Improving the peri-operative management of patients undergoing free tissue transfer for head and neck malignancy

Dr Karen A Eley

Faculty of Medicine & Health Sciences

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(By Publication)

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Abstract

The cohort of patients with oral malignancy is typically of advanced age with significant co-morbidity. The causative factors for such malignancies, such as tobacco and alcohol, are also those which result in cardiovascular disease. As a result patients undergoing ablative and reconstructive surgery, with free tissue transfer, are at considerable risk of peri-operative morbidity and mortality from both primary and secondary disease. Free flap failure has a significant impact upon patient outcome, with resultant delayed discharge, and increased morbidity and mortality. By optimising co-morbidity and peri-operative factors such as fluid balance, nutrition, coagulation and blood pressure support, the complications of complex surgery are reduced.

The collective objectives of this thesis were to determine methods, by both routine and novel approaches, to enhance patient care following ablative and reconstructive surgery for head and neck malignancy.

As a result of these investigations, fluid optimisation with LiDCO monitoring, which derives stroke volume from the blood pressure waveform, is advocated in patients undergoing ablative and reconstructive surgery. Peri-operatively when blood pressure cannot be maintained with fluids alone and pressor support is required, low dose noradrenaline is considered the optimal agent in view of the improvements in flap perfusion and reliable elevation of mean arterial pressure. Careful anticoagulation prescribing should be undertaken, with anti-Xa monitoring of low molecular weight heparin to ensure adequate response, in combination with thromboelastography to identify patients most at risk of thrombotic flap complications.

This thesis has made original contributions to the literature in the peri-operative management of patients undergoing free tissue transfer following ablative surgery for head and neck malignancy in terms of pressor support, coagulation, nutrition, fluid management and hospital admission route. Collectively these recommendations may improve patient outcome with significant long term benefits for both patients and the NHS.

For my parents who support me in everything I do.

In loving memory of my Nan and Grandad.

Contents

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Abbreviations and Acronyms

ACE-27	Adult Co morbidity Evaluation 27
ALT	Anterolateral thigh
ASA	American Society of Anaesthesiologists grade
bd	Twice daily
BI	Bleeding Index
BMI	Body Mass Index
BNF	British National Formulary
BP	Blood pressure
CBCT	Cone Beam Computed Tomography
CI	Cardiac Index
CN	Cranial Nerve
CO	Cardiac output
CP	Cancer procoagulant
CT	Computed Tomography
DIEP	Deep Inferior Epigastric Perforator Flap
DVT	Deep vein thrombosis
FNA	Fine needle aspiration
HPV	Human Papilloma Virus
HR	Heart rate
IJV	Internal jugular vein
IL	Interleukin
IU	International units
KAREN	Key to Aid Replacement Enteral Nutrition
LMWH	Low Molecular Weight Heparin
MA	Maximal amplitude (with regard to TEG)
MAP	Mean arterial pressure
MHRA	Medicines and Healthcare products Regulatory Authority
MRI	Magnetic Resonance Imaging
NG	Nasogastric
NGT	Nasogastric tube
NHS	National Health Service
od	Once daily
PAI	Plasminogen activator inhibitor
PE	Pulmonary embolism
PEG	Percutaneous endoscopic gastrostomy
PET	Positron Emission Tomography
SCC	Squamous Cell Carcinoma
SD	Standard deviation
SE	Standard error
SPSS	Statistics Package for Social Scientists
SVR	Systemic vascular resistance
SVV	Stroke volume variance
TEG	Thromboelastography
TF	Tissue Factor
TNF	Tumour necrosis factor
TNM	Tumour Nodes Metastases
cTNM	Clinical TNM stage
pTNM	Pathological TNM stage
tPA	Tissue plasminogen activator
TPU	Tissue Perfusion Units
TRAM	Transverse Rectus Abdominis Myocutaneous
UFH	Unfractionated Heparin
UK	United Kingdom
USA	United States of America
VEGF	Vascular endothelial growth factor
VTE	Venous Thromboembolism

Manufacturer details

The following software and hardware are utilised throughout the thesis:

- CaseNotes Version 5, Build B268R0, OHIS, Oxford, UK
- Centricity© Enterprise Version 3.0, GE Medical Systems, Buckinghamshire, UK
- Matlab, Version 7.11.0.584 (R2010b), Mathworks, Natick, Massachusetts, USA
- Microsoft Access 2007, Microsoft, Redmond, Washington, USA
- Microsoft Excel 2007, Microsoft, Redmond, Washington, USA
- Statistical Package for the Social Sciences, SPSS Version 18.0, IBM Corp, Somers, NY, USA
- Transonic Laser Doppler, Transonic Systems Inc, Ithaca, NY, USA
- LiDCO Rapid, LiDCO Ltd, Cambridge, UK
- AcqKnowledge Software Version 3.9.1.6, Biopac Systems Inc, California, USA

Acknowledgements

First and foremost I would like to thank Mr Stephen Watt-Smith and Dr Duncan Young who first introduced me to, and continue to inspire me on my academic path. Without their support and encouragement much of the work included in this thesis would not have been possible.

I would like to thank all of the staff and patients who have assisted in each of the included studies; particular thanks go to the intensive care team whose assistance with the pressor study was invaluable.

I am most grateful for the ongoing support of my family and friends who, as always, have provided me with the encouragement and time to permit completion of the included papers and thesis.

Finally I would like to thank the Oxfordshire Health Services Research Committee (OHSRC) for funding the work on pressor agents, both in the form of a research fellowship and small research grant.

1. Introduction

1.0 Introduction

The incidence of head and neck cancer, particularly oral cancer continues to rise. Whilst once considered a malignancy of advanced age as a result of exposure to alcohol and tobacco, the greatest rise in recent years has been amongst a younger cohort, more frequently associated with the human papilloma virus (HPV). Whilst the mainstay of treatment for HPV positive oropharyngeal carcinomas is primarily radiotherapy, curative management for the majority of tumours (HPV negative) includes surgical resection and reconstruction, often in combination with chemo/radiotherapy.

The surgical management of patients following ablative surgery has been revolutionised by advances in microsurgical techniques. Such surgery is frequently prolonged and complex, with associated morbidity and mortality. Optimised peri-operative management is paramount to maximise survival of transplanted tissues and minimise associated morbidity.

This thesis, via a collection of published work, explores a number of factors in peri-operative optimisation in patients undergoing free tissue transfer following ablative surgery for head and neck (oral) cancer.

1.1 Thesis Structure

This thesis explores the peri-operative management of patients undergoing free tissue transfer following ablative surgery for oral malignancy. This work has made original contributions to the field with publications in the following key areas:

1. Pressor support and their effects on transplanted tissues
2. The management of coagulation
3. Nutritional support
4. Fluid management and cardiac events

The thesis commences with a general overview of oral malignancy, surgical management and factors impacting upon patient outcome, with subsequent sections devoted to each of the above topics with a focused literature review. A pertinent discussion is included at the end of each section, with the main discussion and critical appraisal of the published works on which this thesis is based, in the general discussion at the end of the thesis.

1.2 Thesis Objectives

The key objectives for this body of work, with respect to patients undergoing ablative surgery for oral cancer with free flap reconstruction, were to:

1. Identify the optimal agent for blood pressure support following free tissue transfer
2. Identify methods for predicting those patients likely to develop thrombotic complications to permit early intervention and prevent flap loss
3. Determine the efficacy of standard anticoagulation prescription and associated complications
4. Identify the complication rate following surgery in terms of myocardial infarction
5. Develop a method to aid in appropriate selection of feeding adjuncts

Collectively these objectives aim to improve outcome by optimising peri-operative management of patients.

This work was conducted in the departments of Oral & Maxillofacial Surgery and the Intensive Care Unit at the John Radcliffe Hospital, Oxford.

1.2 List of Published Works Submitted for Thesis

The publications upon which this work is based are included in **Appendix C**, and include:

1. **Eley KA**, Young JD, Watt-Smith SR. Epinephrine, norepinephrine, dobutamine, and dopexamine effects on free flap skin blood flow. Plast Reconstr Surg 2012; 130(3):564-70.[3]

2. **Eley KA**, Young JD, Watt-Smith SR. Power spectral analysis of the effects of epinephrine, norepinephrine, dobutamine and dopexamine on microcirculation following free tissue transfer. Microsurgery 2013; 33(4):275-81[4]

3. **Eley KA**, Young D, Watt-Smith. Assessment of the effects of pressors on graft blood flow after free tissue transfer surgery: interim findings. Br J Oral Maxillofac Surg 2009; 47(7): e41-42 [Published abstract].[5]

4. **Eley KA**, Young D, Watt-Smith. Assessment of the effects of pressors on graft blood flow after free tissue transfer surgery: Phase I results. Br J Oral Maxillofac Surg 2010; 48(Supp 1): S13 [Published abstract]. [6]

5. Parker RJ, **Eley KA**, Von Kier S, Pearson O, Watt-Smith SR. Functional fibrinogen to platelet ratio using thromboelastography as a predictive parameter for thrombotic complications following free tissue transfer surgery: a preliminary study. Microsurgery 2012; 32(7): 512-9.[7]

6. **Eley KA**, Watt-Smith SR. Low molecular weight heparin in patients undergoing free tissue transfer following head and neck ablative surgery: a review of efficacy and associated complications. Br J Oral Maxillofac Surg 2013; Oct;51(7):610-4.[8]

7. **Eley KA**, Watt-Smith SR. Coagulopathies and the use of LiDCO Plus Rapid monitoring in patients following head and neck cancer resection and reconstruction. Br J Oral Maxillofac Surg 2010; 48(6): 466.[9]

8. **Eley KA**, Parker R, Bond SE, Watt-Smith SR. Are routine prophylactic dalteparin doses appropriate in patients undergoing head and neck cancer resection? Int J Oral Maxillofac Surg 2009; 38(5): 584-5 [Published abstract].[10]

9. Parker R, **Eley KA**, Bond SE, Watt-Smith SR. Is the ratio of functional fibrinogen to platelets as measured by thromboelastography a predictive parameter for thrombotic complications in free tissue transfer surgery? Int J Oral Maxillofac Surg. 2009; 38(5): 585 [Published abstract].[11]

10. **Eley KA**, Shah R, Bond SE, Watt-Smith SR. A review of post-operative feeding in patients undergoing resection and reconstruction for oral malignancy and presentation of a pre-operative scoring system. Br J Oral Maxillofac Surg 2012; 50(7):601-5.[12]

11. **Eley KA**, Watt-Smith SR. Routine use of percutaneous endoscopic gastrostomy (PEG) in head and neck oncology: benefits and pitfalls. Br J Oral Maxillofac Surg 2010; 48(Supp 1): S20 [Published abstract].[13]

12. **Eley KA**, Watt-Smith SR. Myocardial infarction diagnosed by troponin concentration in post-operative patients with head and neck cancer admitted on the day of operation. Br J Oral Maxillofac Surg 2009; 47(3):245-6.[14]

13. **Eley KA**, Watt-Smith SR. Re: Post-operative fluid balance in patients having operations on the head and neck. Br J Oral Maxillofac Surg 2009; 47(3):249.[15]

14. **Eley KA**, Watt-Smith SR. Intra-operative use of LiDCO – is there an effect on the volume of intravenous fluids used by anaesthetists during free flap surgery for head and neck cancer? Br J Oral Maxillofac Surg 2009; 47(7):e15 [Published abstract]. [16]

15. **Eley KA**, Watt-Smith SR. Post-operative troponin positive cardiac events in patients undergoing head and neck cancer resection admitted on the day of surgery. Br J Oral Maxillofac Surg 2009; 47:e38 [Published abstract].[17]

1.3 Declaration of Published Work

For all of the publications on which this thesis is based, I played a fundamental role in study design, data collection and data analysis. I wrote the first draft of the manuscripts, completed required revisions, and was the first and corresponding author. My involvement in each publication is further detailed below:

1. **Eley KA**, Young JD, Watt-Smith SR. Epinephrine, norepinephrine, dobutamine, and dopexamine effects on free flap skin blood flow. Plast Reconstr Surg 2012; 130(3):564-70.[3]

   I completed the literature review and subsequently developed the research question in collaboration with my co-authors. I obtained ethical approval from the Oxfordshire Research ethics committee with assistance from SR Watt-Smith. I successfully obtained funding in the form of a research fellowship and small research grant for this work. I completed all of the data collection overnight on the intensive care unit. I worked with JD Young in the analysis of the results. I wrote the first draft of the manuscript, with subsequent contributions by my co-authors. I submitted the paper for publication, and responded to the reviewers comments. I am the corresponding author.

2. **Eley KA**, Young JD, Watt-Smith SR. Power spectral analysis of the effects of epinephrine, norepinephrine, dobutamine and dopexamine on microcirculation following free tissue transfer. Microsurgery 2013; 33(4):275-81.[4]

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5. Parker RJ, **Eley KA**, Von Kier S, Pearson O, Watt-Smith SR. Functional fibrinogen to platelet ratio using thromboelastography as a predictive parameter for thrombotic complications following free tissue transfer surgery: a preliminary study. Microsurgery 2012; 32(7): 512-9.[7]

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6. **Eley KA**, Parker RJ, Watt-Smith SR. Low molecular weight heparin in patients undergoing free tissue transfer following head and neck ablative surgery: a review of efficacy and associated complications. Br J Oral Maxillofac Surg 2013; Oct;51(7):610-4.[8]

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7. **Eley KA**, Watt-Smith SR. Coagulopathies and the use of LiDCO Plus Rapid monitoring in patients following head and neck cancer resection and reconstruction. Br J Oral Maxillofac Surg 2010; 48(6): 466.[9]

   I reviewed the publication in the British Journal of Oral & Maxillofacial Surgery and identified differences between this and local practice. I completed the literature review. I had previously completed data collection and analysis. I wrote the first draft with contribution from SR Watt-Smith. I submitted the letter for publication and responded to the reviewers comments.

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2. Background

2.0 Background

This chapter provides a brief overview of the anatomy, physiology, pathology and surgical techniques on which this thesis focuses. As the primary motivation for the thesis was to improve peri-operative management in patients with oral malignancy, it is pertinent to commence with an overview of relevant anatomy prior to reviewing the pathology and peri-operative management.

2.1 Anatomy of the Oral Cavity

The oral cavity extends from the vermilion border of the upper and lower lips, extending posteriorly to the V-shaped terminal sulcus of the tongue, the junction of the hard and soft palates and the anterior border of the anterior faucal arch. The oral cavity is sub-divided into seven bilateral sub-sites, demonstrated in **Figure 1**. The soft palate, the posterior one third of the tongue and the fauces are considered to be part of the oropharynx rather than the oral cavity.

Within the floor of the oral cavity, the mucosa overlies the mylohyoid, hyoglossus and genioglossus muscles, which provide structural support. The vermilion border of the lips provides the commencement of the transition zone between external skin and oral mucosa. Continuous with the lips, the cheeks and buccal mucosa provide the lateral limits of the oral cavity.

The blood supply to the oral cavity is via the lingual, facial and maxillary branches of the external carotid artery, with venous drainage ultimately entering the internal jugular vein (IJV). Sensory innervation is via the maxillary and mandibular branches of the trigeminal nerve (CN V2 and CN V3). Motor innervation is by the facial nerve (CN VII) and the motor branches of the mandibular trigeminal nerve (CN V3). The intrinsic muscles of the tongue, the extrinsic muscles except the palatoglossus, and the geniohyoid receive motor innervation from the hypoglossal nerve (CN XII). The palatoglossus is supplied by the cranial root of the glossopharyngeal nerve (CN IX).

The lymphatic drainage of the oral cavity is via the cervical lymph nodes. These basins consist of fifty to seventy lymph nodes divided into seven discrete levels by the anatomic structures of the neck. The lateral structures of the oral cavity tend to drain to ipsilateral cervical lymph nodes. However, midline structures drain bilaterally.

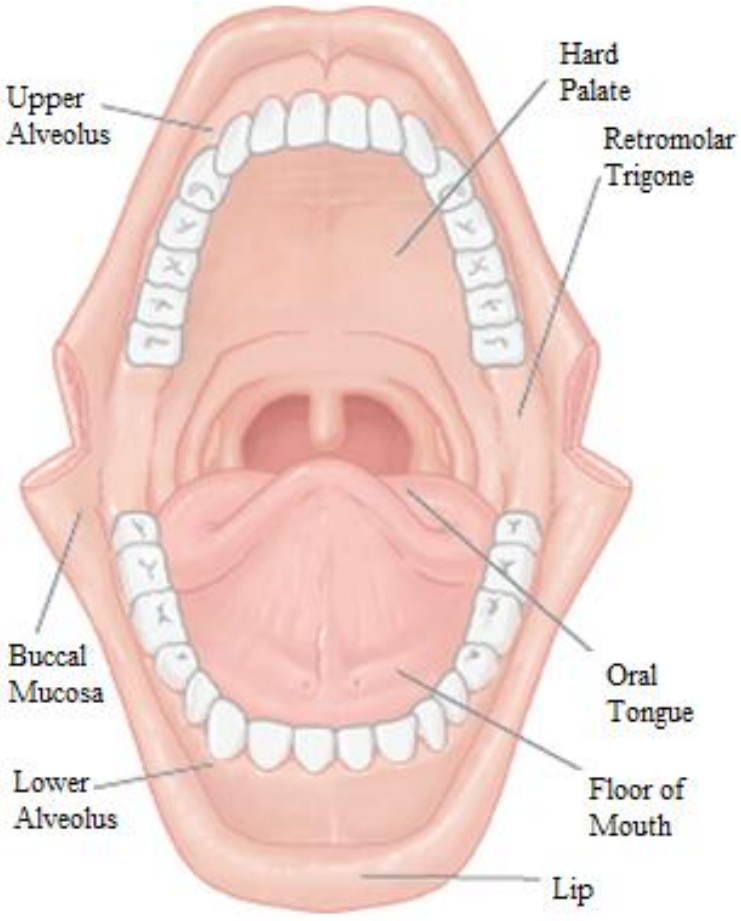

Figure 1: Diagram of the oral cavity.
The oral cavity is sub-divided into seven bilateral subsites; these include the alveolus, palate, floor of mouth and retromolar trigones [source [2]].

2.2 Oral Malignancy

Accounting for approximately 30% of all head and neck malignancies, oral cancer is responsible for 2% of all malignant tumours in northern Europe and USA, and 30% in the Indian subcontinent.[18,19] Over 90% of these tumours are squamous cell carcinomas (SCC). Clinical presentation is usually with a non-healing ulcer, mass, or tooth mobility. However, in some cases initial presentation is with an area of leukoplakia, erythroleukoplakia, erythroplakia, or alternatively as a result of metastatic spread. Pain is usually a late feature, although referred otalgia is a common manifestation.

2.2.1 Incidence & Aetiology

The incidence of head and neck cancer, particularly oral cancer continues to rise and is currently the 15th most common form of cancer in the UK.[20] The tongue is the most frequently affected site in the oral cavity, with ethnicity resulting in some variation in incidence at the remaining oral cavity sub-sites.[21] Overall, the floor of mouth is the second most frequently affected sub-site, with the remainder of sub-sites being almost equally affected.

Head and neck cancer is more common in advanced age, and is strongly associated with alcohol, tobacco use (in any form) and Khat or Betel chewing. [22-24] Since many smokers are also drinkers, and vice versa, it is difficult to separate these particular aetiological factors. Blot *et al*[25] conducted a large case control study in the USA, identifying that both alcohol and tobacco contribute to the occurrence of oropharyngeal carcinoma. They reported a strong dose-response relationship with both substances, with the risks of oropharyngeal cancer combining in an additive fashion in those who both smoke and drank alcohol. The dehydrating effect of alcohol on cell membranes enhances the ability of tobacco-associated carcinogens to permeate mouth tissues.[21] The irritation and chemicals within Khat, Betel, tobacco and alcohol result in dysplasia, from which a significant proportion of tumours are thought to arise.

Leukoplakia presents as a white patch which cannot be scraped off of the tissues, with approximately 5-30% of untreated lesions undergoing malignant transformation. Erythoplakia is seen as a red patch, with insitu or invasive carcinoma found in approximately 50% of lesions.[19]

In approximately 25% of cases the aetiological factor is demonstrated to be the human papilloma virus (HPV), with the most common sub-types being HPV-16 and HPV-18.[26,27] HPV-16 is increasingly identified as the aetiological factor in oropharyngeal SCC of younger patient cohorts.

Other predisposing factors include diseases such as syphilis, chronic oral candidiasis, lichen planus and lupus.

2.2.2 Lymphatic Spread

The lymphatic drainage from the oral cavity is to the cervical lymph nodes in the neck. The cervical lymph nodes are classified into six levels (I-VI), which represent the drainage order and therefore metastatic involvement (**Figure 2**). Tumours affecting the maxillary complex (maxilla, hard palate and paranasal sinuses), typically present late, resulting in locally advanced disease and metastatic nodal involvement.[28,29] The presence or absence of extracapsular spread of tumour in metastatic cervical nodes is the most important single prognostic factor.[18]

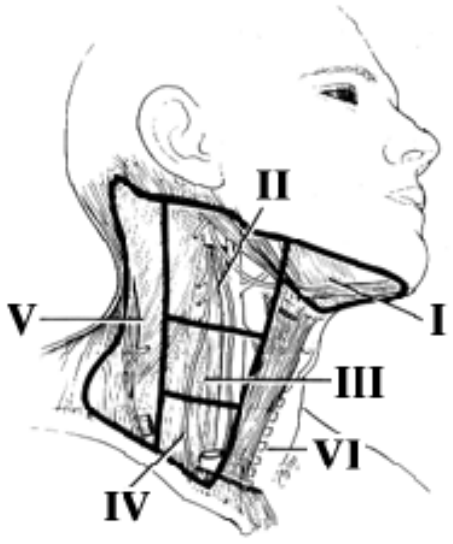

Figure 2: The cervical lymph node levels of the neck.
Tumours involving the head and neck tissues drain to these lymph nodes. Surgical clearance of the nodes in levels I-III is typically completed in head and neck cancers.

2.2.3 Investigation

The first key step in the investigation of oral carcinoma is a full history with systematic clinical examination, which provides an initial clinical stage of the disease (cTNM). A plain radiograph (orthopantogram) provides information on the presence of pathology and can be obtained at the time of the first clinic visit. Fine needle aspiration (FNA) of any neck masses and biopsy of the region of concern provides histological confirmation of the diagnosis, and may be performed with ultrasound guidance. Magnetic Resonance Imaging (MRI) and/or Computed Tomography (CT) or Cone Beam CT (CBCT) imaging should be obtained to define the extent of the tumour and demonstrate any clinically undetectable lymphatic involvement in the neck. The accurate identification of bony invasion is particularly important to determine whether bony resection is required, and provide accurate tumour staging.[30] CT examination should include the chest and abdomen to identify any metastatic involvement; where tumours are small, and therefore unlikely to have metastasised, or where resources are limited, a chest radiograph may be substituted for CT. As synchronous tumours (occurring within 6 months of the first tumour) are found in 1-6% of patients, panendoscopy with biopsy is advocated. In cases where patients present with metastatic disease and the primary site is not clear, or where there is a question regarding the extent of tumour spread, Positron Emission Tomography (PET) in combination with CT or MRI may be useful.

2.2.4 Tumour Staging

Clinical tumour staging is completed using the TNM system (Tumour Nodes Metastasis) (clinical stage, cTNM), first developed in 1977 by the American Joint Committee on Cancer (AJCC).[31] All available information from clinical examination and imaging is utilised to determine this initial stage. The final TNM staging of the patient is completed following resection of the tumour with histological analysis of the tumour and draining lymph nodes (pathological stage, pTNM). The TNM criteria for oral cavity tumours are included in **Appendix A**.

2.3 Management of Oral Cancer

The primary management of oral cavity SCC is with a combination of surgical resection and/or chemo- and radiotherapy. For T1 or T2 tumours brachytherapy (implant radiotherapy) provides an alternative to surgery with similar control rates, but with potential risk of osteoradionecrosis of the bone. Surgical resection requires enbloc excision of the tumour with a margin of approximately 1cm of normal surrounding tissue.

Where there is evidence of bony invasion into the mandible, resection of bone is required in addition to the overlying soft tissues. This may be via a rim resection, which involves resection of the alveolus with preservation of the body of the mandible, or segmental resection where there is significant bony invasion or a history of irradiation. Tumours of the hard palate, maxillary alveolus, maxillary sinus or maxilla require enbloc resection of the soft and hard tissues.

Approximately 40% of patients with tongue cancers have nodal involvement at the time of presentation, with 20% having bilateral disease. Neck dissection in cases where nodal involvement is present is recommended, but prophylactic neck dissection is a contentious issue.[19] The majority of surgeons offer patients with T3 or T4 tumours elective node dissection. The dissection of Levels I-IV on the ipsilateral side to the tumour (bilateral in midline tumours) is most common. In addition to clearance of the lymph nodes, reducing the risk of lymphatic spread, the neck incision provides access to the vessels of the neck for subsequent microsurgical reconstruction, as discussed in the following sections.

HPV positive tumours are typically chemo/radio sensitive, and this forms the basis of treatment in these cases. They may however require salvage surgery with or without clearance of the lymph nodes in the neck.

2.4 Surgical Reconstruction

Following ablative surgery, the resultant defect requires reconstruction to restore both form and function. Reconstructive options are dependent upon the site and size of the defect. The simplest methods, limited to small defects, include leaving the site to heal by secondary intention, directly closing the incision or applying a skin graft or moving local tissues to fill the void (local flap). Direct closure results in scar tissue which may cause difficulty in distinguishing scar from tumour recurrence. As a result mucosal grafts are typically preferred for smaller tumours.

The options for mandibular reconstruction include spanning the defect with a reconstruction plate rigidly fixed to either end of the defect, which is the simplest method for patients not suited to other methods of reconstruction, have lateral defects with good soft tissue coverage and who have not and will not require radiotherapy. Alternatively the bony defect can be reconstructed with non-vascularised tissue such as a bone graft, which is used in combination with a reconstruction plate. However, the optimal method of reconstruction is with vascularised bone.[19] This is discussed later in this chapter.

Maxillary defects and their reconstructive options are defined by the Brown classification[1] (**Figure 3**). The simplest method of reconstruction is to utilise an extended denture (obturator). The resultant bony defect may necessitate a complete multi-part obturator which requires fixations, usually magnetic, to hold it in place and restore the function of chewing. The removal and cleaning of such obturators requires a level of manual dexterity from the patient. More definitive methods of reconstruction, as demonstrated in the classification by Brown *et al*[1] require composite flaps, but these do not necessarily result in improved function.

A flap is defined as a unit of tissue of variable composition which, when transferred from a donor to a recipient site, brings its own blood supply and intrinsic circulation.[32] A flap may be local or distant. In many cases the defect is too large for reconstruction from the local tissues and surgical reconstruction is reliant upon distant flaps in the form of pedicled or free flaps. These may contain a combination of skin, muscle, bone, fat or fascia (fasciocutaneous flap). The transfer usually leaves a secondary defect which is usually either directly closed, or covered with a skin graft.

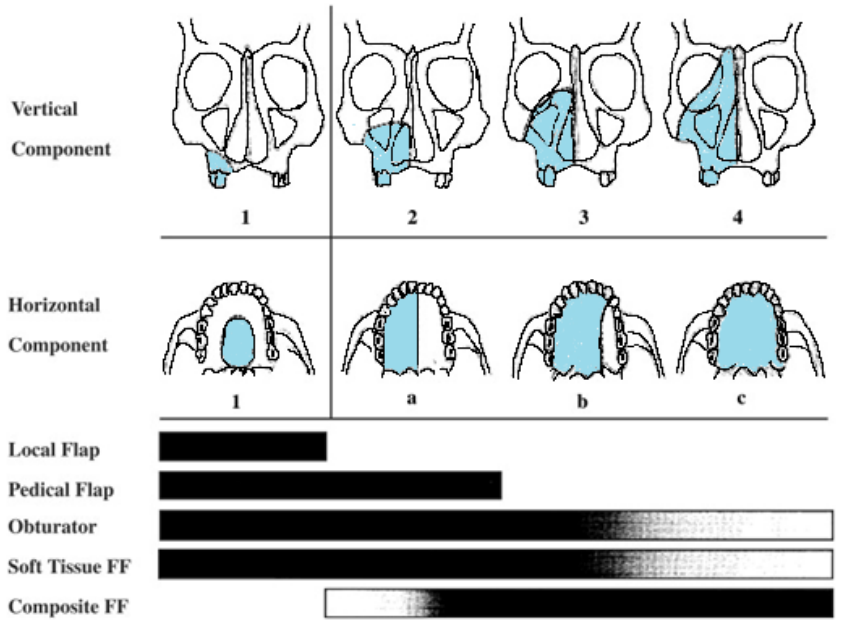

Figure 3: Brown Classification of maxillary defects.
Brown *et al*[1] classified maxillary defects into horizontal and vertical components, highlighting that whilst obturators can be utilised for even the most complex of defects, composite flaps are deemed to be the most optimal method of reconstruction.

2.4.1 Distant Pedicled Flaps

A distant flap can be transferred to its destination in several ways. It can be directly applied to the primary defect, it can be waltzed, pivoted on its pedicle (blood supply) or it may be attached to a carrier (e.g. the wrist) on which it is conveyed to its destination.[33] The distant flaps most frequently utilised in head and neck reconstruction are pedicled (island flaps). In such flaps, the pedicle is reduced in size, in some cases down to just the vessels. The flap pivots on the pedicle and the distal end, which is frequently muscle with an overlying skin paddle, fills the defect, by passing underneath the intermediary tissues which provides protection and prevents drying out of pedicle. Reconstructive options following ablative surgery for head and neck malignancy include pedicled pectoralis major and latissimus dorsi muscle flaps. Failure of these flaps may occur as a result of twisting of the pedicle causing compromise of the blood supply. The main limitations of these flaps include the physical distance the flap can provide cover, and the often poor cosmetic result. This is because it is more difficult to customise the pedicled flap to the defect due to the constraints of the pedicle, and associated tethering and scarring. However, these are generally reliable flaps and are therefore valuable in patients who are poor candidates for more extensive and lengthier surgery.

2.4.2 Free Tissue Transfer

Free tissue transfer is the process of transferring tissues from one site to another, requiring separation of the blood supply at the donor site and surgical anastomosis at the recipient site. Microsurgery utilises magnification either using an operating microscope or loupes to enable the anastomosis of small vessels or nerves.[34]

The foundation for microvascular anastomoses began in 1897 when John B Murphy an American surgeon successfully united the femoral artery after a gunshot wound. Murphy documented that "not a drop of blood escaped at the line of suture" and "pulsation was immediately restored."[35] It was a further 60 years until microscopes were utilised in vascular surgery permitting anastomoses of vessels 1.4mm in diameter, and the term "microvascular surgery" coined by Jules Jacobson.[34] However, it is the American plastic surgeon, Harry J Bunke who is considered the pioneer of contemporary microsurgery. Bunke replanted a rabbit ear, successfully anastomosing vessels of 1mm in diameter, and subsequently developing many of the microsurgical instruments in use today. These developments permitted the successful replantation of digits, and toe to hand transfers, and in 1972 the first human free flap was reported by McLean and Bunke[36] - an omentum flap for a scalp defect.

The possibility of composite tissue transfer was subsequently explored and the implementation of free groin flaps and iliac bone grafts demonstrated superb results in classically hopeless defects.[37] Subsequent developments in microsurgical tissue transfer evolved at an exponential rate, providing the reconstructive surgeon with a toolbox of techniques and flaps for a myriad of defects.

Free flaps are classified according to their composition, which may be cutaneous, fascio-cutaneous, musculo-cutaneous, osseo-cutaneous, muscle, bone, fascia, tendon or any combination.[32]

Musculocutaneous flaps are based on perforators that reach the skin through the muscle. The musculocutaneous system predominates on the torso and this is the location of most of these flaps.[19] Mathes and Nahai in 1981 classified muscle flaps into 5 types based upon the anatomical relationship between the muscle and its vascular pedicle and the intra-muscular anastomoses (**Figure 4**).[19,32,38,39]

- Type 1: one vascular pedicle (e.g. gastrocnemius, tensor fasciae latae)
- Type 2: one dominant vascular pedicle usually entering close to the origin or insertion of the muscle with additional smaller vascular pedicles entering the muscle belly (e.g. gracilis, trapezius)
- Type 3: two dominant pedicles from different sources, either of which can support the whole muscle (e.g. rectus abdominis, serratus anterior)
- Type 4: segmental supply each of which only supplies its segment and an immediately adjacent segment (e.g. sartorius, sternomastoid)
- Type 5: one dominant pedicle near the insertion which can supply the whole muscle and several minor pedicles near the origin which can also supply the muscle (e.g. latissimus dorsi)

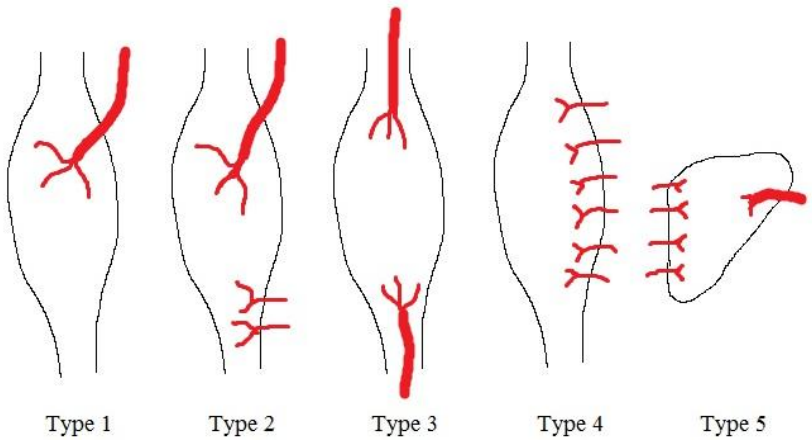

Figure 4: Mathes & Nahai classification of muscle flaps based upon their vascular supply.

Fasciocutaneous flaps are based on vessels running either within or near the fascia. Blood reaches these flaps from fasciocutaneous vessels (also called septocutaneous vessels) running from the deep arteries of the body to the fascia. The fasciocutaneous system predominates on the limbs and this is the location for the majority of these flaps.[19] The main classification system was described by Cormack and Lamberty in 1984.[40,41] This system classifies flaps on the route to reach the skin and directness of supply of the vascular pedicle (**Figure 5**):

- Type A: (broad based with perforators unseen): multiple perforators at the flap base with vessels orientated longitudinally along the flap axis
- Type B: (perforator, axial): single consistent perforator feeding a fascial vascular plexus which may run along flap axis (e.g. groin)
- Type C (ladder type): longitudinal septal vessel sending multiple perforators to fascia and skin as it travels (e.g. radial forearm)
- Type D (osteo-fasciocutaneous): Type C with bone (e.g. radial forearm with bone).

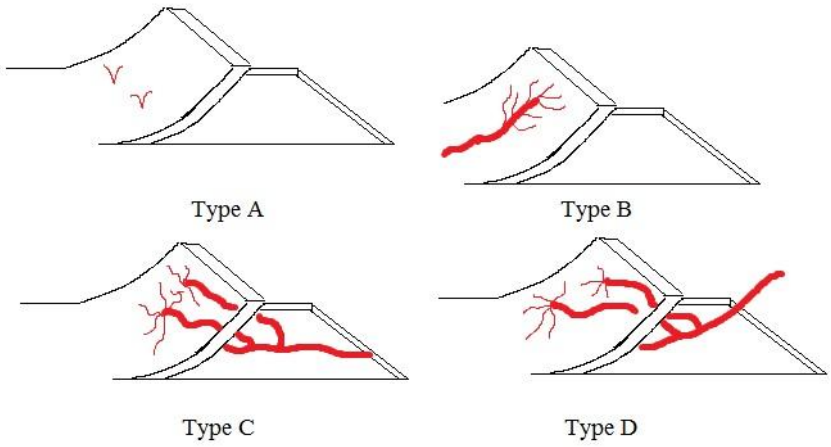

Figure 5: Cormack and Lamberty classification of fasciocutaneous flaps based upon the vascular pedicle.

Numerous variations to these classification systems have been described and these modifications are beyond the scope of this thesis. Reconstruction following resection for head and neck malignancy is most frequently with the radial forearm, fibula, anterolateral thigh, fibula, and/or latissimus dorsi free flaps. These are discussed in further detail below.

2.4.2.1 Radial Forearm Free Flap

The radial forearm free flap was first described in 1978 as a proximally based free flap.[42] It is a Type C flap according to the Cormack and Lamberty classification. The radial forearm flap is raised on the flexor aspect of the forearm. The radial vessels supply the plexus of the investing layer of deep fascia, from which blood is distributed to the overlying skin.[33] The flap can be limited to skin and fascia, or include a length of the radius bone. For a fascicocutaneous flap the plane of elevation lies between the muscles and investing layer of fascia, a subfascial dissection. The flap can also be raised suprafascially. The radial artery and its venae comitantes, with or without a superficial vein such as the cephalic vein are elevated with the flap. With sacrifice of the radial artery, perfusion of the hand becomes dependent upon the ulnar artery. In 12% of cases the radial artery is the dominant supply to the hand, with 3% having an incomplete palmar arch.[42] It is therefore necessary to confirm pre-operatively that the ulnar artery can maintain the blood supply of the hand by performing an Allen's test. The donor site can be covered with a skin graft without any long term functional deficit. However, the superficial radial nerve may need to be sacrificed resulting in some sensory deficit over the extensor aspect of the thumb and first webspace. With a long pedicle the radial forearm flap is a very reliable flap in the reconstruction of oral defects.

2.4.2.2 Anterolateral Thigh Free Flap

The anterior lateral thigh (ALT) flap is a fasciocutaneous flap that has become popular in recent years. It is classified as a Type B flap if one perforator is included and as a Type C if multiple perforators are included.[32] The flap is located over the middle third of the thigh anterior and lateral to the rectus femoris and the vastus lateralis muscles. It is usually used for coverage of defects when a relatively thin flap is required. It is based on perforators from the descending branch of the lateral circumflex artery, which provides a good length of pedicle. The donor site can often be closed directly.

2.4.2.3 Fibula Free Flap

The fibula is elevated on the peroneal vessels, running distally alongside the fibula behind the interosseous membrane. Septocutaneous perforators from the peroneal vessels pass laterally behind the fibula in the intermuscular septum between the peroneal muscles and soleus, and perfuse the overlying skin. These allow the fibula to be transferred as an osteocutanous free flap, as well as a vascularised bone graft.[33] Raised as an osteocutaneous flap, this is classified as a Type D flap. Bearing 10-15% of the load the fibula can be removed without functional impairment, and the ankle remains stable if the middle third of the fibula is harvested.[32]

2.4.2.4 Latissumus Dorsi Free Flap

The latissimus dorsi can be transferred as a muscle only, or myocutaneous flap. It is a Type V flap according to the Mathes and Nahai classification.[39] The dominant blood supply is the thoracodorsal artery, a continuation of the subscapular artery arising from the third part of the axillary artery. It is also supplied segmentally by intercostals and lumbar perforators.[32] It is a reliable free flap, with a long pedicle, good muscle bulk and vessels of a large diameter.

2.5 Free Flap Survival

Since its introduction, free flap viability has improved significantly, with reported success rates of over 95%.[43,44] The flap remains ischaemic after detachment from the blood supply at the donor site until completion of the anastomosis (primary ischaemia). Any later hypoperfusion or ischaemia (secondary ischaemia) due to impaired inflow or outflow from the flap is even less well tolerated and may result in flap failure.[45]

Anaerobic metabolism in the tissues during ischaemia increases the production of superoxide radicals. Following reperfusion, free radical scavengers (e.g. superoxide dismutase) attack the radicals, injuring the cells.[32] This results in endothelial swelling and leakage of fluid into the interstitial space further narrowing the vessel lumen. This is followed by intravascular platelet aggregation. This process is referred to as ischaemia-induced reperfusion injury.[32] Clinically, the result is referred to as "no-reflow," where initial flap perfusion gradually decreases resulting in irreversible flap ischaemia.

Flap necrosis, whether partial or total, is an undesirable complication of reconstructive surgery. These complications can be avoided to a large extent by meticulous surgical technique with careful attention to detail, avoidance of tension, and close post-operative surveillance.[46] Even if the vascular anastomosis is perfect, blood flow may be disturbed by twisting, tension, kinking or external compression of the pedicle.[47]

Peri-operative optimisation is vital to ensure flap survival. This includes measures to maintain adequate blood supply to the flap, minimising risk of thrombosis within the feeding vessels and minimising external compression of the flap vessels.

2.5.1 Flap Flow

The interrelation of factors influencing flow through a vessel, whilst more complex than a rigid tube, can reasonably be described using the Poiseuille-Hagan formula[48]:

$$Flow = (P_A - P_B)x\ \frac{\pi}{8}\ x\frac{1}{\eta}\ x\ \frac{r^4}{L}$$

Where (P_A- P_B) = pressure difference between the two ends of the vessel; η = viscosity; r=radius of vessel; L=length of vessel. As flow is related to the fourth power of the vessel radius, small changes in vessel size results in a large increase in flow.

The muscular tone of vessels is controlled by four main factors:

1. Pressure of the blood within the vessels (myogenic theory) – This theory states that increased intraluminal pressure results in constriction of the vessels and vice versa. This mechanism helps to maintain blood flow at a constant.[19]
2. Neural innervation – The arterioles, arteriovenous anastomoses connecting the arterioles to the efferent veins, and pre-capillary sphincters are innervated by sympathetic fibres.[49] Increased arteriolar tone results in a decrease in cutaneous blood flow, and increased pre-capillary sphincter tone reduces the blood flow into the capillary networks.[19]
3. Humoral factors – These include the effects of adrenaline and noradrenaline which result in vasoconstriction, and histamine and bradykinin which result in vasodilatation. Low oxygen saturation, high carbon dioxide saturation and acidosis also result in vasodilatation.[19]
4. Temperature – Increased heat produces cutaneous vasodilatation and increased flow which predominantly bypasses the capillary beds via the arteriovenous anastomoses.[19]

As a result, several oscillatory components are observed in the blood flow signal spanning from the cardiac frequency (~1 Hz) down to endothelium related frequencies (~0.01Hz).[49,50]

2.6 Maintaining Peri-operative Blood Pressure

Adequate flap perfusion is dependent upon both adequate flow and systemic blood pressure (BP). BP is dependent upon cardiac output and systemic vascular resistance (SVR). SVR is the resistance against which the heart pumps, so vasoconstriction results in an increase in SVR whilst vasodilatation reduces it.[51] Cardiac output is the product of heart rate and stroke volume, where stroke volume is defined as the volume of blood that is ejected by the ventricle with a single contraction, having three major determinants: contractility, preload and afterload. Mean arterial pressure (MAP) is the average arterial blood pressure throughout the cardiac cycle, recognising that diastole makes up two thirds of the time. It is less liable to error due to measuring techniques.

In low cardiac output states leading to hypoperfusion, the heart rate, preload, afterload and then contractility should be addressed, since there is little point in attempting to pharmacologically improve the contractility of the heart when it is either too empty or too distended to eject.[51]

In addition to maintaining blood pressure, accurate fluid balance is required in flap management to prevent oedema of the flap tissues which are at increased risk due to the absence of lymphatic drainage.[52] Accurate replacement of fluid depends upon an understanding of the distribution of water, sodium, and colloid in the body.[51] There are two major fluid compartments: the water within cells (intracellular fluid), which accounts for about 65% of the body total, and the water outside cells (extracellular fluid). Approximately 65% of the extracellular fluid comprises the tissue fluid found between cells (interstitial fluid), and the remainder is plasma.[53]

Pre-operative dehydration, prolonged surgery, intra-operative blood loss and insensible losses can make fluid optimisation in patients undergoing resection and free flap reconstruction of oral malignancy particularly challenging. Clinical examination including BP, heart rate and urine output provide only limited information on fluid balance. As a result the majority of patients undergoing such surgery have both central venous catheters and arterial lines placed to provide central venous pressure and MAP. It is the response of the CVP to fluid challenges that aids volume assessment.

A more useful method is transoesophageal Doppler which provides an estimate of stroke volume; however the use of such probes is often difficult due to accurate and consistent positioning in oral cancer cases. An alternative method is to utilise a system which derives stroke volume from the arterial pressure waveform, such as LiDCO™ (**Figure 6**), which is discussed later in the thesis.

Following optimisation of fluid balance, pharmacological intervention is frequently required to maintain MAP.

Within the circulatory system there are three main types of receptor– alpha, beta, and dopamine receptors. Alpha and beta receptors are collectively termed adrenoreceptors (adrenergic receptors). These are a class of G protein-coupled receptors that are the targets for catecholamines, particularly noradrenaline and adrenaline. Binding of these receptors results in stimulation of the sympathetic nervous system.

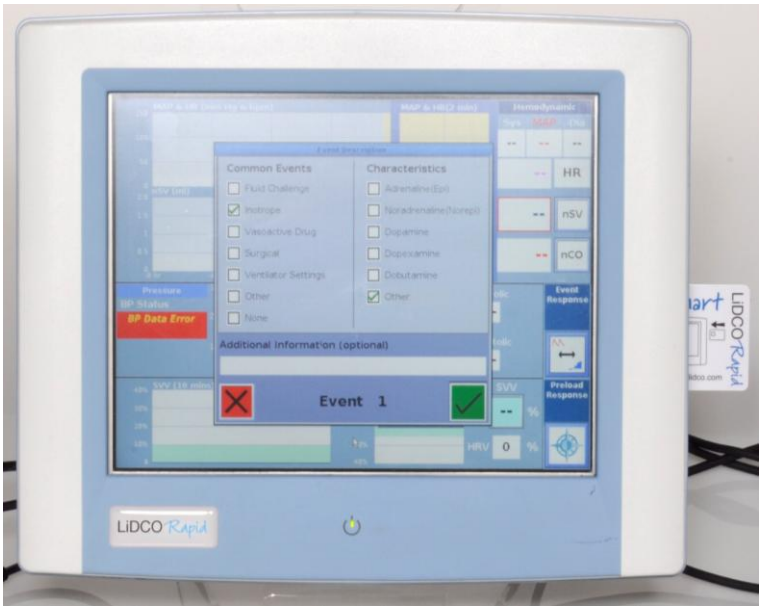

Figure 6: LiDCO Rapid system
This system utilises pulse contour analysis from the arterial pressure waveform to calculate stroke volume variance.

Alpha receptor stimulation results in vasoconstriction of blood vessels, and decreased motility of the smooth muscle of the gastrointestinal tract. The alpha receptors are broadly classified into two groups – α_1 which are located on the post-synaptic membrane and α_2 located on both pre-synaptic neurons and post-synaptic cells. The specific actions of the α_1 receptor include vascular smooth muscle contraction and constriction of smooth muscle within the genitourinary tract. Studies demonstrated that post-junctional responses mediated by α_1 adrenergic receptors could not be explained adequately on the basis of a single population of receptors.[54] This concept was further advanced by the radioligand binding work of Morrow and Creese who suggested a sub-division of α_1 into α_{1A} and α_{1B}, based upon the finding of different binding profiles for various ligands.[54,55] The classification was further complicated by genetic subtyping, with the identification of a third sub-type, α_{1D}. The initial description of the α_{1C} sub-type was later shown to be the homologue of the pharmacologically defined α_{1A} and was as such reclassified into this group.

The α_2 receptor is located both pre- and post-synaptically and serve to produce inhibitory functions including feedback inhibition of neurotransmitter release from pre-synaptic neurons. Post-synaptic α_2 receptors are located on liver cells, platelets and smooth muscle of blood vessels. Four distinct sub-types have been identified, α_{2A}, α_{2B}, α_{2C}, and α_{2D}, with the α_{2D} sub-type being identified only in rats to date.[56]

The alpha receptors have been identified in both the intima and adventitia of blood vessels; α_1-adrenoreceptors appear to be uniformly distributed, whereas α_2-adrenoreceptors are located nearer the intima.[57,58]

Using techniques of molecular cloning three distinct beta adrenergic receptor sub-types have been identified – β_1, β_2 and β_3.[59] $Beta_1$ receptors are located mostly within the heart, where their stimulation results in an increased rate and force of contraction. $Beta_2$ receptors are located within blood vessels and the lungs, and cause vasodilation and bronchodilatation. $Beta_3$ receptors are involved in the enhancement of lipolysis in adipose tissue and thermogenesis in skeletal tissue.

The precise roles for each of these multiple sub-types of adrenoceptors in the regulation of blood pressure have not been completely defined.

Sympathomimetic drugs mimic the effects of transmitter substances of the sympathetic nervous system. These can be utilised to manage hypotension in the peri-operative period. Direct acting drugs include adrenergic receptor agonists which stimulate the α- and β- receptors, and dopaminergic agonists which stimulate the D1 receptors. Indirect acting agents act by blocking and reversing noradrenaline transporter activity. Sympathomimetics have relatively short biological half-lives, achieving a steady state plasma concentration within 5-10 minutes of commencing IV infusion.[60]

Many of the sympathomimetic agents are also considered to be vasoactive agents. Vasoactive agents are a group of bioactive chemicals, which change vasomotor tone through their influence on various peripheral receptors.[61] Vasoactive drugs affect heart rate and stroke volume. They can broadly be classified into inotropes and vasopressors. An inotrope is an agent that alters myocardial contractility.[51,60] A vasopressor is an agent that causes vasoconstriction. Vasopressor agents increase MAP, which increases organ perfusion and preserves distribution of cardiac output to the organs. Vasopressor agents also improve cardiac output and oxygen delivery by decreasing the compliance of the venous compartment and thus augmenting venous return.[62]

The sympathomimetics available within the UK are subdivided in the British National Formulary (BNF) into inotropic sympathomimetics (dobutamine, dopamine, dopexamine and isoprenaline), and vasoconstrictor sympathomimetics (ephedrine, metaraminol, noradrenaline, phenylephrine). However many of these drugs have both vasopressor and inotropic effects. A more useful method of classification is based on their site of action:

1. Directly: adrenoceptor agonists e.g. adrenaline, noradrenaline, isoprenaline, metaraminol (entirely); and dopamine and phenylephrine (mainly).
2. Indirectly: by causing a release of preformed noradrenaline from stores in nerve endings e.g. ephedrine
3. By both mechanisms, though usually one predominates.

	α	β_1	β_2	Dopaminergic	Direct Action	Indirect Action
Adrenaline	✓	✓	✓		✓	
Dobutamine	✓	✓	✓		✓	
Dopexamine			✓	✓	✓	✓
Metaraminol	✓	✓			✓	✓
Noradrenaline	✓	✓			✓	

Table 1: Summary of actions of the most frequently used sympathomimetics in the ICU.

The most commonly utilised agents in the intensive care unit to maintain MAP include adrenaline, noradrenaline, dobutamine, dopexamine and metaraminol. Their actions are summarised in **Table 1**, and are further considered in the following sections. In the USA ephedrine and phenylephrine are also popular.

2.6.1 Adrenaline (Epinephrine)

Adrenaline (**Figure 7**) is a very potent vasoconstrictor and cardiac stimulant, via β_1, β_2, and α effects.[51,63,64] It causes BP to rise rapidly, to a peak proportional to the dose and with a greater rise in diastolic than systolic pressure due to myocardial stimulation (inotropic) increasing the strength of contraction, increased heart rate (chronotropic), and vasoconstriction. At low doses (0.04-0.1mcg/kg/min) the β_1 effects predominate, including increased heart rate, CO and stroke volume, and decreased peripheral vascular resistance. There is also some effect on β_2 receptors in some vessels resulting in dilation and potentially a fall in total peripheral resistance. However, BP tends to rise as β_1 effects predominate. At higher doses, alpha stimulation dominates resulting in vasoconstriction and a resultant increase in BP. It has a half life of 2 minutes.

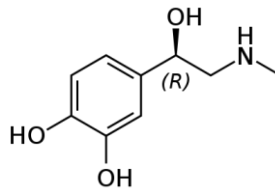

Figure 7: The chemical structure of adrenaline.

2.6.2 Noradrenaline (Norepinephrine)

Noradrenaline (**Figure 8**) exerts its effects on α and β_1 receptors. It has minimal effect on β_2 receptors. Noradrenaline results in an increase in peripheral resistance. It is a potent α agonist and causes a rise in BP by increasing SVR. Since it stimulates both α and β adrenergic receptors, its haemodynamic effects are variable depending on the dosage and clinical setting.[65] At low doses cardiac output and BP are increased, mainly due to predominant β adrenergic stimulation of the heart. However, at higher doses cardiac output may fall as a result of an increase in vascular resistance, despite the positive inotropic effects. It has a half life of 2 minutes.

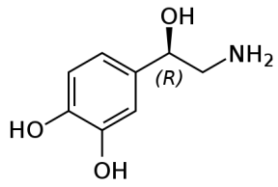

Figure 8: The chemical structure of noradrenaline.

2.6.3 Dobutamine

Dobutamine (**Figure 9**) is a synthetic catecholamine with potent inotropic and modest vasodilatory properties.[66] Dobutamine is a relatively β_1 selective synthetic catecholamine.[63] β_1 effects result in elevation of heart rate and increased contractility and therefore increased cardiac output. Additionally, dobutamine has mild β_2 and α_1 effects. The half life is approximately two minutes, which provides for rapid onset and prompt dose escalation.[66] Despite increases in CO, BP may be reduced or unchanged because of reduction in SVR through β_2 receptor and baroreceptor-mediated vasodilation.[66]

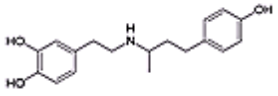
Figure 9: The chemical structure of dobutamine.

2.6.4 Dopexamine

Dopexamine (**Figure 10**) is a synthetic catecholamine acting mainly through activation of dopaminergic and β_2-adrenoceptors. Dopexamine is a synthetic analogue of dopamine.[51] It is characterised by a rapid onset and short duration of action.[67] It exerts its effects as a β_2 agonist. It causes an increase in heart rate and cardiac output and causes peripheral vasodilation and an increase in renal and splanchnic blood flow.

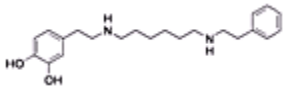
Figure 10: The chemical structure of dopexamine.

2.6.5 Metaraminol

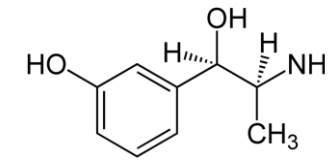

Figure 11: The chemical structure of metaraminol.

Metaraminol (**Figure 11**) is a sympathomimetic drug with a direct effect on vascular-adrenergic receptors and an indirect mechanism of action related to the stimulation of noradrenaline release.[62,68] It has both α and β adrenergic activity, with alpha action being predominant. Metaraminol is a potent peripheral vasoconstrictor. Metaraminol has been utilised to counteract the hypotensive effects of spinal and epidural anaesthesia for many years.[69] It does not tend to cause a change in heart rate.[69] Metaraminol has a longer duration of action than adrenaline or noradrenaline. Effects are seen 1 to 2 minutes after intravenous injection with a duration of action of about 20 minutes.[68] It has an inotropic effect and acts as a peripheral vasoconstrictor, thus increasing cardiac output, peripheral resistance, and BP. Coronary blood flow is increased and the heart rate slowed.[68,70]

2.6.6 Dopamine

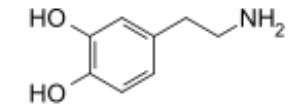

Figure 12: The chemical structure of dopamine.

Dopamine (**Figure 12**) stimulates adrenoreceptors and dopaminergic receptors. The effects change with increasing dose.[51] Low dose dopamine dopaminergic stimulation predominates resulting in increases in renal and mesenteric blood flow. Increasing the dose results in a predominance of β_1 effects, increasing heart rate, cardiac output and myocardial contractility. At high dose, α effects predominate causing a rise in SVR and reduction in renal blood flow. Its half life is 2 minutes. The main problems associated with dopamine are tachycardia and arrhythmias, myocardial ischaemia and excessive peripheral vasoconstriction.

2.6.7 *Isoprenaline*

Isoprenaline (**Figure 13**) is a non-selective beta-adrenergic agonist, thus activating both β_1 and β_2 receptors. It is structurally similar to adrenaline. Isoprenaline relaxes smooth muscle and has negligible metabolic or vasoconstrictor effects.[71] Its main disadvantage is that it results in a marked tachycardia. It has a half life of 2 minutes.

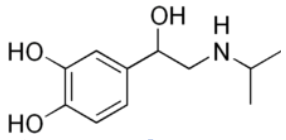

Figure 13: The chemical structure of isoprenaline.

2.6.8 *Ephedrine*

Ephedrine (**Figure 14**) is a plant alkaloid with indirect sympathomimetic actions that resemble those of adrenaline peripherally and amphetamine centrally.[71] It has actions on α and β adrenergic receptors and displaces noradrenaline from adrenergic terminals.[72] It has a half life of approximately 6 hours. Ephredrine has been linked to serious cardiovascular toxicity, including hypertension, vasospasm, angina, coronary artery disease, arrhythmia, myocardial infarction, stroke and death.[72]

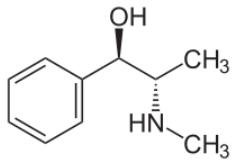

Figure 14: The chemical structure of ephedrine.

2.6.9 *Phenylephrine*

Phenylephrine (**Figure 15**) is a selective α_1 adrenergic receptor agonist. It has the advantage of not being inotropic or chronotropic, and so strictly elevates BP without increasing the heart rate or contractility. However, a reflect bradycardia may result. The elimination half life is approximately 3 hours.

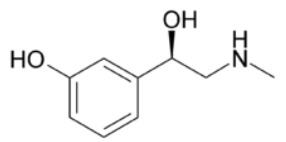

Figure 15: The chemical structure of phenylephrine

2.7 Vasoactive drugs in free tissue transfer

Hypotension under general anaesthesia occurs in 40 to 60 percent of hypertensive patients as a result of decreased systemic vascular resistance. In addition induced hypotension is a widely accepted technique to reduce intraoperative blood loss.[52] However, systemic hypotension may result in flap hypoperfusion, stroke, myocardial infarction, renal failure and death.[73] Hypotension is particularly problematic in patients requiring prolonged peri-operative sedation for ventilation, particularly in combination with alcohol withdrawal. To counteract the effects of hypotension following appropriate fluid administration, anaesthetists and intensivists may require the use of vasoactive drugs. Many surgeons are wary of using inotropic agents as a method of improving perfusion of the transplanted tissue.[46,74] However, flap loss has not been correlated with vasopressor use in recent retrospective studies.[75]

Free flap surgery results in the disruption of the autonomic nerves running around the feeder vessels of the flap. The microcirculatory effect of sympathectomy causes vasodilatation of vessels in muscle and in skin thus potentially improving microcirculation.[76] However, some research suggests that denervation supersensitivity can develop after sympathectomy, leading to excessive vasoconstriction in response to catecholamines.[77] This may be further heightened due to the surgical stress response resulting in release of adrenaline and noradrenaline and consequent vasoconstriction. Any additional circulating sympathomimetic agents may further heighten these effects and result in flap necrosis. Godden *et al*[78] in 2000 reported the findings of the invitro effect of increasing concentrations of phenylephrine (an α_1 agonist) on the rat femoral artery after microvascular anastomosis. The vascular tone on the test side confirmed supersensitivity to the alpha agonist, which was blocked by the alpha blocker phentolamine (a non-selective α-adrenergic blocker). It was concluded that the sympathetic denervation during preparation of the vessels for anastomosis resulted in the increased sensitivity of the blood vessels to the exogenous stimulation. This work provides evidence for the survival of vascular alpha receptors following transplantation, thus providing a potential basis for flap failure due to vasoconstriction of the feeding vessels. The effects of pressor agents on free flaps are further explored in Chapter 3.

2.8 Thrombotic Complications

Virchow in 1856 postulated that venous thrombosis was related to three factors, commonly referred to as Virchow triad: (1) abnormalities in the vessel wall, (2) alterations in blood flow, and (3) alterations in the constituents of the blood.[79]

Coagulation is a complex process which can be divided into intrinsic and extrinsic pathways involving numerous clotting factors prior to the final common pathway where fibrinogen is converted to fibrin to form a stable clot. This complex interaction is one of the first processes to occur after tissue injury. It is reliant upon a number of co-factors, including calcium and vitamin K in addition to regulators such as Protein C and anti-thrombin.

Since the description of thrombophlebitis migrans in association with gastric cancer by Trousseau in 1865 hypercoaguability has been well recognised in association with malignancy.[79] Malignancy has a procoagulant effect through interactions with the coagulation cascade and the release of fibrinolytic factors and proinflammatory cytokines. As a result patients are at increased risk of thrombotic complications, including venous thrombotic events (VTE) and flap thrombosis.

Standard prophylaxis against such complications includes the use of chemical agents, such as heparin. Heparin interacts with anti-thrombin III causing its activation which results in the inactivation of thrombin and other proteases involved in clotting, most notably factor Xa. Alternatives include aspirin which inhibits both prostaglandin synthesis and platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase, and Dextrans which are macromolecules composed of glucose subunits. Dextrans have anti-platelet and anti-fibrin actions, and also improve microcirculation by decreasing blood viscosity and impeding erythrocyte aggregation.

In flaps that demonstrate venous congestion, Leeches can be used to permit time for neovascularisation. Leeches secrete hirudin, a powerful anticoagulant, which inhibits thrombin and encourages bleeding for several hours after the leech has finished feeding. Early detection of a failing flap due to thrombotic complications increases the chances of successful salvage.

2.9 Flap Monitoring

Maintenance of blood flow to the flap is of paramount importance and may be adversely affected by hypothermia, hypovolaemia, peripheral vasoconstriction, reduced cardiac output, hypoxia, and hypocarbia.[80]

Post operative anastomotic problems requiring immediate re-exploration, occurs in 6-25% of cases.[43,81-83] Successful salvage is dependent upon the time interval between flap compromise and anastomotic repair. Regular observation of the flap is paramount in the early post-operative period to identify early signs of compromise.

Clinical assessment includes colour, capillary refill, turgor, and temperature. Pin prick provides further information in cases of concern, since a flap with venous congestion will rapidly bleed venous blood on pricking, and in cases of arterial obstruction bleeding will be significantly delayed or absent. However, clinical observation of intra-oral flaps can be challenging as a result of their location, particularly where the flap is buried (e.g. fibula free flap) with no skin paddle.[84]

Adjuncts to enhance detection of the failing flap continue to be actively sought, and microsurgeons are increasingly utilising such monitoring devices to complement clinical assessment.[85,86] Such a monitor capable of identifying perfusion compromise prior to the development of objective clinical signs would allow earlier intervention and potentially improved outcome following flap salvage.[87] The ideal method for the assessment is non-invasive, simple in application, inexpensive, rapidly responsive to changes in microcirculation, reliable and reproducible.[88] Currently, one of the most popular devices is laser Doppler.

2.9.1 Laser Doppler

The laser Doppler flow meter measures red cell flux in the skin by illuminating an area of skin with monochromatic light, and measuring the amount of light reflected from moving erythrocytes and the Doppler shift (change in wavelength) of the reflected light.[89]

The laser Doppler is not calibrated to measure absolute blood flow in view of variable optical properties of different tissues.[77] It indicates microcirculation in terms of Tissue Perfusion Units (TPU) defined by the manufacturer, a number which corresponds to variations in wavelength. Erroneously high values can be the result of tissue motion, either extrinsic (room vibration) or intrinsic (muscle fasciculation, respiration, or excessive patient movement).[87] However, the use of laser Doppler is non-invasive, allows for continuous recording, and has been shown to be reliable.[47,49,90,91] An alternative to external laser Doppler monitoring is to use an implantable Doppler probe attached to the pedicle. A probe implanted around the outflow vein of a flap will detect cessation of venous flow almost immediately; interruption of arterial flow will cause a near-immediate loss of the Doppler signal.[92] The main difficulties associated with this system is that patients either require a second operation to remove the probe, or in Doppler probes designed to detach without surgery, such blind removal carries a potential risk of damage to the anastomosis.

2.9.2 Temperature monitoring

The monitoring of temperature forms one aspect of routine clinical assessment of flaps; a decrease in blood flow results in a decrease in temperature. An alternative to simple palpation and thermometers is the utilisation of infrared thermometry (thermography) and thermoelectric thermometers. However, these can be unreliable in intraoral flaps where a decrease in surface temperature occurs less readily.[84] As a result an implantable device may offer more reliability. A thermocouple is placed adjacent to the inflow artery distal to the anastomosis with a control thermocouple adjacent to the recipient artery proximal to the anastomosis.[92] Reduced blood flow due to arterial or venous thrombosis results in a decrease in temperature of the distal compared to the proximal probe. The main difficulties associated with this method include accurate placement and the avoidance of dislodgement.

2.9.3 Microdialysis

Microdialysis is a sampling technique that monitors the metabolism of the flap. Ischaemia can be detected by monitoring the changes in glucose, lactate and pyruvate levels in the interstitial fluid of monitored tissue. The technique requires the passage of a microdialysis catheter into the flap tissues; the catheter is infused with isotonic Hartmann's solution at a constant speed thus creating a concentration gradient. Diffusion of low-molecular weight substances occur across the catheters' membrane, representing the composition of the interstitial fluid.[92,93] Ischaemia is characterised by a very low glucose concentration, a rising lactate concentration, and a high lactate/pyruvate ratio. The main disadvantages of this system are the high costs, and intermittent nature of testing.

Other potential solutions include the monitoring of tissue pH, glucose, transcutaneous partial oxygen pressure and colour Doppler sonography.[94,95] However, laser Doppler monitoring has been most widely accepted by microsurgeons and is one of the most cost effective methods currently available. This is further explored in the following section of the thesis.

Chapter Conclusion

As a result of a combination of extensive surgery and associated co-morbidity, patients undergoing surgical management of head and neck cancer are at increased risk of post-operative complications with significant morbidity and mortality. At the time of surgery, patients present a high incidence of difficult intubations, which may be due to a combination of tumour mass, anatomical distortion from previous surgery.[80] Older patients are also more sensitive to propofol and its induction of hypotension in these patients may critically reduce tissue perfusion and oxygenation.[69] Peri-operative optimisation is vital for both free flap and patient survival.

The following sections further explore the effects of pressor agents, nutrition, anticoagulation and fluid balance on morbidity following ablative and reconstructive surgery.

3. Pressor Support

3.0 Pressor Support

Patients with oral malignancies are frequently of advanced age and have chronically abused tobacco and alcohol with resulting co-morbidities.[22,23,25] Many patients require BP support both intra-operatively and during the early post-operative recovery period to counteract the hypotensive effects of sedation or anaesthesia compounded by co-morbidities and concurrent medication. Whilst the sympathomimetic pressor agents used may increase systemic blood pressure and hence the driving pressure perfusing the flap, the associated vasoconstriction (assuming denervated flaps maintain such control), may paradoxically reduce flap perfusion resulting in flap ischaemia. As a result, many surgeons remain wary of using such agents.[74] The optimal agent to maintain blood pressure without adverse effect on flap blood flow remains unclear.

This section of the thesis concentrates on the peri-operative support of patients undergoing ablative surgery and free flap reconstruction in terms of blood pressure support. The section commences with a literature review, before review of the methodology and results in:

1. **Eley KA**, Young JD, Watt-Smith SR. Epinephrine, norepinephrine, dobutamine, and dopexamine effects on free flap skin blood flow. Plast Reconstr Surg 2012; 130(3):564-70.[3]
2. **Eley KA**, Young JD, Watt-Smith SR. Power spectral analysis of the effects of epinephrine, norepinephrine, dobutamine and dopexamine on microcirculation following free tissue transfer. Microsurgery 2013; 33(4):275-81.[4]
3. **Eley KA**, Young D, Watt-Smith. Assessment of the effects of pressors on graft blood flow after free tissue transfer surgery: interim findings. Br J Oral Maxillofac Surg 2009; 47(7): e41-42 [Published abstract].[5]
4. **Eley KA**, Young D, Watt-Smith. Assessment of the effects of pressors on graft blood flow after free tissue transfer surgery: Phase I results. Br J Oral Maxillofac Surg 2010; 48(Supp 1): S13 [Published abstract].[6]

3.1 Literature Review

A comprehensive review of the literature was conducted to determine the current understanding of the effects of pressor agents following free tissue transfer. This was completed using NCBI Pubmed and Google Scholar with the following MeSH terms:

(Free Tissue Flaps or Surgical Flaps [All fields]) and ("Cardiotonic agents" or "hemodynamics" or "Catecholamines" or "Ethylamines" or "Biogenic monoamines").

The titles and abstracts were reviewed to identify those papers with clinical relevance, with subsequent review of related citations and references.

Free flap surgery results in the disruption of the autonomic nerves surrounding the feeder vessels of the flap. Lecoq *et al*[77] investigated the early effects of surgical sympathectomy on the reactivity of cutaneous microcirculation when challenged by adrenergic agents. Using epigastric flaps in rats, they compared the effects of adventitiectomy to intact vessels following infusions of phenylephrine, adrenaline and prazosin (a specific α_1 blocker) utilising laser Doppler flowmeter monitoring. The authors found that immediately after surgical adventitiectomy, the vasoconstriction produced by α-adrenergic agents was prevented without denervation induced hypersensitivity, however they only measured the response of each drug for 6 minutes. The authors concluded that this may result in protection of free flap microcirculation. This was further confirmed by McKee *et al*[96] who examined the blood flow and pressure in the vessels supplying a free skin flap (inferior epigastric) in 25 mongrel dogs. They found that blood flow in the epigastric artery and vein increased significantly between exposure of the vessels and elevation of the flap.

Further animal work was conducted by Massey *et al*,[73] who evaluated the dose-dependent changes in the pedicle artery blood flow and microvascular perfusion of a porcine vertical rectus abdominis myocutaneous rotational flap with the systemic administration of phenylephrine and adrenaline. The microvascular perfusion to the skin of the flap in the 6 pigs was measured using a laser Doppler probe, with a further probe on the thigh to act as a control. The blood flow

through the pedicle artery was measured using an ultrasonic transit time flow probe on the superior epigastric artery. The effects of phenylephrine, adrenaline and sodium nitroprusside (a potent vasodilator) were investigated. Phenylephrine and adrenaline both increased systemic mean arterial pressures, whereas only adrenaline increased cardiac output. The microvascular perfusion of the flap decreased in a dose dependent fashion whilst that of the control increased, with phenylephrine. Pedicle artery blood flow was increased with increasing doses of adrenaline in all but one case. Conversely, Banic *et al*[52] in their study of 9 pigs undergoing latissimus dorsi free flaps reported a 40% decrease in total flow in the flap with systemic sodium nitroprusside, and no change with systemic infusion of phenylephrine. Sun *et al*[97] also explored the effects of sodium nitroprusside, phentolamine and phenylephrine on epigastric skin in rats. Power spectral analysis and laser Doppler flowmetry was performed. They found that sodium nitroprusside and phentolamine increased cutaneous perfusion, whilst phenylephrine decreased perfusion. Cordeiro *et al*[46] examined the effects of vasoactive drugs on blood flow in island musculocutaneous flaps in pigs. They found that dobutamine had the most positive effect on flap flow. At increasing doses, it both increased cardiac output and flap flow. Hiltunen *et al*[98] reported that in their experiments looking at the effects of hypotension and noradrenaline on pedicled rectus abdominis myocutaneous flaps in pigs, that moderate normovolaemic hypotension or its correction with noradrenaline did not affect flap perfusion as assessed by microdialysis.

Investigations into the effects on microvascular anastomoses includes that by Godden *et al*[99] who investigated the changes in sensitivity of rat femoral artery to phenylephrine after microvascular anastomosis, and if these changes could be blocked by the addition of phentolamine, an α-adrenergic blocker. Bilateral groin flaps were raised, with division and anastomosis of the femoral artery on one side only. They found that after microsurgery, the phenylephrine sensitivity of the anastomosed vessels was increased. The increased vascular sensitivity of the denervated rat femoral artery could be prevented by the addition of phentolamine. This therefore provides evidence for the survival of α-receptors following microvascular repair. However, anastomosis was performed to the donor vessel and not to an

alternative site, and it would appear that there was minimal ischaemic time between division and repair of the artery.

Further investigation in living patients includes the work by Suominen *et al.*[100] They assessed the effect of intra-operative administered inotropic agents on blood flow in the recipient and donor vessels during breast reconstruction with a muscle sparing transverse rectus abdominis myocutaneous (TRAM) flap. Patients were randomised into three groups, and received one of dobutamine, dopamine or saline (placebo) for 15 minutes. Dobutamine (8 µg/kg/min) was found to systemically increase CO and heart rate while it decreased SVR. A simultaneous increase in donor and recipient artery flow was noted with dobutamine, but not with dopamine which resulted in a mixed response with decreased flow seen in some patients.

Dobutamine was further investigated by Scholz *et al*[74] in patients following microvascular anastomosis. They investigated the effects of three infusion rates of dobutamine (2, 4 and 6µg/kg/min) for a 10 minute period each, performed intra-operatively in 18 patients. Flow in the artery distal to the anastomosis was measured with a flowmeter. They found that with increasing doses of dobutamine there was a significant increase in heart rate, systolic blood pressure and cardiac index. Dobuamine at 4 and 6µg/kg/min significantly increased blood flow to the flap above baseline values.

More recently, Chen *et al*[101] retrospectively reviewed the medical records of 187 consecutive patients undergoing DIEP flaps, and free TRAM flaps for breast reconstruction. Of the patients studied, 102 received vasopressors (ephedrine and phenylephrine) during surgery. They found that there was no statistical difference in outcome, including flap loss and re-operation, between those who received vasopressors and those who did not. Additionally, they found no difference between the timing of vasopressor use intra-operatively, and outcome.

In most investigations researchers have utilised Doppler monitoring to assess the effects on the transplanted tissue or feeding vessels. Further analysis of the Doppler waveform provides information on the intrinsic control of the tissues. These effects were explored by Lansverk *et al*[102] who examined the effects of pharmacological interruption of the sympathetic innervation

to the arm during brachial plexus blocks. Using two laser Doppler probes, they were able to compare the effects of brachial plexus block on one arm compared to the normal contralateral limb in 13 patients. They found that in the anaesthetised arm there were reduced relative amplitudes in the 0.021 to 0.052Hz and 0.0095 to 0.02Hz frequency intervals. These frequency intervals represent neurogenic and endothelial activity, respectively, and indicate an inhibitory effect on the sympathetic and endothelial activity, suggesting it is denervation rather than another operative factor that alters the low frequency oscillations in transplanted tissue.

There are two previous studies of spectral analysis of free flap and control tissue blood flow signals. Liu *et al*[103] examined the spectral analysis of 18 patients undergoing free latissimus dorsi transfer. The authors used a laser Doppler flowmeter to measure skin blood perfusion at the flap and a control site on the contralateral limb in patients with soft tissue injury of the lower extremity. They found that the spectral power and average amplitude of oscillations in the frequency range 0.0095-1.6Hz were dramatically lowered in the flaps. They concluded that a decrease in both the endothelial cell metabolic processes and sympathetic control, and an increase in the intrinsic myogenic activity occurred. Similar findings were reported by Sun *et al*[50] who examined the spectral analysis changes prior to and following free radial forearm flap harvest and transplantation. They reported significantly increased high frequency (0.15-0.4Hz) and decreased very low frequency (0003-0.04 Hz) power fraction after flap transfer.

In summary, of the pressor agents currently available, the studies to date demonstrate that dopamine and phenylephrine appear detrimental to flap flow. Noradrenaline appears to have limited effect on flap flow, whilst adrenaline and dobutamine are beneficial. Retrospective studies of ephedrine suggest that this agent does not have adverse effects on free flaps. There are no studies available in the literature that have explored the effects of dopexamine, metaraminol, or isoprenaline.

Overall, whilst these studies provide valuable information on the potential effects of pressor agents on transplanted tissues, they have failed to address the important clinical question of which agent should be utilised first line in patients undergoing free tissue transfer following ablative surgery for head and neck malignancy.

The following section explores the methodology of the presented papers, with the aim of identifying the effects of four commonly utilised pressor agents on flap perfusion thus providing guidance on which agent should be utilised in the peri-operative period.

3.2 Materials & Methods

A prospective study investigating the effects of four pressor agents was completed in patients presenting with head and neck malignancy between 2008 and 2010. In total 24 patients (16 male; 8 female) were recruited to the study. One patient re-presented during the study period with a second primary tumour, and was recruited to the study on both occasions, resulting in 25 sets of results. The inclusion criteria were patients undergoing free flap surgery for head and neck cancer resection with a planned post-operative intensive care unit admission for overnight sedation and ventilation, which is standard local practice. The only exclusion criteria were pregnancy or a bodyweight above 100kg.

All patients had both a central venous line and an arterial line sited at the time of anaesthesia as part of routine clinical care. Intra- and post-operatively in the intensive care unit, fluid management was optimised with the aid of the LiDCO™ Rapid system, which uses a pulse contour analysis algorithm ("PulseCO") to estimate stroke volume.[104] Stroke volume variation below 10% was taken to indicate optimal fluid loading throughout the study.

Free flap reconstruction was with a free radial forearm flap (n=16), latissimus dorsi (n=2), anterolateral thigh flap (n=1) or free fibula flap (n=2). In the remaining 4 cases reconstruction was with two simultaneous free flaps (ALT and fibula n=3, radial forearm and fibula n=1) (**Table 2**). At the end of the surgical procedure, two Transonic laser Doppler red blood cell velocimetry probes were attached to the skin – one central on the free flap skin paddle, and one acting as a control (**Figure 16 & 17**). To standardise the control site, and to minimise impact upon vascular access, the skin over the deltoid muscle was used in all cases.

The Transonic device calculates skin blood flow as the product of the number of red cells moving in the illuminated field, and their mean velocity, to provide a measure of red cell flux (blood flow). This is expressed in tissue perfusion units (TPU), a unitless measure, as it is not possible to calibrate the probes. Flap skin blood flow was logged from the Transonic device using AcqKnowledge version 3.9.1.6 software on a personal computer at 40 samples per second.

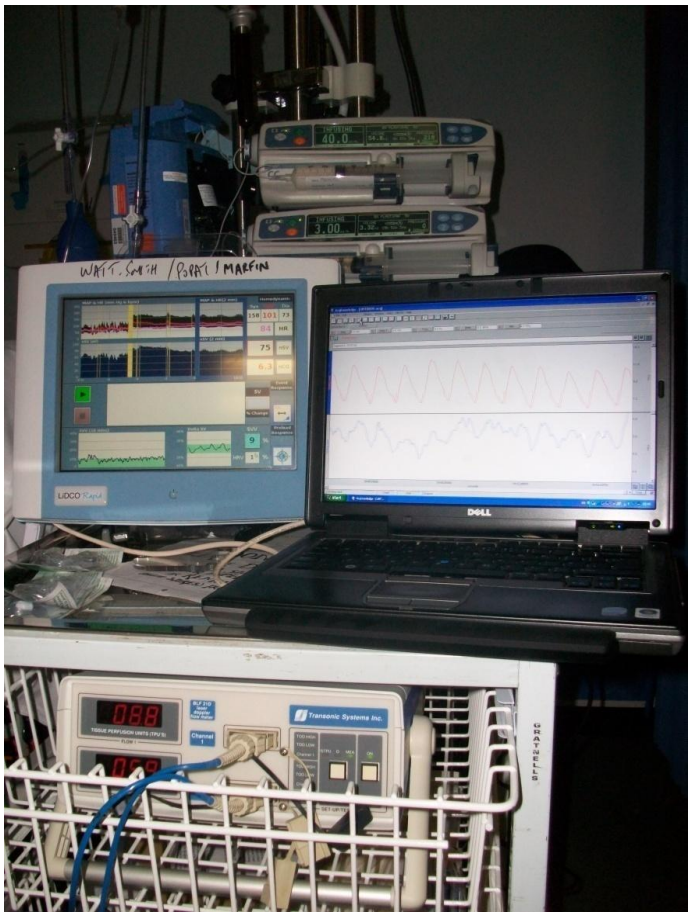

Figure 16: Equipment set up in the intensive care unit for the pressor study.
Continuous Doppler monitoring of the flap and control sites was conducted using Transonic laser Doppler probes.
Fluid management was optimised using LiDCO™ Rapid.

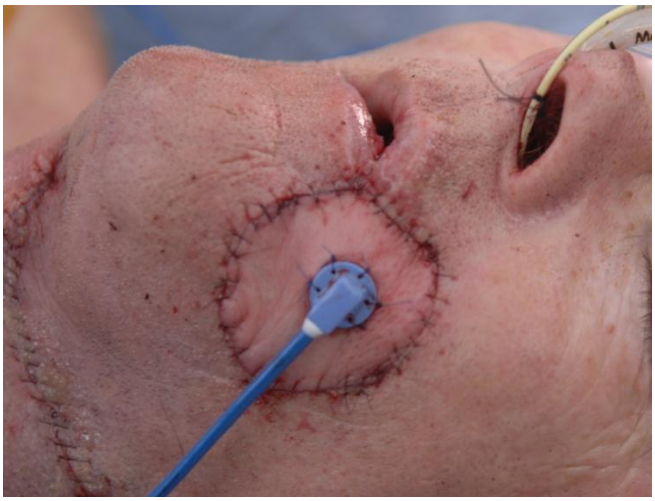

Figure 17: Laser Doppler probe sited on the centre of a cheek flap.

Red cell transfusion to maintain a haemoglobin concentration above 8.0g/dL was completed before the study commenced. Once the patient was stabilised on the intensive care unit, and if the mean arterial pressure (MAP) was below 80mmHg, the patients received four pressor drugs (adrenaline, noradrenaline, dobutamine and dopexamine) infused at four increasing doses (**Table 3**). The order of drug administration was randomly pre-determined and concealed in an opaque envelope until commencement of the trial. The research and medical teams were unblinded to the infusion drug and rate.

Each drug was administered for 5 minutes at each rate intravenously via the central line. The infusion was stopped if the MAP increased by more than 30mmHg, the heart rate reached 150 beats per minute or there was an adverse effect. At the end of each infusion, 5ml of blood was aspirated and discarded from the central line, and the line flushed with 10ml of normal (0.9%) saline. A 20 minute period elapsed prior to commencing the next drug in the sequence to permit adequate time for physiological variables to return to baseline. Throughout the periods of baseline recording and drug infusions, sedation was maintained at a steady rate, and only maintenance fluids were administered.

At the end of the trial, if the patient required continued pressor support, the drug producing the best increase in flap skin blood flow from the trial data was selected.

The final two minutes of the five minute recording period of each drug rate was used for subsequent analysis. The time period was identified on the AcqKnowledge system, and the data transferred to a Microsoft Excel spreadsheet. The recording (in tissue perfusion units) over the two minute period was averaged to obtain a mean value for the flap and the control skin. This was completed for each of the four drugs for all of the four drug infusion rates, and at baseline prior to commencing any drug infusion. The fractional change from the baseline was calculated for each of the infusion rates.

Patient:	Age	Sex	BMI	Resection	Free flap donor site
1	67	M	25.3	Left hemiglossectomy	Radial
2	62	F	24.9	Left hemiglossectomy	Radial
3	62	F	23.4	Total glossectomy	Latissimus dorsi
4	65	M	24.2	Hemi-mandibulectomy	Fibula
5	58	M	32.8	Hemi-mandibulectomy	Fibula
6	61	F	18.0	Resection floor of mouth/mandible	ALT + Fibula
7	53	F	22.4	Left hemiglossectomy	Radial
8	43	M	24.3	Maxillectomy and orbital enucleation	Latissimus dorsi
9 *	68	M	25.0	Resection right buccal sulcus	Radial
10	54	F	24.7	Left hemimandibulectomy	Radial + Fibula
11	63	M	19.4	Resection right tongue/mandible	ALT + Fibula
12	48	M	24.3	Left partial glossectomy	Radial
13 *	69	M	24.7	Right hemimandibulectomy	ALT + Fibula
14	60	F	24.7	Right hemiglossectomy	ALT
15	47	M	26.3	Resection left buccal mucosa	Radial
16	64	M	17.5	Resection floor of mouth	Radial
17	57	F	25.4	Right hemiglossectomy	Radial
18	64	M	26.0	Resection adhesions tongue	Radial
19	54	M	27.1	Right hemiglossectomy	Radial
20	69	M	23.9	Right hemiglossectomy	Radial
21	67	M	30.4	Resection right tonsillar fossa	Radial
22	56	M	17.8	Resection right posterior tongue	Radial
23	66	M	24.7	Resection left tonsillar fossa	Radial
24	57	M	24.7	Resection ventral tongue	Radial
25	73	F	24.4	Right hemiglossectomy and partial maxillectomy	Radial

Table 2: Demographics of the 25 patients recruited to the pressor study.
(*BMI=Body mass index ; ALT=anterolateral thigh flap*).
***Patient 9 & 13 are the same patient, enrolled in the study on two separate occasions, having presented with a second primary tumour during the study period.**

Drug	Concentration (mcg/ml)	1st infusion rate (mcg/kg/min)	2nd infusion rate (mcg/kg/min)	3rd infusion rate (mcg/kg/min)	Final infusion rate (mcg/kg/min)
Adrenaline	20	0.05	0.1	0.15	0.2
Noradrenaline	20	0.05	0.1	0.15	0.2
Dobutamine	500	2	4	6	8
Dopexamine	1000	1.25	2.5	3.75	5

Table 3: Drug infusion rates for the four agents used in the pressor study

Corresponding data from LiDCO™ Rapid was entered onto the Microsoft Excel spreadsheet and corresponding flap conductance ($\frac{Tissue\ Perfusion\ (TPU)}{Mean\ Arterial\ Pressure\ (mmHg)}$) calculated. This result was also converted to a fractional change from baseline.

Spectral analysis (**Figure 18**) of the Doppler data was performed using Matlab version 7.11.0.584 (R2010b). This was completed by using the last 4096 samples (102.4 seconds of recording). The total power (the amount of variation in blood flow) in the signal was calculated as the variance. A standard signal processing approach was used to determine the frequency components of the blood flow signal. Three 2048 sample (51.2 second) segments with 50% overlap were derived by dividing up the total period of 4096 samples. Each underwent linear trend removal (to remove baseline drift) and was then windowed with a Hamming window function (required to remove artefacts generated at the start and end of the recordings) before conversion to zero mean unit variance format, which allowed comparison between patients irrespective of the total blood flow.

Power spectra (the plot of blood flow oscillations at each frequency) were computed using a standard fast Fourier transform algorithm, and the resulting three spectra averaged to give the final result. Only the frequencies below 3Hz were used for graphing. This analysis was performed for each of the four drugs and four drug concentrations, and prior to commencement of any drug infusion, for all 25 sets of results and both recording sites.

For each patient the power in the baseline (pre-drug) period was used to normalise the subsequent results for both control and flap sites. The results from all patients were averaged. In addition for each patient and each dose the control site spectrum was subtracted from the flap site spectrum to highlight any differences between the sites.

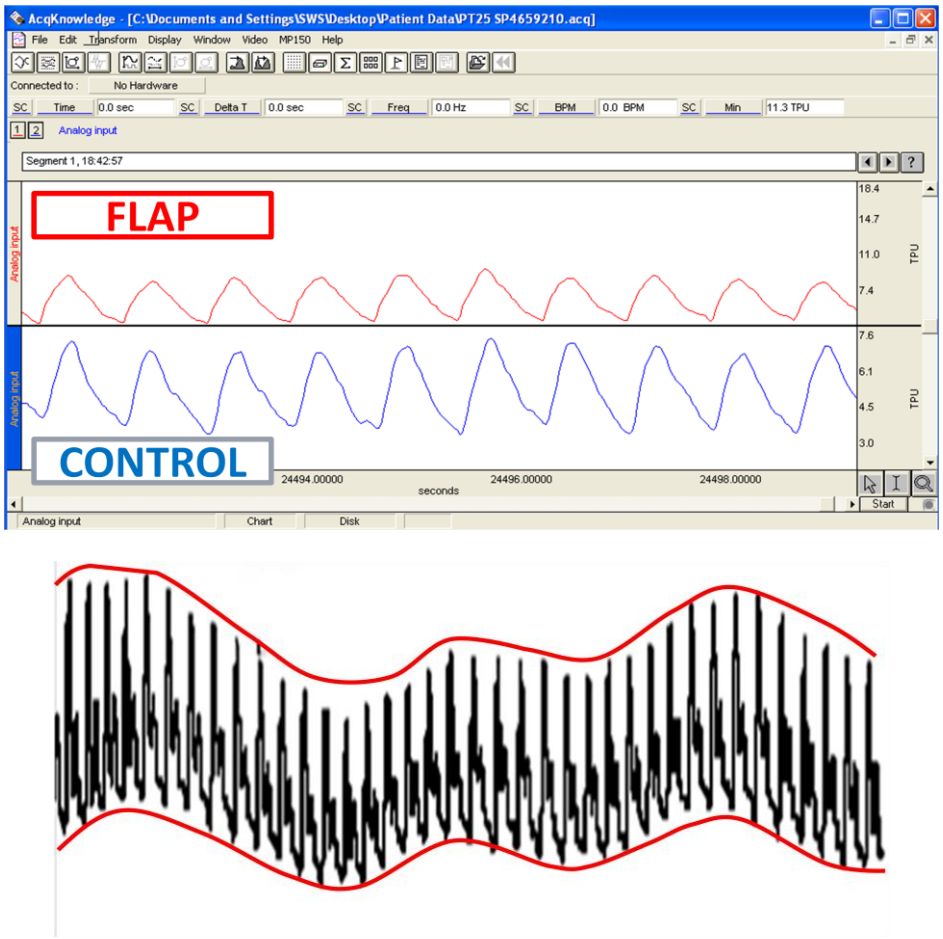

Figure 18: The Doppler waveform and spectral analysis.
Shown above is an example of the Doppler waveform of the flap and control tissues. The waveform if visualised more closely, as shown below, is composed of oscillations representative of the intrinsic control. These are demonstrated via spectral analysis.

Ethical Considerations

Ethical approval was granted from the Oxfordshire Research Ethics Committee (08/H0606/31), and written informed consent obtained from all participants.

Statistical Analysis

Data was analysed using line graphs to identify trends in flow and conductance. Statistical analysis for differences in variance (variability) between control site and flap was completed using t-tests, with Šidák correction for multiple comparisons, on SPSS (Statistical Package for the Social Sciences). The probability of differences between regions of the normalised power spectra arising by chance could not be tested statistically and so differences reported are based on simple interpretation of the graphs.

3.3 Results

The mean values for each of the cardiovascular variables at baseline and for each infusion are shown in **Table 4**. Only five patients received the maximum noradrenaline infusion rate (0.15mcg/kg/min) as the others all reached the upper safety limit for blood pressure at a lower dose.

All of the drugs except noradrenaline resulted in an increased heart rate. Noradrenaline and adrenaline caused an increase in mean arterial pressure, whilst dobutamine and dopexamine caused a modest decrease. All drugs increased cardiac output.

Figure 19 shows graphically the mean and standard error of fractional change in skin perfusion from baseline for both the control and flap. For adrenaline and dopexamine tissue perfusion (flap flow) decreased, whilst that at the control site decreased and increased respectively. For noradrenaline and dobutamine flap flow increased at lower infusion rates, whilst the control site decreased and increased respectively. The greatest increase in flap skin blood flow occurred with 0.1-0.15mcg/kg/min noradrenaline.

To examine the vasodilator or vasoconstriction effects of the drugs independent of the MAP, skin blood flow conductance was calculated (**Figure 20**), with an increase signifying vasodilatation. Only dopexamine caused an increase in conductance for both flap and control with increasing infusion rates. Adrenaline and noradrenaline were both vasoconstrictors (reduced conductance), though noradrenaline had less effect on the flap compared to control tissue.

For the one patient recruited twice into the study, the findings on both occasions yielded similar results for flow and conductance, with all drugs except adrenaline. With adrenaline, it was noted that the first study for this patient (Patient 9) resulted in increased flow for both flap and control, which was not consistent with the repeat study (Patient 13) nor with the mean overall findings for all of the patients combined.

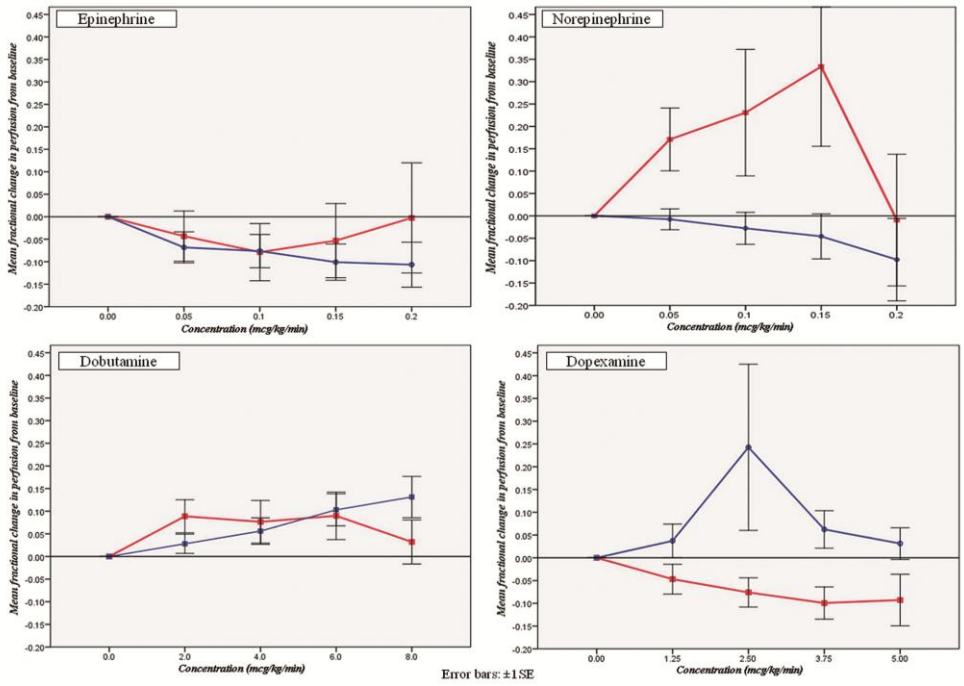

Figure 19: Graphs of mean fractional change in perfusion from baseline for each drug infusion for the flap and control tissues.
Red indicates free flap flow, blue indicates control.

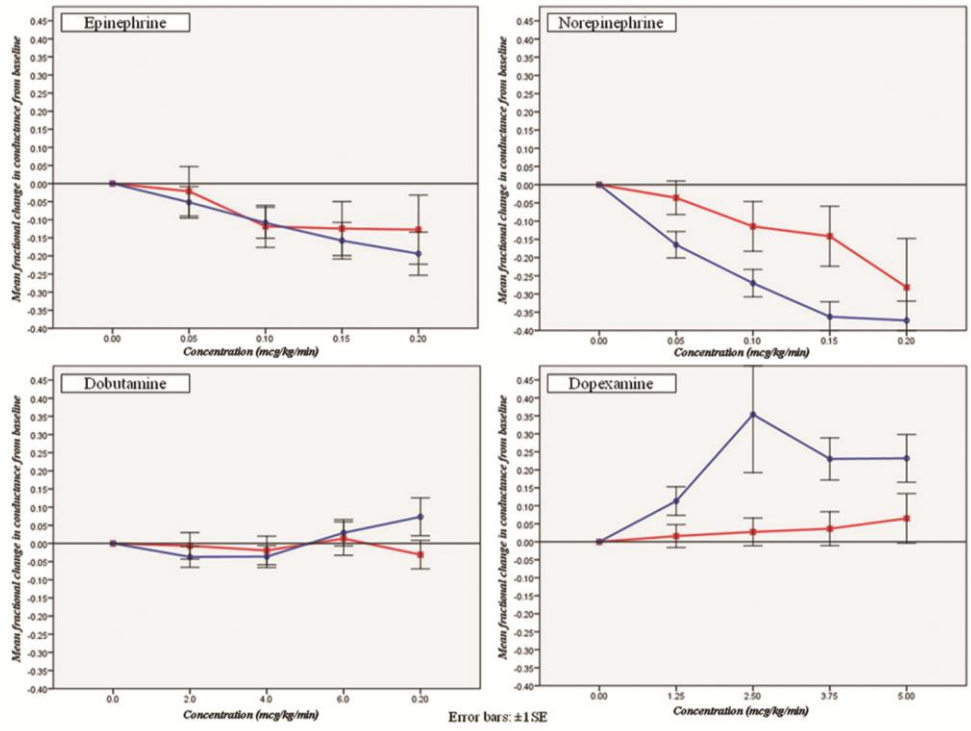

Figure 20: Graphs of mean fractional change in conductance from baseline for each infusion. A decrease in conductance signifies vasoconstriction, as was seen with adrenaline and noradrenaline. Red indicates the free flap, blue indicates the control tissues.

	Concentration (mcg/kg/min)	Mean (SD) HR (beats/min)	Systolic (mmHg)	MAP (mmHg)	CO (L/min)	CI (L/min/m^2)
Baseline	-	77 (13)	113/57 (17/7)	76	5.2 (1.3)	2.9 (0.5)
Adrenaline	0.05	86 (15)	116/53 (22/8)	73	6.7 (2.1)	3.7 (1.1)
	0.1	92 (16)	129/55 (24/7)	77	8.2 (2.7)	4.5 (1.4)
	0.15	99 (17)	139/57 (26/7)	80	9.5 (3.0)	5.2 (1.5)
	0.2	106 (17)	147/61 (24/8)	85	10.5 (3.5)	5.9 (1.8)
Noradrenaline	0.05	76 (15)	136/66 (30/10)	89	5.7 (1.4)	3.1 (0.6)
	0.1	76 (14)	14871 (26/9)	98	6.2 (1.6)	3.38 (0.8)
	0.15	76 (16)	161/76 (21/9)	106	6.8 (1.6)	3.6 (0.8)
	0.2	84 (13)	168/72 (13/7)	103	6.9 (2.0)	3.9 (0.7)
Dobutamine	2	84 (16)	126/58 (25/9)	80	6.5 (2.0)	3.6 (0.9)
	4	91 (18)	131/58 (21/11)	80	7.3 (2.5)	4.0 (1.1)
	6	99 (20)	132/56 (22/8)	78	8.2 (2.9)	4.5 (1.4)
	8	107 (18)	134/55 (23/7)	76	9.8 (3.2)	5.3 (1.4)
Dopexamine	1.25	88 (15)	107/52 (20/9)	68	6.6 (2.0)	3.6 (0.9)
	2.5	95 (15)	105/48 (22/8)	66	7.6 (2.9)	4.2 (1.4)
	3.75	102 (16)	104/46 (22/8)	64	8.4 (2.9)	4.6 (1.3)
	5	109 (17)	103/45 (23/8)	62	9.2 (3.2)	5.0 (1.5)

Table 4: Mean cardiovascular variables at each pressor infusion rate.
Results are shown as mean (SD). (HR=heart rate; MAP=mean arterial pressure; CO=cardiac output; CI=cardiac index.)

	Infusion Rate (mcg/kg/min)	Number of patients receiving dose	Mean HR (beats/min)	MAP (mmHg)	CI (l/min/m^2)	Flap Mean normalised power	Control Mean normalised power
Baseline	-		77±13	76	2.9±0.5	1.00±0.00	1.00±0.00
Adrenaline:							
25%	0.05	25	86±15	73	3.7±1.1	1.23±0.83	1.67±2.93
50%	0.1	25	92±16	77	4.5±1.4	1.57±1.39	1.34±0.97
75%	0.15	24	99±17	80	5.2±1.5	1.87±1.89	1.34±0.96
100%	0.2	21	106±17	85	5.9±1.8	1.76±1.83	1.34±0.75
Noradrenaline:							
25%	0.05	25	76±15	89	3.1±0.6	2.74±3.69	1.26±0.84
50%	0.1	19	76±14	98	3.4±0.8	3.57±7.57	1.37±0.88
75%	0.15	13	76±16	106	3.6±0.8	4.42±6.59	1.34±0.82
100%	0.2	5	84±13	103	3.9±0.7	1.90±1.76	0.79±0.52
Dobutamine:							
25%	2	25	84±16	80	3.6±0.9	1.55±1.10	1.24±0.53
50%	4	23	91±18	80	4.0±1.1	1.50±1.08	1.75±1.93
75%	6	23	99±20	78	4.5±1.4	1.48±1.19	1.48±0.99
100%	8	22	107±18	76	5.3±1.4	1.28±0.77	1.71±1.34
Dopexamine:							
25%	1.25	25	88±15	68	3.6±0.9	1.02±0.57	1.19±0.77
50%	2.5	25	95±15	66	4.2±1.4	1.48±1.93	1.28±0.94
75%	3.75	25	102±16	64	4.6±1.3	1.23±1.37	1.23±0.60
100%	5	25	109±17	62	5.0±1.5	1.83±2.44	1.13±0.74

Table 5: Drug infusion rates, cardiovascular variables and mean total power of the laser Doppler blood flow signal at both sites for all drug doses.
The power has been normalised to the baseline (pre-drug) reading. Values are shown as mean± SD.

By analysing the power spectra contained within the Doppler waveform the effects of these agents on local tissue control could be determined. For each dose the average normalised power, standard deviation of the normalised power and the changes in the power of the blood flow signal (the variance of the signal) are shown in **Table 5.** There was no statistically significant difference between the variability in the control site and flap at any drug dose ("t" tests, Šidák correction for multiple comparisons, all p values >0.05), despite the power spectra for the flap flow appearing to exhibit far more variability with noradrenaline. **Figure 21** shows the power spectrum from the control site of one of the patients in the study. The cardiac, respiratory and myogenic components are seen as discrete peaks, the neurogenic and local endothelial-based control cannot be separately distinguished in this example.

The control (pre-drug) averaged power spectra is shown in **Figure 22,** and at maximum dose (adrenaline, dobutamine and dopexamine) and 75% maximum dose noradrenaline, (as only 5 patients reached maximum dose) are shown in **Figure 23**. Intervening doses showed similar changes. Nearly all the oscillation in blood flow was in the range of 0-3Hz with almost none in higher frequency bands. **Figure 22** shows the control (pre-drug) spectra. The power in the region below 0.1Hz was reduced. As the spectra were normalised there was a corresponding increase in the power in the 0.8-1.7Hz range representing the heart rate. The differing heart rates of the subjects broadened this peak. At the maximum adrenaline infusion rate the heart rate increased and the spread of heart rates also increased. As a result the heart rate dependent peak moved to higher frequencies and broadened. The proportion of the total power in the lower frequencies increased. At the maximum dobutamine infusion rate there was little effect on the distribution of the control of blood flow, though as with all drugs studied the cardiac related peak increased in frequency and broadened. Dopexamine demonstrated the same findings as dobutamine. However with noradrenaline at 75% of maximum dose, low frequency activity below 0.1Hz was higher in the flap compared to control, and the difference between flap and control in the 0.1-0.4Hz band was less marked than with other drugs.

No adverse events or flap failures were noted in any of the patients as a result of the pressor infusions.

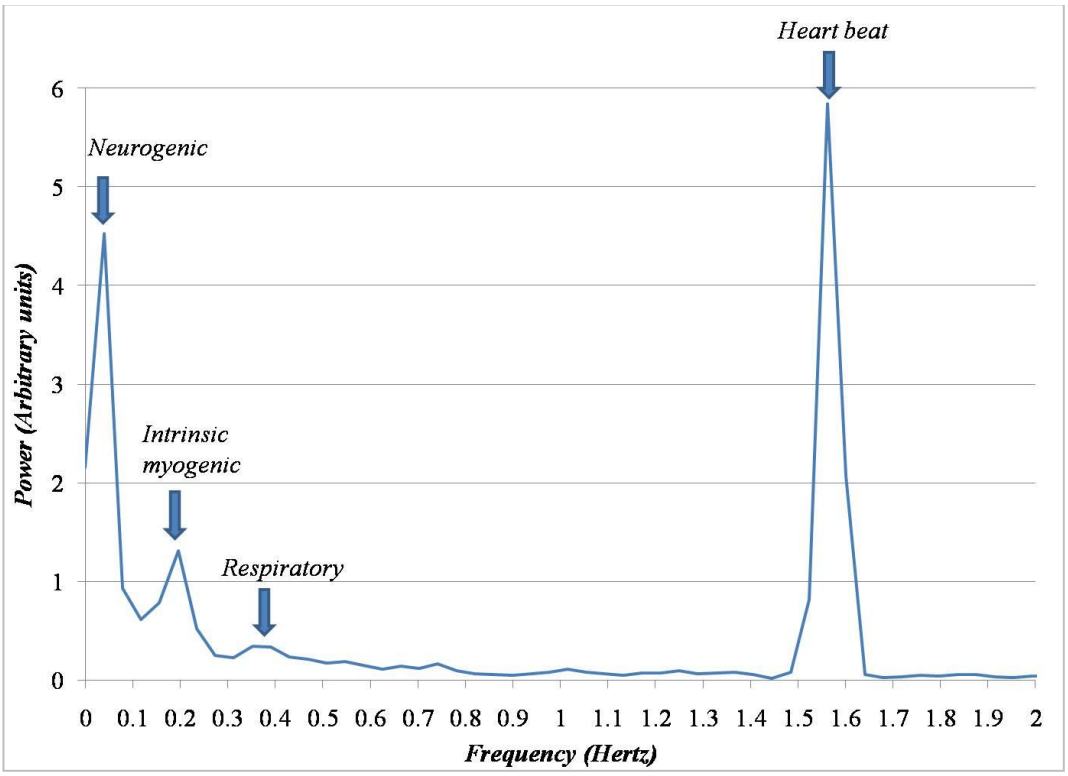

Figure 21: Power spectra at baseline.
This demonstrates the characteristic peaks extracted from the Doppler waveform, corresponding to heart beat, respiration, intrinsic myogenic and neurogenic control.

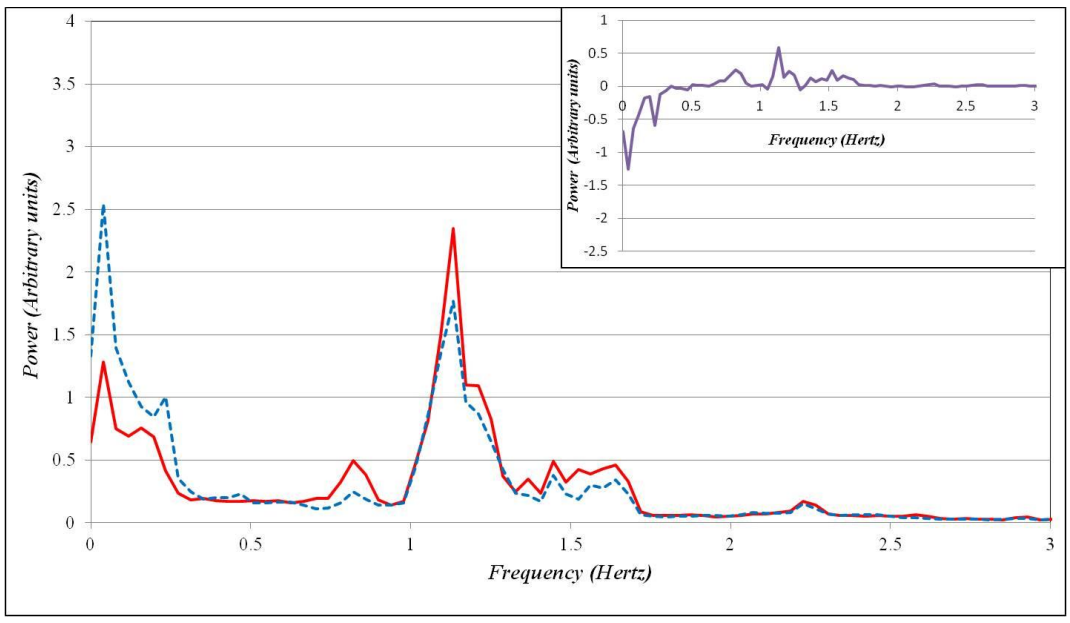

Figure 22: Power spectra for flap and control tissues at baseline.
The flap tissues are shown in red, and the control tissues in blue. Inset: The differential between flap and control tissues (flap-control).

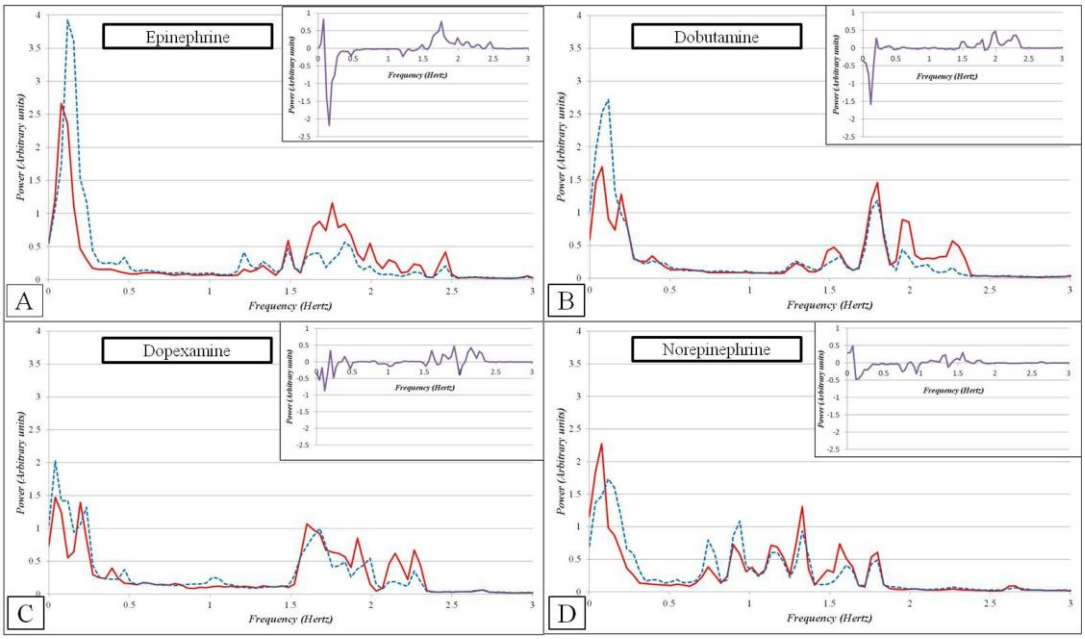

Figure 23: Power spectra for the flap and control tissues with pressor infusions.
Shown are the power spectra for flap (red) and control (blue) tissues for (A) adrenaline 0.2mcg/kg/min (B) dobutamine 8mcg/kg/min (C) dopexamine 5mcg/kg/min and (D), noradrenaline 0.15mcg/kg/min.
Inset panels in each graph show the averaged differences (flap spectrum-control spectrum) to assist interpretation.
Note that the spectra were all normalised (i.e. set to the same area under the curve) by the zero mean unity variance processing, so total power cannot be compared with these graphs.

3.4 Discussion

It has been demonstrated that whilst noradrenaline results in vasoconstriction in both the flap and the control tissue, the effect is more marked in the control tissues. This vasoconstrictor effect on the flap is more than overcome by the resultant increase in blood pressure caused by noradrenaline, resulting in a significant increase in flap perfusion. Dobutamine also reliably increased flap and control site blood flow by about 10% (compared with the 30% maximum seen with noradrenaline) without causing a change in conductance and with little effect on blood pressure.

The power spectra confirmed a number of anticipated findings following free tissue transfer. All drugs increased the power (overall variability) of the blood flow signal at both sites, and this was more marked for adrenaline and especially noradrenaline. At the maximum dobutamine infusion rate there was little effect on the distribution of the control of blood flow. However with noradrenaline at 75% of maximum dose, low frequency activity below 0.1Hz was higher in the flap compared to control, and the difference between flap and control in the 0.1-0.4Hz band was less marked than with other drugs. This suggests that the noradrenaline infusion increases the local myogenic control of blood flow in the free flap to a greater extent than the other drugs studied.

Chapter Conclusion

Noradrenaline most consistently elevated the mean arterial pressure and caused by far the largest increase in flap skin blood flow, making it the pressor agent of choice (of those studied), following free tissue transfer. This is supported by the finding that the control of blood flow shifts towards low frequency vasomotion where blood flow depends mostly on average blood pressure.

4. Coagulation

4.0 Coagulation

In 2005, the House of Commons Health Committee reported that an estimated 25,000 people in the UK die from preventable hospital-acquired venous thromboembolism (VTE) every year. [105]

The NICE guidelines on VTE state that any patient undergoing a surgical procedure with a general anaesthetic and surgical time of more than 90 minutes should be considered at increased risk of VTE. Patients with cancer, aged over 60 years, have a critical care admission, or have one or more significant medical co-morbidities are further risk factors.

These risk factors are further compounded in patients with head and neck malignancy due to the procoagulant effects of malignancy.

In combination with the significant risks of VTE in patients undergoing free flap surgery for head and neck malignancy, there remains an appreciable risk of anastomotic thrombosis, most notable within the first 48 hours, with resultant disastrous consequences.[106] As a result, the majority of surgeons utilise pharmacological antithrombotic agents.[44,107,108] However, such practice remains controversial since inappropriate anticoagulation may result in external haematoma formation and compromise of flap perfusion.

This section of the thesis focuses on peri-operative management of coagulation in patients undergoing ablative surgery and free flap reconstruction. The section commences with a literature review, prior to review of the methodology and results of:

5. Parker RJ, **Eley KA**, Von Kier S, Pearson O, Watt-Smith SR. Functional fibrinogen to platelet ratio using thromboelastography as a predictive parameter for thrombotic complications following free tissue transfer surgery: a preliminary study. Microsurgery 2012; 32(7): 512-9.[7]
6. **Eley KA**, Watt-Smith SR. Low molecular weight heparin in patients undergoing free tissue transfer following head and neck ablative surgery: a review of efficacy and associated complications. Br J Oral Maxillofac Surg 2013; Oct;51(7):610-4.[8]
7. **Eley KA**, Watt-Smith SR. Coagulopathies and the use of LiDCO Plus Rapid monitoring in patients following head and neck cancer resection and reconstruction. Br J Oral Maxillofac Surg 2010; 48(6): 466.[9]
8. **Eley KA**, Parker R, Bond SE, Watt-Smith SR. Are routine prophylactic dalteparin doses appropriate in patients undergoing head and neck cancer resection? Int J Oral Maxillofac Surg 2009; 38(5): 584-5 [Published abstract].[10]
9. Parker R, **Eley KA**, Bond SE, Watt-Smith SR. Is the ratio of functional fibrinogen to platelets as measured by thromboelastography a predictive parameter for thrombotic complications in free tissue transfer surgery? Int J Oral Maxillofac Surg. 2009; 38(5): 585 [Published abstract].[11]

4.1 Literature Review

A comprehensive review of the literature was conducted to explore the current practices in peri-operative management of coagulation following free tissue transfer. This was completed using NCBI Pubmed and Google Scholar with the following MeSH terms:

(Free Tissue Flaps or Surgical Flaps [All fields]) and ("Blood coagulation" or "Blood coagulation factors" or "Blood coagulation tests" or "Anticoagulants").

The titles and abstracts were reviewed to identify those papers with clinical relevance, with subsequent review of related citations and references.

Flap failure may occur due to vascular complications despite meticulous microvascular technique, with venous thrombosis being more common than arterial occlusion.[109] This thrombogenic effect may be the result of several factors. Expression of the proteolytic enzyme CP (cancer procoagulant, a cysteine proteinase) by malignant tumour cells is known to directly activate factor X without interaction with the intrinsic or extrinsic coagulation pathways.[110-112] Increased levels of TF (tissue factor), PAI-1 (plasminogen activator inhibitor), the inflammatory cytokines TNF (tumour necrosis factor), IL1, IL8 (interleukins) and VEGF (vascular endothelial growth factor) are all associated with tumour related thrombosis.[112,113] Additionally reduced expression of regulators of coagulation such as tPA (tissue plasminogen activator) and TM (thrombomodulin) on the endothelial surface and concomitant increased production and deposition of fibrin are also observed in tumour related thrombosis. Higher flap failure rates in malignancy cases would therefore be anticipated; however, reported rates do not appear to support this.[114-117]

Fibrinogen is synthesised in the liver and forms the final step in the clotting cascade when it is converted to fibrin with formation of the clot. In addition to its well known roles in blood coagulation, recent studies have shown that fibrinogen plays important roles in a variety of processes, which include cell-to-cell interactions, inflammation, and cancer progression.[118]

Concentrations of fibrinogen can increase by as much as 200-400% during times of physiological stress, primarily due to the actions of macrophage-derived IL6.

High plasma fibrinogen levels have been correlated with increased thromboembolic risk in patients with cancer or cardiovascular disease.[119] Wayman *et al*[79] noted that fibrinogen concentration was significantly higher in patients with oesophageal carcinoma than in age and sex matched control patients with benign disease. Fibrinogen concentration was also higher in patients who had a greater depth of tumour invasion and those with metastatic disease.

Kuo *et al*[119] investigated the impact of hyperfibrinogenemia on patency of microvascular anastomoses. Using a rodent model, they performed femoral artery and vein anastomosis with and without intravenous administration of fibrinogen. Laser Doppler flowmetry was used to assess the patency of the anastomosis pre-operatively and 2 hours post-operatively. Vascular patency was assessed 7 days post-operatively. They found that there was no statistical difference in patency of the femoral vessels after vessel division and re-anastomosis. This experimental data did not support their clinical findings that 20% of patients with hyperfibrinogenemia suffered post-operative thrombotic events resulting in flap failure.

Wang *et al*[120] highlighted the problems associated with free tissue transfer in hypercoagulable patients. Of the 2032 flaps performed over a 5 year period, 58 flaps were identified to have been performed in patients having thrombophilia or previous thromboembolic event. The rate of thrombosis was 20.7% (12 flaps), including those occurring intra-operatively, with a flap loss rate of 15.5%. Most of these flaps failed late, outside of the typical 48 hour window. Whilst the authors advocated careful pre-operative assessment to identify patients at risk, Davison *et al*[121] presented four patients in whom flap failure occurred due to unrecognised hypercoagulation, highlighting that no routine, inexpensive, specific screening test predicts for the development of hypercoagulopathy-related peri-operative complications.

In their review of pharmacologic optimisation of microsurgery, Conrad and Adams[122] following an extensive review of the literature, reported their experience with 500 free flaps. They found that Dextran resulted in several cases of volume overload and pulmonary oedema and therefore

advocated the use of low dose aspirin for two weeks post-operatively, and intra-operative heparin. Dextran impairs platelet function, prolongs bleeding time and destabilises fibrin polymerisation. It is related to anaphylactic reactions and systemic effects, making its use in patients over 50 years of age unadvisable. As recommended by Conrad and Adams[122] aspirin and heparins are more suitable for patients with head and neck malignancy, who are typically of advanced age. Low molecular weight heparins (LMWH) have broadly replaced unfractionated heparin (UFH) due to more preferable pharmacokinetics and an improved safety profile.[123] Reiter *et al*[124] reviewed the outcome and peri-operative complications of 137 free flap procedures using low molecular weight enoxaparin prophylaxis. The overall flap survival was 97.1%, and the overall return to theatre rate was 15.3%. A similar retrospective study was completed by Chen *et al*.[125] They reviewed 6,759 surgical procedures for oncologic reconstruction, with comparisons made between those undergoing head and neck reconstruction (n=1,591) with all other surgical procedures (n=5,168) during the same period. Of those undergoing free flaps to the head and neck (n=473), there were 4 cases of symptomatic DVT, and 7 cases of PE. Post-operatively head and neck free flap patients received aspirin and LMWH in addition to pneumatic compression devices; despite this the incidence of VTE was higher than in non head and neck patients.

It is well documented that patients with malignant disease are at increased risk of VTE, with malignancy being the aetiological factor in 20% of VTE events in the community, and resulting in a 100-fold increase in incidence in hospitalised patients.[126-127] In patients undergoing free tissue transfer, this risk is further compounded by immobility and prolonged surgical procedures.

Locally, dalteparin is usually the preferred LMWH. Blackburn *et al*[128] assessed the safety of a change in protocol in which the first dose of dalteparin was increased from 2500 to 5000 units 12 hours pre-operatively in patients undergoing major head and neck surgery with microvascular reconstruction. In total they reviewed 68 patients evenly distributed across the two dalteparin regimens. The primary outcome measure was the bleeding index and the secondary outcome measure was post-operative return to theatre for bleeding or evacuation of a

haematoma. Pre-operative use of warfarin was considered a factor for exclusion. The bleeding index (BI) over 5 days (range 40–60) was used as an objective, surrogate measure of peri-operative bleeding, where:

BI = [pre-operative haemoglobin (g/L) - day 4-6 post-operative haemoglobin (g/L)] + number of units of packed cells transfused in the interim.

They found no significant difference in the mean bleeding index between the two groups, and the authors concluded that an increased dose of dalteparin did not seem to increase bleeding complications. The efficacy of the increased dose was not studied. The benefit of commencing LMWH pre-operatively has been debated. Strebel *et al*[129] in their systematic review of LMWH regimens in patients undergoing elective hip surgery found no convincing evidence that starting prophylaxis pre-operatively is associated with a lower incidence of VTE than starting post-operatively.

With only a moderate prolonging effect on the activated partial thromboplastic time, anti-Xa levels are preferentially used to monitor LMWH therapy.[130] For dalteparin the recommended peak anti-Xa level is 0.5-1.0 IU/ml or 1.0–2.0 IU/ml for full anticoagulation with twice daily and once daily dosing, respectively, and 0.2-0.4 IU/ml for prophylactic VTE anticoagulation.[130,131] The same dose regimen for prophylaxis is routinely used for all patients post-operatively, irrespective of their body mass index (BMI).

In an attempt to predict risk there are various scoring systems available. In patients with head and neck malignancy, one such system, the Caprini score[132] would result in the majority of patients being deemed high risk – since patients are mostly over the age of 60 years (2 points), have malignancy (2 points), are having major surgery (2 points), and depending upon the donor site, will have an immobilising plaster (2 points).[132] In view of smoking and alcohol use, many will also score additional points for co-morbidity.

Early identification of the failing flap is paramount for successful salvage. A method to reliably predict those patients most at risk would permit additional measures to be instigated in an attempt to minimise flap failure.

Thrombelastography (TEG®) has been used for many years to detect coagulopathy and hypercoagulable states, and is now widely used as a near-site haemostasis monitor.[133-135] TEG® technology analyses the functional activities of the cellular elements, such as platelet cytoplasmic granules and platelet surfaces, in conjunction with plasma components. Because the TEG® analyser monitors the shear elasticity of clotting blood, it is sensitive to all of the interacting cellular and plasmatic components. These include coagulation and fibrinolytic factors, activators, and inhibitors which may affect the rate or structure of a clotting sample and its breakdown. The TEG® analyser can be used to calculate the ratio of functional fibrinogen to platelets (the "functional" component being only the fibrinogen which is biologically active) by utilising an additional reagent. There are no published findings in the literature (apart from the presented paper) exploring the use of TEG® in free tissue transfer.

The following section explores the methodology used in the presented papers, with the aim of determining: a) if the ratio of functional fibrinogen to platelets, as measured by TEG®, is a reliable predictor of intra- and post-operative thrombotic complications following free tissue transfer surgery, and b) the therapeutic response to standard LMWH dose in patients (using anti-Xa levels) following ablative and reconstructive surgery for head and neck cancer.

4.2 Materials and Methods

The methodology is divided into two discrete phases:

4.2.1 TEG

A retrospective review of patients undergoing surgery for head and neck pathology with free flap reconstruction, performed between April 2006 and June 2007 was conducted.

Functional fibrinogen to platelet ratio was determined at induction of anaesthesia and this baseline result used for subsequent analysis. All patients, as per local routine practice, had regular TEG® analyses (without the additional functional fibrinogen to platelet ratio) performed throughout the peri-operative period in addition to routine haematology and biochemistry investigations (including a coagulation screen).

TEG® analysis was completed using the TEG® 5000 haemostasis analyser (Haemoscope Corp, Niles, IL) (**Figure 24**). This measures the visco-elastic properties of blood, and the resulting haemostasis profile is a measure of the time it takes for the first fibrin strand to be formed, the kinetics of clot formation and the strength and dissolution of the clot (**Figure 25**). Approximately 80% - 90% of the strength of the maximum amplitude (MA) is related to platelet numbers and function.

A "Clauss correlated" functional fibrinogen level (TEG-Fib) achieved through the addition of the monoclonal antibody c7E3 (abciximab (ReoPro®, Eli Lilly, Indiana, USA)) which binds the glycoprotein IIb/IIIa receptor on the platelet surface, was used to remove the platelet component of the clot to measure the fibrinogen contribution to clot strength, expressed as MA_R.

Figure 24: TEG haemostasis analyser.
TEG analyses the viscoelastic properties of blood.

With the concurrent use of an unmodified TEG® sample, the independent contribution of fibrinogen and platelets to the overall clot strength could be determined**.** For standard TEG® analysis, a 1ml sample of whole blood was added to a kaolin activator vial. After inverting the vial to ensure adequate mixing, 360µgs of kaolin activated whole blood was transferred to the analyser. To test the functional fibrinogen level, 355µgs of the remaining kaolin activated whole blood was added to a second cup which contained 5µgs abciximab (**Figure 26**). Analytical software within the TEG® software (version 4.2.3) was used to calculate the functional fibrinogen level (FLEV) through the transformation of the MA value.

As the maximal amplitude (MA) of thromboelastography using whole blood (MA_W) measures clot strength and represents the collective contribution of both fibrinogen and platelets it was possible to firstly inhibit the platelet function, and subsequently calculate the functional fibrinogen to platelet ratio using the equation:

$$Functional\ Fibrinogen\ to\ Platelet\ Ratio = \frac{MA_R}{MA_w} x\ 100$$

In total, 29 patients (male n=17; female n=12), with a mean age of 58 years (32 – 83 years) had functional fibrinogen to platelet ratios available (**Table 6**). Pre-operative anticoagulation in line with local protocol at the time of the study was not used.

The functional fibrinogen to platelet results were compared to data previously obtained from a healthy adult control group (n=42). Participants in this group were freely consenting laboratory staff, who each donated 1ml of blood for baseline modified functional fibrinogen and standard TEG® testing. This data was collected to permit familiarity with the methodology, and as such no demographic data was stored.

Ethical Considerations

Since blood analysis utilising TEG® constitutes routine patient care (with no additional blood samples required), and the control group were laboratory staff, ethical approval was not considered necessary.

Statistical Analysis

Statistical analysis was performed with an Independent samples Mann Whitney U Test and Fishers Exact Test on SPSS version 17, with results displayed as mean±SD.

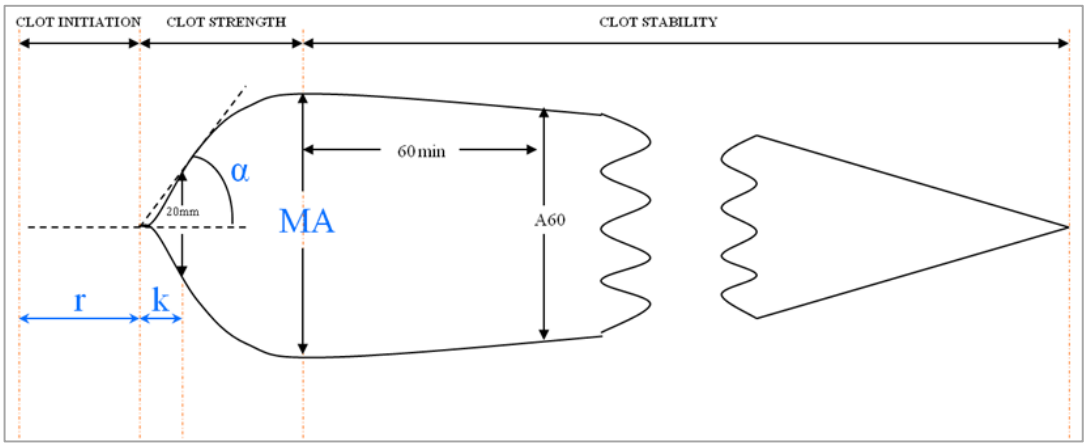

Figure 25: Schematic diagram of TEG trace.
The TEG parameters illustrate the functional activity of clot initiation, kinetics, maximal strength and clot stability.

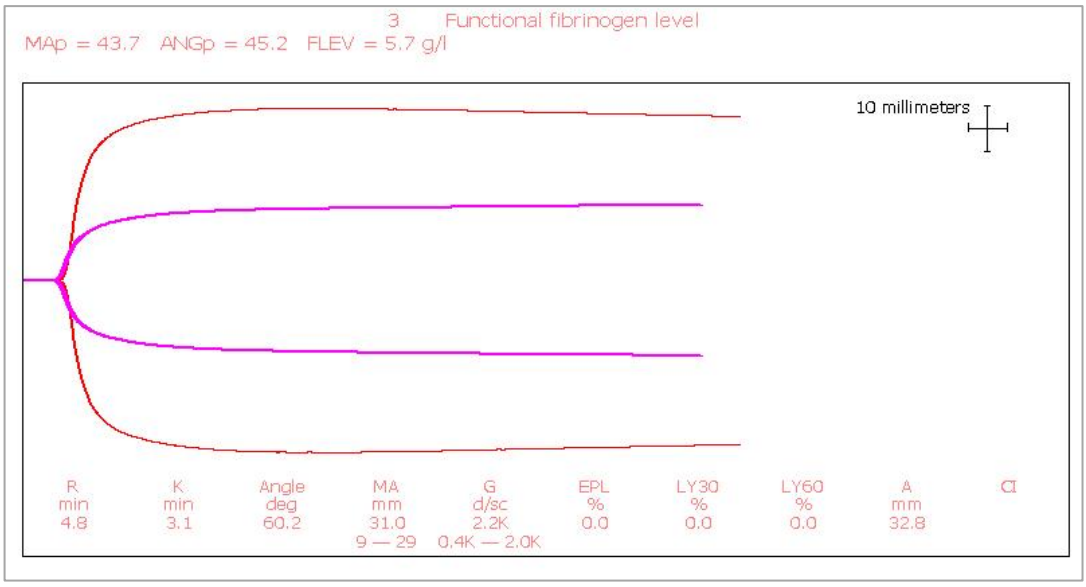

Figure 26: Schematic diagram of the TEG trace.
This shows: Large trace (red) the MA as a function of fibrinogen and platelet activity on whole blood (MA_w); Small trace (pink) the MA as a function of fibrinogen contribution alone, after exposure to Reopro (MA_R). Allowing for the determination of the independent contributions of fibrinogen and platelets to overall clot strength. MA_R/MA_w x100

Patient	Sex	Age	Site of resection	Flap(s)	Baseline FF:Plt	Thrombotic Complications
1	M	83	Mandible	Latissimus Dorsi, & Radial	55	Intra-operative anastomotic thrombus
2	M	43	Mandible	Fibula & Latissimus Dorsi	55	Arterial anastomotic thrombus
3	M	34	Mandible	Fibula	39	
4	M	59	Mandible	Fibula & Radial	36	
5	M	83	Mandible	Fibula & Radial	50	Intra-operative IJV thrombus
6	F	61	Mandible	Fibula & Radial	34	Arterial anastomotic thrombus
7	M	32	Maxilla	Radial	26	
8	F	63	Mandible	Radial & Scapular	45	Venous anastomotic thrombus
9	M	75	Floor of Mouth	Radial	35	
10	M	57	Floor of Mouth	Radial	50	Intra-operative IJV thrombus
11	F	52	Tongue	Radial	46	
12	F	57	Mandible	Fibula	35	
13	M	48	Floor of Mouth	Radial	44	Intra-operative IJV thrombus
14	F	55	Mandible	Radial	39	
15	F	32	Right cheek	Groin	37	
16	M	69	Pharynx	Radial	42	
17	M	53	Mandible	Fibula	32	
18	F	79	Mandible	Fibula	30	
19	F	73	Maxilla	Radial	32	
20	M	75	Mandible	Radial	44	
21	M	45	Mandible	Fibula	39	
22	M	50	Floor of Mouth	Radial	41	
23	F	77	Mandible	Fibula	49	Arterial anastomotic thrombus
24	M	49	Lateral tongue	Radial	38	
25	F	76	Tonsillar fossa	Radial	36	
26	M	55	Lateral tongue	Radial	51	
27	F	54	Lateral tongue	Radial	42	
28	M	50	Lateral tongue	Radial	39	
29	F	46	Lateral tongue	Radial	42	Venous anastomotic thrombus

Table 6: Demographics for the patients included in the TEG study.
Included are the baseline functional fibrinogen to platelet ratio (FF:Plt) and corresponding thrombotic complications

4.2.2 LMWH and Anti-Xa

A retrospective review of all patients undergoing ablative surgery for head and neck cancer with free tissue transfer between 2006 and 2009 was completed. Patient medical records and the departmental database were utilised to obtain information relating to anticoagulation prescription, pre-operative weight, co-morbidity and post-operative morbidity. Co-morbidity was assessed using the Adult Co-morbidity Evaluation-27 (ACE-27) scoring system grading patients into four groups of no, mild, moderate or severe decompensation (**Appendix B**).[136] The presenting tumour was not included in this scoring process.

At the time of the study, routine prophylaxis included dalteparin 5000 IU once daily (od) with or without aspirin 75mg od post-operatively. The incidence of bleeding complications requiring return to the operating theatre was determined. In those cases where anti-Xa levels were available, these results were reviewed. An anti-Xa level 4 hours following administration of the initial dalteparin dose was requested (introduced at the end of 2008), and the dose adjusted to ensure optimal LMWH therapy. Only those anti-Xa results which could be confidently confirmed as being performed at the correct time interval were included for data analysis. The prophylactic range was considered a peak (4-hour) result of 0.2-0.4 IU/ml.

Post-operative haematoma and bleeding complications, for which no cause was identifiable, were considered to be related to anticoagulation administration for the purpose of this study.

Ethical Considerations

This aspect of the thesis was considered to be an audit of clinical practice, and therefore formal ethical approval was not considered necessary. All patients included in the study had undergone surgical intervention, and had agreed to the use of their medical records for the purposes of research and audit during the formal written consent process.

Statistical Analysis

Statistical analysis was performed using SPSS. Descriptive analysis was first completed using histograms, box plots, and scatter plots. Statistical comparison was performed using paired Student's *t*-tests and chi square tests. Probabilities of ≤ 0.05 were considered significant.

4.3 Results

4.3.1 TEG

The functional fibrinogen to platelet ratio results were significantly higher in the surgery group (40.8±7.4) compared to healthy controls (32.4±6.1) ($p<0.05$; Independent samples Mann Whitney U Test). Within the surgery group, patients with malignancy (n=26) had higher ratios compared to those with benign pathologies (n=3), with mean functional fibrinogen to platelet ratios of 41±7% and 38±2% respectively (**Table 6**).

Of the 29 patients studied, 31% (n= 9) had some form of thrombotic event (**Table 6**). One patient had an early venous anastomotic thrombotic event, which was detected prior to wound closure, with no post-operative flap complications following thrombus removal and repeat anastomosis. Five patients experienced flap complications necessitating return to the operating theatre where anastomotic thrombosis was identified as the cause. Of these, 3 were arterial thromboses, with successful salvage in one case; two were venous thromboses, with both flaps ultimately lost. In the remaining 3 cases thrombosis within the internal jugular vein (IJV) was noted and removed at the time of primary surgery, with no further complication. There were no incidents of deep vein thrombosis or pulmonary emboli.

The functional fibrinogen to platelet ratio results were stratified into 2 groups, based upon the apparent clustering of thrombotic complications in those with ratios above 42% (**Table 7**). In Group A (ratio < 42%) one patient experienced flap complications (ratio 34%), with ultimate loss of both fibula and radial flaps on post-operative day 11 (**Figure 27**).

In Group B (ratio ≥42%) 8 patients experienced thrombotic complications; with three flap failures on days 1, 5 and 9 respectively. In the first case (ratio 45%) repeat surgery was complicated with further anastomotic thrombosis, but salvage successful. In the second patient (ratio 55%) both free flaps (fibula & latissimus dorsi) were lost, with subsequent failure of a repeat free flap. In the final patient (ratio 42%), repeat surgery was uneventful. The incidence of all thrombotic complications was statistically higher in Group B ($p=0.003$; Fishers Exact Test) (**Figure 28**).

The groups were similar for both age and BMI (**Table 7**). Only one patient had a previous history of VTE (deep vein thrombosis), and there were no prior incidences of anastomotic complications for any of the patients studied. The patient with a past history of DVT had a functional fibrinogen to platelet ratio of 46% at induction of anaesthesia for flap surgery, but did not experience any thrombotic complications at or following surgery.

A functional fibrinogen to platelet ratio of ≥42% resulted in a sensitivity of 89% and specificity of 75% for predicting thrombotic events.

During the study period, a further 19 free flaps were completed, resulting in 48 flap procedures by the same surgical team. In this group one patient underwent successful flap salvage for anastomotic venous occlusion. The overall free flap success rate for the study period was 92%. However, a free flap survival rate of 86% was achieved in the 29 patients studied, lower than would be expected. This discrepancy is likely to represent a combination of chance, and an increased request rate for a functional fibrinogen to platelet ratio in patients who may have been clinically perceived to be at increased risk of flap thrombosis.

Group	A	B
FF: Plt	<42%	≥42%
	n=16	n=13
Age (years)	55±15	62±14
BMI (kg m^{-2})	27±6	23±5
Thrombotic events	n=1	n=8
Flap loss	n=1	n=3

Table 7: Comparison of thrombotic and flap complications with age and BMI for the two subgroups of functional fibrinogen to platelet ratio.

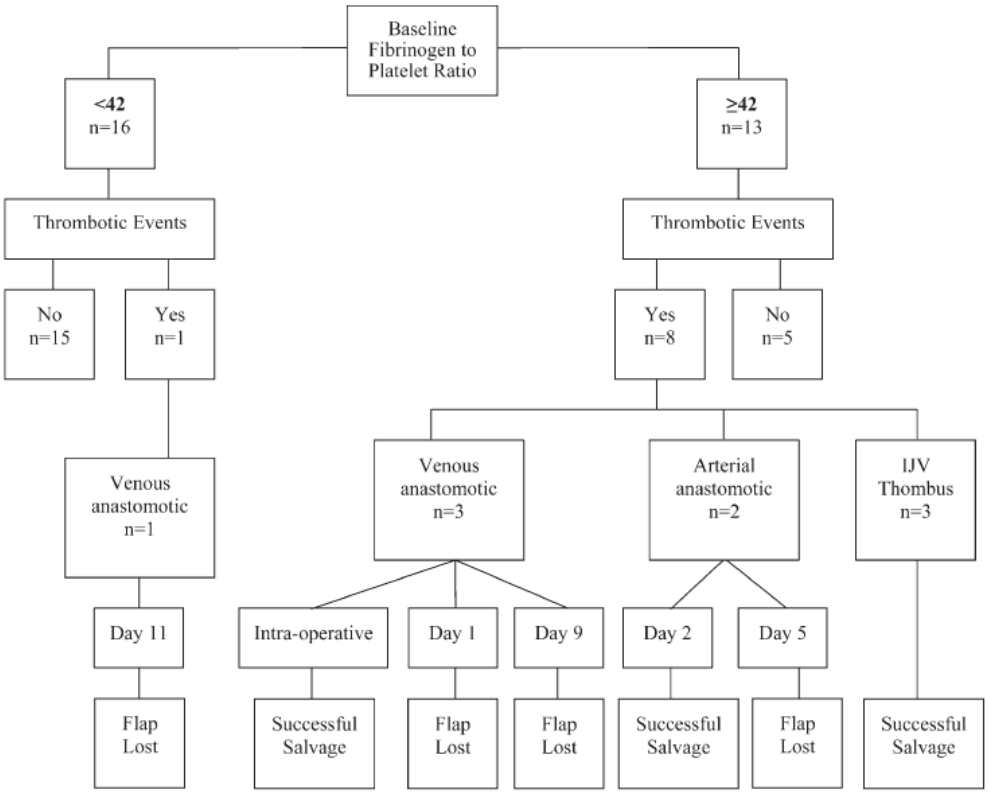

Figure 27: Flow diagram correlating flap outcomes with functional fibrinogen to platelet ratio.

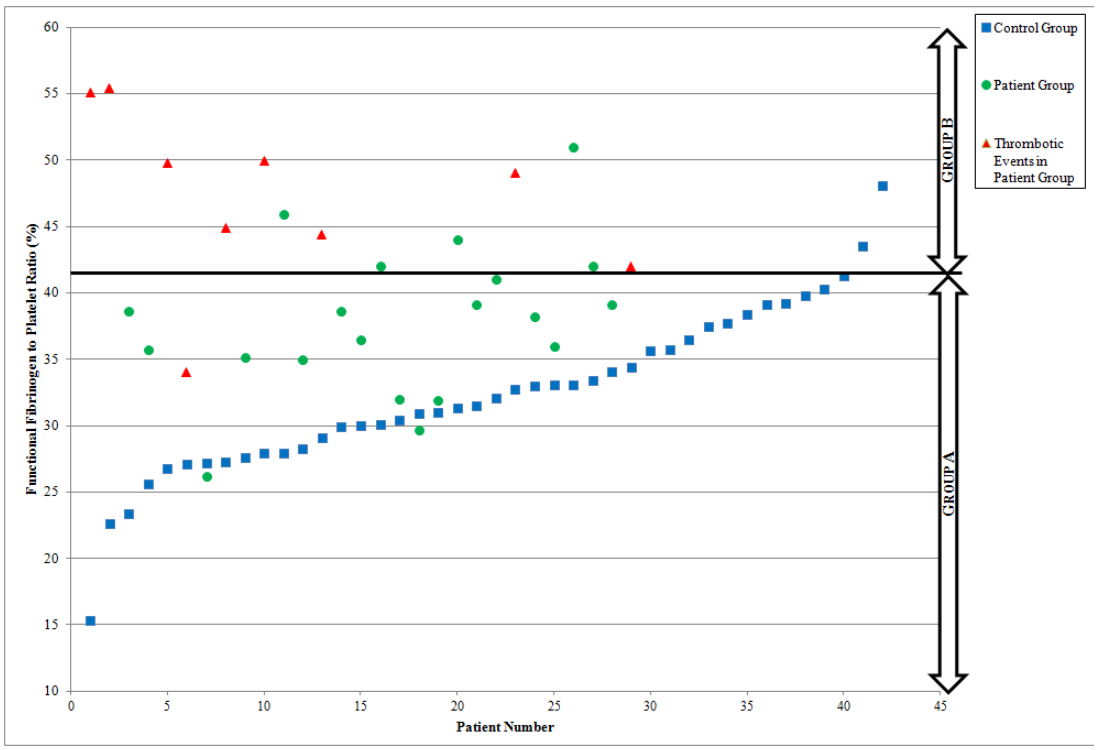

Figure 28: Graph of the functional fibrinogen to platelet ratios for the patients studied and the healthy controls.
The functional fibrinogen contributions of the patient group are shown in green, and healthy controls in blue. Patients who experienced thrombotic events are highlighted in red.

4.3.2 LMWH and Anti-Xa

During the 4 year period, 173 free flap procedures were completed following resection of primary or recurrent tumours of the head and neck, and were included in the study. This consisted of 153 patients, of whom 18 patients underwent more than one free flap procedure (two procedures n=16; three procedures n=2) as a result of tumour recurrence (n=3), a second primary tumour (n=3), to aid function (n=7) or due to flap failure (n=7) (**Table 8**). There were three further flap failures in the patient cohort, who subsequently underwent delayed or pedicled reconstruction. Successful flap salvage (including successful leech therapy n=1) was performed in 5 cases, with a further 2 patients experiencing an area of skin paddle loss.

Fourteen patients required return to theatre because of bleeding complications. In 8 of these, an active bleed was identified secondary to loose vascular clips (n=1), bleeding from the anastomosis (n=1), erosion of a vessel by a drain (n=1) or another identified vessel bleed (n=5). However, in 6 cases, no active bleeding was identified, and a haematoma evacuated. The distribution of unexplained haematoma was similar for all dalteparin regimens (**Table 9**), with no significant difference between groups (p=0.712). The distribution in terms of ACE-27 score, age and weight for the three groups are displayed in **Table 8**. The majority of patients received dalteparin with or without aspirin (**Table 10**). Nine patients were managed with intravenous unfractionated heparin (UFH) post-operatively, with five patients ultimately being commenced on warfarin in view of thrombosis within the IJV and/or problematic flap salvage. There were no significant complications in those managed with UFH.

Anti-Xa results were available in 47 cases, with a further test performed in 3 patients following dose adjustment (**Figure 29**). Of these, 44% (n=22) of the results were within the prophylactic range (≥0.2 U/ml) (**Table 11**). The average weight of patients with an anti-Xa <0.2 IU/ml was 84kg ±24 (range 48.5 – 157kg), and for those ≥0.2 IU/ml 65kg±12 (range 45 – 86kg). Paired samples t test, demonstrated a strong negative correlation (p=0.01) with anti-Xa result with increasing patient weight. In the 3 patients with repeat anti-Xa results following dose adjustment, there was an improvement in anti-Xa result in 2 cases.

Of the 47 flap cases with anti-Xa results, there were 6 flap complications. This included successful flap salvage, in one case, but 5 flaps ultimately lost. All but two anti-Xa results were below 0.2 IU/ml, with patients receiving a dalteparin dose of 5000od. Of the 14 patients who required return to theatre because of bleeding/haematoma, anti-Xa results were available in 8. Of these, 5 were patients with identified vessel bleeding, in whom only 2 patients had an anti Xa in the prophylactic range (mean 0.13; range 0.01-0.24). For the remaining 3 patients with haematoma, 2 of the anti-Xa results were in range (mean 0.26; range 0.1 – 0.47). One patient was treated for suspected post-operative VTE (pulmonary embolism), although there was some doubt associated with the diagnosis. This was an 82 year old male weighing 70kg who underwent mandibulectomy, and a fibula free flap reconstruction. He had been prescribed a dalteparin dose of 5000 IU bd, with no adjuvant aspirin. An anti-Xa was not performed.

	Return to theatre for bleeding complication (n=14)		**No bleeding complications (n=159)**
	Cause of bleed identified (n=8)	No cause for bleeding identified (n=6)	
Sex:			
Male	n=5	n=3	n=93
Female	n=3	n=3	n=66
Age (years)	54±16	66±16	61±14
Weight (kg)	82±14	60±7	71±18
ACE-27:			
0	n=3	n=2	n=55
1	n=4	n=4	n=89
2	n=1	n=0	n=15
Free Flap:			
Radial	n=4	n=4	n=93
ALT	n=1	n=1	n=18
Fibula	n=2		n=21
Latissimus dorsi		n=1	n=9
Fibula + Radial	n=1		n=8
Fibula + ALT			n=5
Fibula + Latissimus dorsi			n=1
Other			n=4

Table 8: Patients' details, co-morbidities, and free-flap reconstruction by bleeding complications

Dalteparin dose (IU)	No bleeding complications (n=159)	Active bleeding identified at return to theatre (n=8)	Unexplained haematoma (n=6)
2500 od	7 (5%)	0	0
5000 od	100 (63%)	5	4
5000 bd	34 (21%)	1	2
7500 or more od	18 (11%)	2	0

Table 9: Dalteparin prescription in patients with no bleeding or haematoma and those with unexplained post-operative haematoma.

	Dalteparin dose								
	2500od		5000od		5000bd		≥7500od		Total
	with aspirin	no aspirin	with aspirin	no aspirin	with aspirin	no aspirin	with aspirin	no aspirin	
No Problems	5	2	71	29	19	15	13	5	159
Identified bleed	0	0	4	1	1	0	2	0	8
Haematoma	0	0	3	1	2	0	0	0	6
Total:	5	2	78	31	22	15	15	5	173

Table 10: Anticoagulation regimen and frequency of associated bleeding complications.

Dalteparin dose (IU)	Anti-Xa Concentration	
	<0.2	≥0.2
2500 od	6	0
5000 od	18	14
5000 bd	2	5
7500 od or more	2	3

Table 11: Result of anti-Xa in 47 cases with varying doses of dalteparin (3 patients had repeat tests).

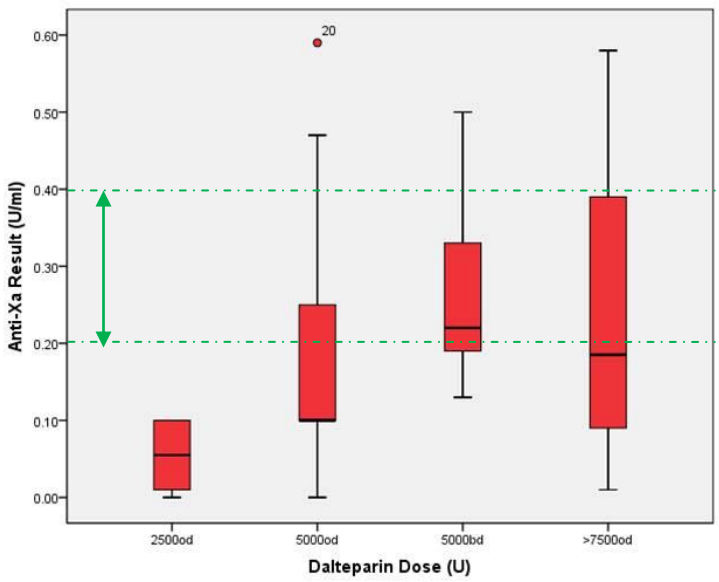

Figure 29: Boxplot of anti-Xa results for varying doses of dalteparin. The prophylactic range is highlighted in green.

4.4 Discussion

It has been demonstrated that anti-Xa results are strongly correlated with mean patient weight, consistent with studies examining the anti-Xa response to dalteparin in obese patients.[137] This would imply that standard dose regimens of dalteparin are not suitable for all patients. However, despite a variable anti-Xa response to prophylactic dalteparin dose regimens, prescribing is rarely adjusted according to patient weight in routine clinical practice.

In the presented cohort, 56% had anti-Xa results which were below 0.2 IU/ml, and therefore deemed insufficient for prophylaxis. The risk, in terms of bleeding/haematoma complications, did not appear to be influenced by dalteparin dose, or aspirin prescription.

Targeting anticoagulant therapy to those patients most at risk of VTE or thrombotic flap events appears more complex than BMI alone. Functional fibrinogen to platelet ratio performed at induction of anaesthesia may therefore be a useful pre-operative predictor of patients likely to experience thrombotic complications. By identifying those in a cohort of patients all deemed "high risk" that are more likely to develop thrombotic flap complications additional measures to prevent or identify early flap failure can be instituted. These additional measures may include additional chemical thromboprophylaxis such as unfractionated heparin (particularly intra-operatively), or monitoring devices such as Doppler probes or microdialysis.[138]

However, patients included in this study had the functional fibrinogen to platelet ratio measured at the time of induction of anaesthesia (when the first routine TEG® is ordinarily performed) to avoid the need for an additional blood sample, and as a result, high risk patients were not identified at a sufficiently early time to institute pre-operative additional anticoagulation.

Whilst included as a thrombotic complication, the significance of thrombosis within the internal jugular vein seen at primary surgery is unclear. This was found in 3 patients, at the time of surgery, without subsequent flap complication. Where IJV thrombus was removed, additional anticoagulation measures, including intra-operative unfractionated heparin, were instigated with close clinical surveillance. This is likely to have reduced potential adverse sequelae in these patients. Certainly this represents an increased incidence of IJV thrombosis detected at primary surgery than is alluded to in the literature.[9,139]

Chapter Conclusion

Standard prophylactic LMWH dosing appears inadequate in patients with head and neck cancer and dose adjustment with anti-Xa monitoring is advocated. Anticoagulation could be further guided by functional fibrinogen to platelet ratio levels which appear useful in identifying patients likely to experience post-operative thrombotic events.

5. Nutritional Support

5.1 Nutritional Support

Malnutrition occurs in 35 to 60% of patients with head and neck malignancy. Optimised nutritional support is vital for post-operative recovery, including wound healing and immune function.[140-143] Despite improvements in reconstruction following ablative surgery, the impairment of post-surgical functions such as articulation, mastication and swallowing remain problematic for patients, compounded by oedema, trismus, loss of muscle, and reconstruction with nonsensate and nonmotile flaps.[144,145] Radiotherapy adds to these problems through mucositis, xerostoma, trismus, and further alters swallowing dynamics often resulting in dysphagia.[146,147] It is therefore often necessary to provide enteral feeding to bypass the oral cavity and pharynx to permit recovery of swallowing, and to allow the site to heal. In the early 1990's the use of Percutaneous Endoscopic Gastrostomy (PEG) tubes were popularised as the feeding method of choice in patients with head and neck malignancy; however, they carry significant morbidity and mortality risks.[148]

This section of the thesis focuses upon the peri-operative management of nutrition in patients undergoing free tissue transfer following ablative surgery for head and neck malignancy. The section commences with a literature review before describing the methodology and results of:

10. **Eley KA**, Shah R, Bond SE, Watt-Smith SR. A review of post-operative feeding in patients undergoing resection and reconstruction for oral malignancy and presentation of a pre-operative scoring system. Br J Oral Maxillofac Surg 2012; 50(7):601-5.[12]
11. **Eley KA**, Watt-Smith SR. Routine use of percutaneous endoscopic gastrostomy (PEG) in head and neck oncology: benefits and pitfalls. Br J Oral Maxillofac Surg 2010; 48(Supp 1): S20 [Published abstract].[13]

5.2 Literature Review

A comprehensive review of the literature was conducted to explore the current practices in peri-operative management of nutrition following free tissue transfer. This was completed using NCBI Pubmed and Google Scholar with the following MeSH terms:

("Free Tissue Flaps" or "Surgical Flaps" or "Mouth neoplasms" or "Head & neck neoplasms" [All fields]) and ("Enteral nutrition" or "Feeding methods" or "Nutritional support" or "intubation, gastrointestinal" or "Gastrostomy").

The titles and abstracts were reviewed to identify those papers with clinical relevance, with subsequent review of related citations and references.

It is recognised that patients with head and neck cancer are frequently affected with swallowing difficulties as a result of their primary tumour, surgical resection, reconstruction or adjuvant therapy. This results in malnutrition, and the potential sequelae of delayed wound healing. Early nutritional input is paramount to optimise enteral feeding, often with the need for nasogastric or gastostomy tubes.[149] The main difficulties associated with nasogastric tubes include blockage or their inadvertent removal. They may additionally cause nasopharyngeal pressure and irritation that can interfere with recovery of independent swallowing function and possibly lead to septal necrosis and sinusitis.[150]

It is hoped that swallowing function improves in the post-operative period to permit early removal of feeding tubes; however this belief is not supported in the literature. Tei *et al*[147] assessed the swallowing function in 25 patients pre- and post-operatively in patients undergoing resection of tongue, floor of mouth, lower gum and/or retromolar trigone carcinomas with free flap reconstruction. Of these, 21 patients underwent pre-operative radiotherapy. Swallowing performance was assessed pre-operatively, and at 1, 6, and 12 months after surgery. Assessments were completed using barium liquid and paste swallowing investigations. The authors reported that after surgery, as expected, swallowing worsened. Only 9 of the 25 patients' demonstrated improvement in swallowing at 24 months post surgery; function

appeared to remain unchanged 6 months following surgery. Those with the worst dysfunction were patients with tumours affecting the floor of mouth or tongue. It is therefore likely that any patient requiring nutritional support at 6 months post-surgery is likely to require this long term. It should be noted however, that the majority of patients included in Tei *et al*[147] study had undergone pre-operative radiotherapy increasing the likelihood of post-operative swallowing difficulties.

Gastrostomy provides a longer term route to maintain adequate nutrition in those patients with prolonged swallowing dysfunction, however this is not without risk. O'Dwyer *et al*[151] reported their experience with percutaneous gastrostomy feeding in 55 patients with head and neck malignancy. In their cohort, gastrostomy was performed by a radiologist under fluoroscopy, following ultrasound confirmation of the absence of viscera between the stomach and anterior abdominal wall. Of the 55 patients, 1 died of peritonitis and septic shock 72 hours after the procedure, due to dislodgement of the tube with leakage of feed into the peritoneum. Perforation of the small bowel occurred in one further case, requiring laparotomy, and three further patients experienced minor complications. Whilst the authors concluded that percutaneous gastrostomy using the Seldinger technique under fluoroscopy was useful in patients with head and neck tumours, endoscopy is often preferred. Endoscopy provides direct confirmation of the siting of the gastrostomy tube, and provides adjunct investigation of the upper gastrointestinal tract in patients at risk of synchronous gastrointestinal tumours. However, as with radiologically inserted gastrostomy, endoscopic assisted gastrotomy insertion is associated with similar complications.

Walton[152] reported the complications of PEG in 40 patients with head and neck cancer. In the majority of cases PEG was placed by the "pull" method one week prior to surgery; where endoscopy was not possible, gastrostomy was placed under fluoroscopic control. Nine patients experienced major complications, including premature tube removal, migration of the gastrostomy tube through the stomach wall and pneumonia. Seven patients experienced minor complications, including wound site infections and leakage around the tube. The author concluded that whilst useful, PEG is not without potentially life-threatening complications and

careful pre-operative selection is required. Fewer complications were reported by Hujala *et al*.[153] In their cohort of 79 patients with upper aerodigestive tract malignancies, PEG tubes were placed by the "pull" technique in the pre-operative period. In 5 cases open gastrostomy was needed mainly due to stricture or obstruction. There were no major complications, and the incidence of minor complications was low.

The insertion of gastrostomy tubes in the pre-operative period results in patients requiring an additional procedure at a time when the airway may become compromised by tumour bulk. Oakley *et al*[154] noted that peri-operative airway events in patients undergoing PEG insertion for head and neck cancer was reduced by the introduction of a tumour assessment protocol. In their initial audit cycle of 33 patients who had PEG insertion under sedation, there were two patients who had major airway complications resulting in one fatality. The protocol introduced included dynamic and static assessment of the tumour by endoscopy in addition to imaging review, prior to PEG to identify those tumours at risk of causing airway compromise. Following introduction of this protocol, 96 patients had PEG insertion under sedation, 16 under GA and 5 under radiological guidance, without complication.

Cunliffe *et al*[155,156] reported the benefits of PEG insertion at the time of tumour resection. They noted the significant risks associated with intravenous sedation in patients with advanced oral malignancy, with a requirement for the patient to be positioned supine. PEG placement at the time of definitive surgery once the airway was secured with an endotracheal tube, ensured that the airway was protected, and minimised the number of procedures for the patient. Lloyd and Penfold[142] reported similar findings. PEG insertion was completed by the "pull" method, in 52 patients over a 3 year period. Of these, the median duration of use was 18 weeks. There were no major complications, and 10 minor complications. The authors concluded that the insertion of a PEG could be performed safely at the time of surgical resection following intubation to secure the airway. In their study, Chandu *et al*[144] reviewed the complication rate associated with PEG insertion in 49 patients undergoing resection of oral malignancy. In the majority of cases (n=41) PEG insertion was via the "pull" technique at the time of surgical tumour resection. Seven tubes were inserted pre-operatively and 2 post-operatively. In total, there were 4 major complications

and 5 minor complications. Major complications included accidental removal, tube migration and abdominal wall abscess. Endoscopy revealed Barrett's metaplasia in one case and an ulcer on the greater curvature of the stomach in a second case, diagnosed as poorly differentiated adenocarcinoma. This again highlights the benefit of endoscopy in this patient group, with a similar complication rate associated with PEG insertion in the peri-operative period. Similar findings in terms of peri-operative morbidity have been reported by other authors with PEG insertion either at the time of tumour resection, or in the early pre-or post-operative period.[157-159]

Available guidance [160-163] suggests that PEG tubes should be considered if it is anticipated that nutritional intake is likely to be inadequate for a period exceeding 2-3 weeks. Sobani *et al*[145] compared patients managed with nasogastric feeding with those provided with a gastrostomy tube. In their cohort of 32 patients, they reported lower mean weight loss in those managed with gastrostomy. The complication rate was higher in the nasogastric group, with aspiration pneumonia due to dislodged tubes being problematic.

One of the key difficulties in patients with head and neck malignancy is identifying which patients are most likely to require longer term nutritional support, and who would therefore most benefit from the insertion of a PEG tube. Locher *et al*[164] conducted a retrospective analysis of surveillance, epidemiology and end results data of 8306 patients with locoregionally advanced stage head and neck cancer. PEG tube was more likely in patients with cancer of the larynx or oropharynx compared with those with cancer of the nasopharynx or oral cavity, in patients who had regional rather than local cancer, and who did not receive surgery as part of treatment.

Schweinfurth *et al*[150] also attempted to identify the factors common to patients who require enteral feeding long after the immediate post-operative period. They reviewed the medical records of 142 patients treated by surgical resection of carcinomas of the sinus, oral cavity, tongue base, larynx and pharynx. They found that a heavy use of alcohol was an absolute risk factor for post-operative gastrostomy dependence. The addition of post-operative radiation also placed patients at increased risk for gastrostomy dependence. TNM staging was not predictive of significant risk. Mekhail *et al*[141] retrospectively reviewed patients with SCC of the head and

neck treated with definitive radiation therapy or combined chemoradiotherapy; surgical resection was only used in those patients where non-operative management failed. As anticipated, there was a greater need for feeding tube placement in those patients with hypopharyngeal primary tumours, larger primary tumours, and after treatment with the more intensive chemoradiotherapy. Patients managed with a PEG were dependent upon their feeding tube longer than those managed with NG tube. This was speculated by the authors to be related to the discomfort and appearance of the NG tube producing a more aggressive and motivated swallowing rehabilitation. However, selection bias of patients being provided with a PEG because of a perceived increased requirement could not be excluded. Gardine *et al*[146] reviewed 109 patients treated surgically for SCC of the oral cavity, larynx or pharynx. 37.6% of their patients required tube feeding for more than 30 days post-operatively. The patient's age, sex and pre-operative serum albumin levels did not predict which patients would require prolonged enteral supplementation. Stage IV cancers, combined treatment with surgery and radiotherapy, and pre-operative weight loss of more than 10 pounds were significantly associated with the need for long term post-operative nutritional support.

Gibson *et al*[165] reported that in patients with tonsil lesions, the hospital stay was 48 days for the nasogastric group, and 19 days for the PEG group; however there were only 20 patients with tonsil tumours. Similar claims have been made by other authors.[159] Morton *et al*[166] explored the impact upon quality of life of PEG in head and neck cancer patients receiving chemoradiotherapy. They found that longer PEG duration was associated with poorer swallowing function, anticipated as more severely affected patients are likely to require longer periods of tube feeding. Longer PEG duration also predicted poorer overall quality of life and speech.

Whilst these authors have identified potential contributory factors to assist in the selection of enteral feeding tube in patients with head and neck malignancy, further guidance is required. The following section explores the methodology of the presented paper, with the aim of reviewing the complications associated with PEG and NG feeding in a local patient cohort, and developing a potential scoring system to aid tube selection.

5.3 Materials and Methods

A retrospective review of all patients undergoing primary or secondary head and neck cancer resection with immediate free flap reconstruction between January 2006 and 2010 was conducted. In total 144 patients were identified, and their medical records, and the electronic reporting systems (Centricity PACS and CaseNotes©) were reviewed to obtain details on tumour type, co-morbidity, surgery, post-operative feeding method, length of feeding and associated complications.

Routine practice at the time of the study included (where required) the insertion of a PEG by the upper gastrointestinal surgeons using the "pull" technique (which provides direct endoscopic visualisation of the upper gastrointestinal tract) immediately prior to surgery. PEG placement was performed once the anaesthetist had secured the airway. For patients managed with NG tubes, these were placed at the end of surgery with the aid of a flexible scope, with post-operative radiological confirmation of position.

Typically the operating surgeon selected a PEG rather than NGT when nutritional support was likely for ≥4 weeks, with consideration given to tumour volume, site and post operative adjuvant therapy.

Patients were ventilated for the first post-operative night on the Intensive Care Unit (ICU) as per routine practice. All patients received standard post-operative antibiotic prophylaxis (usually a cephalosporin and metronidazole), and gastric protection (usually a H_2 receptor antagonist).

Ethical Considerations

Patient consent for the use of medical records for audit and research purposes is routinely obtained as part of the consent process for surgical procedures. All patients included in this retrospective study had undergone surgical resection, with no objections given at the consent process for the use of their medical records for audit or research. As this work was considered to be part of an audit of clinical practice, with the aim of improving patient outcome, ethical approval was not considered necessary.

Statistical Analysis

Data was collected using data collection sheets, with the information transferred to an Excel spreadsheet and Access database to aid data interrogation. Data was randomly cross-referenced to confirm accuracy. SPSS was used for statistical analysis, with preliminary interpretation completed with histograms and box plots, followed by binary logistic regression.

Following data analysis, review of the decision making processes, and results of the literature review, the Key to Appropriate Replacement Enteral Nutrition (*KAREN*) scoring system was developed to assist in identifying those patients most likely to require prolonged nutritional support and who should receive a PEG tube. Whilst created retrospectively, this scoring system provides a basis for future prospective analysis.

5.4 Results

Of the 144 patients (male n=88; female n=56) the average age was 62 years (29 – 88 years). The pathology in all but 4 patients was squamous cell carcinoma (SCC); 3 were sarcomas and 1 patient had a malignant ossifying fibromyxoid tumour. In 126 cases resection was performed for a primary tumour, 9 for second primary tumours, and 9 cases for recurrent tumours. The site of excision and method of reconstruction are shown in **Table 12**.

	ALT	Radial	Fibula	Latissimus Dorsi	Scapular	ALT + Fibula	Radial + Fibula	TOTAL
Alveolus/Mandible/ Retromolar Trigone	2	11	12	2	1	3	10	**41**
Maxilla	0	1	0	1	0	1	0	**3**
Floor of Mouth/ Ventral Tongue	1	18	0	0	0	0	0	**19**
Lateral/ Posterior Tongue	6	48	0	3	0	0	0	**57**
Buccal mucosa/ Cheek/Lip	5	13	0	1	0	0	0	**19**
Tonsillar fossa/ pharynx/soft palate	0	5	0	0	0	0	0	**5**
TOTAL	**14**	**96**	**12**	**7**	**1**	**4**	**10**	**144**

Table 12: Tumour excision site and free flap used for reconstruction.

5.4.1 Nasogastric Tube Feeding

In total, 24 patients were managed post-operatively with NGT. Of these, 3 patients ultimately required a PEG tube; 2 because of post-operative complications (unrelated to their NGT) prolonging their need for nutritional support (one case of hypoxic brain injury following a respiratory arrest and one post-operative pneumonia), inserted at 21 and 30 days respectively. The final patient had a PEG tube placed as a separate outpatient procedure following discharge, prior to commencing radiotherapy to the pharynx.

The average length of NGT use was 13 days (5 – 63 days). In addition to the two patients ultimately progressing to PEG, 2 further patients were reliant upon NGT for longer than 28 days (33 and 63 days respectively). In the first case this was due to perforation of a colonic diverticulum unrelated to the primary surgery. The second patient had an NGT for 63 days, following resection of a commisure and cheek tumour with reconstruction using a radial forearm free flap and local rotation flap. Early return to oral nutrition was anticipated, but post-operative recovery was eventful with return to the critical care unit due to respiratory failure. The use of NG feeding was discontinuous with times of full oral nutrition before succumbing to further complication.

Patients required the insertion of a mean of 1.9 NGT's (1 – 5 tubes per patient), as a result of accidental removal or dislodgement. Two patients experienced complications directly related to their NGT resulting in a prolonged in-hospital stay (aspiration pneumonia in both cases).

5.4.2 Percutaneous Endoscopic Gastrostomy (PEG)

The remaining 120 patients received PEG tubes. Five were inserted in the pre-operative period in the endoscopy suite at an average of 14 days pre-operatively (2 – 26 days), the remainder (n=115) at the time of surgery. This group included one patient requiring open jejunostomy in view of co-existing pancreatic disease.

In the pre-operative insertion group (n=5) there were no serious PEG related complications. One patient experienced complex feeding problems (autonomic neuropathy related diabetic gastroparesis), ultimately requiring supplemental Total Parental Nutrition (for one month) in addition to jejunal gastrostomy extension.

Post-operative imaging of the abdomen was required in 10 patients (CT n=7; Fluroscopy n=3) having PEG or jejunostomy tubes inserted at the time of surgery. The indications for imaging included significant abdominal pain, early sepsis, and confusion, raising concern of a PEG leak. This occurred on an average of 6.3 days post insertion (3 – 12 days). In one case, CT revealed a colonic injury secondary to PEG insertion and the patient proceeded to laparotomy and removal of the PEG. A PEG leak was found on imaging in one patient and he also underwent laparotomy. In both cases subsequent recovery was uneventful. In a further 3 patients imaging identified an abdominal cause for their symptoms which was unrelated to their gastrostomy (ischaemic bowel, acute pancreatitis, and perforated colonic diverticulum). In the remaining 5 patients imaging was normal.

Of the 120 patients managed with PEG, 19 experienced minor complications (16%). These included abdominal pain not warranting investigation (n=4), problems associated with the feed (n=3), leakage of feed around the stoma (n=2), overgranulation of the stoma (n=7), skin site infection (n=2) and accidental removal of the tube (not requiring replacement or further intervention) (n=1).

To date, 13 patients continue to use their PEG tube and their average length of use is currently 795 days (310 – 1344). Thirty patients died with their PEG tubes still in use, resulting in an average length of use at the time of death of 186 days (2 – 654). The remaining 77 patients have had their PEG tubes removed as a separate outpatient endoscopic procedure or at the time of further surgery. The average length of use from insertion to request for removal was 141 days (13- 636), and to the date of actual removal 212 days (27 – 733).

Selection of post-operative feeding route

In those patients managed with a PEG tube, 9 patients used it for less than 28 days, and in these patients NGT may have been more appropriate. All nine patients had minimal co-existing medical problems, with ASA scores of I or II, and underwent partial glossectomy with a radial forearm free flap ≤ 6x4cm in size.

In the NGT group, the four patients who required prolonged nutritional support had unpredictable post-operative complications. The combination of co-morbidity and surgical excision site were not sufficient to predict these events pre-operatively.

Development of a pre-operative scoring system

The scoring system (**Table 13**) was devised from a combination of statistical analysis of the retrospective review, and additional information from the medical records. Not every patient required feeding for the whole period prior to radiotherapy commencing.

Binary logistic regression between the NG and PEG groups, utilising only those patients who were deemed appropriately managed, revealed no statistical difference between the groups for age or sex. ASA score (grouped for ASA I-II, and III-IV), alcohol intake, and free flap type all met or approached 95% significance (p=0.063, p=0.012, p=0.092 respectively).

ASA score, alcohol intake and free flap type were insufficient in isolation to accurately select the feeding method. Further factors typically utilised in the decision making process, including clinical tumour stage, tumour site, and planned radiotherapy (& number of sites) were therefore also included to improve the scoring system. Patient's prescribed large numbers of oral medications frequently remain reliant upon their PEG tube for these medications despite almost full return to oral nutrition. The number of medications was therefore considered a further contributing factor in tube selection.

Using this method, all nine patients using their PEG tube for less than 28 days would have been identified as suitable for an NGT rather than a PEG. For the NG group, the *KAREN* score would have identified only one out of four of the patients who required prolonged nutrition. However, two patients suffered unpredictable post-operative complications (perforated colonic diverticulum, hypoxic brain injury). Taking these two patients into consideration, and applying the scoring system to the remaining 142 patients (**Table 14**), resulted in a prediction rate of 92%.

		Score
K	**Known clinical tumour stage T3 or T4**	3
A	**ASA Grade:** III-V	3
	Alcohol Consumption: >40 units/week	3
R	**Reconstruction:**	
	Fibula / ALT / Latissimus dorsi	2
	≥ 2 simultaneous free flaps	3
	Radiotherapy: More than one field following surgery planned	2
E	**Excision of tumour:**	
	Anterior 2/3 of tongue+/- Floor of mouth	1
	Posterior 1/3 tongue	2
	Total glossectomy	4
	Mandibulectomy	2
	Tonsillar fossa/ pharyngeal/ soft palate	2
N	**Number of regular medications**: >3	2
	Method of Nutritional Support:	
	Nasogastric Tube	**0 - 3**
	PEG Tube	**≥ 4**

Table 13: K.A.R.E.N (Key to Appropriate Replacement Enteral Nutrition) Score.

	Correctly Predicted	Incorrect	Total
NGT	21	1	22
PEG	110	10	120
Total	131	11	142

Table 14: Application of KAREN scoring system to patient cohort.

5.5 Discussion

The complication rate associated with NGT was low, with two cases of aspiration pneumonia most likely secondary to dislodgement of the NGT during feeding, despite confirmation of position prior to the commencement of feeding. A higher incidence of complications were noted in the PEG tube group, with two major complications directly related to the PEG tube (1.7%), and a minor complication rate of 16%, resulted in an overall complication rate of 18%. This is in keeping with previously reported rates in the literature.[148,167]

For the cohort of patients studied, the *KAREN* scoring method appears reliable, with the correct tube selection in 92% of patients, providing the basis for prospective review to permit refinement and the creation of a highly accurate and reliable tool.

Chapter Conclusion

Nutritional support in patients undergoing ablative surgery for head and neck cancer is paramount. Whilst the major complication rate associated with NGT and PEG is relatively low, careful selection of the most appropriate tube is required. The scoring system developed provides a novel and simple method of scoring the key factors which have been found to be related to requirement for prolonged nutritional support post-operatively.

6. Fluid Balance & Cardiac Events

6.1 Fluid Balance & Cardiac Events

The risk factors associated with head and neck cancer – tobacco and alcohol use, are also associated with coronary artery disease and myocardial infarction (MI). Myocardial injury is a common and major contributor to surgical morbidity and mortality.[168] Patients experiencing an MI after non cardiac surgery have an in-hospital mortality rate of 15-25%, and non fatal peri-operative MI is an independent risk factor for cardiovascular death and non fatal MI during the 6 months following surgery.[169] Cardiac troponin assays are highly sensitive and almost exclusively specific to myocardium, and have increased the detection rate of atypical and silent MI's.

Prolonged surgery for head and neck cancer involves large fluid shifts and blood loss. Complications resulting from inappropriate fluid management are thought to occur in as many as 50% of peri-operative patients, and their adverse outcome well documented.[68,170] Measurement of cardiac output or stroke volume has been regarded as a necessary facet of caring for critically ill patients.[171] Previously only possible using invasive pulmonary artery catheters, the LiDCO™ Rapid system is one method of minimally invasive monitoring that is now available.[172] The Stroke Volume Variance (SVV) is derived directly from the arterial pressure waveform, providing reliable information regarding the filling status of the patient.

Traditionally patients undergoing surgery were admitted in the pre-operative period to hospital where all necessary assessments and optimisation were completed. Hospital admission on the day of surgery was introduced as a means to increase patient throughput and produce efficiency savings. Initial reports about same day surgical admissions in vascular and colorectal surgery have been favourable.[173,174]

This section of the thesis focuses upon hospital admission route and peri-operative fluid balance in patients undergoing free tissue transfer following ablative surgery for head and neck malignancy. The section commences with a literature review before describing the methodology and results of:

12. **Eley KA**, Watt-Smith SR. Myocardial infarction diagnosed by troponin concentration in post-operative patients with head and neck cancer admitted on the day of operation. Br J Oral Maxillofac Surg 2009; 47(3):245-6.[14]

13. **Eley KA**, Watt-Smith SR. Re: Post-operative fluid balance in patients having operations on the head and neck. Br J Oral Maxillofac Surg 2009; 47(3):249.[15]

14. **Eley KA**, Watt-Smith SR. Intra-operative use of LiDCO – is there an effect on the volume of intravenous fluids used by anaesthetists during free flap surgery for head and neck cancer? Br J Oral Maxillofac Surg 2009; 47(7):e15 [Published abstract].[16]

15. **Eley KA**, Watt-Smith SR. Post-operative troponin positive cardiac events in patients undergoing head and neck cancer resection admitted on the day of surgery. Br J Oral Maxillofac Surg 2009; 47:e38 [Published abstract].[17]

6.2 Literature Review

A comprehensive review of the literature was conducted to explore the current practices in peri-operative management of nutrition following free tissue transfer. This was completed using NCBI Pubmed and Google Scholar with the following MeSH terms:

("Free Tissue Flaps" or "Surgical Flaps" or "Mouth neoplasms" or "Head & neck neoplasms" [All fields]) and ("Fluid Therapy" or "Cardiovascular diseases" or "Physiological processes" or "surgery")

The titles and abstracts were reviewed to identify those papers with clinical relevance, with subsequent review of related citations and references.

The World Health Organisation definition for diagnosis of myocardial infarction is two of: a) history of chest pain, b) diagnostic ECG, c) elevated biochemical markers. Arterial thrombosis is the underlying cause of the majority of non operative MI's, however, the pathophysiology in the operative setting is less clear.[169] Surgery initiates an inflammatory response due to increases in tumour necrosis factor-α, interleukin 1, IL6 and CRP. Surgical stress involves increased levels of catecholamines (adrenaline and noradrenaline) and cortisol.

Cardiac troponins, which are structural proteins unique to the heart, are sensitive and specific biochemical markers of myocardial damage, often more reliable than electrocardiography.[175] Troponin I is a highly specific marker for cardiac injury with a sensitivity and specificity approaching 100%. Troponin I is elevated at 12 hours following a cardiac event and remains elevated for 5 days.

Nagele *et al*[168] completed a retrospective study of 378 patients undergoing major head and neck cancer surgery. They utilised Troponin I concentration as the primary outcome measure. Measurements were completed routinely in all patients immediately post-operatively, at 8 hours and at 16 hours. Of their patient cohort, 57 patients developed an elevated Troponin I, with 90% of these occurring within the first 24 hours post-operatively. The authors identified that pre-

existing renal insufficiency, hypertension and preceding combined chemotherapy and radiation were predictive factors for post-operative MI. Patients with post-operative MI had a significantly longer stay in hospital and mortality. Only 30% of patients who developed a post-operative Troponin I elevation had a pre-operative diagnosis of coronary artery disease.

Troponin levels were utilised in a similar study by Nouraei *et al*[176] who reviewed the incidence and risk factors for MI following head and neck surgery. They retrospectively reviewed 65 patients undergoing surgery for upper aerodigestive tract SCC. Troponin I was performed on the 3rd post-operative day. Post operative elevated troponin I was found in 16 patients. Factors identified as independent predictors of post-operative myocardial injury were blood pressure level, intra-operative heart variability and degree of post-operative inflammatory response.

Datema *et al*[177] conducted a retrospective review of 135 patients undergoing extensive ablative and reconstructive surgery for SCC of the oral cavity or oropharynx. Medical records were reviewed for evidence of post-operative cardiovascular complications. The mean combined surgery and anaesthetic time was 11.3 hours. Of the 135 patients, there were 4 confirmed MI's, 18 patients with heart failure and 1 patient with ventricular fibrillation. The mean length of hospital stay was lengthened by 7 days in those experiencing cardiovascular complications compared to those who did not. ACE-27 score positively correlated with cardiovascular complications.

Tanaka *et al*[178] conducted a retrospective analysis of 1249 patients undergoing head and neck ablative surgery with free flap reconstruction to determine the mortality rate associated with surgery. The in-hospital mortality rate was 1.84%. The 30-day mortality rate was 0.88% and significantly correlated with age; however this was not the case for in-patient mortality. Only one of the 23 in-hospital deaths was attributed to acute MI. Similar findings were reported by Clark *et al*[179] who identified an in-patient mortality rate of 1.6% in their study of 185 patients undergoing free flap reconstruction following ablative head and neck surgery. There was a major morbidity rate of 40%, including MI in 3.2% of all patients. Predictors for major complications including ASA grade 3 and 4, age greater than 65 years and current smokers.

Predictors for medical complications included crystalloid replacement of >130ml/kg over 24 hours; volume of colloid replacement was a predictor for length of hospital stay.

Optimising peri-operative fluid balance is important to minimise cardiovascular complications, and for maintaining flap survival. Excessive intra-operative fluid administration may jeopardise the success of free flap transfer by several mechanisms, including, contrary to what would be anticipated, enhancing coagulation.[180] Flaps have a lack of lymphatic drainage, are denervated and have reduced ability to reabsorb excess interstitial fluid.[181] Conversely, negative fluid balance is equally detrimental.

Haughey *et al*[182] in their retrospective review of 236 patients who had undergone free flap reconstruction to the head and neck found that more than 7L of crystalloid during surgery was significantly associated with major medical and flap complications. The duration of anaesthesia and use of blood products and pressors did not predict complications.

Optimisation of fluid balance using Doppler ultrasound has been shown to improve stroke volume and cardiac output and speed of post-operative recovery; however, this is often impractical in head and neck surgery in view of the difficulty accessing the surgical field for repositioning of the Doppler probe.[183,184] Routine invasive monitoring with central venous cannulation has been shown to be unreliable in head and neck surgery.[185]

LiDCO™ Rapid derives stroke volume from the arterial pressure waveform using the pulseCO algorithm. Abdel-Galil *et al*[183] reported their initial experience with LiDCO™ with plans for conducting a randomised controlled trial; these results are not yet available. Chalmers *et al*[181] conducted a survey of 32 head and neck units to ascertain the peri-operative monitoring in patients following free tissue transfer. They found that very few units currently use cardiac output monitoring, but reported that their own experience with LiDCO™ monitoring resulted in a mean reduction of 25% of intra-operative fluid administration.

Pre-operative optimisation is equally important to minimise post-operative complications, particularly in terms of co-morbidity. As a result it has been traditional for patients to be admitted to hospital pre-operatively. In the 1990's same day hospital admission (Theatre direct

admissions, TDA), whereby patients for elective operations attend a holding bay on the day of operation, became routine practice across the United States of America and Australia. Boothe and Finegan[186] assessed the cost-effectiveness of this process in patients undergoing laparoscopic cholecystectomy with discharge from hospital the day following surgery. One of the main benefits highlighted by the authors for same day admission was that pre-operative assessment by the anaesthetist in the outpatient clinic rather than on the night prior to surgery in hospital prevented inappropriate hospital admissions in patients not fit for anaesthesia and therefore in whom surgery would have been cancelled. They calculated an overall cost saving per patient of 18% for same day surgery. Similar findings were reported by Calligaro *et al*[174] in their comparative study of patients undergoing elective infrarenal aortoilliac surgery. They reported a significant cost saving, with no differences in terms of post-operative mortality, complications or readmission rates. Interestingly post-operative stay was also shorter for those admitted on the day of surgery. However, patients admitted pre-operatively to optimise their medical status were excluded from the study, which may have biased the results. Vijay *et al*[187] reported their experience of such practice within the NHS using a dedicated elective surgery centre, concluding that this offered considerable cost-savings although these savings were not calculated.

The only study identified in the literature exploring the use of same day admission in head and neck patients is by Kulasegarah *et al*.[188] In their prospective review of 75 patients, 34% were oncology patients. The oncology group were significantly older than the non oncology group and were more likely to be delayed going to theatre; however, there was no difference in terms of post-operative complication rates. The authors however concluded that for major surgery same day admission is not appropriate for all patients.

Whilst these authors have identified potential contributory factors to enhance care in head and neck patients, further guidance is required. The following section explores the methodology of the presented papers, with the aim of further evaluating the benefit of intra-operative LiDCO™ monitoring and same day hospital admission.

6.3 Materials and Methods

The methodology is divided into two discrete phases evaluating firstly fluid balance and secondly same day hospital admission.

6.3.1 Peri-operative fluid balance

A retrospective review of all patients undergoing free flap procedures for head and neck cancer between January 2006 and April 2009 was conducted. During this period LiDO Rapid monitoring was introduced as part of the pressor study described in Chapter 3. LiDCO™ monitoring was additionally utilised in patients not recruited to the pressor study where it was deemed beneficial by the operating surgeon. Comparisons were made with those patients treated prior to the introduction of LiDCO™ monitoring.

Medical records, including anaesthetic charts, were reviewed to determine the intra-operative fluid status, post-operative morbidity, and length of hospital stay. For patients in whom LiDCO™ Rapid monitoring was used the data was exported from LiDCO™ to a Microsoft Excel spread sheet to permit calculation of the mean intra-operative SVV.

In total, 157 free flap procedures were completed during 140 surgical sessions. The notes for 7 patients were unavailable for review, the anaesthetic chart missing in the notes of a further patient, and the LiDCO™ data corrupt in a further two patients. These patients were therefore excluded from the study. In total, 116 free flaps were completed during 103 surgical sessions on 89 patients for primary head and neck cancer resection or reconstruction of associated problems. LiDCO™ monitoring was used for 27 free flap sessions (24 patients; 3 patients undergoing two separate surgical procedures).

Ethical Considerations

The study was considered to be an audit of clinical practice, for which ethical approval was not considered necessary. All patients underwent surgical intervention providing consent for the use of their medical records for audit and research.

Statistical Analysis

Data collection sheets were used during review of the medical records, and the data transferred to a Microsoft Excel spreadsheet. Statistical analysis was completed with SPSS, with significance level set to 0.05.

6.3.2 Theatre Direct Admission

An audit of clinical practice was completed following a perceived increased risk of morbidity following the introduction of TDA in 2007 for patients with head and neck malignancy. All patients admitted via TDA underwent routine pre-operative assessment, and those deemed high risk were admitted in the traditional manner via the ward pre-operatively.

A comparative study was completed between those admitted pre-operatively to the ward and those admitted via TDA.

Myocardial infarction was used as the primary outcome measure of post-operative morbidity. Elevation in Troponin I was used to define MI to avoid potential bias associated with the documentation of chest pain or ECG changes.

A retrospective review of all patients undergoing major operations for head and neck cancer between 2003 and 2007 was completed. During this time period 131 patients were admitted pre-operatively to the ward in the traditional manner, and 15 patients were admitted via TDA. The electronic biochemistry results system (CaseNotes®) was interrogated for each patient to determine if a Troponin had been requested, and all subsequent results. Troponin was only requested by the clinical team where there was concern that the patient had suffered a cardiac event.

Following a change of practice, the audit was repeated with a further 49 patients between 2007 and 2008.

Ethical Considerations

As the study formed part of clinical practice with the intention of improving patient care, ethical approval was not considered necessary. All patients included in the study underwent surgical intervention, providing informed consent for the use of their medical records for audit and research purposes.

6.4 Results

6.4.1 Peri-operative fluid balance

Of the two patient groups, with and without LiDCO™ monitoring, the distribution in terms of free flap type, age, sex, weight and length of procedure (combined anaesthetic and surgical time) were similar (**Table 15**).

On analysis of the intra-operative anaesthetic charts in the LiDCO™ group colloids were more frequently used ($p<0.03$) than in the non-LiDCO™ group where crystalloids were preferred. Overall, when urine output and procedure length were taken into account, the LiDCO™ group received less fluid per hour than the routine group ($p<0.04$).

There were no in-hospital deaths in the 27 patients included in the LiDCO™ group. In the 103 patients in the routine group, there were 7 post-operative deaths due to MI in two cases, an upper GI bleed (n=1), perforated sigmoid diverticulum (n=1), TB pneumonia (n=1) and ischaemic bowel (n=1).

Post-operative hospital stay was significantly less in the LiDCO™ group ($p<0.02$), with a mean length of stay of 13.6±5 days in the LiDCO™ group, compared to 21.7±18 days in the routine group.

		LiDCO™	Routine
Sex	Male	52%	52%
	Female	48%	48%
	Age (years)	58 ± 9	62 ± 15
	Weight (Kg)	76 ± 24	69 ± 14
Free flap	ALT	n=15	n=12
	Fibula	n=7	n=16
	Latissimus Dorsi	n=19	n=5
	Radial	n=44	n=54
	Other	n=0	n=2
	Combined two free flaps	n=15	n=12
	Procedure Length (Hours)	8 ± 1.3	7 ± 1.8
	Average Hospital Stay (Days)	13.6 ± 5	21.7 ± 18
Intra-operative Fluid Balance			
	Crystalloid (Litres)	6.0 ± 1.5	6.4 ± 1.9
	Colloid (Litres)	0.7 ± 0.7	0.4 ± 0.8
	Blood (Units)	0.7 ± 1	0.8 ± 1
	Total Fluid In (Litres)	7.0 ±1.7	7.0 ± 2.1
	Urine Output (Litres)	1.1 ± 0.7	1.2 ± 1.0
	Balance (Litres)	5.9 ± 1.7	5.9 ± 1.8
	Balance/procedure length (ml/hr)	728 ± 169	814 ± 250

Table 15: Distribution of age, sex, weight and procedure length in the two groups in terms of LiDCO™ monitoring.

6.4.2 Theatre Direct Admission

Of the 131 patients admitted to the ward pre-operatively, troponin concentrations were requested for 33 patients, and were significant in nine (7%). In the 15 patients admitted by TDA, troponin concentrations were requested in seven patients, and were positive in three (20%). During the period of TDA admission, 15 patients were also admitted pre-operatively via the ward, either because of patient factors, such as co-morbidity or lack of transport for the morning of surgery, or clinician factors, such as an inability to complete the required pre-operative assessment prior to the date of surgery. Of these 15 patients, troponins were requested in 6 patients, and these were all negative (**Table 16**).

As a result of these findings pre-operative ward admission for all patients undergoing ablative and reconstructive surgery for head and neck malignancy was reinstituted. Following full reintroduction of pre-operative ward admission a re-audit was completed. On re-audit, of the 49 patients admitted via the ward, there were 12 troponin requests, with only 1 elevated result (2%) (**Table 17**).

	2003-2004	2004-2005	2005-2006	2006-2007		2007-2008		2008 -
				Ward	TDA	Ward	TDA	Ward	Ward
n	33	36	30	18	8	14	7	22	27
Troponin Requests	6	9	7	6	3	5	4	7	5
	18%	25%	23%	33%	38%	36%	57%	32%	19%
Troponin Positive	4	2	2	1	1	0	2	0	1
% Positive	12	6	7	6	13	0	29	0	4

Table 16: Frequency of troponin requests and percentage positive of whole group, per year between 2003 and mid 2008.

Cohort	Admission Type	Troponin				Total
		Positive	Negative	Total Requests	Total not requested	
1	Ward Admission	9 (7%)	24	33 (25%)	98	131
2	Theatre Direct Admission	3 (20%)	4	7 (47%)	8	15
3	Ward Admission	1 (2%)	11	12 (24%)	37	49

Table 17: Frequency of Troponin I request and results in the three cohorts of patients.

Overall, the timing for post-operative MI was at a median of day 3 post-operative (range 0-21 days post-operative). This occurred at a mean of 3 days post-operative (range 1 – 6 days post-operative) for those admitted via TDA, and a mean of 5 days (range 0 – 21 days post-operative) for those admitted via the ward.

6.5 Discussion

The results of these studies suggests that the intra-operative use of LiDCO™ Rapid monitoring results in an increased use of colloids and an overall decrease in fluid administration intra-operatively. Post-operative in-hospital stay was significantly reduced in the LiDCO™ group, with an associated fall in post-operative complications.

The high incidence of myocardial infarction associated with the TDA group may reflect a cluster that would have occurred at this time irrespective of the route of admission. However, subsequent repeat audit showed significant improvement in post-operative cardiac morbidity, when pre-operative ward admission was reinstituted. The combination of a patient's anxiety associated with admission to hospital, and the serious stress response from an extensive operation, are probable contributory factors to post-operative complications such as myocardial infarction.[189]

Chapter Conclusion

LiDCO™ Rapid is an additional source of patient monitoring suitable for patients undergoing free flap surgery, permitting goal directed therapy, and resulting in decreased post-operative morbidity. Post-operative morbidity may be further reduced by careful attention to pre-operative factors including route of hospital admission, as TDA may not be appropriate for all patients having major operations.

7. General Discussion & Conclusions

7.0 General Discussion

The collection of publications which form the basis of this thesis highlight a number of factors which contribute to peri-operative mortality and morbidity in patients undergoing ablative and reconstructive surgery for head and neck malignancy.

It has been demonstrated that operative risks in this patient group are compounded by co-morbidity as a result of age, alcohol and tobacco use. A cardiovascular history is likely since the causative agents for oral malignancy and cardiovascular disease are largely the same. As a result patients are likely to require blood pressure support during the peri-operative period due to decreased vessel compliance and antihypertensive medications.

Four commonly utilised pressor agents were studied for their effects on free tissue transfer. It was found that whilst noradrenaline resulted in vasoconstriction (demonstrated by a decreased conductance), in both the flap and the control tissue, the effect was more marked in the control tissues. This may suggest that the flap tissues have some level of protection, likely as a result of surgical sympathectomy. However, unlike the findings of Lecoq *et al*[77] vasoconstriction did occur in the flap tissues. This vasoconstrictor effect on the flap was more than overcome by the increase in blood pressure, so that there was a significant increase in flap perfusion with the increased blood pressure up to a dose of 0.15mcg/kg/min of noradrenaline. The paradoxical results that were seen at 0.2mcg/kg/min of noradrenaline, whereby there was a sudden and profound decrease in flap perfusion, are likely to be unreliable. Only 5 patients received this maximal dose of noradrenaline with the remaining patients having already reached the maximum blood pressure increase permitted in the study (30mmHg MAP rise) at lower doses. This highlights one of the inherent problems of the analysis methods used for this study. It was noted on review of the individual patient results that half of the cohort demonstrated profound changes from baseline with noradrenaline, whilst the remainder of the group had more modest changes. This variable response may be due to varying levels of vessel compliance due to age and cardiovascular disease, or variable alpha receptor survival.

Dobutamine also reliably increased flap and control site blood flow by about 10% (compared with the 30% maximum seen with noradrenaline) without causing a change in conductance and with little effect on blood pressure. The effects on MAP with dobutamine were surprisingly variable. The sole reason for instituting pressor support in patients in the peri-operative period is to increase MAP; the potential benefits of improved flap flow are outweighed by an unpredictable effect on blood pressure. This is a recognised problem with dobutamine as despite increases in CO (on average this was increased by 50% in the patients studied), the reduction in SVR through β_2 receptor and baroreceptor-mediated vasodilation results in BP being reduced or unchanged.[66] A more concerning adverse effect of dobutamine in the patient group studied was the frequency with which it resulted in a tachycardic response requiring premature termination of the drug infusion. This effect is again in keeping with the known ino-dilator effects of dobutamine. Since patients with head and neck malignancy are already at high risk of cardiac ischaemia these side effects are likely to cause concern and dobutamine may therefore not be the most useful agent despite its positive flap effects.

Adrenaline caused a decrease in both flap flow and conductance in spite of an increase in both blood pressure and cardiac output, and there was little difference between flap and control skin. It also resulted in a tachycardic response. Of the 25 patients studied, 21 received the maximum infusion rate of adrenaline, the remaining 4 patients having reached the safe limits at lower infusion rates.

Dopexamine preferentially vasoconstricted the flap compared with the control skin, making it entirely unsuitable for maintaining flap perfusion. It was also ineffective at increasing blood pressure at the doses studied. Dopexamine is now a less popular agent in the ICU compared to the time at which the study was planned. This is an inevitable consequence of such studies due to significant time periods between designing the study, obtaining necessary approvals, including ethics, MHRA, and local research and development, and the completion of data collection.

However, the prolonged data collection period provided the opportunity to recruit the same patient to the study on two occasions, as a result of a second primary tumour which also required resection with free flap reconstruction. Consistency of findings on two separate occasions with different free flaps could therefore be explored. Overall, the results were largely consistent on both occasions and with the mean results for all patients with all of the drugs, except adrenaline. Adrenaline resulted in both increased flow and conductance for both flap and control on the first occasion, but decreased flow and conductance (consistent with the overall results) on the second study. This may simply reflect an erroneous result, but raises the possibility that there is some variability in free flap alpha receptor survival. On the first occasion reconstruction had been completed with a radial forearm free flap, and on the second by combined reconstruction with an ALT and fibula free flap, with the Doppler sited on the ALT. Anastomosis of the fibula free flap was completed whilst the ALT was raised, making prolonged primary ischaemia an unlikely contributor to alpha receptor survival. In the majority of the 24 patients studied, reconstruction had been completed with a radial forearm free flap, thus why the results were not consistent in this patient on the first occasion is more difficult to understand.

It is postulated that the ischaemic time during free flap transplantation results in apoptosis of a proportion of alpha receptors. It is most likely that the intimal receptors survive this process, but the added contribution of denervation results in loss of the adventitial receptors. Age and co-morbidity are also likely to be contributory factors in receptor survival. This would explain why the findings were not consistent in all of the patients studied. Since the ischemic time was not recorded in the patients studied it was not possible to correlate this with the results in this study.

Certainly, the findings should be interpreted in light of the limitations of the study. In all cases the laser Doppler probe was sited at the centre of the flap, based upon the assumption that any changes in blood flow through the flap would be uniform. However, this may not be the case, and variabilities in flap flow, particularly in cases where the skin paddle of a fibula flap was used, may have resulted in discrepancies in the results.

The exclusion criteria for patient recruitment were largely limited to pregnancy and obesity, due to drug administration safety. As a result the patient cohort consisted of tumour resection from a range of oral cavity sub-sites, with varying patient BMI, age, sex and free flap types. Whilst it would have been particularly ideal to standardise the free flap across all patients, this would have resulted in difficulties in recruitment in a study which took over a year to complete the patient recruitment and data collection phases. Of the 25 datasets, 17 were from radial forearm free flaps, and only 2 required the Doppler probe to be sited on a skin paddle of a fibula flap. Any effects as a result of inconsistencies between flap types should therefore be minimal. As a result of the small numbers of each flap data analysis was completed for the whole group rather than sub-groups. Any sub-group analysis would have resulted in four groups, with as few as two patients in some of these groups. A power calculation demonstrated that a sample size of 25 was required to detect a difference, making sub-set analysis unlikely to approach significance.

In four cases reconstruction had been completed with two simultaneous free flaps, with a fibula flap and either a radial forearm free flap or ALT. Arterial anastomosis was typically end to end for both of the flaps, with end to side venous anastomosis to the internal jugular vein. Since the flaps were not "piggybacked" to the same arterial supply it is unlikely that the effects of the pressor agents would have differed by using two rather than one free flap.

Laser Doppler probes are both safe and convenient to use. The benefit of using a Doppler probe on the skin paddle of the flap was the ability to confirm positioning and permit easy removal following completion of data collection. Only the skin paddle of the flap was examined, which may not be representative of the entire free flap. In all cases the Doppler probe was sited at the centre of the flap; this occasionally resulted in the probe lying directly over the feeding vessels which, at the time of data collection, appeared to result in more pronounced variability of the Doppler reading on the monitor. However, such extreme variability was not seen at data analysis, and the overall consistency of the results is reassuring.

Since the Doppler probe was sutured directly to the flap, they were simply removed without further requirement for surgery and without risk to the anastomosis. The simplicity of the technique and the good correlation with other measures of flap blood flow has made laser

Doppler monitoring a popular research and clinical monitoring technique. The laser Doppler device interrogates a hemisphere of about $1mm^3$ volume under the probe, and provides an output that is the product of the red cell velocity (from the Doppler shift in reflected light) and the number of red cells in motion (from the amount of reflected, Doppler-shifted light). The probe cannot be calibrated against a known blood flow, so the unitless "tissue perfusion units" are used to express blood flow. This means the use of a control tissue or stable comparator baseline is required. Laser Doppler monitoring of skin blood flow in free flap tissue transfer has been used successfully to assess changes in intra-oral flap perfusion over time.[47,190,191] However, these studies used blood flow measured prior to flap elevation as a baseline rather than using a control area of normally innervated skin, and as a result could not determine if the responses were unique to free flaps or a global response to surgery and the recovery period. There are some inherent difficulties associated with using Doppler monitoring. Since measurements are in TPU, comparisons cannot be made across patients, thus necessitating calculation of change from baseline. The Doppler probes are sensitive to movement and light. As a result extra care was necessary to keep these factors constant throughout the data collection period. A good Doppler trace, as evidenced by the waveform, was ensured prior to commencing data collection in all cases. There was an inevitable learning curve associated with the method used to suture the probe to the flap; however this is unlikely to have impacted upon the results obtained. Between infusions the flap was monitored in the traditional manner (colour, warmth, consistency) to confirm viability. Any blood that had accumulated in the region was suctioned to ensure a good Doppler trace was maintained. A baseline recording period was completed before starting each drug infusion which was used for data analysis.

Changes were calculated as a fractional change from baseline (prior to the infusion of any drugs) for each patient for both the control and flap sites, and a mean result obtained for the patient group. An alternative method of analysis would have been to standardise the results by determining the difference between the control and flap tissues (by subtracting one from the other), however, this would have eliminated the ability to compare the flap tissues to the control site. It may also have heightened inaccuracy, due to the effects of ambient temperature on the

peripheral control site. The control site in all cases was the deltoid region. This region was selected as it was remote from arterial and venous access sites. Being close to the operative site, any differences associated with temperature are likely to have been minimised. For comparative purposes, the tissue corresponding to the donor site on the opposite limb would be considered to be most representative of the flap tissues, however, access to these sites are likely be have been problematic in terms of confounding factors, such as temperature (due to ambient changes and as a result of infusion of fluids) and light. The effects of the pressor agents due to vasoconstriction of the peripheries is also likely to have been problematic had a more distal peripheral site been utilised for the control site.

Skin blood flow was used as a surrogate measure of total flap blood flow. There is only one study of total blood flow to free flaps in human subjects, largely obtaining similar results to those seen in this study. Scholz *et al*[74] investigated the effect of dobutamine on total blood flow of free tissue transfer flaps during head and neck surgery. Following completion of the anastomoses, the flow in the anastomosed donor artery was measured with an ultrasonic flowmeter. Dobutamine at rates up to 6µg/kg/min was infused. They found a doubling in flow from baseline to 6µg/kg/min accompanied by increased cardiac output, concluding that dobutamine may be useful in improving free flap perfusion. The authors noted that there was no significant increase in MAP with the three rates trialled. The maximum dobutamine infusion utilised in the presented study was 8µg/kg/min, a small increase in the doses used by Scholz *et al*; however, the often insignificant increase in MAP was also noted.

Any effect on cardiovascular parameters and Doppler readings were considered to be solely the result of the pressor agent infused. However, there are numerous contributory factors. Despite the best efforts to achieve optimum fluid balance and maintain all variables constant during data collection, this was difficult to fully achieve during the immediate post-operative period being also reliant upon intra-operative fluid optimisation. The study was not commenced until patients had been adequately stabilised on the ICU, this included where required, transfusion to maintain haemoglobin above 8g/dL. A SVV of ≤10% was considered optimal filling and this was achieved in the majority of patients prior to the commencement of pressor infusions. The

accuracy of the LiDCO™ results were dependent upon achievement of a good arterial line trace. In one case the patency of the arterial line was lost during data collection necessitating the drug infusion to be recommenced. Difficulties also arose with sedation; whilst a constant level of sedation was achieved throughout the study period in the majority of cases, a small number required additional bolusing to prevent patient movement affecting the Doppler trace. The contributory effects of sedation and fluid administration on the overall results of the study are difficult to quantify.

In addition to electronic recording of results, cardiovascular parameters and Doppler results were recorded manually throughout the baseline periods and drug infusions. This provided a further method to cross-reference the results obtained during data analysis to enhance accuracy. In one patient the LiDCO™ data was corrupt, and the manual dataset was utilised for analysis.

Conducting such a study on the intensive care unit requires full understanding by the intensive care team to avoid any additional confounding factors. Patient care is paramount, and this was maintained throughout data collection by good communication with the nursing and medical staff on the ICU to ensure that necessary tasks, such as access to the arterial line for blood gases, were not conducted during pressor infusion periods which would have impacted upon the LiDCO™ results. As such, there were no adverse events for any of the patients during data collection.

Overall, the most striking result found was the decreased sensitivity of the flap to the vasoconstrictor effects of noradrenaline when compared with control tissue. It was this that caused the increase in blood flow to the flap as the blood pressure increased with increasing noradrenaline doses, whilst in control tissue vasoconstriction dominated and the blood flow decreased as the noradrenaline dose increased. Chronic denervation of tissues is generally believed to lead to a heightened vasoconstrictor response to α adrenergic agents such as noradrenaline in the denervated tissue, which may begin as early as two days.[99,192-195] As a result it would be anticipated that the control tissues would have demonstrated less vasoconstriction compared to the flap tissues. However, in this acute situation the ability of systemically-administered noradrenaline to cause vasoconstriction in the denervated free flap was markedly

attenuated when compared with the control tissue. A similar effect has been observed when innervated and denervated pedicle flaps were raised in a rat model.[77] Why this reduction in α_1 adrenergic receptor sensitivity occurs in acutely denervated vessels is unknown. It is possible that noradrenaline-induced vasoconstriction of fully vasodilated denervated vessels results in insufficient calibre reduction to significantly alter blood flow, though this is unlikely given the exquisite sensitivity of flow to vessel diameter. Reduced pulsatility in denervated, dilated vessels may reduce the secretion of endothelium-derived vasoconstrictive factors, or there may be a direct effect at the α_1 adrenergic receptor level. Certainly, there was some inherent delay between completion of surgery and the stabilisation of the patient on the ICU prior to commencing the study equating to approximately 4 hours from the time of microsurgical anastomosis.

Spectral analysis of the Doppler waveform was completed to further explore this. Examining the frequency components helps to distinguish local from humeral effects, and has been shown to be useful and accurate.[89,196] Characteristic frequency peaks exist in signals of cardiovascular origin.[197] The spectrum is conventionally divided into 5 frequency intervals centred on 1Hz, 0.3Hz, 0.1Hz, 0.04Hz, and 0.01Hz.[103,197] Of interest are those occurring at a slower rate than the oscillations caused by respiratory rate at about 0.3Hz. Studies have demonstrated that these slow oscillations are influenced by the sympathetic nervous system and microvascular wall activity.[102] Blood flow is controlled by the combined effect of all of these periodic oscillations of both local and central origin, which are transduced to vascular smooth muscle cells, resulting in a specific vascular tone.[103]

The power spectra confirmed a number of anticipated findings following free tissue transfer. Since the flaps were denervated the power in the region below 0.1Hz, which contains sympathetic activity, and in the respiratory frequencies centred on 0.2-0.3Hz (12-18 breaths/minute) which are partially neurally mediated, were both reduced as expected.

As the spectra were normalised (the area under the curve was fixed) there was a corresponding increase in the power in the 0.8-1.7Hz range representing the heart rate. As the results for the

cardiovascular variables demonstrated, there was a dose dependent increase in heart rate with adrenaline, dopexamine and dobutamine but an unchanged heart rate with noradrenaline until the maximum dose was reached. The differing heart rates of the subjects broadened the associated peak of the power spectra. At the maximum adrenaline infusion rate the heart rate increased and the spread of heart rates also increased, so the heart rate dependent peak moved to higher frequencies and broadened. The proportion of the total power in the lower frequencies increased, as local control of blood flow rather than global hemodynamics dominated blood flow control, though in general as with the control spectra, the effects of denervation were maintained.

All drugs increased the power (overall variability) of the blood flow signal at both sites, and this was more marked for adrenaline and especially noradrenaline. As a result of the processing techniques any differences between flap and control spectra in one frequency band must have equivalent changes in the opposite direction at other frequencies. The difference spectra demonstrated this best, the area defined by the 0 baseline and the spectral difference above the baseline being matched by an equivalent area between the 0 baseline and the spectral difference below the baseline. The technique used for sampling and processing meant the frequency resolution was limited to 0.05Hz and thus the 0.04Hz, and 0.01Hz peaks corresponding to the neurogenic activity of the vessel wall and the endothelial cell metabolic processes could not be resolved independently.

At the maximum dobutamine infusion rate there was little effect on the distribution of the control of blood flow, though as with all drugs studied the cardiac related peak increased in frequency and broadened. Dopexamine demonstrated the same findings as dobutamine. However with noradrenaline at 75% of maximum dose, low frequency activity below 0.1Hz was higher in the flap compared to control, and the difference between flap and control in the 0.1-0.4Hz band was less marked than with other drugs. This suggests that the noradrenaline infusion increases the local myogenic control of blood flow in the free flap to a greater extent than the other drugs studied.

With increasing doses of adrenaline and noradrenaline there was increased dependence on local control, as evidenced by the increasing proportion of power in the 0-0.1Hz frequency band. This occurred in both control and flap tissue, though with noradrenaline the effect was more marked in the flap tissue. This would imply that there is survival of alpha receptor activity in the transplanted tissues, and possibly that these receptors are more sensitive to exogenous alpha agonists after denervation.

The sampling period used limited the resolution of the spectral analysis to 0.05Hz, thus the two lower frequency bands could not be resolved independently. All the spectra were normalised to allow an averaged spectrum containing all patient data to be constructed with each patient contributing equally, but this normalisation causes increases in power in one frequency band to always be associated with a change in the opposite direction in other frequency bands, making interpretation more difficult. The probability of differences between regions of the normalised power spectra arising by chance could not be tested statistically. Changes in the power in the cardiac cycle frequency were made more difficult to interpret due to the increase in heart rate and the widening of the range of heart rates caused by the drugs. Drug infusion times were selected to minimise the effects of slow overall changes in the patient's haemodynamics biasing the results. A minimum of 5 minutes (2-3 half-lives for the drugs studied[198-200]) was used to ensure a steady state drug effect.

The β_1 and β_2 agonists dobutamine and dopexamine showed no change in the power spectrum from the control state, with the denervation effect preserved and no other changes. The known vasodilator properties of β_2 agonists, at the doses studied, had no apparent effect on the local control mechanisms or the effects of global haemodynamics. Adrenaline and especially noradrenaline, have significant α_1 agonist activity, and this did alter the relative effects of local and haemodynamic control on blood flow, with an apparent increase in local control. In the case of noradrenaline this seemed to overcome the effect of denervation, so there was more power at the very low frequencies in the denervated flap compared with the control site. It is postulated that the vasomotion at low frequencies became wholly dependent on exogenous α_1 agonist, swamping any local neural or other effects. This is in agreement with the results from the

hydraulic conductance, which showed both flap and control tissue vasoconstriction. However, it was noted that overall flap blood flow increased with noradrenaline, as the increase in blood pressure more than compensated for the decreased conductance. This was not reflected as an increase in the power at cardiac frequencies in the power spectral studies. Coupled with the changes in power at low frequencies, this suggests the flap blood flow is more determined by the average blood pressure interacting with low frequency vasomotion, rather than the pulsatile (systolic/diastolic) component of blood pressure.

As noted previously,[3] there appears to be a brief period after denervation when tissue blood flow is less responsive to exogenous α_1 agonists, but later the tissues become more sensitive. The results from this study may therefore not be generalised to longer term blood flow control. Furthermore, vasopressor drugs acting via pathways other than alpha-adrenergic receptors, such as vasopressin or nitric oxide antagonists, may produce different results.

It was assumed that skin flow reflected changes in other tissues, but this could not be proven with the technology used. However, similar findings were seen for all of the flaps included in the study. It is likely that other drugs mediating activity through alpha receptors will produce similar improved perfusion in denervated flaps.

It appears that noradrenaline is effective and safe in free flaps once the tissue has been denervated, with only the intimal alpha-adrenergic receptors being responsive to noradrenaline. This is supported by the finding that the control of blood flow shifts towards low frequency vasomotion where blood flow depends mostly on average blood pressure. It is, however, assumed that the flap skin paddle response to noradrenaline is representative of the remaining flap tissues. The results may not be generalisable to treatment in the longer term, when a heightened sensitivity of denervated vessels to α adrenergic agents has been reported.

Indeed acceptance of a small vasoconstrictor effect in return for a significant improvement in flap perfusion will further validation before concerns about the adverse effects of α adrenergic agents on free tissue transfer are fully addressed. However, the enhanced effects of alpha receptor stimulation causing vasoconstriction of the flap vessels appears to be largely balanced

by the denervation of the flap vessels, which results in reduced vascular tone and small vessel dilatation, resulting in an overall increase in flap perfusion; although as previously discussed this is likely to represent a somewhat over simplified explanation.

Metaraminol is a sympathomimetic agent with direct α and β_1 effects, which also indirectly stimulates noradrenaline release. This agent was not in common use in the Trust when the study was planned, but is now frequently employed intra-operatively and in the ICU to elevate MAP. Metaraminol has three properties that set it apart from the inotropes and pressors used in the study. Metaraminol produces a reflex reduction in heart rate, and so avoids the tachycardia almost invariably caused by the sympathomimetic amines. It constricts the central venous circulation and so increases the central venous pressure and therefore cardiac output. Unlike the sympathomimetic amines it can be used as a peripheral venous infusion, which though not relevant to this study (all patients have central venous catheters) is relevant in other branches of reconstructive surgery. A comparative study further investigating dobutamine, noradrenaline and metaraminol was commenced and data collection completed in two patients, however it was not possible to complete the study as a result of departmental restructuring. Data from these two patients were not included in this thesis as the small number of patients would not permit any conclusions to be made. This work is vital to fully address the concerns relating to pressor effects on transplanted tissues.

As already discussed, patients undergoing such extensive surgery frequently have significant co-morbidity that not only has an impact upon pressor selection, but also increases their general risk of post-operative morbidity. Co-existing cardiovascular disease is particularly prevalent as a result of the overlapping causative factors with oral malignancy. In combination with the surgical stress response cardiac ischaemia peri-operatively is likely, making adequate perfusing pressure vital. The surgical stress response is a systemic reaction to injury that includes endocrine, immunological, and haematological effects, with a magnitude and duration proportional to the injury.[201,202] The route of hospital admission, whether pre-operatively to the ward, or on the day of surgery via theatre direct admission, was considered to be a potential

contributor to a heightened stress response. It is inevitable that patients undergoing ablative and reconstructive surgery for head and neck malignancy will have anxieties regarding surgery, post-operative recovery and their resultant appearance. The consenting process for such surgery includes the discussion of all potential peri-operative complications which will have a resultant impact upon mental state of the patient. Whilst pre-operative assessment is completed in the weeks preceding surgery, the structuring of junior doctor rotas, certainly in the Trust where these studies were conducted, resulted in the consent form being signed on the day of surgery for those patients admitted via TDA. This is compounded by the additional anxiety of travelling to the hospital on the day of surgery, finding the admission unit which is often unfamiliar, and awaiting surgery in an area very close to the operating theatres. Pre-operative hospital admission provides time for patients to become accustomed to being in hospital and usually on the same ward which they will return to post-operatively from ICU. The written consent is obtained on the night prior to surgery, providing further opportunity to ask any further questions. For the surgical team, it provides the opportunity to review investigations and complete a systematic up to date examination of the patient. Any potential cancellations due to the patient being unfit on the day prior to surgery does provide an opportunity, albeit short, to admit another patient on the waiting list for surgery. Conversely, some patients may prefer being admitted on the day of surgery, since it avoids being an in-patient during a time when they consider themselves to be well.

The impact of TDA on patients undergoing ablative head and neck surgery was considered by review of post-operative troponin positive myocardial infarction. Between 2003 and 2004 there were 33 patients admitted pre-operatively via the ward, with a troponin requested in 6 cases. Of these, 4 were positive, resulting in a troponin positive MI rate for the year of 12%. Between 2004 and 2006 this rate dropped, until the introduction of TDA when there was a troponin positive MI rate of 13% and 29% between 2006-7 and 2007-8, respectively. Most profound is that for those admitted to the ward between 2007-8, including those patients preferentially admitted via the ward despite TDA being operational, and following return to ward admission for all patients, the troponin positive MI rate was 0%.

The increased incidence of MI in patients admitted via TDA may reflect a cluster that occurred at this time, irrespective of admission method. This was a new method of admitting patients, and patients may not have been adequately optimised in the pre-operative period. In many centres, including the Trust where this work was conducted, pre-operative assessment is largely led by nursing staff with clinical examination by the medical team. The patients included in this cohort were at a time when the junior medical staff were dentally but not medically qualified. As a result it is likely that on the balance of probabilities co-morbidity was not adequately investigated nor optimised. As a result it is impossible to state if this increased incidence of MI was solely the result of patients being admitted via TDA. However, the results were of sufficient concern to change practice and return to pre-operative ward admission for all patients undergoing ablative and reconstructive surgery for head and neck cancer. Certainly on re-audit the incidence of MI returned to a more satisfactory level.

Troponin measurements were used in isolation to diagnose MI for the purpose of the study. In clinical practice, the triad of chest pain, ECG changes and troponin levels are utilised with a diagnosis of MI being made when at least two of these factors are positive. Troponin is highly sensitive and specific and therefore considered to be more accurate than any attempt at both locating a history of chest pain and an ECG in the medical records, and identifying any changes on ECG. Incorrect timing of the ECG could result in detection of ST changes which signify reversible ischaemia rather than MI. Conversely, troponin levels may have been requested too early for elevation to be detected, thus resulting in an increased under-diagnosis rate. The electronic biochemistry reporting system was used to review the results of all troponin levels requested, with the majority of patients having more than one troponin result on the system. As a result, it is unlikely that an elevated result would have been missed since troponins remain elevated for 5 days after a cardiac event. Troponins were only requested by the medical team when there was concern that the patient had suffered a cardiac event. The frequency of requests therefore provided a further method to evaluate post-operative morbidity. The incidence of troponin requests increased between 2006-8, and subsequently decreased again in 2008. This may simply reflect an increased availability of the test, or its popularity at the time. Most striking is the request rate of 57% in the TDA group between 2007-8, compared to around 30%

in those admitted to the ward during the same time period. However, it should be noted that there were only 7 patients admitted via TDA during this time period.

Previous studies have reported positive troponin rates following head and neck surgery to be as high as 46% when routinely measured.[176] Conversely, reported rates of post operative MI have been as low as 3%.[177,179] It is therefore likely that the incidence of post-operative MI is higher than reported in view of this patient cohort being at particular risk of silent MI. This raises the question of whether routine post-operative troponin monitoring should be utilised in routine practice. The main difficulty is identifying the optimal time, coinciding with the greatest risk, as to when the test should be conducted. Whilst it is reported that the majority of post-operative MI's occur in the first 48 hours post surgery, in the cohort studied the range was between the day of surgery and 21 days post-operatively. The most frequent time interval appeared to be within 4 days of surgery. However, routinely measuring troponin levels would incur additional cost to the NHS. The overall benefit of routine testing is difficult to ascertain.

One of the main limitations of the study is that retrospective note review was not formally conducted. Whilst there was some overlap of patients with the other studies reported in this thesis, it was not possible to calculate the in-hospital mortality rate for this particular cohort. It was therefore not possible to determine the incidence of silent MI or the longer term effects of MI in the post-operative period in this particular cohort. Reports suggest that MI following surgery results in an in-hospital mortality rate of 15-25%, and that non fatal peri-operative MI is an independent risk factor for cardiovascular death and nonfatal MI during the 6 months following surgery.[168] The management of peri-operative MI includes the use of anti-platelet agents and anticoagulants, which can be problematic in the first 24 hours following surgery when flap complications may necessitate return to the operating theatre.

Without review of co-morbidity and other potential contributory factors it is not possible to accurately determine if the increased MI rate was associated with TDA or due to patients already at risk of MI. Data available for the three patients admitted via TDA who experienced peri-operative MI demonstrates that only one of these patients had a history of claudication indicative of cardiovascular disease, but for which the patient was not on any treatment; the remaining patients were ASA I, with no past medical history of note and were not on any

medications. Their mean age was 66 years (range 58 – 71 years) at the time of surgery, with a mean BMI of 23 kg/m^2 (range 19 – 28 kg/m^2). However, they all had a positive smoking history, underwent resection with neck dissection (bilateral in two cases), with radial forearm free flap reconstruction. The mean combined anaesthetic and surgery time was 6 hours (range 5 – 7 hours), with 6 – 8 L of crystalloid administered intra-operatively. None of these factors would identify these patients as being at high risk of MI. However, in one case it is likely that a PEG leak requiring laparotomy was a major contributory factor.

To fully assess the potential risks associated with TDA, a randomised trial is required. However, there are potential ethical dilemmas associated with this approach as there are already concerns regarding the admission of patients on the day of surgery for major procedures.[188]

As previously discussed there are many other potential contributory factors to the increased MI rate seen in the cohort of patients admitted via TDA. In patients with oral malignancy, where nutritional status is recognised to frequently be deficient, pre-operative ward admission provides the opportunity to optimise fluid and electrolyte balance, both of which are of significant importance in terms of peri-operative morbidity. The surgical stress response is further compounded by insulin resistance. The benefit of glucose loading pre-operatively on post-operative outcome requires further investigation in head and neck malignancy.

Complications resulting from inappropriate fluid management are thought to develop in as many as 50% of peri-operative patients, and their adverse outcomes are well documented.[68,170]

Targeted fluid administration has been demonstrated to result in decreased post-operative morbidity. Following resection and reconstruction of oral cancer, patients typically remain intubated and ventilated for the first post-operative night. Hypotensive episodes are common as a consequence of anaesthesia maintained with propofol and morphine or other similar agents. Potential consequences of this are inadequate flap perfusion and fluid overload secondary to fluid boluses given in an attempt to normalise blood pressure. The unresolved dilemma is the relation between flap perfusion, systemic blood pressure, cardiac output, and which drugs have the most influence on flap perfusion. The work on pressor support has gone someway to address this, however, adequate fluid filling is required to optimise the effects of pressor agents and maintain flap perfusion; a fine balance between adequate fluid input and overload resulting in

pulmonary and flap oedema. The pressor study in view of the introduction of LiDCO™ based stroke volume variance monitoring, provided the opportunity to evaluate the effects on intra-operative fluid balance. Only the intra-operative period was utilised for analysis as post-operative LiDCO™ monitoring was not routinely used outside of the pressor study, and with multiple clinicians involved in the care of patients post-operatively, significant variability was likely. However, surgery was largely completed by the same surgical and anaesthetic team all of whom were familiar with LiDCO™ Rapid. Arterial cannulation is routine for such surgery, and a good trace ensured optimal LiDCO™ monitoring. The system calculates the variations in pulse pressure, systolic pressure, and stroke volume that occur through the respiratory cycle, providing reliable information regarding the patient's response to fluids. The system does not require calibration, which resulted in set up in the operating room without any delays; however, the utilisation of a pulse contour analysis without formal calibration does raise question of accuracy. The consistency of findings in the studies reported suggests that this is not problematic.[171,172] Patients' height and weight are required to obtain accurate results, and as is often the case, some patients did not have a recent record of these in their medical records at the time of surgery, which may have resulted in some error, albeit small.

At the time of the study of the 130 major cases included in the retrospective review LiDCO™ monitoring had only been used in 27 cases intra-operatively. However, the key factors including age, sex, flap type, weight and length of the combined surgical and anaesthetic procedure were largely consistent between the two groups. Of the 27 patients included in the LiDCO™ group, 13 of these were patients recruited to the pressor study.

Whilst the fluid balance and urine output appeared consistent between the two groups, colloids were more frequently used in the LiDCO™ group, and in terms of hourly fluid balance this group received less fluid. For the LiDCO™ group the mean intra-operative crystalloid volume was 6.0±1.5L and for the routine group not using LiDCO™ it was 6.4±1.9L. Haughey *et al*[182] reported that in their retrospective review of 236 patients that more than 7L of crystalloid intra-operatively was significantly associated with major medical and flap complications. However, in our patient group a number of patients received more than 7L of crystalloid intra-operatively without complication. This included 9 out of 27 patients (33%) in the LiDCO™ group, and 45

of the 103 patients (44%) of the routine group. Utilising the volume of crystalloid in isolation is not an accurate method to assess intra-operative fluid balance. There are multiple factors that influence the volume of fluid given intra-operatively including the patient's pre-operative status; it is well recognised that patients with oral malignancy are frequently malnourished and probably dehydrated pre-operatively. Other factors include the length of the procedure, the size of the patient, and the fluid output. A more accurate assessment is to incorporate as many of these factors as possible, by calculating the fluid balance per hour. In the patient cohort studied, this demonstrated that for the LiDCO™ group less fluid per hour was administered when urine output had been deducted (728±169ml/hr compared to 814±250ml/hr).

Most striking was a significant reduction in length of hospital stay from a mean of 21.7±18 days to 13.6±5 days. Whilst this is likely to be multi-factorial, it should be noted that LiDCO™ monitoring was utilised in patients outside of the pressor study generally when there was concern regarding the impact of co-morbidity on fluid balance. As such it would be expected that this patient group would have a longer hospital stay, which was not the case. However, of the 27 patients studied in the LiDCO™ group 13 were also in the pressor study, which may have impacted upon their post-operative recovery. Anecdotally it was noted that patients in the pressor study had improved post-operative recovery; it is postulated that this was the result of the continuing fluid optimisation of the patient during data collection on the ICU. The pressor study took on average 5 hours to complete, and during this time I was present at the patient bedside, and co-ordinated all patient interventions. Certainly, the provision of a personal doctor for the patient is not possible for patients post-operatively, however the fluid balance results provide further evidence that intra-operative fluid optimisation has a significant effect in reducing post-operative morbidity.

The use of LiDCO™ monitoring provides an additional indicator to clinicians in management of fluid status and is particularly useful intra-operatively when routine methods, such as central venous pressure monitoring can be more problematic. The introduction of LiDCO™ monitoring on the ICU for the first post-operative night may be particularly useful in helping to prevent fluid overload. This is frequently a problem compounded by hypotension, avoidance of pressor agents, and crystalloid rather than colloid bolusing. However, it should be noted that the system

is not infallible, significant changes, for example, in SVV can be seen just by the infusion of a pressor agent.

The reduction in hospital stay seen in this preliminary work provides evidence for routine LiDCO™ monitoring in all patients undergoing ablative and reconstructive head and neck surgery. The main limiting factor to routine use is the associated cost of the required access cards; however, this would be more than compensated for by the cost saving of earlier post-operative discharge. Further confirmation is undoubtedly required with a larger cohort study with a full cost analysis.

Despite patient optimisation unpredictable flap complications may result in discharge delay. Early detection of a failing flap is vital to maximise successful flap salvage potential. Loss of a free flap has significant impact upon the patient, in terms of associated morbidity and delayed hospital discharge, with a further long operative procedure usually required. The financial consequences of flap failure are profound. Pre-selecting patients with the lowest risk factors is often not an option in head and neck malignancy. The cohort as a whole is often of advanced age with significant co-morbidity and the options in terms of local and pedicled reconstruction are limited with poorer outcomes in terms of cosmesis and function.

If patients who are at increased risk of flap failure due to anastomotic thrombosis can be identified in the pre-operative period, the patient can be further counselled in terms of their increased risk, and if still deemed appropriate to proceed with free tissue transfer, additional methods can be instigated to both minimise and identify flap failure early.

It has been demonstrated in the novel work on thromboelastography that functional fibrinogen to platelet ratio performed at induction of anaesthesia may be a useful pre-operative predictor of patients likely to experience thrombotic complications.

Of the 29 patients studied the majority of cases of thrombotic complications could have been predicted in the immediate pre-operative period with high functional fibrinogen to platelet ratios. One of the 16 patients (6%) in Group A (Ratio <42%), and eight of the 13 patients (62%) patients in Group B (Ratio ≥42%) experienced thrombotic flap complications. It should be noted that this patient group was small, and the overall flap complication rate was far higher than

would ordinarily be anticipated (86%), most likely due to inadvertent pre-selection of patients most at risk. During the study period, a further 19 free flaps were completed in addition to those included in the study, resulting in 48 flap procedures. In this additional group one patient underwent successful flap salvage for anastomotic venous occlusion, and the overall free flap success rate for the entire study period was 92%. Certainly the discrepancy may have been the result of chance, but it is more likely that there was an increased request rate for functional fibrinogen to platelet ratio in patients who may have been clinically perceived to be at increased risk of flap thrombosis.

Functional fibrinogen to platelet ratio was only measured at the time of induction of anaesthesia (when the first routine TEG® is ordinarily performed) to avoid the need for an additional blood sample. As a result, high risk patients were not identified sufficiently early enough to institute pre-operative additional anticoagulation. It would be interesting to determine if performing the test on the day prior to surgery yields similar results thus permitting preventative measures to be implemented.

The main limitation was the small number of patients included in the study. Further validation in a prospective study is required, with recruitment of consecutive patients. However, the difference between the cohort of surgical patients, particularly those with thrombotic complications, and normal controls was marked. The mean functional fibrinogen to platelet ratio in the control group was 32.4, but 40.8 in the surgical group. Even excluding those patients who experienced thrombotic flap complications, the mean functional fibrinogen to platelet ratio was 37.9. This finding is consistent with the procoagulant effects of malignancy.

No demographic data were available for the healthy control group. Age, sex and ethnicity have been demonstrated to impact upon TEG® results,[203,204] and it is likely that the age distribution of the control group was lower than the study group. Two patients in the control group had ratios above 42% defined as the limit at which adverse thrombotic flap complications were likely. With no data available for the control group it is impossible to draw any conclusions regarding these two controls. It is of course possible that these volunteers had contributory morbidity resulting in a procoagulant state. There are indeed a wide range of conditions predisposing

patients to increased risk of thrombosis, including Protein C and Factor V Leiden deficiencies. However, there is no information regarding the individual effects of any of these conditions specifically on functional fibrinogen to platelet ratio. This finding does highlight the fact that patients with seemingly no risk factors for thrombosis can have unrecognised reasons for flap complications. Whilst the difference between surgical patients and healthy controls is of interest, it is the correlation of a high ratio with thrombotic complications, rather than comparison to healthy controls which is of most importance.

Although all patients undergoing free tissue transfer have standard TEG® analysis, functional fibrinogen to platelet ratios (which is an additional test) were not routinely obtained. Full pre-operative screening for hereditary thrombophilia is not routinely undertaken, and often the first indication of problems is a failing flap. The short time to obtain a functional fibrinogen to platelet ratio at the induction of anaesthesia is one of the key benefits of the test.

Whilst included as a thrombotic complication, the significance of thrombosis within the internal jugular vein seen at primary surgery is unclear, and may simply be the result of central line insertion at the time of anaesthesia. This was found in 3 patients, at the time of surgery, without subsequent flap complication. Where IJV thrombus was removed, additional anticoagulation measures, including intra-operative unfractionated heparin, were instigated with close clinical surveillance. This is likely to have reduced potential adverse sequelae in these patients. Overall, an increased incidence of IJV thrombosis was detected at primary surgery than appears to be reported literature.[9,139] Such finding at surgery raises suspicion for post-operative flap complications.

The main benefits of TEG® analysis include performing the test near the bedside, with a result obtained more quickly than routine laboratory analyses. TEG® analysis also provides information of clot formation taking into consideration all of the constituents involved in its formation.

Flap failure may occur as a result of extrinsic compression of the pedicle, interpositional vein grafts, or technical error.[109] However, despite sound surgical technique, a hypercoagulable state

may still predispose a patient to thrombotic events that may ultimately jeopardise the microvascular anastomosis.[119] It has been reported that 96% of microsurgeons routinely use anticoagulants in an attempt to minimise post-operative thrombotic complications.[205] Without a mechanism to detect high risk patients, targeted therapy is not possible, subjecting all patients to the potential adverse effects of these measures. The recognised risk factors for thrombosis are related to one or more elements of Virchow's triad – stasis, vessel injury and hypercoagulability; factors frequently encountered in oncology patients undergoing free tissue transfer. High plasma fibrinogen levels have been correlated with increased thromboembolic risk in patients with cancer or cardiovascular disease.[119] Kuo *et al*[119] investigated the impact of hyperfibrinogenemia on patency of microvascular anastomoses. Using a rodent model, they performed femoral artery and vein anastomoses with and without intravenous administration of fibrinogen. Laser Doppler flowmetry was used to assess the patency of the anastomosis pre-operatively and 2 hours post-operatively. Vascular patency was assessed 7 days post-operatively. They found that there was no statistical difference in patency of the femoral vessels after vessel division and re-anastomosis. This experimental data did not support their clinical findings of 20% of patients with hyperfibrinogenemia suffering post-operative thrombotic events resulting in flap failure. The increased functional fibrinogen to platelet ratio seen in those patients experiencing thrombotic complications in this study is consistent with the finding of microvascular complications associated with hyperfibrinogenemia; elevated fibrinogen being a recognised finding in patients with malignancy.[206]

Wang *et al*[207] reviewed the outcome of 58 flaps in patients with recognised hypercoaguability. They reported an increased flap thrombosis rate of 20.7% compared to the average for all flap cases of 4.2%. In their patient cohort, none of the failing flaps were salvageable. The authors discussed the potential of flap complications being amenable to mechanical thrombolytics, systemic anticoagulation and change of the target donor vessels, making pre-operative identification of at-risk patients of key importance. In the presented cohort, the only successful post-operative successful salvage was in the case of an arterial thrombus on post-operative day 2, in whom the baseline functional fibrinogen to platelet ratio was 49%. As a result, functional

fibrinogen to platelet ratio levels may be a useful tool to identify patients likely to experience post-operative thrombotic events.

Whilst TEG® is increasingly being utilised in post-operative surgical management, the current study is the first to highlight the potential predictive benefit of the technique in free flap surgery. Further prospective validation is required, however, the results of this preliminary study suggest that this method may aid clinicians in targeting additional anticoagulation methods and close surveillance to those patients most at risk, reducing patient morbidity. This is particularly relevant in the NHS, where due to financial constraints, it is necessary to target therapy to those most in need. These additional measures may include additional chemical thromboprophylaxis such as unfractionated heparin (particularly intra-operatively), or monitoring devices such as Doppler probes or microdialysis.[138] Using unfractionated heparin needs to be fully justified, and the use of devices such as implantable Dopplers are expensive, and are a luxury which cannot be afforded to every patient. By identifying those in a cohort of patients all deemed "high risk" that are more likely to develop thrombotic flap complications additional measures to prevent or identify early flap failure can be instituted.

Patients who are at increased risk of thrombotic flap complications due to the procoagulant effects of malignancy or alternative cause are additionally at increased risk of VTE. There are numerous scoring methods to identify patients at high risk for VTE; however such methods are often unreliable in patients undergoing resection and reconstructive surgery for head and neck malignancy. Certainly, the use of the Caprini score in such a patient cohort would result in the majority of patients being deemed high risk – since they are mostly over the age of 60 years (2 points), have malignancy (2 points), are having major surgery (2 points), and depending upon the donor site, will have an immobilising plaster (2 points).[132] In view of smoking and alcohol use, many will also score additional points for co-morbidity.

Despite the increased risk of VTE in patients with malignancy, standard prophylactic LMWH dosages are the same for all patients. It is therefore unsurprising to find that dalteparin doses are inadequate in terms of anti-Xa response in a large number of patients. Anti-Xa results were strongly correlated with mean patient weight, consistent with studies examining the anti-Xa

response to dalteparin in obese patients.[137] However, despite a variable anti-Xa response to prophylactic dalteparin dose regimens, prescribing is rarely adjusted according to patient weight in routine clinical practice. The results available from the manufacturer state a mean peak (4 hour) levels of anti-Xa level in trials following single doses of 2500, 5000 and 10,000 IU of 0.19±0.04, 0.41±0.07 and 0.82±0.10 IU/ml, respectively.[208] However, it was found that a dose of 2500 IU was rarely sufficient to bring the anti-Xa result into the prophylactic range.

Anti-Xa measurement is the only method to accurately determine the effect of LMWH; however, routine testing is not advocated in clinical practice. Whilst in healthy patients without malignancy this routine prophylactic dosing regimen is likely to be adequate, this is not the case in patients with malignancy.

The measurement of anti-Xa levels in patients, with subsequent dose adjustment, appears a safe and reliable method to ensure efficacy. In the presented cohort, 56% had anti-Xa results which were below 0.2 IU/ml, and therefore deemed insufficient for prophylaxis. The potential consequences of this include significant peri-operative morbidity. Whilst adjustment in dalteparin dose was undertaken in those patients with sub-prophylactic levels, few patients had a repeat anti-Xa performed to determine the resultant effect. In the 3 patients that did, 1 still failed to bring the anti-Xa level into range.

The findings should be interpreted with the limitations of the retrospective nature in which it was conducted. The accuracy of the anti-Xa level was reliant upon clear documentation of both the time of dalteparin administration, and venepuncture. Whilst the majority of patients were cared for on the ICU which utilises electronic administration records, it is anticipated that some anti-Xa levels were not perfectly timed. Venepuncture too soon after administration would result in an artificially high anti-Xa result, and too long following administration, an artificially low result. In most cases venepuncture timing was overseen by a coagulation practitioner, thus enhancing the accuracy.

Despite a high proportion of patients having sub-prophylactic anti-Xa results, the incidence of VTE in this cohort was low, with only one case identified. However, since an anti-Xa was not performed in this patient, it is impossible to ascertain if the dalteparin dose was appropriate. It is

possible that the incidence of VTE was under reported as a result of patients being treated at peripheral hospitals following hospital discharge, although it would be expected that such treatment would be reported to the operating surgeon and documented in the medical records. Further contributing factors reducing VTE in this cohort include the intra- and early post-operative use of pneumatic compression devices, antithrombotic stockings, and where possible, early mobilisation.

The adverse outcomes in patients with acute coronary syndrome with subtherapeutic anti-Xa levels have been reported,[209] however no such relationship has yet been reported following flap surgery. A number of factors may interfere with the effectiveness of subcutaneous administered LMWHs in head and neck cancer patients, including low cardiac output, decreased peripheral blood flow, or subcutaneous oedema during the early post-operative period.[210] This further highlights the benefit of routine anti-Xa monitoring.

Whilst LMWH reduces the risk of VTE, the benefits for free flaps remain uncertain. Animal studies have demonstrated that LMWH dalteparin prevents arterial thrombosis as effectively as UFH.[211-212] Of the ten flap losses, anti-Xa results were available in 5, with only 2 of these being in the therapeutic prophylactic range. In the majority of cases, flap failure occurred after the critical 48 hour post-operative period. Potential contributing factors leading to failure include pregnancy, diabetes mellitus, and cardio-respiratory diseases. Olsson *et al*[206] noted that of the two patients experiencing anastomotic thrombotic events in their patient cohort, both had an anti-Xa level below 0.3 IU/ml, and that pre-operative anticoagulation with 2500-5000 IU was unreliable.

The ideal anticoagulant for free flap surgery would not only effectively reduce pedicle thrombosis, but would do so with minimal adverse side effects. The literature is replete with recommended regimens with such aims. Statins, in view of their vasoprotective action, anticoagulation and anti-inflammatory properties, are potential alternatives to traditional anticoagulants; however, there are currently no intravenous preparations available. In the cohort studied, 20% of patients (n=35) were on statins, and of these 5 experienced flap and/or haematological complications (flap loss n=2; identified bleed n= 2; haematoma n=1). In view of

the small numbers the data fails to yield any statistically significant correlations, but certainly provides scope for future research.

The risk, in terms of bleeding/haematoma complications, did not appear to be influenced by dalteparin dose, or aspirin prescription. Since all patients received heparin in some form, with only a very small number of patients managed with UFH, it is not possible to compare these findings with what would be encountered with UFH or in the absence of anticoagulation. Previous studies have reported that LMWH carries a substantially reduced risk of adverse side effects, including haematoma formation when compared to UFH.[213] However small, the use of LWMH carries risk, but this risk appears to be outweighed by the prophylactic benefits.

In a recent amendment of the hospital protocol for the pre-operative management of surgical patients it has been decided that all patients should now receive a dose of 2500 IU of dalteparin the night prior to surgery. The benefit of this small additional dose is questionable. Certainly in their systematic review of elective hip surgery patients Strebel *et al*[129] found no convincing evidence that starting prophylaxis pre-operatively was associated with a lower incidence of VTE than starting post-operatively.

Whatever dose of LMWH is used, the response should be measured by an anti-Xa concentration. Patients should be encouraged to mobilise as soon as possible to minimise the risk of VTE. In order to facilitate early mobilisation, patients need to be free of as many intravenous lines and feeding tubes as possible, and their nutritional status should be adequate enough to provide the calorific intake to permit post-operative recovery, wound healing and mobilisation.

Such early mobilisation is only possible in patients who are physically able. Patients with oral malignancy are frequently malnourished, both as a result of their primary tumour and secondary effects of malignancy. Extensive surgery and delayed recovery often results in patients losing further weight during their hospital stay. Optimisation of nutrition is therefore vital. As a result of surgical resection and reconstruction a method to bypass the oral cavity is required. Nasogastric and gastrostomy feeding tubes are often the preferred methods since they maintain the gastrointestinal tract; total parental nutrition carries significant risks, is highly expensive

with potentially high complication rates, and is rarely required following head and neck cancer resection.

The main problems associated with NG tubes are displacement. Patients required a mean of 1.9 tubes post-operatively in the cohort studied, a finding similar to those previously reported.[148] Reinsertion of an NGT in patients following head and neck cancer resection and reconstruction can be challenging. The swallow mechanism is often inhibited, in combination with anaesthesia of the tissues and post-operative swelling obstructing passage of the tube. Other reported problems include nasal irritation, pharyngeal and mucosal ulceration.[141] The diameter of the NGT is relatively small, making the administration of medication through them more difficult.[153] This is particularly problematic in head and neck cancer patients who frequently have multiple co-morbidities requiring multiple medications. For patients requiring only short term support NGT is the ideal method for nutritional support. The potential social stigma of a NGT in situ has been suggested as a factor for early return to oral feeding.

Only 24 patients were included in the study that were initially managed with NGT, with 3 of these ultimately requiring the insertion of a gastrostomy. Whilst the mean duration of use of NGT was 13 days, well within the recommended period of less than 3 weeks, the range was wide (between 5 and 63 days). However, only 2 patients were dependent upon NGT for longer than 28 days; in both cases this prolonged requirement could not have been predicted. Both patients experienced post-operative complications which resulted in their increased dependence. With such a small number of patients included in this cohort it is difficult to make any direct comparisons between the NGT and PEG groups.

In total, 120 patients were reviewed who were managed with gastrostomies. All but 5 of these were inserted at the time of surgery. The small number of patients who underwent insertion of gastrostomy in the pre-operative period was not sufficient enough to permit comparison between pre-operative insertion and insertion at the time of surgery. Insertion at the time of surgery does have significant benefits for the patient, this includes insertion only after the airway has been secured and minimises the number of procedures the patient has to undergo. Insertion at the time of surgery reduces demand on the routine endoscopy lists, and can be

completed with only minimal prolonging of the anaesthetic time. The main disadvantages are that any upper gastrointestinal pathology that is detected cannot be fully investigated or treated prior to surgery. The seeding of malignant cells as a result of upper GI endoscopy prior to oral cancer resection is a potential risk but is not one encountered in any of the patients studied.

Iatrogenic injury to the colon at the time of PEG insertion is particularly rare, and in reported cases may not present for many weeks following PEG insertion.[214] Two patients experienced major complications – a colonic injury, and a PEG leak, both requiring laparotomy. The minor complication rate of 16% resulted in an overall complication rate of 18%. This is lower than previously reported in the literature.[148,167] It is likely there are a number of contributory factors to this. PEG insertion is only completed by a senior member of the surgical team, and only after the airway is secured. The nursing staff follow a protocol of flushing prior to use of the tube, and the patient is taught how to manage their PEG as soon as they are able. Patients are closely followed up in the outpatient department following discharge, with support from the Dieticians and Clinical Nurse Specialists. This ensures that the stoma site is frequently inspected, and preventative mechanisms put in place to avoid wound complications. However, it should also be noted that minor complications, such as local infection may have been treated by general practitioners and not documented in the patient medical records. By combined use of data from retrospective note review and both a database and records held by the dieticians it is hoped that these inaccuracies were minimised.

The mean time of PEG use to removal request was 141 days, and to actual removal 212 days. This represents an average of 71 days from the point of referral to removal – a significant delay. Subsequent changes have been instigated in the patient pathway, with resultant reduction in waiting times for endoscopic PEG removal. In addition, the requirement for endoscopic removal may be reduced with the use of "cut and push" tubes which are currently being evaluated. All patients are assessed and followed up by the dietician and speech and language teams. The decision for PEG removal is multi-factorial, and whilst discussion of PEG removal may have occurred sooner during patient follow-up care, the date of referral for removal was considered to be more accurately documented.

Further concern related to PEG use is a delay in return to normal feeding which may result from protracted disuse of the muscles of deglutition.[141,215] Rogers *et al*[216] reported decreased quality of life scores in patients continuing to use their PEG compared to those who had undergone removal or had not used a PEG tube at all. However, the cohort continuing to use their PEG were also more likely to have undergone adjuvant therapy with more advanced disease; both significant contributors for quality of life scores. The impact on quality of life of a delay in reestablishing oral nutrition is difficult to quantify. It is difficult to accurately compare patient satisfaction between NG tubes and PEG tubes since this would entail randomisation of feeding tubes, which would be inappropriate in a number of cases.

The correct selection of feeding tube in patients with head and neck cancer can be particularly problematic, as identifying patients who require longer enteral support can be difficult. It was demonstrated that the key factors likely to result in prolonged nutritional support include tumour size, location, method of reconstruction, and extent of planned post-operative radiotherapy. In the cohort of patients studied, the *KAREN* scoring method was reliable, with the correct tube selection in 92% of patients.

The main limitations of the study are related to its retrospective nature. Only those patients who underwent free tissue transfer surgery were included, and as such, tumour volume was much greater than those undergoing local resection and local flaps/mucosal grafts. As a tertiary referral centre large volume disease is frequently encountered which contributed to the increased frequency of PEG selection. The scoring system was developed and assessed only on retrospective data at one centre thus it is heavily biased to local practice. The scores were arbitrarily assigned and it must be noted that a significant proportion of patients would be provided with a PEG based upon this system. Whilst useful for the local population, mainly as a result of being consistent with local practices, the scoring system was developed on a relatively small patient cohort and may not be transferrable to other head and neck units. Indeed the definition of "correct" selection of feeding tube for the patients included in the study was based upon their length of use, whilst important this is not the only consideration in tube selection. Often the decision for adjuvant therapy is only made once the results of pathological analysis of

the resected specimen are available, as a result it is not always possible to assign a score pre-operatively for the number of planned radiotherapy fields. Prospective application of the scoring system is required for further validation with a larger patient cohort and subsequent refinement to permit the creation of a highly accurate and reliable tool.

Potential factors to improve peri-operative care of patients following ablative and reconstructive surgery for head and neck malignancy have been investigated. There was a certain amount of overlap between the patient cohorts studied and certainly a full retrospective study on a larger cohort of patients would now be possible.

The departmental database was established through some of the early preliminary studies included in this thesis. The retrospective review of medical records and maintaining the accuracy of this data with regard to investigations and outcome is an extensive task fraught with many challenges. As a result of the growing amount of data available it has been possible in this thesis to cross-reference patients from the published studies, such as that on MI following admission via TDA to further assess causative factors.

However, as previously stated these comparisons are only as accurate as the data collected and stored. The fundamental difficulty associated with all retrospective medical record reviews is the accuracy and completeness of the contemporaneous notes. Certainly for the Trust at which these studies were conducted, filing of medical records provided additional challenges since the notes were often not arranged in chronological order, had sections missing or were illegible.

The factors included in this thesis provide a good basis on which to improve peri-operative care in terms of pressor support, fluid management, nutrition, coagulation and hospital admission route. However, there are numerous other factors in the care of patients undergoing ablative and reconstructive head and neck surgery that could also be considered, such as management of the airway, effects of insulin resistance, and the benefits of a dedicated head and neck surgery unit. This provides further scope for study, for which comparisons can be made between patients cared for on combined surgical wards, and following the recent transfer of head and neck services to the cancer centre, where all head and neck patients under the care of the

Otolaryngologists, Plastic Surgeons and Maxillofacial Surgeons will be cared for on a combined head and neck ward.

The studies discussed also provide further scope for additional investigation and research. In terms of selecting the optimal pressor agent following free tissue transfer, metaraminol requires further investigation. Discussions are currently underway to permit completion of this second phase of the study. Prospective studies are required to further assess the potential of fibrinogen to platelet ratio as measured by TEG® as a screening tool to identify patients at risk of thrombotic complications, and also to determine the accuracy of the Key to Aid Replacement Enteral Nutrition.

Conclusion

This thesis has explored a number of factors in the peri-operative management of patients undergoing ablative surgery for head and neck malignancy with free flap reconstruction. Of the factors studied, fluid optimisation with LiDCO™ monitoring is advocated in patients undergoing ablative and reconstructive surgery and where pressor support is required, low dose noradrenaline should be used. Careful anticoagulation prescribing should be undertaken, with anti-Xa monitoring of LMWH to ensure adequate response, in combination with TEG® monitoring to identify patients most at risk of thrombotic flap complications. These recommendations may improve patient outcome with significant long term benefits for both patients and the NHS.

References

1. Brown J, Rogers S, McNally D. A modified classification for the maxillectomy defect. *Head & neck* 2000;22:17-26.
2. Souba WW, Fink MP, Jurkovich GJ, Kaiser LR, Pearce WH, Pemberton JH, Soper NJ. Oral Cavity Procedures. *ACS Surgery: Principles and Practice*: WebMD Professional Publishing, 2006.
3. Eley KA, Young JD, Watt-Smith SR. Epinephrine, norepinephrine, dobutamine, and dopexamine effects on free flap skin blood flow. *Plastic and reconstructive surgery* 2012;130(3):564-70.
4. Eley KA, Young JD, Watt-Smith SR. Power spectral analysis of the effects of epinephrine, norepinephrine, dobutamine and dopexamine on microcirculation following free tissue transfer. *Microsurgery* 2013;33(4):275-81.
5. Eley KA, Young D, Watt-Smith SR. Assessment of the effects of pressors on graft blood flow after free tissue transfer surgery: interim findings. *British Journal of Oral and Maxillofacial Surgery* 2009;47(7):e41-e42.
6. Eley KA, Young D, Watt-Smith SR. 48 Assessment of the effects of pressors on graft blood flow after free tissue transfer surgery: phase I results. *British Journal of Oral and Maxillofacial Surgery* 2010;48, Supplement 1(0):S13.
7. Parker RJ, Eley KA, Von Kier S, Pearson O, Watt-Smith SR. Functional fibrinogen to platelet ratio using thromboelastography as a predictive parameter for thrombotic complications following free tissue transfer surgery: a preliminary study. *Microsurgery* 2012;32(7):512-9.
8. Eley KA, Parker RJ, Watt-Smith SR. Low molecular weight heparin in patients undergoing free tissue transfer following head and neck ablative surgery: review of efficacy and associated complications. *The British journal of oral & maxillofacial surgery* 2013; Oct;51(7):610-4.
9. Eley KA, Watt-Smith SR. Coagulopathies and the use of LiDCO Plus Rapid monitoring in patients following head and neck cancer resection and reconstruction. *The British journal of oral & maxillofacial surgery* 2010;48(6):486.
10. Eley KA, Parker R, Bond SE, Watt-Smith SR. Are routine prophylactic dalteparin doses appropriate in patients undergoing head and neck cancer resection and reconstruction? *International journal of oral and maxillofacial surgery* 2009;38(5):584-85.
11. Parker R, Eley KA, Bond SE, Watt-Smith SR. Is the ratio of functional fibrinogen to platelets as measured by thromboelastography a predictive parameter for thrombotic complications in free tissue transfer surgery? *International journal of oral and maxillofacial surgery* 2009;38(5):585.
12. Eley KA, Shah R, Bond SE, Watt-Smith SR. A review of post-operative feeding in patients undergoing resection and reconstruction for oral malignancy and presentation of a pre-operative scoring system. *The British journal of oral & maxillofacial surgery* 2012;50(7):601-5.
13. Eley KA, Watt-Smith SR. 75 Routine use of percutaneous endoscopic gastrostomy (PEG) in head and neck oncology: benefits and pitfalls. *British Journal of Oral and Maxillofacial Surgery* 2010;48, Supplement 1(0):S20.
14. Eley KA, Watt-Smith SR. Myocardial infarction diagnosed by troponin concentration in postoperative patients with head and neck cancer admitted on the day of operation. *The British journal of oral & maxillofacial surgery* 2009;47(3):245-6.
15. Eley KA, Watt-Smith SR. Re: Postoperative fluid balance in patients having operations on the head and neck. *The British journal of oral & maxillofacial surgery* 2009;47(3):249.
16. Eley KA, Watt-Smith SR. Intra-operative use of LiDCO—is there an effect on the volume of intravenous fluids used by anaesthetists during free flap surgery for head and neck cancer? *British Journal of Oral and Maxillofacial Surgery* 2009;47(7):e15.
17. Eley KA, Watt-Smith SR. Post-operative troponin positive cardiac events in patients undergoing head and neck cancer resection admitted on the day of surgery. *British Journal of Oral and Maxillofacial Surgery* 2009;47(7):e38-e39.
18. Mitchell DA, Mitchell L. *Oxford Handbook of Clinical Dentistry*. Fourth ed. Oxford: Oxford University Press, 2005.
19. Richards AM. *Key Notes in Plastic Surgery*. Oxford: Blackwell Publishing, 2007.
20. Oral Cancer Incidence Statistics.Cancer Research UK. http://info.cancerresearchuk.org/cancerstats/types/oral/incidence/uk-oral-cancer-incidence-statistics
21. Liu L, Kumar SK, Sedghizadeh PP, Jayakar AN, Shuler CF. Oral squamous cell carcinoma incidence by subsite among diverse racial and ethnic populations in California. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics* 2008;105(4):470-80.

22. Marshall JR, Graham S, Haughey BP, Shedd D, O'Shea R, Brasure J, Wilkinson GS, West D. Smoking, alcohol, dentition and diet in the epidemiology of oral cancer. *Oral Oncol Eur J Cancer* 1992;28B(1):9-15.
23. Rothman K, Keller A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *J Chron Dis* 1972;25:711-16.
24. Fasanmade A, Kwok E, Newman L. Oral squamous cell carcinoma associated with khat chewing. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics* 2007;104(1):e53-5.
25. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, Bernstein L, Schoenberg JB, Stemhagen A, Fraumeni JF. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Research* 1988;48:3282-87.
26. Joseph AW, D'Souza G. Epidemiology of human papillomavirus-related head and neck cancer. *Otolaryngol Clin North Am* 2012;45(4):739-64.
27. Lee LA, Huang CG, Liao CT, Lee LY, Hsueh C, Chen TC, Lin CY, Fan KH, Wang HM, Huang SF, Chen IH, Kang CJ, Ng SH, Yang SL, Tsao KC, Chang YL, Yen TC. Human papillomavirus-16 infection in advanced oral cavity cancer patients is related to an increased risk of distant metastases and poor survival. *PLoS One* 2012;7(7):e40767.
28. Stavrianos S, Camilleri I, McLean N, Piggot T, Kelly C, Soames J. Malignant tumours of the maxillary complex: an 18-year review. *British journal of plastic surgery* 1998;51(8):584-88.
29. Poeschl PW, Russmueller G, Seemann R, Klug C, Poeschl E, Sulzbacher I, Ewers R. Staging and Grading as Prognostic Factors in Maxillary Squamous Cell Carcinoma. *Journal of Oral and Maxillofacial Surgery* 2011.
30. Brown JS, Lewis-Jones H. Evidence for imaging the mandible in the management of oral squamous cell carcinoma: a review. *Br J Oral & Maxilofac Surg* 2001;39:411-18.
31. Le QT, Fu KK, Kaplan M, Terris DJ, Fee WE, Goffinet DR. Treatment of maxillary sinus carcinoma. *Cancer* 1999;86(9):1700-11.
32. Giele H, Cassell O. *Plastic & Reconstructive Surgery*. 1st ed. Oxford: Oxford University Press, 2008.
33. McGregor AD, McGregor IA. *Fundamental techniques of plastic surgery*. London: Churchill Livingstone, 2005.
34. Tyagi S, Kumar S. Microsurgery: An important tool for reconstructive surgery- A review. *International J Pharma Bio Sciences* 2010;1(3):1-11.
35. Cuadros CL. History of sleeve anastomosis. *Plastic and reconstructive surgery* 1988;82(6):1102.
36. McLean DH, Buncke HJ. Autotransplant of omentum to a large scalp defect, with microsurgical revascularization. *Plastic and reconstructive surgery* 1972;49(3):268-74.
37. Shenaq SM, Klebuc MJA, Vargo D. Magnification: Experience with 251 procedures. *Plastic and reconstructive surgery* 1995;95(261-269).
38. Cormack GC, Lamberty BGH. *The arterial anatomy of skin flaps*. Second ed. New York: Chuchill Livingstone, 1995.
39. Mathes SJ, Nahai F. Classification of the vascular anatomy of muscles: experimental and clinical correlation. *Plastic and reconstructive surgery* 1981;67(2):177-87.
40. Cormack GC, Lamberty BG. Fasciocutaneous flap nomenclature. *Plastic and reconstructive surgery* 1984;73(6):996.
41. Cormack GC, Lamberty BG. A classification of fascio-cutaneous flaps according to their patterns of vascularisation. *Br J Plast Surg* 1984;37(1):80-7.
42. Hodges A. *A-Z of Plastic Surgery*. Oxford: Oxford University Press, 2008.
43. Repez A, Oroszy D, Arnez AM. Continuous postoperative monitoring of cutaneous free flaps using near infrared spectroscopy. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS* 2008;61:71-77.
44. Salemark L. International survey of current microvascular practices in free tissue transfer and replantation surgery. *Microsurgery* 1991;12(4):308-11.
45. Banic A, Krejci V, Erni D, Petersen-Felix S, Sigurdsson GH. Effects of extradural anesthesia on microcirculatory blood flow in free latissimus dorsi musculocutaneous flaps in pigs. *Plastic and reconstructive surgery* 1997;100(4):945-55.
46. Cordeiro PG, Santamaria E, Hu QY, Heerdt P. Effects of vasoactive medications on the blood flow of island musculocutaneous flaps in swine. *Ann Plast Surg* 1997;39(5):525-30.
47. Yoshino J, Nara S, Endo M, Kamata N. Intraoral free flap monitoring with a laser doppler flowmeter. *Microsurgery* 1996;17:337-40.
48. MacDonald DJF. Anaesthesia for microvascular surgery. *Br J Anaesth* 1985;57:904-12.
49. Soderstom T, Stefanovska A, Verber M, Svensson H. Involvement of sympathetic nerve activity in skin blood flow oscillations in humans. *Am J Physiol Heart Circ Physiol* 2003;284:H1638-H46.

50. Sun T-B, Kuo TBJ, Yang CCH. Power spectral analysis of perfusion signals on free radial forearm flap transplantation in humans. *Microsurgery* 2009;29:636-43.
51. Cooper N, Cramp P. *Essential Guide to Acute Care*. London: BMJ, 2003.
52. Banic A, Krejci V, Erni D, Wheatley AM, Sigurdsson GH. Effects of sodium nitroprusside and phenylephrine on blood flow in free musculocutaneous flaps during general anesthesia. *Anesthesiology* 1999;90(1):147-55.
53. Ward J, Clarke R, Linden R. *Physiology at a glance*. Oxford: Blackwell Publishing Ltd, 2006.
54. Graham RM, Perez DM, Hwa J, Piascik MT. α1-Adrenergic Receptor Subtypes : Molecular Structure, Function, and Signaling. *Circulation Research* 1996;78(5):737-49.
55. Morrow AL, Creese I. Characterization of alpha 1-adrenergic receptor subtypes in rat brain: a reevaluation of [3H]WB4104 and [3H]prazosin binding. *Molecular Pharmacology* 1986;29(4):321-30.
56. Philipp M, Brede M, Hein L. Physiological significance of α2-adrenergic receptor subtype diversity: one receptor is not enough. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* 2002;283(2):R287-R95.
57. Rajanayagam MA, Rand MJ. Differential activation of adrenoceptor subtypes by noradrenaline applied from the intimal or adventitial surfaces of rat isolated tail artery. *Clin Exp Pharmacol Physiol* 1993;20(12):793-9.
58. Bevan JA, Duckles SP. Evidence for alpha-adrenergic receptors on intimal endothelium. *Blood Vessels* 1975;12(5):307-10.
59. Chruscinski A, Brede ME, Meinel L, Lohse MJ, Kobilka BK, Hein L. Differential Distribution of β-Adrenergic Receptor Subtypes in Blood Vessels of Knockout Mice Lacking β1 - or β2-Adrenergic Receptors. *Molecular Pharmacology* 2001;60(5):955-62.
60. Graver J. Inotropes--an overview. *Intensive Crit Care Nurs* 1992;8(3):169-79.
61. Husedzinovic I, Bradic N, Goranovic T. Vasoactive agents. *Signa Vitae* 2006;1(1):9-12.
62. Holmes CL. Vasoactive drugs in the intensive care unit. *Curr Opin Crit Care* 2005;11(5):413-17.
63. Katzung BG. *Basic & Clinical Pharmacology*. 6th ed: Appleton & Lange, 1995.
64. Westfall TC, Westfall DP. Adrenergic agonists and antagonists. In: Harman J, Limbird LE, editors. *Goodman & Gilman's the pharmacological basis of therapeutics*: New York: McGraw Hill, 1996.
65. Bourdarias JP, Dubourg O, Gueret P, Ferrier A, Bardet J. Inotropic agents in the treatment of cardiogenic shock. *Pharmac Ther* 1983;22:53-79.
66. Coons JC, Seidl E. Cardiovascular pharmacotherapy update for the intensive care unit. *Crit Care Nurs Q* 2007;30(1):44-57.
67. Fitton A, Benfield P. Dopexamine hydrochloride. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in acute cardiac insufficiency. *Drugs* 1990;39(2):308-30.
68. Walsh SR, Cook EJ, Bentley R, Farooq N, Gardner-Thorpe J, Tang T, Gaunt ME, Coveney EC. Perioperative fluid management: prospective audit. *Int J Clin Pract* 2008;62(3):492-7.
69. Chiu CL, Tew GP, Wang CY. The effect of prophylactic metaraminol on systemic hypotension caused by induction of anaesthesia with propofol in patients over 55 years old. *Anaesthesia* 2001;56:879-905.
70. Malmcrona R, Schroder G, Werko L. Hemodynamic effects of metaraminol. *American Journal Cardiology* 1964.
71. Bennett PN, Brown MJ, Sharma P. *Clinical Pharmacology*. 50th ed: Churchill Livingstone, 2012.
72. Liles JT, Dabisch PA, Hude KE, Pradhan L, Varner KJ, Porter JR, Hicks AR, Corll C, Baber SR, Kadowitz PJ. Pressor responses to ephedrine are mediated by a direct mechanism in the rat. *J Pharmacol Exp Ther* 2006;316(1):95-105.
73. Massey MF, Gupta DK. The effects of systemic phenylephrine and epinephrine on pedicle artery and microvascular perfusion in a pig model of myoadipocutaneous rotational flaps. *Plastic and reconstructive surgery* 2007;120:1289-99.
74. Scholz A, Pugh S, Fardy M, Shafik M, Hall JE. The effect of dobutamine on blood flow of free tissue transfer flaps during head and neck reconstructive surgery. *Anaesthesia* 2009;64:1089-93.
75. Harris L, Goldstein D, Hofer S, Gilbert R. Impact of vasopressors on outcomes in head and neck free tissue transfer. *Microsurgery* 2012;32(1):15-9.
76. Pollock DC, Li Z, Rosencrance E, Krome J, Koman LA, Smith TL. Acute effects of periarterial sympathectomy on the cutaneous microcirculation. *J Orthopaedic Research* 1997;15:408-13.
77. Lecoq JH, Joris JL, Nelissen XP, Lamy ML, Heymans OY. Effect of adrenergic stimulation on cutaneous microcirculation immediately after surgical adventitiectomy in a rat skin flap model. *Microsurgery* 2008;28:480-6.

78. Godden DR, Little R, Weston A, Greenstein A, Woodwards RT. Catecholamine sensitivity in the rat femoral artery after microvascular anastomosis. *Microsurgery* 2000;20(5):217-20.
79. Wayman J, O'Hanlon D, Hayes N, Shaw I, Griffin SM. Fibrinogen levels correlate with stage of disease in patients with oesophageal cancer. *Br J Surg* 1997;84(2):185-8.
80. Inglis MS, Robbie DS, Edwards J, Breach NM. The anaesthetic management of patients undergoing free flap reconstructive surgery following resection of head and neck neoplasms - a review of 64 patients. *Annals Royal College Surgeons England* 1988;70:235-38.
81. Agostini T, Lazzeri D, Agostini V, Spinelli G, Shokrollahi K. Delayed free flap salvage after venous thrombosis. *The Journal of craniofacial surgery* 2012;23(3):e260-1.
82. Mirzabeigi MN, Wang T, Kovach SJ, Taylor JA, Serletti JM, Wu LC. Free flap take-back following postoperative microvascular compromise: predicting salvage versus failure. *Plastic and reconstructive surgery* 2012;130(3):579-89.
83. Pohlenz P, Klatt J, Schon G, Blessmann M, Li L, Schmelzle R. Microvascular free flaps in head and neck surgery: complications and outcome of 1000 flaps. *International journal of oral and maxillofacial surgery* 2012;41(6):739-43.
84. Abdel-Galil K, Mitchell D. Postoperative monitoring of microsurgical free tissue transfers for head and neck reconstruction: a systematic review of current techniques--part I. Non-invasive techniques. *The British journal of oral & maxillofacial surgery* 2009;47(5):351-5.
85. Jallali N, Ridha H, Butler PE. Postoperative monitoring of free flaps in UK plastic surgery units. *Microsurgery* 2005;25(6):469-72.
86. Whitaker IS, Gulati V, Ross GL, Menon A, Ong TK. Variations in the postoperative management of free tissue transfers to the head and neck in the United Kingdom. *Br J Oral & Maxilofac Surg* 2007;45:16-18.
87. Clinton MS, Sepka RS, Bristol D, Pederson WC, Barwick WJ, Serafin D, Klitzman B. Establishment of normal ranges of laser doppler blood flow in autologous tissue transplants. *Plastic and reconstructive surgery* 1991;87(2):299-309.
88. Nabawi A, Gurlek A, Patrick CW, Amin A, Ritter E, Elsharaky M, Evans GRD. Measurement of blood flow and oxygen tension in adjacent tissues in pedicles and free flap head and neck reconstruction. *Microsurgery* 1999;19:254-57.
89. Young JD, Cameron EM. Dynamics of skin blood flow in human sepsis. *Intensive Care Med* 1995;21:669-74.
90. Hellner D, Schmelzle R. Laser Doppler monitoring of free microvascular flaps in maxillofacial surgery. *J Craniomaxillofac surg* 1993;21:25-29.
91. Fischer JC, Parker PM, Shaw WW. Waveform analysis applied to laser Doppler flowmetry. *Microsurgery* 1986;7(2):67-71.
92. Abdel-Galil K, Mitchell D. Postoperative monitoring of microsurgical free-tissue transfers for head and neck reconstruction: a systematic review of current techniques--part II. Invasive techniques. *The British journal of oral & maxillofacial surgery* 2009;47(6):438-42.
93. Rogers ML, Brennan PA, Leong CL, Gowers SA, Aldridge T, Mellor TK, Boutelle MG. Online rapid sampling microdialysis (rsMD) using enzyme-based electroanalysis for dynamic detection of ischaemia during free flap reconstructive surgery. *Anal Bioanal Chem* 2013;405(11):3881-8.
94. Hara H, Mihara M, Iida T, Narushima M, Todokoro T, Yamamoto T, Koshima I. Blood glucose measurement for flap monitoring to salvage flaps from venous thrombosis. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS* 2012;65(5):616-9.
95. Nabawi A, Gurlek A, Patrick CW, Jr., Amin A, Ritter E, Elsharaky M, Evans GR. Measurement of blood flow and oxygen tension in adjacent tissues in pedicled and free flap head and neck reconstruction. *Microsurgery* 1999;19(5):254-7.
96. McKee NH, Clarke HM, Nigra CAL, Manktelow RT. A study of blood flow and pressure in the vessels supplying a free flap. *Plastic and reconstructive surgery* 1982;69(1):68-73.
97. Sun TB, Kuo TB, Yang CC. Nonparallel cutaneous microcirculatory responses to pharmacologic alterations of systemic arterial pressure in rats. *Microsurgery* 2009;29(4):319-25.
98. Hiltunen P, Palve J, Setala L, Mustonen PK, Berg L, Ruokonen E, Uusaro A. The effects of hypotension and norepinephrine on microvascular flap perfusion. *J Reconstr Microsurg* 2011;27(7):419-26.
99. Godden DRP, Little R, Weston A, Greenstein A, Woodwards RTM. Catecholamine sensitivity in the rat femoral artery after microvascular anastomosis. *Microsurgery* 2000;20:217-20.
100. Suominen S, Svartling N, Silvasti M, Niemi T, Kuokkanen H, Asko-Seljavaara S. The effect of intravenous dopamine and dobutamine on blood circulation during a microvascular TRAM flap operation. *Ann Plast Surg* 2004;53(5).

101. Chen C, Nguyen M, Bar-Meir E, Hess PA, Lin S, Tobias AM, Upton J, Lee BT. Effects of vasopressor administration on the outcomes of microsurgical breast reconstruction. *Ann Plast Surg* 2010;65:28-31.
102. Landsverk SA, Kvandal P, Kjelstrup T, Benko U, Bernjak A, Stefanovska A, Kvernmo H, Kirkeboen KA. Human skin microcirculation after brachial plexus block evaluated by wavelet transform of the laser Doppler flowmetry signal. *Anesthesiology* 2006;105:478-84.
103. Liu X, Zeng B, Fan C, Jiang C, Hu X. Spectral analysis of blood perfusion in the free latissimus dorsi myocutaneous flap and normal skin. *Phys Med Biol* 2006;51:173-83.
104. Jonas M, Fennell J, Brudney CS. Haemodynamic optimisation of the surgical patient revisited. *Anaesthesia International* 2008;2(1).
105. NICE. CG92 Venous thromboembolism - reducing the risk: NICE guideline. *National Institute for Health and Clinical Excellence* 2010. http://www.nice.org.uk/nicemedia/live/12695/47195/47195.pdf
106. Ashjian P, Chen CM, Pusic A, Disa JJ, Cordeiro PG, Mehrara BJ. The effect of postoperative anticoagulation on microvascular thrombosis. *Ann Plast Surg* 2007;59:36-40.
107. Fosnot J, Jandali S, Low DW, Kovach SJ, Wu LC, Serletti JM. Closer to an understanding of fate - the role of vascular complications in free flap breast reconstruction. *Plastic and reconstructive surgery* 2011;Epub ahead of print June 15.
108. Chen CM, Ashjian P, Disa JJ, Cordeiro PG, Pusic AL, Mehrara BJ. Is the use of intraoperative heparin safe? *Plastic and reconstructive surgery* 2008;121(3):49e-53e.
109. Novakovic D, Patel RS, Goldstein DP, Gullane PJ. Salvage of failed free flaps used in head and neck reconstruction. *Head Neck Oncology* 2009;1(33):1-5.
110. Gordon SG, Mielicki WP. Cancer procoagulant: a factor X activator, tumour marker and growth factor from malignant tissue. *Blood Coagul Fibrinolysis* 1997;8(2):73-86.
111. ten Cate H, Falanga A. Overview of the postulated mechanisms linking cancer and thrombosis. *Pathophysiol Haemost Thromb* 2008;36(3-4):122-30.
112. Rickles FR, Falanga A. Molecular basis for the relationship between thrombosis and cancer. *Thrombosis research* 2001;102(6):215-24.
113. Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. *Lancet Oncol* 2005;6(6):401-10.
114. Kesting MR, Holzle F, Wales C, Steinstraesser L, Wagenpfeil S, Mucke T, Rohleder NH, Wolff KD, Hasler RJ. Microsurgical reconstruction of the oral cavity with free flaps from the anterolateral thigh and the radial forearm: a comparison of perioperative data from 161 cases. *Ann Surg Oncol* 2011;18(7):1988-94.
115. Kruse AL, Bredell MG, Lubbers HT, Jacobsen C, Gratz KW, Obwegeser JA. Clinical reliability of radial forearm free-flap procedure in reconstructive head and neck surgery. *The Journal of craniofacial surgery* 2011;22(3):822-5.
116. Townley WA, Nguyen DQ, Rooker JC, Dickson JK, Goroszeniuk DZ, Khan MS, Camp D. Management of open tibial fractures - a regional experience. *Ann R Coll Surg Engl* 2010;92(8):693-6.
117. Ducic I, Brown BJ, Rao SS. Lower extremity free flap reconstruction outcomes using venous coupler. *Microsurgery* 2011;31(5):360-64.
118. Lee SE, Lee JH, Ryu KW, Nam BH, Cho SJ, Lee JY, Kim CG, Choi IJ, Kook MC, Park SR, Kim YW. Preoperative plasma fibrinogen level is a useful predictor of adjacent organ involvement in patients with advanced gastric cancer. *J Gastric Cancer* 2012;12(2):81-7.
119. Kuo Y-R, Jeng S-F, Wu W-S, Lin C-J, Sacks JM, Yang KD. Hyperfibrinogenemia alone does not affect the patency of microvascular anastomosis. Clinical experience and animal study. *Ann Plast Surg* 2005;54(4):435-41.
120. Wang TY, Serletti JM, Cuker A, McGrath J, Low DW, Kovach SJ, Wu LC. Free tissue transfer in the hypercoagulable patient: a review of 58 flaps. *Plastic and reconstructive surgery* 2012;129(2):443-53.
121. Davison SP, Kessler CM, Al-Attar A. Microvascular free flap failure caused by unrecognized hypercoagulability. *Plastic and reconstructive surgery* 2009;124(2):490-95.
122. Conrad MH, Adams WP, Jr. Pharmacologic optimization of microsurgery in the new millennium. *Plastic and reconstructive surgery* 2001;108(7):2088-96; quiz 97.
123. Hammerstingl C. Monitoring therapeutic anticoagulation with low molecular weight heparins: is it useful or misleading? *Cardiovasc hematol agents med chem* 2008;6(4):282-86.
124. Reiter M, Kapsreiter M, Betz CS, Harreus U. Perioperative management of antithrombotic medication in head and neck reconstruction-a retrospective analysis of 137 patients. *Am J Otolaryngol* 2012;33(6):693-6.

125. Chen CM, Disa JJ, Cordeiro PG, Pusic AL, McCarthy CM, Mehrara BJ. The incidence of venous thromboembolism after oncologic head and neck reconstruction. *Ann Plast Surg* 2008;60(5):476-9.
126. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ. Predictors of recurrence after deep vein thrombosis and pulmonary embolism. A population-based cohort study. *Arch Intern Med* 2000;160(6):809-15.
127. Heit JA. The epidemiology of venous thromboembolism in the community. *Arteriosclerosis, Thrombosis, Vascular Biology* 2008;28:370-72.
128. Blackburn TK, Java KR, Lowe D, Brown JS, Rogers SN. Safety of a regimen for thromboprophylaxis in head and neck cancer microvascular reconstructive surgery: non-concurrent cohort study. *The British journal of oral & maxillofacial surgery* 2012;50(3):227-32.
129. Strebel N, Prins M, Agnelli G, Buller HR. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? *Arch Intern Med* 2002;162(13):1451-6.
130. Wilson SJ, Wilbur K, ;, Burton E, Anderson DR. Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low-molecular-weight heparin for the treatment of venous thromboembolism. *Haemostasis* 2001;31(1):42-8.
131. Lim W, Dentali F, Eikelboom JW, Crowther MA. Meta-analysis: Low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann intern med* 2006;144(9):673-84.
132. Pannucci CJ, Bailey SH, Dreszer G, Fisher Wachtman C, Zumsteg JW, Jaber RM, Hamill JB, Hume KM, Rubin JP, Neligan PC, Kalliainen LK, Hoxworth RE, Pusic AL, Wilkins EG. Validation of the Caprini risk assessment model in plastic and reconstructive surgery patients. *J Am Coll Surg* 2011;212(1):105-12.
133. Samama CM. Thromboelastography: The next step. *Anesthesia Analgesia* 2001;92(3):563-64.
134. Falanga A, Marchetti M, Vignoli A, Balducci D. Clotting mechanisms and cancer: implications in thrombus formation and tumor progression. *Clin Adv Hematol Oncol* 2003;1(11):673-8.
135. Ganter MT, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. *Anesthesia Analgesia* 2008;106(5):1366-75.
136. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL, Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA* 2004;291(20):2441-7.
137. Smith J, Canton EM. Weight-based administration of dalteparin in obese patients. *Am J Health System Pharmacy* 2003;60(7):683-7.
138. Smit JM, Zeebregts CJ, Acosta R, Werker PM. Advancements in free flap monitoring in the last decade: a critical review. *Plastic and reconstructive surgery* 2010;125(1):177-85.
139. Felstead AM, Perkins CS. Thrombosis of the internal jugular vein: a rare but important operative finding. *The British journal of oral & maxillofacial surgery* 2010;48(3):195-6.
140. Arosarena O. Perioperative management of the head and neck cancer patient. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons* 2007;65(2):305-13.
141. Mekhail T, Adelstein D, Rybicki L, Larto M, Saxton J, Lavertu P. Enteral nutrition during the treatment of head and neck carcinoma: is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube? *Cancer* 2001;91(9):1785-90.
142. Lloyd CJ, Penfold CN. Insertion of percutaneous endoscopic gastrostomy tubes by a maxillofacial surgical team in patients with oropharyngeal cancer. *The British journal of oral & maxillofacial surgery* 2002;40(2):122-4.
143. Guo CB, Ma DQ, Zhang KH, Hu XH. Relation between nutritional state and postoperative complications in patients with oral and maxillofacial malignancy. *The British journal of oral & maxillofacial surgery* 2007;45(6):467-70.
144. Chandu A, Smith AC, Douglas M. Percutaneous endoscopic gastrostomy in patients undergoing resection for oral tumors: a retrospective review of complications and outcomes. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons* 2003;61(11):1279-84.
145. Sobani ZU, Ghaffar S, Ahmed BN. Comparison of outcomes of enteral feeding via nasogastric versus gastrostomy tubes in post operative patients with a principle diagnosis of squamous cell carcinoma of the oral cavity. *J Pak Med Assoc* 2011;61(10):1042-5.
146. Gardine RL, Kokal WA, Beatty JD, Riihimaki DU, Wagman LD, Terz JJ. Predicting the need for prolonged enteral supplementation in the patient with head and neck cancer. *Am J Surg* 1988;156(1):63-5.

147. Tei K, Maekawa K, Kitada H, Ohiro Y, Yamazaki Y, Totsuka Y. Recovery from postsurgical swallowing dysfunction in patients with oral cancer. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons* 2007;65(6):1077-83.
148. Corry J, Poon W, McPhee N, Milner A, Cruickshank D, Porceddu S, Rischin D, Peters L. Prospective study of percutaneous endoscopic gastrostomy tubes versus nasogastric tubes for enteral feeding in patients with head and neck cancer undergoing (chemo)radiation. *Head & neck* 2009;31(7):867-76.
149. Paccagnella A, Morello M, Da Mosto MC, Baruffi C, Marcon ML, Gava A, Baggio V, Lamon S, Babare R, Rosti G, Giometto M, Boscolo-Rizzo P, Kiwanuka E, Tessarin M, Caregaro L, Marchiori C. Early nutritional intervention improves treatment tolerance and outcomes in head and neck cancer patients undergoing concurrent chemoradiotherapy. *Support Care Cancer* 2010;18(7):837-45.
150. Schweinfurth JM, Boger GN, Feustel PJ. Preoperative risk assessment for gastrostomy tube placement in head and neck cancer patients. *Head & neck* 2001;23(5):376-82.
151. O'Dwyer TP, Gullane PJ, Awerbuch D, Ho CS. Percutaneous feeding gastrostomy in patients with head and neck tumors: a 5-year review. *Laryngoscope* 1990;100(1):29-32.
152. Walton GM. Complications of percutaneous gastrostomy in patients with head and neck cancer--an analysis of 42 consecutive patients. *Ann R Coll Surg Engl* 1999;81(4):272-6.
153. Hujala K, Sipilä J, Pulkkinen J, Grenman R. Early percutaneous endoscopic gastrostomy nutrition in head and neck cancer patients. *Acta Otolaryngol* 2004;124(7):847-50.
154. Oakley R, Donnelly R, Freeman L, Wong T, McCarthy M, Calman F, O'Connell M, Jeannon J, Simo R. An audit of percutaneous endoscopic gastrostomy insertion in patients undergoing treatment for head and neck cancer: reducing the incidence of peri-operative airway events by the introduction of a tumour assessment protocol. *Ann R Coll Surg Engl* 2009;91(3):249-54.
155. Cunliffe DR, Swanton C, White C, Watt-Smith SR, Cook TA, George BD. Percutaneous endoscopic gastrostomy at the time of tumour resection in advanced oral cancer. *Oral Oncol* 2000;36(5):471-3.
156. Cunliffe DR, Watt-Smith SR, George BD, Cook TA. Complications of percutaneous gastrostomy in patients with head and neck cancer--an analysis of 42 consecutive patients. *Ann R Coll Surg Engl* 2001;83(4):295.
157. Roukema JA, van der Werken C, Juttmann JR. Percutaneous endoscopic gastrostomy as a standard procedure in head and neck surgery. *Archives of otolaryngology--head & neck surgery* 1990;116(6):730-1.
158. Saunders JR, Jr., Brown MS, Hirata RM, Jaques DA. Percutaneous endoscopic gastrostomy in patients with head and neck malignancies. *Am J Surg* 1991;162(4):381-3.
159. Koehler J, Buhl K. Percutaneous endoscopic gastrostomy for postoperative rehabilitation after maxillofacial tumor surgery. *International journal of oral and maxillofacial surgery* 1991;20(1):38-9.
160. NICE. Guidance on cancer services: Improving outcomes in head and neck cancers. The manual. 2004. www.nice.org.uk
161. (NICE) NIfCE. Nutrition Support for Adults Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition. *NICE* 20062010(May 16). http://guidance.nice.org.uk/CG32/Guidance/pdf/English
162. Loser C, Aschl G, Hebuterne X, Mathus-Vliegen EMH, Muscaritoli M, Niv Y, Rollins H, Singer P, Skelly RH. ESPEN guidelines on artificial enteral nutrition - Percutaneous endoscopic gastrostomy (PEG). *Clinical Nutrition* 2005;24:848-61.
163. SIGN. Diagnosis and management of head and neck cancer. A national clinical guideline. 2006;Scottish Intercollegiate Guidelines Network.www.sign.ac.uk
164. Locher JL, Bonner JA, Carroll WR, Caudell JJ, Allison JJ, Kilgore ML, Ritchie CS, Tajeu GS, Yuan Y, Roth DL. Patterns of prophylactic gastrostomy tube placement in head and neck cancer patients: A consideration of the significance of social support and practice variation. *Laryngoscope* 2013.
165. Gibson S, Wenig BL. Percutaneous endoscopic gastrostomy in the management of head and neck carcinoma. *Laryngoscope* 1992;102(9):977-80.
166. Morton R, Crowder V, Mawdsley R, Ong E, Izzard M. Elective gastrostomy, nutritional status and quality of life in advanced head and neck cancer patients receiving chemoradiotherapy. *ANZ J Surg* 2009;79(10):713-8.
167. Chandu A, Smith ACH, Douglas M. Percutaneous endoscopic gastrostomy in patients undergoing resection for oral tumors: a retrospective review of complications and outcomes. . *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons* 2003;61(11):1279-84.

168. Nagele P, Rao LK, Penta M, Kallogjeri D, Spitznagel EL, Cavallone LF, Nussenbaum B, Piccirillo JF. Postoperative myocardial injury after major head and neck cancer surgery. *Head & neck* 2011;33(8):1085-91.
169. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ* 2005;173(6):627-34.
170. Wei S, Tian J, Song X, Chen Y. Association of perioperative fluid balance and adverse surgical outcomes in esophageal cancer and esophagogastric junction cancer. *Ann Thorac Surg* 2008;86(1):266-72.
171. Rhodes A, Sunderland R. Arterial pulse power analysis: The LiDCOTM plus system. Functional harmodynamic monitoring. *Update in Intensive care and emergency medicine* 2005;42:183-92
172. Pearse RM, Ikram K, Barry J. Equipment review: an appraisal of the LiDCO plus method of measuring cardiac output. *Crit Care* 2004;8(3):190-5.
173. Rothwell LA, Bokey EL, Keshava A, Chapuis PH, Dent OF. Outcomes after admission on the day of elective resection for colorectal cancer. *ANZ J Surg* 2006;76(1-2):14-9.
174. Calligaro KD, Dandura R, Dougherty MJ, DeLaurentis DA, Raviola CA. Same-day admissions and other cost-saving strategies for elective aortoiliac surgery. *J Vasc Surg* 1997;25(1):141-4.
175. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *The New England journal of medicine* 2009;361(9):858-67.
176. Nouraei SA, Al-Yaghchi C, Sandhu GS, Giussani DA, Doyle P, Clarke PM. Incidence and significance of myocardial injury after surgical treatment of head and neck cancer. *Laryngoscope* 2007;117(9):1581-7.
177. Datema FR, Poldermans D, Baatenburg de Jong RJ. Incidence and prediction of major cardiovascular complications in head and neck surgery. *Head & neck* 2010;32(11):1485-93.
178. Tanaka K, Sakuraba M, Miyamoto S, Hayashi R, Ebihara M, Miyazaki M, Shinozaki T, Daiko H, Yano T. Analysis of Operative Mortality and Post-operative Lethal Complications after Head and Neck Reconstruction with Free Tissue Transfer. *Japanese Journal of Clinical Oncology* 2011;41(6):758-63.
179. Clark J, McCluskey S, Hall F, Lipa J, Neligan P, Brown D, Irish J, Gullane P, Gilbert R. Predictors of morbidity following free flap reconstruction for cancer of the head and neck. *Head & neck* 2007;29(12):1090-101.
180. Pattani KM, Byrne P, Boahene K, Richmon J. What makes a good flap go bad?: a critical analysis of the literature of intraoperative factors related to free flap failure. *Laryngoscope* 2010;120:717-23.
181. Chalmers A, Turner MWH, Anand R, Puxeddu R, Brennan PA. Cardiac output monitoring to guide fluid replacement in head and neck microvascular free flap surgery—what is current practice in the UK? *British Journal of Oral and Maxillofacial Surgery* 2012;50(6):500-03.
182. Haughey B, Wilson E, Kluwe L, Piccirillo J, Fredrickson J, Sessions D, Spector G. Free flap reconstruction of the head and neck: analysis of 241 cases. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery* 2001;125(1):10-7.
183. Abdel-Galil K, Craske D, McCaul J. Optimisation of intraoperative haemodynamics: early experience of its use in major head and neck surgery. *The British journal of oral & maxillofacial surgery* 2010;48(3):189-91.
184. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PS. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology* 2002;97(4):820-6.
185. Jensen NF, Todd MM, Block RI, Hegtvedt RL, McCulloch TM. The efficacy of routine central venous monitoring in major head and neck surgery: a retrospective review. *J Clin Anesth* 1995;7(2):119-25.
186. Boothe P, Finegan BA. Changing the admission process for elective surgery: an economic analysis. *Can J Anaesth* 1995;42(5 Pt 1):391-4.
187. Vijay V, Kazzaz S, Refson J. The same day admissions unit for elective surgery: a case study. *Int J Health Care Qual Assur* 2008;21(4):374-9.
188. Kulasegarah J, Lang EE, Carolan E, Viani L, Gaffney R, Walsh RM. Day of surgery admission--is this safe practise? *Ir Med J* 2008;101(7):218-9.

189. Kehlet H. The surgical stress response: should it be prevented? *Can J Surg* 1991;34(6):565-7.
190. Hölzle F, Loeffelbein DJ, Nolte D, Wolff KD. Free flap monitoring using simultaneous non-invasive laser Doppler flowmetry and tissue spectrophotometry. *J Craniomaxillofac surg* 2006;34(1).
191. Hölzle F, Rau A, Loeffelbein DJ, Mücke T, Kesting MR, Wolff KD. Results of monitoring fasciocutaneous, myocutaneous, osteocutaneous and perforator flaps: 4-year experience with 166 cases. *International journal of oral and maxillofacial surgery* 2010;39(1):21-8.
192. Banbury J, Siemionow M, Porvasnik S, Petras S, Zins JE. Muscle flaps' triphasic microcirculatory response to sympathectomy and denervation. . *Plastic and reconstructive surgery* 1999;104:730-37.
193. Rizzoni D, Perlini S, Mircoli L, Porteri E, Franzelli C, Castellano M, Agabati RE, Ferrari AU. Enhanced vascular reactivity in the sympathectomized rat: Studies in vivo and in small isolated resistance arteries. *J Hypertens* 2000;18:1041-49.
194. Bickel A, Axelrod FB, Schmelz M, Marthol H, Hilz MJ. Dermal microdialysis provides evidence for hypersensitivity to noradrenaline in patients with familial dysautonomia. *J Neurol Neurosurg Psychiatry* 2002;73:299–302
195. Moore GK, Trachy RE, Cummings CW. The effect of alpha-adrenergic stimulation and blockade on perfusion of myocutaneous flaps. *Otolaryngol Head Neck Surg.* 1986;94(4):489-96.
196. Rossi M, Carpi A, Galetta F, Franzoni F, Santoro G. The investigation of skin blood flowmotion: a new approach to study the microcirculatory impairment in vascular diseases? *Biomed Pharmacotherapy* 2006;60:437-42.
197. Bracic M, Stefanovska A. Wavelet-based analysis of human blood-flow dynamics. *Bull Math Biol* 1998;60(5):919-35.
198. Goldstein RA, Passamani ER, Roberts R. A comparison of digoxin and dobutamine in patients with acute infarction and cardiac failure. *The New England journal of medicine* 1980;303(15):846-50.
199. Kates RE, Leier CV. Dobutamine pharmacokinetics in severe heart failure. *Clin Pharmacol Ther* 1978;24(5):537-41.
200. Dimsdale JE, Moss J. Short-term catecholamine response to psychological stress. *Psychosom Med* 1980;42(5):493-7.
201. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000;85(1):109-17.
202. Wilmore DW. From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. *Ann Surg* 2002;236(5):643-8.
203. Roeloffzen WW, Kluin-Nelemans HC, Mulder AB, Veeger NJ, Bosman L, de Wolf JT. In normal controls, both age and gender affect coagulability as measured by thrombelastography. *Anesth Analg* 2010;110(4):987-94.
204. Singhal D, Smorodinsky E, Guo L. Differences in coagulation among Asians and Caucasians and the implication for reconstructive microsurgery. *J Reconstr Microsurg* 2011;27(1):57-62.
205. Askari M, Fisher C, Weniger FG, Bidic S, Lee WP. Anticoagulation therapy in microsurgery: a review. *J Hand Surg Am* 2006;31(5):836-46.
206. Olsson E, Svartling N, Asko-Seljavaara S, Lassila R. Activation of coagulation and fibrinolysis during reconstructive microsurgery in patients with cancer. *Microsurgery* 2001;21(5):208-13.
207. Wang TY, Serletti JM, Cuker A, McGrath J, Low DW, Kovach SJ, Wu LC. Free tissue transfer in the hypercoagulable patient: a review of 58 flaps. *Plastic and reconstructive surgery* 2011;Epub ahead of press(Oct 7).
208. Pfizer. Fragmin dalteparin sodium injection. 2007.www.pfizer.com/files/products/uspi_fragmin.pdf
209. Montalescot G, Collet J, Tanguy M, Ankri A, Payot L, Dumaine R, Choussat R, Beygui F, Gallois V, Thomas D. Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin. *Circulation* 2004;110(4):392-8.
210. Rommers M, Van Der Lely N, Egberts T, van den Bemt P. Anti-Xa activity after subcutanous administration of dalteparin in ICU patients with and without subcutanous oedema: a pilot study. 2006;10(3).
211. Karsenti G, Le Manach Y, Bouvier S, Chaine A, Bertolus C. Statins: a new pharmacological agent for free flap surgery? *Journal of plastic, reconstructive & aesthetic surgery : JPRAS* 2010;63(5):870-4.
212. Malm K, Dahiback B, Arnlijots B. Low-molecular-weight heparin (dalteparin) effectively prevents thrombosis in a rat model of deep arterial injury. *Plastic and reconstructive surgery* 2003;111(5):1659-66.
213. De A, Roy P, Garg VK, Pandey NK. Low-molecular-weight heparin and unfractionated heparin in prophylaxis against deep vein thrombosis in critically ill patients undergoing major surgery. *Blood Coagul Fibrinolysis* 2010;21(1):57-61.

214. Friedmann R, Feldman H, Sonnenblick M. Misplacement of Percutaneously inserted Gastrostomy Tube into the colon: Report of 6 cases and review of the literature. *J Parenter Enteral Nutr* 2007;31(6):469-67.
215. Murphy BA. Adcances in quality of life and symptom management for head and neck cancer patients. *Current Opinion Oncology* 2009;21(3):242-47.
216. Rogers SN, Thomson R, O'Toole PO, Lowe D. Patients experience with long-term percutaneous endoscopic gastrostomy feeding following primary surgery for oral and oropharyngeal cancer. *Oral Oncol* 2007;43:499-507.
217. Sobin LH, Gospodarowicz MK, Wittekind C, International Union against Cancer. *TNM classification of malignant tumours*. 7th ed. Chichester, West Sussex, UK ; Hoboken, NJ: Wiley-Blackwell, 2010.

Appendices

Appendix A: Staging of head & neck malignancy

The current staging system for head and neck malignancy is by the TNM classification of Malignant Tumours, by the International Union Against Cancer (UICC), Seventh Edition.

Lip & Oral Cavity

The classification applies to carcinomas of the vermilion surfaces of the lips and of the oral cavity, including those of minor salivary glands.[217]

Anatomical Sites and Subsites

Lip (C00)

1. External upper lip (vermilion border) (C00.0)
2. External lower lip (vermilion border) (C00.1)
3. Commissures (C00.6)

Oral Cavity (C02-06)

1. Buccal mucosa
    a. Mucosa of upper and lower lips (C0.3, 4)
    b. Cheek mucosa (C06.0)
    c. Retromolar areas (C06.2)
    d. Bucco-alveolar sulci, upper and lower (vestibule of mouth) (C06.1)
2. Upper alveolus and gingival (upper gum) (C03.0)
3. Lower alveolus and gingival (lower gum) (C03.1)
4. Hard palate (C05.0)
5. Tongue
    a. Dorsal surface and lateral borders anterior to vallate papillae (anterior two thirds) (C02.2)
    b. Inferior (ventral) surface (C02.2)
6. Floor of mouth (C04)

TNM Classification

T – Primary Tumour

T1	≤ 2cm
T2	>2-4 cm
T3	>4cm
T4a	**Oral Cavity:** through cortical bone, deep/extrinsic muscle of tongue, maxillary sinus, skin of face **Lip:** through cortical bone, inferior alveolar nerve, floor of mouth, skin
T4b	Masticator space, pterygoid plates, skull base, internal carotid artery

N - Regional Lymph Nodes

N0	No regional lymph node metastasis
N1	Ipsilateral single ≤3cm
N2	a. Ipsilateral single >3-6cm b. Ipsilateral multiple ≤6cm c. Bilateral, contralateral ≤6cm
N3	>6cm

M – Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IVA	T4a	N0, N1	M0
	T1, T2, T3, T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Nasal Cavity and Paranasal Sinuses

Anatomical Sites and Subsites

Nasal Cavity (C3.0)
- Septum
- Floor
- Lateral wall
- Vestibule

Maxillary Sinus (C31.0)

Ethmoid Sinus (C31.1)

TNM Classification (Maxillary Sinus)

T – Primary Tumour

T1	Mucosa
T2	Bone erosion/destruction, hard palate, middle nasal meatus
T3	Posterior bony wall maxillary sinus, subcutaneous tissues, floor/medial wall of orbit, pterygoid fossa, ethmoid sinus
T4a	Anterior orbit, cheek skin, pterygoid plates, infratemporal fossa, cribiform plate, sphenoid or frontal sinuses
T4b	Orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, clivus

N – Regional Lymph Nodes

N1	Ipsilateral single ≤3cm
N2	
	a. Ipsilateral single >3-6cm
	b. Ipsilateral multiple ≤6cm
	c. Bilateral, contralateral ≤6cm
N3	>6cm

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Appendix B: ACE-27 Co-morbidity Scoring

Adult Comorbidity Evaluation-27

Identify the important medical comorbidities and grade severity using the index.
Overall Comorbidity Score is defined according to the highest ranked single ailment, except in the case where two or more Grade 2 ailments occur in different organ systems. In this situation, the overall comorbidity score should be designated Grade 3.

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Cardiovascular System			
Myocardial Infarct	☐ MI ≤ 6 months	☐ MI > 6 months ago	☐ MI by ECG only, age undetermined
Angina / Coronary Artery Disease	☐ Unstable angina	☐ Chronic exertional angina ☐ Recent (≤ 6 months) Coronary Artery Bypass Graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA) ☐ Recent (≤ 6 months) coronary stent	☐ ECG or stress test evidence or catheterization evidence of coronary disease without symptoms ☐ Angina pectoris not requiring hospitalization ☐ CABG or PTCA (>6 mos.) ☐ Coronary stent (>6 mos.)
Congestive Heart Failure (CHF)	☐ Hospitalized for CHF within past 6 months ☐ Ejection fraction < 20%	☐ Hospitalized for CHF >6 months prior ☐ CHF with dyspnea which limits activities	☐ CHF with dyspnea which has responded to treatment ☐ Exertional dyspnea ☐ Paroxysmal Nocturnal Dyspnea (PND)
Arrhythmias	☐ Ventricular arrhythmia ≤ 6 months	☐ Ventricular arrhythmia > 6 months ☐ Chronic atrial fibrillation or flutter ☐ Pacemaker	☐ Sick Sinus Syndrome ☐ Supraventricular tachycardia
Hypertension	☐ DBP≥130 mm Hg ☐ Severe malignant papilledema or other eye changes ☐ Encephalopathy	☐ DBP 115-129 mm Hg ☐ DBP 90-114 mm Hg while taking antihypertensive medications ☐ Secondary cardiovascular symptoms: vertigo, epistaxis, headaches	☐ DBP 90-114 mm Hg while not taking antihypertensive medications ☐ DBP <90 mm Hg while taking antihypertensive medications ☐ Hypertension, not otherwise specified
Venous Disease	☐ Recent PE (≤ 6 mos.) ☐ Use of venous filter for PE's	☐ DVT controlled with Coumadin or heparin ☐ Old PE > 6 months	☐ Old DVT no longer treated with Coumadin or Heparin
Peripheral Arterial Disease	☐ Bypass or amputation for gangrene or arterial insufficiency < 6 months ago ☐ Untreated thoracic or abdominal aneurysm (≥6 cm)	☐ Bypass or amputation for gangrene or arterial insufficiency > 6 months ago ☐ Chronic insufficiency	☐ Intermittent claudication ☐ Untreated thoracic or abdominal aneurysm (< 6 cm) ☐ s/p abdominal or thoracic aortic aneurysm repair
Respiratory System			
	☐ Marked pulmonary insufficiency ☐ Restrictive Lung Disease or COPD with dyspnea at rest despite treatment ☐ Chronic supplemental O_2 ☐ CO_2 retention (pCO_2 > 50 torr) ☐ Baseline pO_2 < 50 torr ☐ FEV1 (< 50%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which limits activities ☐ FEV1 (51%-65%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which has responded to treatment ☐ FEV1 (66%-80%)
Gastrointestinal System			
Hepatic	☐ Portal hypertension and/or esophageal bleeding ≤ 6 mos. (Encephalopathy, Ascites, Jaundice with Total Bilirubin > 2)	☐ Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms "compensated hepatic failure"	☐ Chronic hepatitis or cirrhosis without portal hypertension ☐ Acute hepatitis without cirrhosis ☐ Chronic liver disease manifested on biopsy or persistently elevated bilirubin (>3 mg/dl)
Stomach / Intestine	☐ Recent ulcers(≤ 6 months ago) requiring blood transfusion	☐ Ulcers requiring surgery or transfusion > 6 months ago	☐ Diagnosis of ulcers treated with meds ☐ Chronic malabsorption syndrome ☐ Inflammatory bowel disease (IBD) on meds or h/o with complications and/or surgery
Pancreas	☐ Acute or chronic pancreatitis with major complications (phlegmon, abscess, or pseudocyst)	☐ Uncomplicated acute pancreatitis ☐ Chronic pancreatitis with minor complications (malabsorption, impaired glucose tolerance, or GI bleeding)	☐ Chronic pancreatitis w/o complications

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Renal System			
End-stage renal disease	☐ Creatinine > 3 mg% with multi-organ failure, shock, or sepsis ☐ Acute dialysis	☐ Chronic Renal Insufficiency with creatinine >3 mg% ☐ Chronic dialysis	☐ Chronic Renal Insufficiency with creatinine 2-3 mg%.
Endocrine System	**(Code the comorbid ailments with the (*) in both the Endocrine system and other organ systems if applicable)**		
Diabetes Mellitus	☐ Hospitalization ≤ 6 months for DKA ☐ Diabetes causing end-organ failure ☐ retinopathy ☐ neuropathy ☐ nephropathy* ☐ coronary disease* ☐ peripheral arterial disease*	☐ IDDM without complications ☐ Poorly controlled AODM with oral agents	☐ AODM controlled by oral agents only
Neurological System			
Stroke	☐ Acute stroke with significant neurologic deficit	☐ Old stroke with neurologic residual	☐ Stroke with no residual ☐ Past or recent TIA
Dementia	☐ Severe dementia requiring full support for activities of daily living	☐ Moderate dementia (not completely self-sufficient, needs supervising)	☐ Mild dementia (can take care of self)
Paralysis	☐ Paraplegia or hemiplegia requiring full support for activities of daily living	☐ Paraplegia or hemiplegia requiring wheelchair, able to do some self care	☐ Paraplegia or hemiplegia, ambulatory and providing most of self care
Neuromuscular	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder and requiring full support for activities of daily living	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but able to do some self care	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	☐ Recent suicidal attempt ☐ Active schizophrenia	☐ Depression or bipolar disorder uncontrolled ☐ Schizophrenia controlled w/ meds	☐ Depression or bipolar disorder controlled w/ medication
Rheumatologic	**(Incl. Rheumatoid Arthritis, Systemic Lupus, Mixed Connective Tissue Disorder, Polymyositis, Rheumatic Polymyositis)**		
	☐ Connective Tissue Disorder with secondary end-organ failure (renal, cardiac, CNS)	☐ Connective Tissue Disorder on steroids or immunosuppressant medications	☐ Connective Tissue Disorder on NSAIDS or no treatment
Immunological System	**(AIDS should not be considered a comorbidity for Kaposi's Sarcoma or Non-Hodgkin's Lymphoma)**		
AIDS	☐ Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)	☐ HIV+ with h/o defining illness. $CD4^+ < 200/\mu L$	☐ Asymptomatic HIV+ patient. ☐ HIV^+ w/o h/o AIDS defining illness. $CD4^+ > 200/\mu L$
Malignancy	**(Excluding Cutaneous Basal Cell Ca., Cutaneous SCCA, Carcinoma in-situ, and Intraepithelial Neoplasm)**		
Solid Tumor including melanoma	☐ Uncontrolled cancer ☐ Newly diagnosed but not yet treated ☐ Metastatic solid tumor	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated within the last 5 years	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated > 5 years ago
Leukemia and Myeloma	☐ Relapse ☐ Disease out of control	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o leukemia or myeloma with last Rx > 1 yr prior
Lymphoma	☐ Relapse	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o lymphoma w/ last Rx >1 yr prior
Substance Abuse	**(Must be accompanied by social, behavioral, or medical complications)**		
Alcohol	☐ Delirium tremens	☐ Active alcohol abuse with social, behavioral, or medical complications	☐ H/o alcohol abuse but not presently drinking
Illicit Drugs	☐ Acute Withdrawal Syndrome	☐ Active substance abuse with social, behavioral, or medical complications	☐ H/o substance abuse but not presently using
Body Weight			
Obesity		☐ Morbid (i.e., BMI ≥ 38)	

OVERALL COMORBIDITY SCORE (Circle one.) **0** None **1** Mild **2** Moderate **3** Severe **9** Unknown

Epinephrine, Norepinephrine, Dobutamine, and Dopexamine Effects on Free Flap Skin Blood Flow

Karen A. Eley, M.R.C.S., M.Sc.
J. Duncan Young, B.M., D.M.
Stephen R. Watt-Smith, F.D.S.R.C.S., M.D.

Oxford, United Kingdom

Background: The optimal sympathomimetic drug to support blood pressure without adverse vasoconstriction of free flap circulation remains unknown. This study examined the effects of four agents (epinephrine, norepinephrine, dobutamine, and dopexamine) on free flaps following resection of head and neck cancer.

Methods: Twenty-four patients (25 data sets) were recruited into the study. Each patient received an infusion of the four drugs in a random order, with an intervening washout period between drugs, at four infusion rates. Continuous free flap skin blood flow monitoring was performed using laser Doppler velocimetry, with a second sensor on normal skin acting as a control. Global cardiovascular variables were monitored using the LiDCO Rapid Pulse Contour Analysis System (LiDCO Ltd., Cambridge, United Kingdom).

Results: Dose-dependent, increased free flap skin blood flow was observed with norepinephrine and dobutamine. Both dopexamine and epinephrine infusions decreased blood flow. Flap skin blood conductance decreased (vasoconstriction) with norepinephrine, but markedly less than in control tissue, so overall the flap skin blood flow increased with increasing arterial blood pressure. Dobutamine increased flap skin conductance, without significantly increasing blood pressure, and modestly increased flap blood flow.

Conclusions: Both dobutamine and norepinephrine had beneficial effects on flap skin blood flow. The maximal improvement in flow occurred with norepinephrine, making it the optimal pressor to use in patients with hypotension after free flap surgery. (*Plast. Reconstr. Surg.* 130: 564, 2012.)

Free flap reconstruction following ablative surgery for intraoral and perioral malignancy has become routine practice. Patients with these malignancies are frequently of advanced age and have chronically abused tobacco and alcohol, with resulting comorbidities.[1–3] Many patients require blood pressure support both intraoperatively and during the early postoperative recovery period to counteract the hypotensive effects of sedation or anesthesia compounded by comorbidities and concurrent medication. Although the sympathomimetic pressor agents used may increase systemic blood pressure and hence the driving pressure that perfuses the flap, the associated vasoconstriction (assuming denervated flaps maintain such control) may paradoxically reduce flap perfusion, resulting in flap ischemia. As a result, many surgeons remain wary of using such agents.[4] The best agent to maintain blood pressure without adverse effect on flap blood flow remains unclear. This study investigated the effects on flap skin perfusion of four common sym-

From the Nuffield Department of Surgical Sciences and Nuffield Division of Anesthesia, University of Oxford.
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pathomimetic agents routinely used in intensive care practice.

PATIENTS AND METHODS

After ethical approval from the Oxfordshire Research Ethics Committee, 24 patients (16 men and eight women) were recruited into the study, and written consent was obtained. One patient re-presented during the study period with a second primary tumor and was recruited into the study on both occasions, resulting in 25 sets of results. The inclusion criteria were patients undergoing free flap surgery for head and neck cancer resection with a planned postoperative intensive care unit admission for overnight sedation and ventilation (standard practice at our institution). The only exclusion criteria were pregnancy or a body weight above 100 kg. All patients had a central venous line and arterial line sited at the time of anesthesia as part of routine clinical care. Intraoperatively and postoperatively in the intensive care unit, fluid management was optimized with the aid of the LiDCO Rapid system (LiDCO Ltd., Cambridge, United Kingdom), which uses a pulse contour analysis algorithm (PulseCO) to estimate stroke volume.[5] Stroke volume variation below 10 percent was taken to indicate optimal fluid loading throughout the study. At the end of the surgical procedure, two Transonic laser Doppler red blood cell velocimetry probes (Transonic Systems Inc., Ithaca, N.Y.) were attached to the skin—one central on the free flap skin paddle and one acting as a control. To standardize the control site, and to minimize impact upon vascular access, the skin over the deltoid muscle was used in all cases. The Transonic device calculates skin blood flow as the product of the number of red cells moving in the illuminated field and their mean velocity to provide a measure of red cell flux (blood flow). This is expressed in tissue perfusion units, a unitless measure, as it is not possible to calibrate the probes. Flap skin blood flow was logged from the Transonic device using AcqKnowledge version 3.9.1.6 software (Biopac Systems Inc., Goleta, Calif.) on a personal computer at 40 samples per second.

Red cell transfusion to maintain a hemoglobin concentration above 8.0 g/dl was completed before the study commenced. Once the patients were stabilized in the intensive care unit, and if the mean arterial pressure was below 80 mmHg, the patients received four pressor drugs (epinephrine, norepinephrine, dobutamine, and dopexamine) infused at four increasing doses (Table 1). The order of drug administration was randomly predetermined and concealed in an opaque envelope until commencement of the trial. The research and medical teams were unblinded to the infusion drug and rate.

Each drug was administered for 5 minutes at each rate. The infusion was stopped if the mean arterial pressure increased by more than 30 mmHg or there was an adverse effect. At the end of each infusion, 5 ml of blood was aspirated and discarded from the central line and the line flushed with 10 ml of normal (0.9%) saline. A 20-minute period elapsed before commencing the next drug in the sequence to permit adequate time for physiological variables to return to baseline. Throughout the periods of baseline recording and drug infusions, sedation was maintained at a steady rate, and only maintenance fluids were administered.

At the end of the trial, if the patient required continued pressor support, the drug producing the best increase in flap skin blood flow from the trial data was selected. The final 2 minutes of the 5-minute recording period of each drug rate was used for subsequent analysis. The time period was identified on the AcqKnowledge system and the data were transferred to a Microsoft Excel (Redmond, Wash.) spreadsheet. The recording (in tissue perfusion units) over the 2-minute period was averaged to obtain a mean value for the flap and the control skin. This was completed for each of the four drugs for all of the four drug infusion rates and at baseline before commencing any drug infusion. The fractional change from the baseline was calculated for each of the infusion rates. Corresponding data from LiDCO Rapid were entered onto the Microsoft Excel spreadsheet and corresponding flap conduc-

Table 1. Drug Infusion Rates

Drug	Concentration (μg/ml)	First Infusion Rate (μg/kg/min)	Second Infusion Rate (μg/kg/min)	Third Infusion Rate (μg/kg/min)	Final Infusion Rate (μg/kg/min)
Epinephrine	20	0.05	0.1	0.15	0.2
Norepinephrine	20	0.05	0.1	0.15	0.2
Dobutamine	500	2	4	6	8
Dopexamine	1000	1.25	2.5	3.75	5

tance $\left(\frac{\text{Tissue Perfusion (TPU)}}{\text{Mean Arterial Pressure (mmHg)}}\right)$ was calculated. This result was also converted to a fractional change from baseline.

RESULTS

Of the 24 patients recruited into the study, the majority had reconstruction completed with a radial forearm free flap ($n = 17$) (Table 2). All patients were American Society of Anesthesiologists grade II to IV, with a mean age of 60 years (range, 43 to 73 years). Patient demographics are shown in Table 2.

The mean values for each of the cardiovascular variables at baseline and for each infusion are shown in Table 3. All of the drugs except norepinephrine resulted in an increased heart rate. Norepinephrine and epinephrine caused an increase in mean arterial pressure, whereas dobutamine and dopexamine caused a modest decrease. All drugs increased cardiac output. Figure 1 shows a mean (SE) fractional change in skin perfusion from baseline for the control and flap. For epinephrine and dopexamine, tissue perfusion (flap flow) decreased, whereas that at the control site decreased and increased, respectively. For norepinephrine and dobutamine, flap flow increased at lower infusion rates, whereas the control site decreased and increased, respectively. The largest increase in flap skin blood flow occurred with 0.1 to 0.15 μg/kg/minute of norepinephrine.

To examine the vasodilator or vasoconstriction effects of the drugs independent of the mean arterial pressure, skin blood flow conductance was calculated (Fig. 2), with an increase signifying vasodilatation. Only dopexamine caused an increase in conductance for both flap and control with increasing infusion rates. Epinephrine and norepinephrine were both vasoconstrictors (reduced conductance), though norepinephrine had less effect on the flap compared with control tissue.

For the one patient recruited twice into the study, the findings on both occasions yielded similar results for flow and conductance, with all drugs except epinephrine. With epinephrine, it was noted that the first study for this patient (patient 9) resulted in increased flow for both flap and control, which was not consistent with the repeat study (patient 13) or the overall results for all patients.

DISCUSSION

It has been demonstrated that whereas norepinephrine results in decreased conductance (vasoconstriction) in both the flap and the control

Table 2. Patient Demographics

Patient	Age (yr)	Sex	BMI	Resection	Free Flap Donor Site
1	67	M	25.3	Left hemiglossectomy	Radial
2	62	F	24.9	Left hemiglossectomy	Radial
3	62	F	23.4	Total glossectomy	Latissimus dorsi
4	65	M	24.2	Hemimandibulectomy	Fibula
5	58	M	32.8	Hemimandibulectomy	Fibula
6	61	F	18.0	Resection floor of mouth/mandible	ALT + fibula
7	53	F	22.4	Left hemiglossectomy	Radial
8	43	M	24.3	Maxillectomy and orbital enucleation	Latissimus dorsi
9*	68	M	25.0	Resection right buccal sulcus	Radial
10	54	F	24.7	Left hemimandibulectomy	Radial + fibula
11	63	M	19.4	Resection right tongue/mandible	ALT + fibula
12	48	M	24.3	Left partial glossectomy	Radial
13*	69	M	24.7	Right hemimandibulectomy	ALT + fibula
14	60	F	24.7	Right hemiglossectomy	ALT
15	47	M	26.3	Resection left buccal mucosa	Radial
16	64	M	17.5	Resection floor of mouth	Radial
17	57	F	25.4	Right hemiglossectomy	Radial
18	64	M	26.0	Resection adhesions tongue	Radial
19	54	M	27.1	Right hemiglossectomy	Radial
20	69	M	23.9	Right hemiglossectomy	Radial
21	67	M	30.4	Resection right tonsillar fossa	Radial
22	56	M	17.8	Resection right posterior tongue	Radial
23	66	M	24.7	Resection left tonsillar fossa	Radial
24	57	M	24.7	Resection ventral tongue	Radial
25	73	F	24.4	Right hemiglossectomy and partial maxillectomy	Radial

BMI, body mass index; M, male; F, female; ALT, anterolateral thigh flap.
*Patients 9 and 13 are the same patient, enrolled in the study on two separate occasions, having presented with a second primary tumor during the study period.

Table 3. Mean Cardiovascular Variables at Each Infusion Rate

	Concentration (μg/kg/min)	Mean (SD)				
		HR (Beats/min)	Systolic (MmHg)	MAP (MmHg)	CO (Liter/min)	CI (Liter/min/m²)
Baseline	—	77 (13)	113/57 (17/7)	76	5.2 (1.3)	2.9 (0.5)
Epinephrine	0.05	86 (15)	116/53 (22/8)	73	6.7 (2.1)	3.7 (1.1)
	0.1	92 (16)	129/55 (24/7)	77	8.2 (2.7)	4.5 (1.4)
	0.15	99 (17)	139/57 (26/7)	80	9.5 (3.0)	5.2 (1.5)
	0.2	106 (17)	147/61 (24/8)	85	10.5 (3.5)	5.9 (1.8)
Norepinephrine	0.05	76 (15)	136/66 (30/10)	89	5.7 (1.4)	3.1 (0.6)
	0.1	76 (14)	14871 (26/9)	98	6.2 (1.6)	3.4 (0.8)
	0.15	76 (16)	161/76 (21/9)	106	6.8 (1.6)	3.6 (0.8)
	0.2	84 (13)	168/72 (13/7)	103	6.9 (2.0)	3.9 (0.7)
Dobutamine	2	84 (16)	126/58 (25/9)	80	6.5 (2.0)	3.6 (0.9)
	4	91 (18)	131/58 (21/11)	80	7.3 (2.5)	4.0 (1.1)
	6	99 (20)	132/56 (22/8)	78	8.2 (2.9)	4.5 (1.4)
	8	107 (18)	134/55 (23/7)	76	9.8 (3.2)	5.3 (1.4)
Dopexamine	1.25	88 (15)	107/52 (20/9)	68	6.6 (2.0)	3.6 (0.9)
	2.5	95 (15)	105/48 (22/8)	66	7.6 (2.9)	4.2 (1.4)
	3.75	102 (16)	104/46 (22/8)	64	8.4 (2.9)	4.6 (1.3)
	5	109 (17)	103/45 (23/8)	62	9.2 (3.2)	5.0 (1.5)

HR, heart rate; MAP, mean arterial pressure; CO, cardiac output; CI, cardiac index.

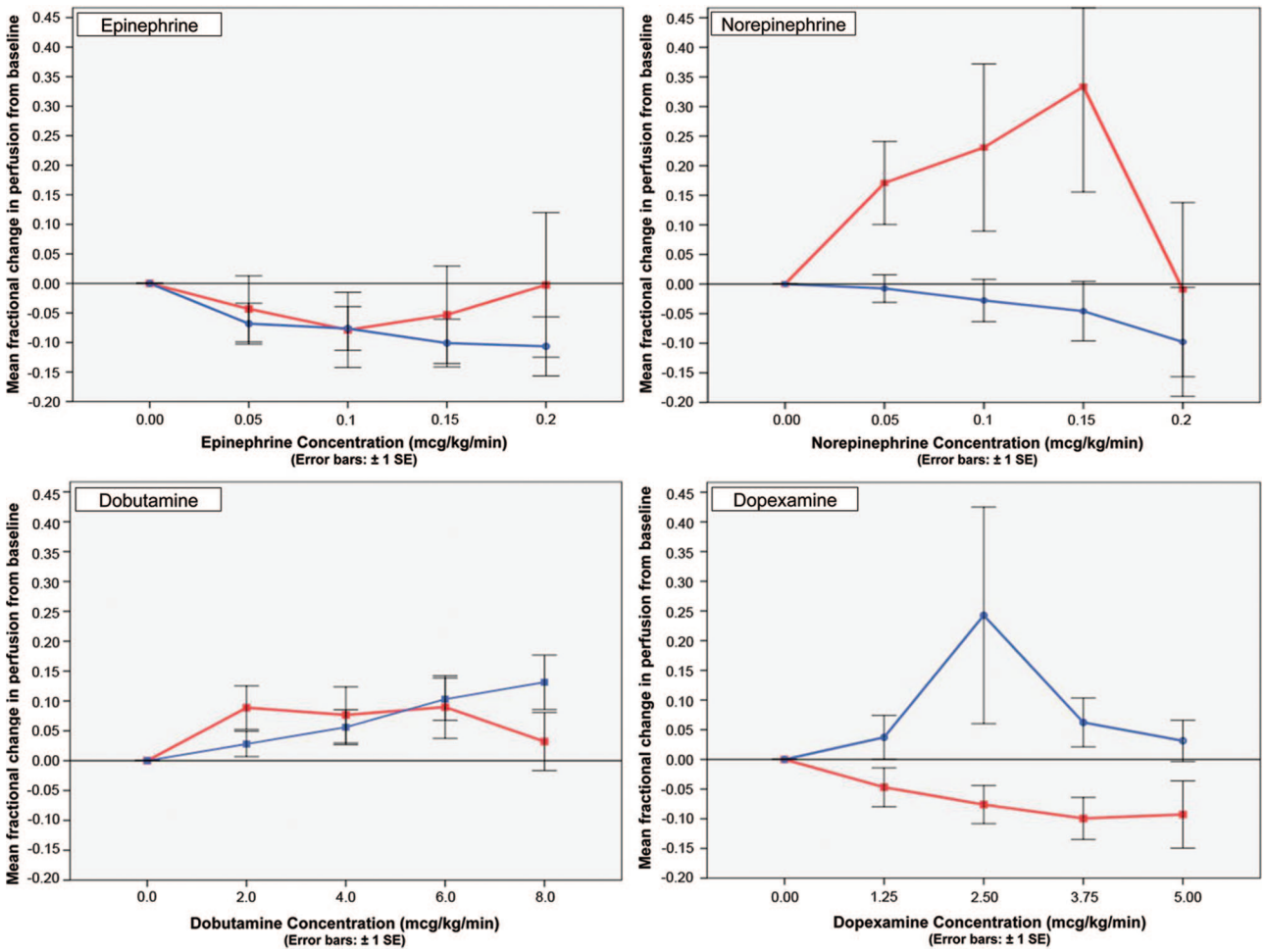

Fig. 1. Mean fractional change in perfusion from baseline for each drug infusion for flap and control. *Red* indicates free flap, and *blue* indicates control.

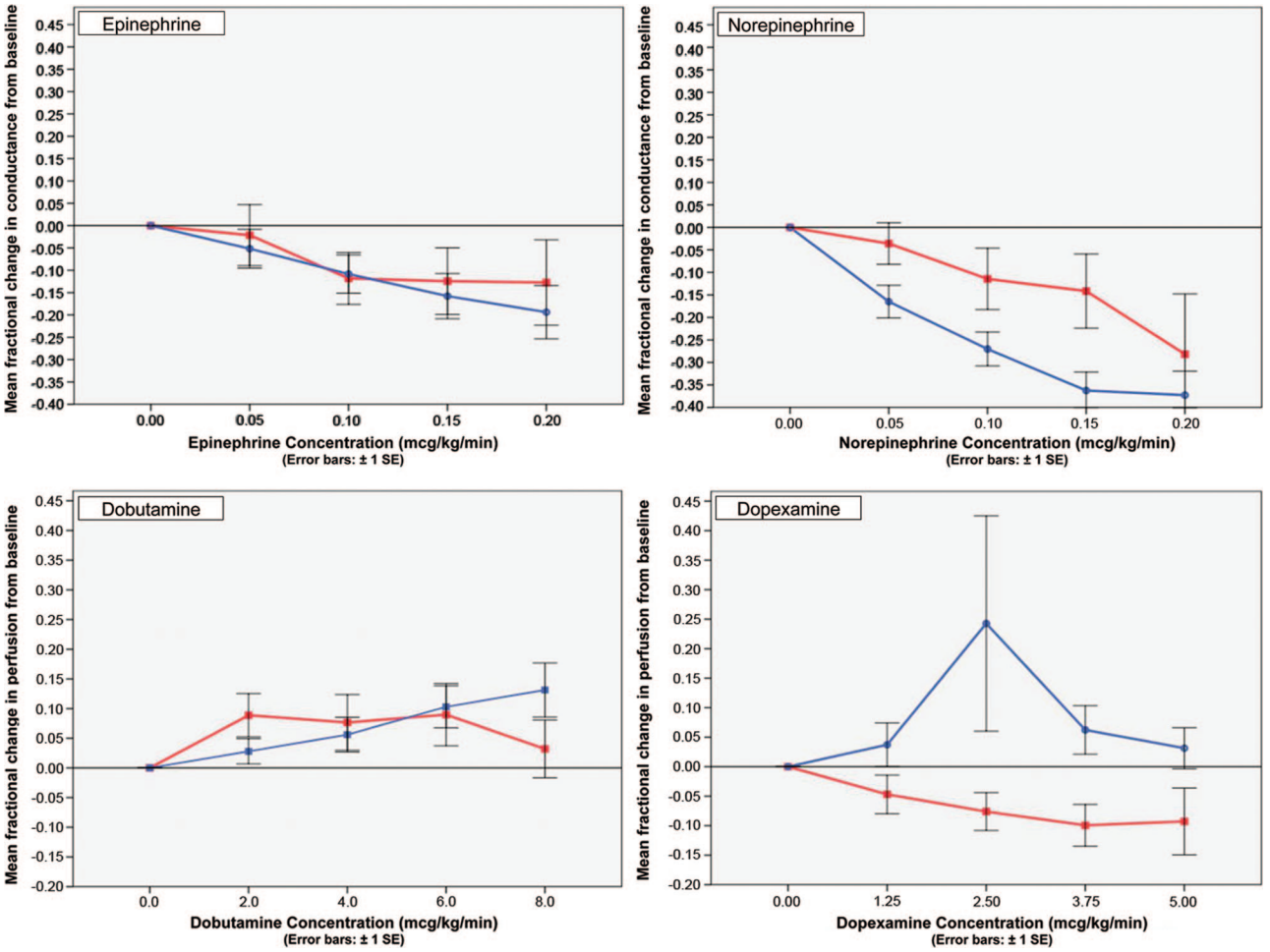

Fig. 2. Mean fractional change in conductance from baseline for each infusion. *Red* indicates free flap, and *blue* indicates control.

tissue, the effect is more marked in the control tissues. The vasoconstrictor effect on the flap is more than overcome by the increase in blood pressure, so a significant increase in flap perfusion arises with the increased blood pressure up to a dose of 0.15 μg/kg/minute. The paradoxical results at 0.2 μg/kg/minute may be unreliable, as only five patients received this dose, the remaining patients having reached the maximum blood pressure increase permitted in the study (30-mmHg mean arterial pressure rise) at lower doses. Dobutamine also reliably increased flap and control-site blood flow by about 10 percent (compared with the 30 percent maximum seen with norepinephrine) without causing a change in conductance and with little effect on blood pressure. It, however, frequently resulted in a tachycardia, requiring premature termination of the drug infusion in a number of cases, and increased the cardiac output by 50 percent on average. These effects are all in keeping with the known inodilator effects of dobutamine. With this patient group at high risk of cardiac ischemia, these side effects might cause concern. Epinephrine caused a decrease in both flap flow and conductance, despite an increase in both blood pressure and cardiac output, and there was little difference between flap and control skin. Dopexamine preferentially vasoconstricted the flap compared with the control skin, making it entirely unsuitable for maintaining flap perfusion.

The recruitment of the same patient on two occasions has provided a unique opportunity to examine the consistency of findings on two separate occasions with different free flaps. The results were largely consistent on both occasions and with the overall results for all patients in all drugs except epinephrine. This resulted in both increased flow and conductance for both flap and control on the first occasion but a decreased flow and conductance (consistent with the overall results) in the second study. This may simply reflect an

erroneous result but raises the possibility that there is some variability in free flap α receptor survival.

The findings should be interpreted with regard to the limitations of the study. The laser Doppler probes were sited at the center of the flap in all cases, based on the assumption that any changes in blood flow through the flap would be uniform. Only the skin paddle of the flap was examined, and there was variability in the free flap type. In addition, despite best efforts to achieve optimal fluid balance and maintain all variables constant during the study, this is difficult to fully achieve during the immediate postoperative period.

Doppler laser blood flow probes are both safe and convenient to use. Because the Doppler probes are sutured directly to the flap, they can simply be removed without further requirement for surgery, unlike probes attached around the flap vessels. The simplicity of the technique and the good correlation with other measures of flap blood flow have made laser Doppler monitoring a popular research and clinical monitoring technique. The laser Doppler device interrogates a hemisphere of about 1-mm^3 volume under the probe and provides an output that is the product of the red cell velocity (from the Doppler shift in reflected light) and the number of red cells in motion (from the amount of reflected, Doppler-shifted light). The probe cannot be calibrated against a known blood flow, so the unitless "tissue perfusion units" are used to express blood flow. This means the use of a control tissue or stable comparator baseline is required. Laser Doppler monitoring of skin blood flow in free flap tissue transfer has been used successfully to assess changes in intraoral flap perfusion over time.[6–8] These studies, however, used blood flow measured before flap elevation as a baseline rather than using a control area of normally innervated skin and, as a result, could not determine whether the responses were unique to free flaps or a global response to surgery and the recovery period.

The most striking result in this study was the decreased sensitivity of the flap to the vasoconstrictor effects of norepinephrine when compared with control tissue. It was this that caused the increase in blood flow to the flap as the blood pressure increased with increasing norepinephrine doses, whereas in control tissue, vasoconstriction dominated and the blood flow decreased as the norepinephrine dose increased. Chronic denervation of tissues is generally believed to lead to a heightened vasoconstrictor response to α adrenergic agents, such as norepinephrine, in the denervated tissue, which may begin as early as 2 days.[9–13] In this acute situation, however, the ability of systemically administered norepinephrine to cause vasoconstriction in the denervated free flap was markedly attenuated when compared with the control tissue. A similar effect has been observed when innervated and denervated pedicle flaps were raised in a rat model.[14] In these studies, the denervated flaps had an increase in blood flow after norepinephrine or phenylephrine (α_1 agonist) administration, with a simultaneous reduction in flow in the innervated flap. The effect was blocked by prazosin, a selective blocker of α_1 receptors on vascular smooth muscle, suggesting the effect was due to a decreased sensitivity to α_1 agonists. In this study, epinephrine was also studied, a drug that has α_1 agonist activity at high doses but that showed parallel changes in flap and control tissue perfusion in this study, suggesting the β effects of epinephrine were predominating at the doses used.

Why this reduction in α_1 adrenergic receptor sensitivity occurs in acutely denervated vessels is unknown. It is possible that norepinephrine-induced vasoconstriction of fully vasodilated denervated vessels results in insufficient caliber reduction to significantly alter blood flow, though this is unlikely given the exquisite sensitivity of flow to vessel diameter. Reduced pulsatility in denervated, dilated vessels may reduce the secretion of endothelium-derived vasoconstrictive factors, or there may be a direct effect at the α_1 adrenergic receptor level. Examining the frequency components of the blood flow signal may at least help distinguish local from humeral effects.[15]

Dopexamine is a synthetic analogue of dopamine that causes systemic vasodilatation through the stimulation of β_2 adrenoceptors and peripheral dopamine receptors, and weak inotropic properties through the stimulation of β1 adrenoceptors. In this study, dopexamine increased control-site conductance more than flap conductance and, coupled with a modest reduction in blood pressure caused by β_2 adrenoceptor stimulation systemically, caused a reduction in flap flow. As dopaminergic stimulation causes local release of norepinephrine, this differential effect on control tissue and flap conductance might be mediated through the same mechanism as norepinephrine.

Dobutamine is predominantly a β_1 adrenergic agonist, with weak β_2 and α_1 activity and is therefore primarily an inotropic and chronotropic drug. It had little effect on either flap conductance

or flow and was of limited practical value due to the β_1-induced tachycardia it caused.

This study used the skin blood flow as a surrogate measure of total flap blood flow. There is only one study of total blood flow to free flaps in human subjects. Scholz et al.[4] investigated the effect of dobutamine on total blood flow of free tissue transfer flaps during head and neck surgery. After completion of the anastomoses, the flow in the anastomosed donor artery was measured with an ultrasonic flow meter. Dobutamine at rates up to 6 μg/kg/minute was infused. They found a doubling in flow from baseline to 6 μg/kg/minute accompanied by increased cardiac output, concluding that dobutamine may be useful in improving free flap perfusion. The authors noted that there was no significant increase in mean arterial pressure with the three rates trialed. Similar findings, but of much less magnitude, were obtained in this study.

Acceptance of a small vasoconstrictor effect in return for a significant improvement in flap perfusion will require further validation before concerns about the adverse effects of α adrenergic agents on free tissue transfer are fully addressed, and the pure α_1 adrenergic agents, phenylephrine and metaraminol, require further investigation. This study was limited to the perioperative period, and the results may not be transferable to treatment in the longer term, when a heightened sensitivity of denervated vessels to α adrenergic agents has been reported.

CONCLUSION

Norepinephrine most consistently elevated the mean arterial pressure and caused by far the largest increase in flap skin blood flow, making it the pressor agent of choice (of those studied), following free tissue transfer.

Karen A. Eley, M.B.Ch.B., M.Sc.
Nuffield Department of Surgical Sciences
University of Oxford
John Radcliffe Hospital
Headley Way
Oxford OX3 9DU, United Kingdom
karen.a.eley@gmail.com

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REFERENCES

1. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res.* 1988;48:3282–3287.
2. Marshall JR, Graham S, Haughey BP, et al. Smoking, alcohol, dentition and diet in the epidemiology of oral cancer. *Oral Oncol Eur J Cancer* 1992;28B:9–15.
3. Rothman K, Keller A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *J Chron Dis.* 1972;25:711–716.
4. Scholz A, Pugh S, Fardy M, Shafik M, Hall JE. The effect of dobutamine on blood flow of free tissue transfer flaps during head and neck reconstructive surgery. *Anaesthesia* 2009;64: 1089–1093.
5. Jonas M, Fennell J, Brudney CS. Haemodynamic optimisation of the surgical patient revisited. *Anaesthesia Int.* 2008;2: 1–5.
6. Yoshino J, Nara S, Endo M, Kamata N. Intraoral free flap monitoring with a laser Doppler flowmeter. *Microsurgery* 1996;17:337–340.
7. Hölzle F, Loeffelbein DJ, Nolte D, Wolff KD. Free flap monitoring using simultaneous non-invasive laser Doppler flowmetry and tissue spectrophotometry. *J Craniomaxillofac Surg.* 2006;34::25–33.
8. Hölzle F, Rau A, Loeffelbein DJ, Mücke T, Kesting MR, Wolff KD. Results of monitoring fasciocutaneous, myocutaneous, osteocutaneous and perforator flaps: 4-year experience with 166 cases. *Int J Oral Maxillofac Surg.* 2010;39:21–28.
9. Banbury J, Siemionow M, Porvasnik S, Petras S, Zins JE. Muscle flaps' triphasic microcirculatory response to sympathectomy and denervation. *Plast Reconstr Surg.* 1999;104:730–737.
10. Rizzoni D, Perlini S, Mircoli L, Porteri E, Franzelli C, Castellano M, et al. Enhanced vascular reactivity in the sympathectomized rat: Studies in vivo and in small isolated resistance arteries. *J Hypertens.* 2000;18:1041–1049.
11. Godden DRP, Little R, Weston A, Greenstein A, Woodwards RTM. Catecholamine sensitivity in the rat femoral artery after microvascular anastomosis. *Microsurgery* 2000;20:217–220.
12. Bickel A, Axelrod FB, Schmelz M, Marthol H, Hilz MJ. Dermal microdialysis provides evidence for hypersensitivity to noradrenaline in patients with familial dysautonomia. *J Neurol Neurosurg Psychiatry* 2002;73:299–302.
13. Moore GK, Trachy RE, Cummings CW. The effect of alpha-adrenergic stimulation and blockade on perfusion of myocutaneous flaps. *Otolaryngol Head Neck Surg.* 1986;94:489–496.
14. Lecoq JH, Joris JL, Nelissen XP, Lamy ML, Heymans OY. Effect of adrenergic stimulation on cutaneous microcirculation immediately after surgical adventitiectomy in a rat skin flap model. *Microsurgery* 2008;28:480–486.
15. Young JD, Cameron EM. Dynamics of skin blood flow in human sepsis. *Intensive Care Med.* 1995;21:669–674.

POWER SPECTRAL ANALYSIS OF THE EFFECTS OF EPINEPHRINE, NOREPINEPHRINE, DOBUTAMINE AND DOPEXAMINE ON MICROCIRCULATION FOLLOWING FREE TISSUE TRANSFER

KAREN A. ELEY, M.B.C.H.B., M.R.C.S.(ED), M.Sc.,[1*] JOHN DUNCAN YOUNG, B.M., D.M., F.R.C.A.,[2] and STEPHEN R. WATT-SMITH, M.B.B.S., F.D.S.R.C.S., M.D.[1]

Background: The use of pressor drugs after microsurgical free tissue transfer remains controversial because of potential vasoconstrictor effects on the free flap. Noninvasive monitoring of free flaps with laser Doppler flowmetry may provide further information regarding the local regulation of blood flow in the flap tissues during pressor infusions. This study evaluated the effects of four commonly used pressor agents. *Methods:* Twenty four patients (25 data sets) undergoing head and neck cancer resection and free flap reconstruction were recruited. Epinephrine, norepinephrine, dopexamine, and dobutamine were infused in a random order at four infusion rates, after surgery, with free flap and control area (deltoid region) laser Doppler skin blood flow monitoring. Frequency analysis of the Doppler waveform was performed utilizing the time period immediately before the first drug infusion for each patient as baseline. *Results:* At baseline there was less power at the 0.002–0.6 Hz frequency in the flap compared with control tissue consistent with surgical denervation. At maximum epinephrine infusion rates, the control of blood flow moved toward (i.e., proportion of power increased in) the lower frequencies, as smooth muscle mediated (myogenic) control began to dominate blood flow, an effect most marked with norepinephrine. Dobutamine and dopexamine had little effect on control of blood flow. *Conclusions:* Denervation of free flap tissue is demonstrable using spectral analysis of laser Doppler blood flow signals. With norepinephrine the control of blood flow shifts toward low frequency vasomotion where blood flow depends mostly on average blood pressure, making it potentially the most suitable agent following free tissue transfer. © 2013 Wiley Periodicals, Inc. Microsurgery 33:275–281, 2013.

Microsurgical free tissue transfer has become routine practice for reconstruction after the excision of peri-oral malignancies. Patients undergoing surgery for these malignancies frequently require blood pressure support (pressor drug infusions) both intraoperatively and during the early post-operative recovery period to counteract the hypotensive effects of sedation or anaesthesia compounded by co-morbidities and concurrent medication. However, pressors may have vasoconstrictor effects on the transplanted tissues, raising concerns about flap ischaemia, which may contribute to the free flap failure rates of 3% reported by high-volume centres.[1,2] Salvage of a failing flap depends on early detection and intervention with reported success rates between 33 and 83%.[3] Laser Doppler flowmetry provides a measure of microcirculatory blood flow in a small area of tissue illuminated by a laser. This noninvasive method of monitoring blood flow in free flaps is increasingly used in clinical practice to assess changes in intraoral flap perfusion over time.[4–6] As well as providing a convenient method to monitor changes in flap blood flow over time, spectral analysis of the variations in laser Doppler flowmetry signal may provide further information on changes in the regulation of blood flow in the superficial flap tissues and help explain the differing effects of pressor agents on flap blood flow.[7]

The human microcirculation shows rhythmic variations (oscillations) in blood flow produced by central (brain stem) and local (tissue) effects. The most obvious oscillations are caused by the heart rate and respiration.[8] Several studies performed using laser Doppler flowmetry have shown there are an additional three periodic components with varying amplitudes and frequencies, which can be extracted from the Doppler waveform. The five components are centered around 1 Hz (60 cycles per minute), 0.3 Hz (18 cycles per minute), 0.1 Hz (six cycles per minute), 0.04 Hz (2.4 cycles per minute), and 0.01 Hz (six cycles in 10 min) corresponding to heartbeat, respiration, intrinsic myogenic activity of vascular smooth muscle, the neurogenic activity of the vessel wall and the endothelial cell metabolic processes, respectively.[9]

The aim of this study was to determine the effects of epinephrine, norepinephrine, dobutamine, and dopexamine on the local control of blood flow in transplanted tissues using spectral analysis of the laser Doppler flowmetry waveform.

PATIENTS AND METHODS

Following ethical approval from the Oxfordshire Research Ethics Committee, 24 patients (16 male; eight female) undergoing resection of head and neck cancers

[1]Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU
[2]Nuffield Division of Anaesthesia, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU

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*Correspondence to: Miss Karen A Eley, Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU. E-mail: Karen.a.eley@gmail.com
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Table 1. Drug Infusion Rates, Cardiovascular Variables, and Mean Total Power of the Laser Doppler Blood Flow Signal at Both Sites for All Drug Doses

			Mean			Flap	Control
	Infusion rate (mcg/kg/min)	Number of patients receiving dose	Heart rate (beats/min)	Mean arterial blood pressure (mmHg)	Cardiac index (l/min/m^2)	Mean normalized power	Mean normalized power
Baseline	–		77 ± 13	76	2.9 ± 0.5	1.00 ± 0.00	1.00 ± 0.00
Epinephrine							
25%	0.05	25	86 ± 15	73	3.7 ± 1.1	1.23 ± 0.83	1.67 ± 2.93
50%	0.1	25	92 ± 16	77	4.5 ± 1.4	1.57 ± 1.39	1.34 ± 0.97
75%	0.15	24	99 ± 17	80	5.2 ± 1.5	1.87 ± 1.89	1.34 ± 0.96
100%	0.2	21	106 ± 17	85	5.9 ± 1.8	1.76 ± 1.83	1.34 ± 0.75
Norepinephrine							
25%	0.05	25	76 ± 15	89	3.1 ± 0.6	2.74 ± 3.69	1.26 ± 0.84
50%	0.1	19	76 ± 14	98	3.4 ± 0.8	3.57 ± 7.57	1.37 ± 0.88
75%	0.15	13	76 ± 16	106	3.6 ± 0.8	4.42 ± 6.59	1.34 ± 0.82
100%	0.2	5	84 ± 13	103	3.9 ± 0.7	1.90 ± 1.76	0.79 ± 0.52
Dobutamine							
25%	2	25	84 ± 16	80	3.6 ± 0.9	1.55 ± 1.10	1.24 ± 0.53
50%	4	23	91 ± 18	80	4.0 ± 1.1	1.50 ± 1.08	1.75 ± 1.93
75%	6	23	99 ± 20	78	4.5 ± 1.4	1.48 ± 1.19	1.48 ± 0.99
100%	8	22	107 ± 18	76	5.3 ± 1.4	1.28 ± 0.77	1.71 ± 1.34
Dopexamine:							
25%	1.25	25	88 ± 15	68	3.6 ± 0.9	1.02 ± 0.57	1.19 ± 0.77
50%	2.5	25	95 ± 15	66	4.2 ± 1.4	1.48 ± 1.93	1.28 ± 0.94
75%	3.75	25	102 ± 16	64	4.6 ± 1.3	1.23 ± 1.37	1.23 ± 0.60
100%	5	25	109 ± 17	62	5.0 ± 1.5	1.83 ± 2.44	1.13 ± 0.74

The power has been normalized to the baseline (pre-drug) reading. Values are shown as mean ± SD.

with free flap reconstruction were recruited to the study and written informed consent obtained. One patient represented during the study period with a second primary tumor, and was recruited to the study on two occasions, resulting in 25 sets of results. Free flap reconstruction was with a free radial forearm flap ($n = 16$), latissimus dorsi ($n = 2$), anterolateral thigh (ALT) flap ($n = 1$), or free fibula osteocutaneous flap ($n = 2$). In the remaining four cases, reconstruction was with two simulatenous free flaps (ALT and fibula $n = 3$, radial forearm and fibula $n = 1$). At the end of the surgical procedure, a Transonic laser Doppler probe (Transonic type R; Transonic Systems, Ithaca, NY) was sutured to the centre of the free flap, utilizing the soft tissue free flap in cases of more than one flap, and the skin paddle on fibula free flaps. A second Doppler probe was sutured to the skin in the deltoid region to provide a control site. All patients were admitted to the intensive care unit (ICU) and were artificially ventilated overnight as part of the local care pathway. Once the patients had been stabilized on the ICU they received four drugs (epinephrine, norepinephrine, dobutamine, and dopeximine) in increasing concentrations for a period of 5 min at each rate (Table 1). The order of drug administration was random and contained in a sealed envelope, which was opened shortly prior to commencing the trial. The infusions were administered via a syringe pump using weight-based rates. The maximum safe parameters for increase in mean arterial pressure (MAP) and absolute heart rate were set at 30 mmHg and 150 bpm, respectively; with the infusions stopped if these limits were reached. A 20 min wash-out period was allowed before commencing the next drug in the sequence. Continuous Doppler monitoring was performed using a Doppler flow meter (model Transonic BLF—21D, Transonic Systems, Ithaca, NY) with the waveform recorded using analogue-to-digital conversion and AcqKnowledge software (BIOPAC Systems, Goleta, CA) at a sampling frequency of 40 samples per second.

The final 2 min of each drug infusion rate and the 2 min period prior to the commencement of the first drug (baseline) were used for subsequent analysis. Each time period was identified on the AcqKnowledge software and the data exported to Microsoft Excel for further analysis. Spectral analysis of the Doppler data was performed using Matlab version 7.11.0.584 (R2010b) (Mathworks, Natick, MA). This was completed using the last 4,096 samples (102.4 second of recording). The total power (the amount of variation in blood flow) in the signal was calculated as the variance. A standard signal processing approach was used to determine the frequency components of the blood flow signal. Three 2,048 sample (51.2 second) segments with 50% overlap were derived by dividing up the total sample of 4,096 samples. Each underwent linear trend removal (to remove baseline drift) and was then windowed with a Hamming window function (required to remove artefacts generated at the start and end of the

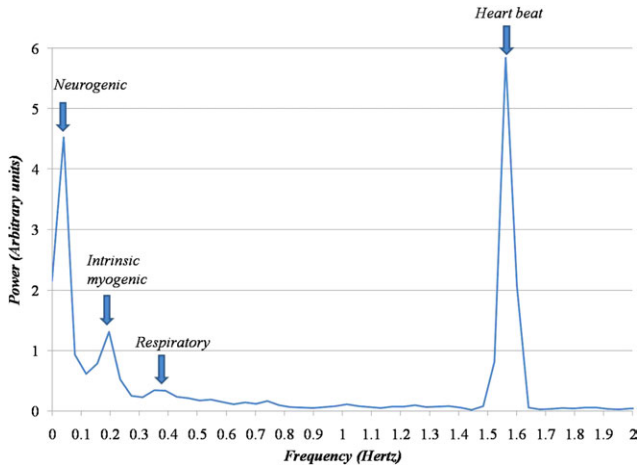

Figure 1. Power spectra at baseline demonstrating the characteristic peaks extracted from the Doppler waveform, corresponding to heart beat, respiration, intrinsic myogenic, and neurogenic control. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

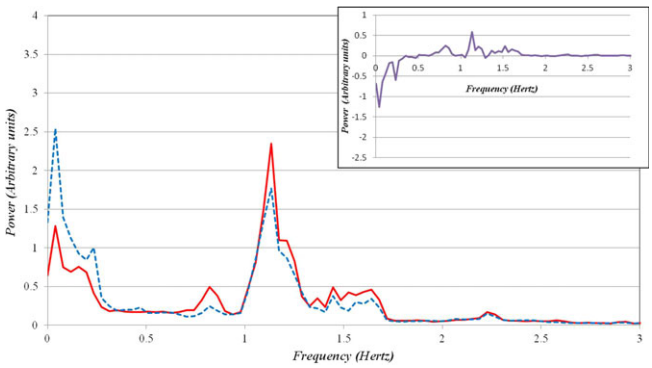

Figure 2. Power spectra for flap (red) and control (blue) tissues for baseline. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

recordings) before conversion to zero mean unit variance format, which allows comparison between patients irrespective of the total blood flow. Power spectra (the plot of blood flow oscillations at each frequency) were computed using a standard fast Fourier transform algorithm, and the resulting three spectra averaged to give the final result. Only the frequencies below 3 Hz were used for graphing. This analysis was performed for each of the four drugs and four drug concentrations, and prior to commencement of any drug infusion, for all 25 set of results and both recording sites. For each patient the power in the baseline (pre-drug) period was used to normalize the subsequent results for both control and flap sites. The results from all patients were averaged. In addition for each patient and each dose, the control site spectrum was subtracted from the flap site spectrum to highlight any differences between the sites. Only five patients received the maximum norepinephrine infusion rate (0.15 mcg/kg/min) as the others all reached the upper safety limit for blood pressure at a lower dose.

Statistical analysis for differences in variance (variability) between control site and flap was completed using *t*-tests, with Šidák correction for multiple comparisons, on Statistical Package for the Social Sciences. The probability of differences between regions of the normalized power spectra arising by chance could not be tested statistically and so differences reported are based on simple interpretation of the graphs.

RESULTS

The cardiovascular variables are shown in Table 1. For each dose the average normalized power, standard deviation of the normalized power, and the changes in the power of the blood flow signal (the variance of the signal) are shown in Table 1.

There was no statistically significant difference between the variability in the control site and flap at any drug dose ("*t*" tests, Šidák correction for multiple comparisons, all P values >0.05), despite the power spectra for the flap flow appearing to exhibit far more variability with norepinephrine.

Figure 1 shows the power spectrum from the control site of one of the patients in this study. The cardiac, respiratory, and myogenic components are seen as discrete peaks, the neurogenic and local endothelial-based control cannot be separately distinguished in this example.

The control (pre-drug) averaged power spectra is shown in Figure 2, and at maximum dose (epinephrine, dobutamine, and dopexamine) and 75% maximum dose norepinephrine, (as only five patients reached maximum dose) in Figure 3. Intervening doses showed similar changes. Nearly all the oscillation in blood flow was in the range of 0–3 Hz with almost none in higher frequency bands.

Figure 2 shows the control (pre-drug) spectra. The power in the region below 0.1 Hz was reduced. As the spectra were normalized there was a corresponding increase in the power in the 0.8–1.7 Hz range representing the heart rate. The differing heart rates of the subjects broadened this peak.

At the maximum epinephrine infusion rate the heart rate increased and the spread of heart rates also increased, so the heart rate dependent peak moved to higher frequencies and broadened. The proportion of the total power in the lower frequencies increased. At the maximum dobutamine infusion rate there was little effect on the distribution of the control of blood flow, though as with all drugs studied the cardiac related peak increased in frequency and broadened. Dopexamine demonstrated the same findings as dobutamine. However,

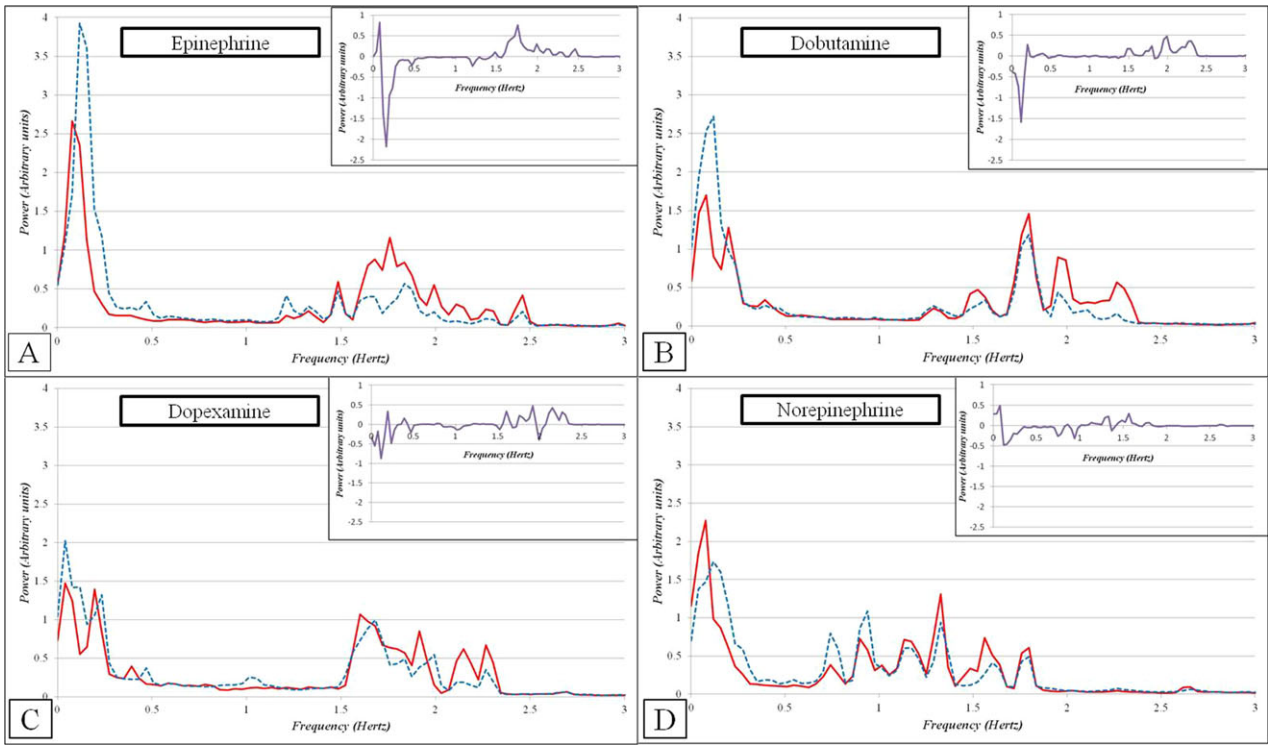

*Figure 3. Power spectra for flap (red) and control (blue) tissues for (**A**) epinephrine 0.2 mcg/kg/min, (**B**) dobutamine 8 mcg/kg/min, (**C**) dopexamine 5 mcg/kg/min, and (**D**), norephineprine 0.15 mcg/kg/min, and inset, the differential results (flap-control). Inset panels in each graph show the averaged differences (flap spectrum-control spectrum) to assist interpretation. Note that the spectra were all normalized (i.e., set to the same area under the curve) by the zero mean unity variance processing, so total power cannot be compared with these graphs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]*

with norepinephrine at 75% of maximum dose, low frequency activity below 0.1 Hz was higher in the flap compared to control, and the difference between flap and control in the 0.1–0.4 Hz band was less marked than with other drugs.

No adverse events or flap failures were noted in any of the patients as a result of the pressor infusions.

DISCUSSION

The power spectra confirmed a number of anticipated findings following free tissue transfer. As the flaps were denervated the power in the region below 0.1 Hz which contains sympathetic activity, and in the respiratory frequencies centered on 0.2–0.3 Hz (12–18 breaths/min) which are partially neurally mediated, were both reduced as expected.

As the spectra were normalized (the area under the curve was fixed) there was a corresponding increase in the power in the 0.8–1.7 Hz range representing the heart rate. As the results for the cardiovascular variables demonstrated, there was a dose dependent increase in heart rate with epinephrine, dopexamine, and dobutamine but an unchanged heart rate with norepinephrine until the maximum dose were seen. The differing heart rates of the subjects broadened the associate peak of the power spectra. At the maximum epinephrine infusion rate the heart rate increased and the spread of heart rates also increased, so the heart rate dependent peak moved to higher frequencies and broadened. The proportion of the total power in the lower frequencies increased, as local control of blood flow rather than global hemodynamics dominated blood flow control, though in general as with the control spectra the effects of denervation were maintained.

All drugs increased the power (overall variability) of the blood flow signal at both sites, and this was more marked for epinephrine and especially norepinephrine. As noted above, as a result of the processing techniques any differences between flap and control spectra in one frequency band must have equivalent changes in the opposite direction at other frequencies. The difference spectra demonstrated this best, the area defined by the 0 baseline and the spectral difference above the baseline is matched by an equivalent area between the 0 baseline and the spectral difference below the baseline. The technique used for sampling and processing meant the frequency resolution was limited to 0.05 Hz and

thus the 0.04 Hz, and 0.01 Hz peaks corresponding to the neurogenic activity of the vessel wall and the endothelial cell metabolic processes could not be resolved independently.

At the maximum dobutamine infusion rate, there was little effect on the distribution of the control of blood flow, though as with all drugs studied the cardiac related peak increased in frequency and broadened. Dopexamine demonstrated the same findings as dobutamine. However, with norepinephrine at 75% of maximum dose, low frequency activity below 0.1 Hz was higher in the flap compared to control, and the difference between flap and control in the 0.1–0.4 Hz band was less marked than with other drugs. This suggests that the norepinephrine infusion increases the local myogenic control of blood flow in the free flap to a greater extent than the other drugs studied.

With increasing doses of epinephrine and norepinephrine there was increased dependence on local control, as evidenced by the increasing proportion of power in the 0–0.1 Hz frequency band. This occurred in both control and flap tissue, though with norepinephrine the effect was more marked in the flap tissue. This would imply that there is survival of alpha receptor activity in the transplanted tissues, and possibly that these receptors are more sensitive to exogenous alpha agonists after denervation.

The laser Doppler flow meter measures red cell flux in the skin by illuminating an approximately 1 mm^3 hemisphere of skin with monochromatic (laser) light, and determining the amount of light reflected from moving erythrocytes and the Doppler shift (change in wavelength) of the reflected light.[10] The product of the two represents red cell flux, a measure of tissue blood flow. Laser Doppler flowmetry records the velocities and concentrations of erythrocytes in the arterioles located in the dermis and in the subepidermal papillary loops. The absolute value recorded depends on the adjacency of one of these vessels to the illuminated area, and is therefore dependent on probe position so it is not possible to convert the Laser Doppler signal to "conventional" bulk blood flow units of blood flow per unit mass of tissue per minute. Instead the laser Doppler device gives results as "tissue perfusion units" derived from the voltages generated by the photodetector in the instrument. For these reasons laser Doppler flowmetry results are usually expressed relative to a baseline state.[11] Spectral analysis of laser Doppler flowmeter signal has been shown to be useful and accurate.[12] It has been shown that characteristic frequency peaks exist in signals of cardiovascular origin.[13] The spectrum is conventionally divided into five frequency intervals centered on 1, 0.3, 0.1, 0.04, and 0.01 Hz.[9,13] Of interest are those occurring at a slower rate than the oscillations caused by respiratory rate at about 0.3 Hz. Studies have demonstrated that these slow oscillations are influenced by the sympathetic nervous system and microvascular wall activity.[8] Blood flow is controlled by the combined effect of all of these periodic oscillations of both local and central origin, which are transduced to vascular smooth muscle cells, resulting in a specific vascular tone.[9]

This study has a number of methodological limitations. The sampling period used limited the resolution of the spectral analysis to 0.05 Hz, thus, the two lower frequency bands could not be resolved independently. All the spectra were normalized to allow an averaged spectrum containing all patient data to be constructed with each patient contributing equally, but this normalization causes increases in power in one frequency band to always be associated with a change in the opposite direction in other frequency bands, making interpretation more difficult. The probability of differences between regions of the normalized power spectra arising by chance could not be tested statistically. Changes in the power in the cardiac cycle frequency were made more difficult to interpret due to the increase in heart rate and the widening of the range of heart rates caused by the drugs. Drug infusion times were selected to minimize the effects of slow overall changes in the patient's haemodynamics biasing the results. A minimum of 5 min (2–3 half-lives for the drugs studied[14–16]) was used to ensure a steady state drug effect.

There are two previous studies of spectral analysis of free flap and control tissue blood flow signals. Liu et al[9] examined the spectral analysis of 18 patients undergoing free latissimus dorsi transfer. The authors used a laser Doppler flowmeter to measure skin blood perfusion at the flap and a control site on the contralateral limb in patients with soft tissue injury of the lower extremity. They found that the spectral power and average amplitude of oscillations in the frequency range 0.0095–1.6 Hz were dramatically lowered in the flaps. They concluded that a decrease in both the endothelial cell metabolic processes and sympathetic control, and an increase in the intrinsic myogenic activity were found. Similar findings were reported by Sun et al.[17] who examined the spectral analysis changes prior to and following free radial forearm flap harvest and transplantation. They reported significantly increased high frequency (0.15–0.4 Hz) and decreased very low frequency (0003–0.04 Hz) power fraction after flap transfer. The results of the current study are in general agreement with the findings of Liu et al.[9] and Sun et al.,[17] though the effects observed in this study were less pronounced.

Landsverk et al[8] examined the effects of pharmacological interruption of the sympathetic innervation to the arm during brachial plexus blocks. Using two laser Doppler probes, they were able to compare the effects of brachial plexus block on one arm compared to the normal

contralateral limb in 13 patients. They found that in the anaesthetized arm there were reduced relative amplitudes in the 0.021–0.052 Hz and 0.0095–0.02 Hz frequency intervals. These frequency intervals represent neurogenic and endothelial activity, respectively, and indicate an inhibitory effect on the sympathetic and endothelial activity, suggesting it is denervation rather than another operative factor that alters the low frequency oscillations in transplanted tissue.

We have previously reported the effects of the drug infusions on flap and control site blood flow and overall hydraulic conductance (average blood flow/MAP).[7] In brief, dobutamine caused little change in conductance, dopexamine preferentially vasoconstricted the flap compared with the control skin, epinephrine caused a decrease in both flap and control flow and conductance, and norepinephrine resulted in decreased conductance in both the flap and the control tissue, with the effect more marked in the control tissues. These four agents were selected for investigation in view of their widespread use within the ICU locally. It appears that norepinephrine is effective and safe in free flaps once the tissue has been denervated, with only the adventitial alpha-adrenergic receptors being responsive to norepinephrine. It is assumed that the flap skin paddle response to norepinephrine is representative of the remaining flap tissues.

The β_1 and β_2 agonists dobutamine and dopexamine showed no change in the power spectrum from the control state, with the denervation effect preserved and no other changes. The known vasodilator properties of β_2 agonists, at the doses studied, had no apparent effect of the relative effects of the local control mechanisms or the effects of global haemodynamics. Epinephrine, and especially norepinephrine, has significant α_1 agonist activity, and this did alter the relative effects of local and haemodynamic control on blood flow, with an apparent increase in local control. In the case of norepinephrine, this seemed to overcome the effect of denervation, so there was more power at the very low frequencies in the denervated flap compared with the control sites. It is postulated that the vasomotion at low frequencies became wholly dependent on exogenous α_1 agonist, swamping any local neural or other effects. This is in agreement with the results from the hydraulic conductance, which showed both flap and control tissue vasoconstriction. However, it was noted that overall flap blood flow increased with norepinephrine, as the increase in blood pressure more than compensated for the decreased conductance. This was not reflected as an increase in the power at cardiac frequencies in the power spectral studies. Coupled with the changes in power at low frequencies, this suggests the flap blood flow is more determined by the average blood pressure interacting with low frequency vasomotion, rather than the pulsatile (systolic/diastolic) component of blood pressure.

As noted previously,[7] there appears to be a brief period after denervation when tissue blood flow is less responsive to exogenous α_1 agonists, but later the tissues become more sensitive. The results from this study may therefore not be generalized to longer term blood flow control. Furthermore, vasopressor drugs acting via pathways other than alpha-adrenergic receptors, such as vasopressin or nitric oxide antagonists, may produce different results. We measured skin flow and assumed that this reflected changes in other tissues, but this could not be proven with the technology used. However, similar findings were seen for all of the flaps included in the study. It is likely that other drugs mediating activity through alpha receptors will produce similar improved perfusion in denervated flaps.

CONCLUSION

This study has confirmed that denervation of free flap tissue is demonstrable using spectral analysis of laser Doppler blood flow signals. It appears from these findings that norepinephrine may be the best agent to preserve flap blood flow in spite of its vasoconstrictor effect, supported by the finding that the control of blood flow shifts toward low frequency vasomotion where blood flow depends mostly on average blood pressure. Further research to confirm this, and that the effect is common to all flap tissues, would probably require flow measurement at the flap pedicle rather than on the skin surface. Statistical analysis may be possible by adjustment of the methods to avoid normalization of the power spectra.

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REFERENCES

1. Davison SP, Kessler CM, Al-Attar A. Microvascular free flap failure caused by unrecognized hypercoagulability. Plast Reconstr Surg 2009;1242:490–495.
2. Harris L, Goldstein D, Hofer S, Gilbert R. Impact of vasopressors on outcomes in head and neck tissue transfer. Microsurgery. 2012;32:15–19.
3. Heller L, Levin LS, Klitzman B. Laser doppler flowmeter monitoring of free-tissue transfers: blood flow in normal and complicated cases. Plast Reconstr Surg 2001;107:1739–1745.
4. Yoshino J, Nara S, Endo M, Kamata N. Intraoral free flap monitoring with a laser doppler flowmeter. Microsurgery. 1996;17:337–340.
5. Hölzle F, Loeffelbein DJ, Nolte D, Wolff KD. Free flap monitoring using simultaneous non-invasive laser Doppler flowmetry and tissue spectrophotometry. J Craniomaxillofac Surg 2006;34:25–33.
6. Hölzle F, Rau A, Loeffelbein DJ, Mücke T, Kesting MR, Wolff KD. Results of monitoring fasciocutaneous, myocutaneous, osteocutaneous and perforator flaps: 4-year experience with 166 cases. Int J Oral Maxillofac Surg 2010;39:21–28.

7. Eley KA, Young JD, Watt-Smith SR. Epinephrine, norepinephrine, dobutamine and dopexamine effects on free flap skin blood flow. Plast Reconstr Surg 2012;130:564–570.
8. Landsverk SA, Kvandal P, Kjelstrup T, Benko U, Bernjak A, Stefanovska A, Kvernmo H, Kirkeboen KA. Human skin microcirculation after brachial plexus block evaluated by wavelet transform of the laser Doppler flowmetry signal. Anesthesiology 2006;105:478–484.
9. Liu X, Zeng B, Fan C, Jiang C, Hu X. Spectral analysis of blood perfusion in the free latissimus dorsi myocutaneous flap and normal skin. Phys Med Biol 2006;51:173–183.
10. Young JD, Cameron EM. Dynamics of skin blood flow in human sepsis. Intensive Care Med 1995;21:669–674.
11. Cracowski JL, Minson CT, Salvat-Melis M, Halliwill JR. Methodological issues in the assessment of skin microvascular endothelial function in humans. Trends Pharmacol Sci 2006;27: 503–508.
12. Rossi M, Carpi A, Galetta F, Franzoni F, Santoro G. The investigation of skin blood flowmotion: A new approach to study the microcirculatory impairment in vascular diseases? Biomed Pharmacotherapy 2006;60:437–442.
13. Bracic M, Stefanovska A. Wavelet-based analysis of human bloodflow dynamics. Bull Math Biol 1998;60:919–935.
14. Goldstein RA, Passamani ER, Roberts R. A comparison of digoxin and dobutamine in patients with acute infarction and cardiac failure. N Engl J Med 1980;303:846–850.
15. Kates RE, Leier CV. Dobutamine pharmacokinetics in severe heart failure. Clin Pharmacol Ther 1978;24:537–541.
16. Dimsdale JE, Moss J. Short-term catecholamine response to psychological stress. Psychosom Med 1980;42:493–497.
17. Sun T-B, Kuo TBJ, Yang CCH. Power spectral analysis of perfusion signals on free radial forearm flap transplantation in humans. Microsurgery 2009;29:636–643.

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Is the ratio of functional fibrinogen to platelets as measured by thromboelastography a predictive parameter for thrombotic complications in free tissue transfer surgery?

Karen Ann Eley*, Rachel Parker, S.R. Watt-Smith

Oxford Radcliffe Hospitals NHS Trust, United Kingdom

The risk of total flap loss after free microvascular tissue transfer is estimated to be between 2 and 6%. Flap failure is most frequently due to anastomotic thrombosis, occurring in the early postoperative period. The exact causes of events leading to thrombotic occlusion are not clear, although authors have observed detrimental effects of increased platelet counts, platelets aggregation, and fibrinogen levels on flap survival.

In patients with hyperfibinogenemia related to oral cancer, the safety of performing a successful microsurgical procedure for complex tissue defects has been debated, and the correlation between hyperfibrinogenemia and vascular thrombosis in microsurgery remains unclear.

We retrospectively reviewed 42 patients undergoing free tissue transfer following head and neck cancer resection. The ratio of pre-operative fibrinogen to platelet was calculated for each patient pre-operatively. A control group of normal fibrinogen to platelet ratio results were obtained from 49 healthy volunteers. Fibrinogen to platelet ratios in patients with head and neck cancer preoperatively were significantly higher ($p < 0.001$) than this control group.

In total, seven patients (17%) experienced major graft failure secondary to thrombotic events. Two of these patients had intraoperative thrombotic events. The pre-operative fibrinogen to platelet ratio was above 50% in six patients, correctly identifying their increased thrombotic tendency. In the one patient with a pre-operative ratio of 34%, post-operative results demonstrated continuing elevating ratios, that may have highlighted forthcoming flap failure.

These preliminary results suggest that the use of pre-operative fibrinogen to platelet ratios may aid in identifying patients at increased risk of anastomotic thrombosis.

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Reducing post-operative blood loss in sagittal synostosis: the role of fibrin glue

Dilip Srinivasan*, D. Rodrigues, N. White, E. Carver, M.S. Dover, H. Nishikawa, S. Magdum, G. Solanki

Birmingham Children's Hospital, United Kingdom

Aims and objectives: Fibrin's haemostatic properties are well known and we report its application prior to scalp closure in order to reduce post-operative blood transfusion.

Patients and methods: Prospective study of 16 calvarial remodellings for sagittal synostosis were performed by the same surgical team. Data collected included post-operative wound drainage at 8 and 48 h. Group A had scalp closure alone (10 cases), while Group B had scalp closure with fibrin (Tisseel) glue (6 cases).

Results: The two groups were comparable with a similar mean age at surgery, peri-operative blood loss and intra-operative blood transfusion. In group A, post-operative drainage in the first 8 h was 246 mls compared to 172 mls in group B ($p = 0.02$) The total post-operative drain volume was 441 mls compared to 301 mls ($p = 0.01$). The fibrin glue group did not require post-operative transfusion (0/6) compared to 2/10 in the untreated group.

Conclusion: Fibrin glue application is associated with reduced post-operative bleeding and post-operative blood transfusion.

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Assessment of the effects of pressors on graft blood flow after free tissue transfer surgery: interim findings

Karen Ann Eley*, D. Young, S.R. Watt-Smith

Oxford Radcliffe Hospitals NHS Trust, United Kingdom

Patients with intra-oral carcinoma frequently require support to mitigate the hypotensive effects of sedation in the early recovery period. Sympathomimetic agents may increase the systemic blood-pressure but the resulting vasoconstriction may paradoxically reduce flap perfusion and result in flap failure (Suominem 2004). The aims of this study are to identify the optimal agent to improve systemic blood pressure whilst maintaining flap perfusion.

All patients presenting with head and neck cancer, requiring free flap surgery, and consenting to participate in the trial are recruited. Following surgery Doppler probes are sited on the flap and at a control site, providing continuous recording of tissue perfusion. All patients remain intubated and ventilated overnight, and are monitored using LiDCO Plus to optimise fluid balance. Four drugs (Dobutamine, Dopexamine, Adrenaline and Noradrenaline), in random order and with an intermediary wash out period, are infused at increasing rates to institute a rise in mean arterial blood-pressure of 15 mmHg.

Interim findings show that both Noradrenaline and Adrenaline reliably increase systemic blood pressure, but unpredictably maintain, elevate or lower tissue perfusion. Dopexamine has so far failed to increase blood pressure in any of our patients, and has always resulted in significant tachycardia. Dobutamine currently appears to be the drug of choice; although it too often results in a tachycardic patient, it reliably elevates blood pressure and elevates or maintains tissue perfusion.

The implications of these initial findings are discussed. The end point of this trial has implications for all tis-

sue transfer surgery including free flap procedures and transplantation.

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Factors associated with blood loss and transfusion requirements in craniofacial surgery: a 5 year single-institution review

Dilip Srinivasan*, E. Carver, D. Rodrigues, R. Vemaraju, R. Marcus, G. Solanki, H. Nishikawa, M.S. Dover

Birmingham Children's Hospital, United Kingdom

Introduction: Blood loss remains a major challenge in craniofacial surgery. Despite major advances in both craniofacial surgery and replacement of blood products, this area of practice remains challenging.

Aims and objectives: To delineate factors associated with blood loss and transfusion by reviewing practice at a designated craniofacial unit in the UK.

Patients and methods: 189 Children operated on between 2002 and 2007 were the subjects of this retrospective review. 108 Fronto-orbital advancement and remodelling (FOAR) and 81 sagittal synostosis corrections were performed. Patient demographics, surgery details and estimate of blood loss were collected. Surgical technique was refined to reduce blood loss. Adjuvant methods were employed to reduce postoperative drainage and transfusion requirements. A specific protocol for blood transfusion was developed.

Results: Mean age at surgery for FOAR was19 months with an upward trend ($15 \geq 25$months) during the period of review. Blood loss decreased from 120% to 80% of blood volume during this period.

In sagittal synostosis, 83% of children undergoing correction were under 18-months. Age at surgery decreased over 5 year. Mean blood loss was 80% of blood volume.Blood loss increased from 60% to 80% coinciding with a change in practice from strip-craniectomy to calvarial remodelling.

Conclusions: Surgical technique, age at surgery, type of surgery and use of fibrin glue influence amount of blood loss. Cell salvage in FOAR helps reduce blood requirements.

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Microdialysis: have we found the ideal flap monitoring device?

Jolie Scannell*, Andrew Lyons

Guy's Hospital, London, United Kingdom

Introduction: Flap monitoring should be reliable, safe, accurate and easy to use in any clinical setting. Microdialysis is a method of monitoring interstitial tissue metabolism of free flaps. Previous studies have shown a 77% flap salvage rate with use of microdialysis monitoring[1] and ischaemia prediction 1–2 h before it became evident clinically.[2] The aim of this study was to assess the usefulness and reliability of microdialysis for continual free flap monitoring.

Methods: 20 Free Microvascular flaps carried out following oral cancer resection were monitored from January 2008 to January 2009 with microdialysis for a 72 h postoperative period. A microdialysis catheter was inserted into the skin or muscle part of the flap at the end of operative procedure. A bedside analyser was used with hourly dialysate samples providing continual trace on the screen showing trends for glucose, lactate and lactate/pyruvate ratio. The readout could be photographed and sent by mobile phone. Flap ischaemia is represented by a falling glucose, increased lactate and lactate/pyruvate ratios.

Results: Successful salvage of a DCIA flap was possible due to early detection of venous failure. No flaps were returned to theatre unnecessarily and microdialysis also predicted partial flap necrosis in 2 cases.

Conclusion: Our experience at Guys has shown microdialysis is safe, provides real time, continual flap monitoring giving early prediction of flap ischaemia.

References

1. Setala, et al. *Journal of Reconstructive Surgery* 2006;**22**(2):87–95.
2. Jyranki, et al. *Annals of Plastic Surgery* 2006;**56**(April (4)):387–93.

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The effective management of high flow vascular malformations of the head and neck

Andrew Monaghan*, I. McCafferty, S. Lamin, H. Nishikawa, R. Williams

University Hospital Birmingham NHS Trust, United Kingdom

Introduction: High flow vascular malformations (arteriovenous malformations) of the head and neck are some of the most challenging lesions to treat. Traditional management includes embolisation followed shortly afterwards by surgical excision. Incomplete excision inevitably leads to recurrence due to recruitment of collateral circulation. Surgery is often associated with massive haemorrhage; the literature has numerous reports of intraoperative deaths.

Method: This presentation will report the results of embolisation of high flow malformations of the head and neck using Onyx. Onyx comprises of an ethylene-vinyl alcohol copolymer with a lava-like flow pattern. Micronized tantalum powder is added to the mixture for radiopacity.

Results/conclusion: Onyx differs from conventional embolisation methods in that it fills the lesion and obliterates the nidus; the recruitment of collateral circulation does not

shown little benefit. The principal aim of this study is to determine whether manual reduction or IMF provides a better result in terms of occlusion and radiographic reduction of mandibular fractures.
Methods: All patients presenting to the Gold Coast hospital with fractures of the mandible not including the condylar head or neck and without midface injuries were offered participation in the study. Randomisation into either manual reduction or intraoperative IMF was undertaken. Data was collected on operative duration, occlusal results, radiographic results, and complications. The patient and assessor were blinded as to the technique used intraoperatively.
Results: 36 patients were randomised during the study period. Patients treated with manual reduction had a significantly shorter operative duration. There was no difference between either the radiograpic interpretation of reduction or the objective occlusal result. Difficulties in maintaining patient followup made assessment of complications difficult.
Discussion: Manual reduction of fractures of the mandible produces equivalent results to the use of intraoperative intermaxillary fixation. In addition this can be undertaken in a shoter duration of time. This translates into less costly procedures as not only is operative time diminished but additional hardware (eg IMF screws, arch bars, wire) are not required.

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Assessment of the effects of pressors on graft blood flow after free tissue transfer surgery: phase I results

K.A. Eley, D. Young, S.R. Watt-Smith. *Oxford Radcliffe Hospitals NHS Trust, UK*

Introduction: Patients with intra-oral carcinoma frequently require support to mitigate the hypotensive effects of sedation in the early recovery period. Sympathomimetic agents may increase the systemic blood pressure but the resulting vasoconstriction may paradoxically reduce flap perfusion and result in flap failure. Difficulty remains in the appropriate management of patients undergoing free flap surgery post-operatively on the Intensive Care Unit.
Aims: To identify the optimal agent to improve systemic blood pressure whilst maintaining flap perfusion.
Method: The effects of four vasopressors (Noradrenaline, Adrenaline, Dobutamine and Dopexamine) upon microsurgically transplanted tissue were investigated in 25 patients. Utilising laser Doppler probes a continuous waveform of tissue perfusion was obtained for the transplanted tissue and compared to a control site. All patients were, in addition to standard ITU care, monitored using LiDCO Plus Rapid, to optimise fluid balance.
Results: The preliminary (mid-point) findings of this research were presented at the Annual Conference 2009. Following recent completion of data collection definitive data analysis is currently being completed.
The effects of the four trialled drugs are dose dependent with Dobutamine frequently improving tissue perfusion of the flap, but with the adverse effect of a tachycardic response.
Conclusions: Dobutamine and Adrenaline rarely have adverse effects upon transplanted tissue, but frequently result in an unacceptably tachycardic patient. Approval (pending funding) has recently been granted for extension of this research project to investigate the optimal concentration of the most efficacious agent determined in this phase, with comparison to metaraminol – which does not appear to result in tachycardia.

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Mandible fracture patterns seen in British servicemen subjected to blast injury

J. Breeze, A.G. Gibbons, N. Hunt, A.M. Monaghan, A. Hepper, M. Midwinter. *Academic Department of Military Surgery and Trauma, Royal Centre for Defence Medicine, UK*

Introduction: Blast injuries are the primary cause of injury to coalition soldiers in Iraq and Afghanistan. There have been isolated case reports and experimental data describing mandible fracture patterns secondary to blast injury but to date no significant case series has been published.
Method: All mandible fractures sustained by British servicemen secondary to blast injury between 01 January 2004 and 30 September 2009 were identified.
Results: During this period 60 mandible fractures were identified in total. 22 servicemen survived to obtain treatment back in the UK while the remaining 38 died from wounds, predominantly from primary brain injury. No British servicemen in this case series died specifically from facial wounds.
Careful analysis of the mandible fractures using radiographs, clinical notes and situational operational reports ascertained that 35 of these fractures were most likely secondary to the blast wave itself and not from associated shrapnel. Unlike previous case reports and experimental data we found no evidence of unusual fracture patterns such as horizontal splits.
Clinical relevance: A number of fractures were found to have been secondary to blunt impacts from a serviceman's weapon or equipment and further research is ongoing to see how this information can change current battlefield protocols.

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Utility of a generic risk prediction score in predicting outcomes after orofacial surgery for cancer.

D. Tighe. *Queen Victoria Hospital, East Grinstead, UK*

Introduction: Head and Neck surgery for cancer is fraught with patient risk. Systematically measuring and auditing risk in Head and Neck Surgery is impossible without a consensus comparator or 'gold standard'. Understanding how individual patient variation and peri-operative events alter risk is fundamental to auditing outcome in a meaningful way.
Methods: Post operative outcomes (n = 305) over a three year period (2005–2008) are reported from one centre of excellence (Queen Victoria Hospital, East Grinstead) treating major Head and Neck surgical cases. The predictive accuracy of a popular generic risk prediction tool, the POSSUM equation for morbidity and P-Possum, is reported for the first time in the discipline of Maxillofacial Surgery.
Results: Morbidity rates are broadly in line with other international published data but lower than expected mortality outcomes. The POSSUM morbidity equation showed reasonable discrimination (C Statistic 0.74) as did the P POSSUM mortality equation (C Statistic 0.75) but both were shown to have poor fit overall [Hosmer and Lemeshow goodness of fit tests for morbidity $\chi^2 = 31.64$ at 8 d.f ($P = 0.00011$) and for mortality was $\chi^2 = 5.51$ at 1 d.f ($P = 0.0189$) respectively]. Of note, no improvement was demonstrated after excluding procedures requiring emergency return to theatre nor extremely minor procedures during the audit period.
Conclusions: A 'Standard of Care' index for major Head and Neck surgery, for the purposes of mortality and morbidity audit is an unmet need. Collaboration within the speciality could produce such a score within 2 years.

FUNCTIONAL FIBRINOGEN TO PLATELET RATIO USING THROMBOELASTOGRAPHY AS A PREDICTIVE PARAMETER FOR THROMBOTIC COMPLICATIONS FOLLOWING FREE TISSUE TRANSFER SURGERY: A PRELIMINARY STUDY

RACHEL J. PARKER, S.O.P.D., M.I.C.R.,[1] KAREN A. ELEY, M.B.Ch.B.(Hons.), M.R.C.S.(Ed), P.G.C.T.L.C.P., F.H.E.A., M.Sc.,[2*] STEPHEN VON KIER, M.I.C.R.,[1] OLIVER PEARSON,[1] and STEPHEN R. WATT-SMITH, M.B.B.S., B.D.S., F.D.S.R.C.S., M.D.[3]

Background: Microvascular free tissue transfer in head and neck surgery has become an indispensable tool. Anastomotic thrombosis is one of the leading causes of flap failure; however, there are no validated methods to accurately identify and quantify those patients most at risk of thrombotic complications. The aim of this study was to determine if functional fibrinogen to platelet ratio using thrombelastography could preoperatively identify patients at risk of thrombotic complications. *Materials and Methods:* Twenty nine patients undergoing free tissue transfer surgery for head and neck pathology underwent routine TEG® analysis, with calculation of functional fibrinogen to platelet ratio at induction of anesthesia. All perioperative thrombotic complications were recorded and crossreferenced with preoperative ratios. Data was further compared to results obtained from 42 healthy volunteers. *Results:* The mean functional fibrinogen to platelet ratio was significantly higher in the surgery group compared to healthy volunteers. Of the 29 patients studied, 31% ($n = 9$) had some form of thrombotic event, with all but one patient having a ratio $\geq$42% (mean 47% $\pm$ 7%). For those patients without thrombotic events, the mean ratio was 37% $\pm$ 5%. *Conclusion:* A functional fibrinogen to platelet ratio above 42% as measured by TEG® may be useful in identifying those patients likely to develop thrombotic complication. © 2012 Wiley Periodicals, Inc. Microsurgery 32:512–519, 2012.

Microvascular free tissue transfer following ablative oncological surgery has become an indispensable tool in head and neck reconstruction, with reported success rates of 90–99%.[1–3] The cohort of patients with perioral malignancy are typically of advanced age, chronically abused alcohol and/or tobacco with associated comorbidity, placing them at increased risk of both flap and general postoperative complications. Additionally, it is well documented that patients with malignant disease are at increased risk of venous thromboembolism (VTE), with malignancy being the etiological factor in 20% of VTE events in the community, and a 100-fold increase in incidence in hospitalized patients.[4,5] In patients undergoing free tissue transfer, this risk is further compounded by immobility and prolonged surgical procedures.

Flap failure may occur due to vascular complications despite meticulous microvascular technique, with venous thrombosis being more common than arterial occlusion.[2] This thrombogenic effect may be the result of several factors. Expression of the proteolytic enzyme CP (cancer procoagulant, a cysteine proteinase) by malignant tumor cells is known to directly activate factor X without interaction with the intrinsic or extrinsic coagulation pathways.[6–8] Increased levels of TF (tissue factor), PAI-1 (plasminogen activator inhibitor), the inflammatory cytokines TNF (tumor necrosis factor), IL1, IL8 (interleukins), and VEGF (vascular endothelial growth factor) are all associated with tumor thrombosis.[8,9] Additionally, reduced expression of regulators of coagulation such as tPA (tissue plasminogen activator) and TM (thrombomodulin) on the endothelial surface and concomitant increased production and deposition of fibrin are also observed in tumor-related thrombosis. Therefore, it would be expected to see higher flap failure rates in malignancy cases; however, reported rates do not appear to support this.[10–13]

Early identification of the failing flap is paramount for successful salvage. A method to reliably predict those patients most at risk would permit additional measures to be instigated in an attempt to minimize flap failure.

Thrombelastography (TEG®) has been used for many years to detect coagulopathy and hypercoagulable states, and is now widely used as a near-site hemostasis monitor.[14–16] TEG ® technology analyses the functional activities of the cellular elements, such as platelet cytoplasmic granules and platelet surfaces, in conjunction with plasma components. Because the TEG® analyzer monitors the shear elasticity of clotting blood, it is sensitive to all of the interacting cellular and plasmatic components. These include coagulation and fibrinolytic factors, activators, and inhibitors which may affect the rate or structure of a clotting sample and its breakdown. The TEG® analyzer can be used to calculate the ratio of functional fibrinogen to platelets (the "functional" component being only the

[1]Hemostasis and Blood Conservation Service, Oxford University Hospitals NHS Trust, Headley Way, Oxford OX3 9DU, UK
[2]Nuffield Department of Surgical Sciences, University of Oxford, Oxford University Hospitals NHS Trust, Headley Way, Oxford OX3 9DU, UK
[3]Department of Oral and Maxillofacial Surgery, Oxford University Hospitals NHS Trust, Headley Way, Oxford OX3 9DU, UK
Rachel J. Parker and Karen A. Eley contributed equally to this work.
*Correspondence to: Karen A. Eley, Nuffield Department of Surgical Sciences, University of Oxford, Level 6, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK. E-mail: karen.a.eley@gmail.com
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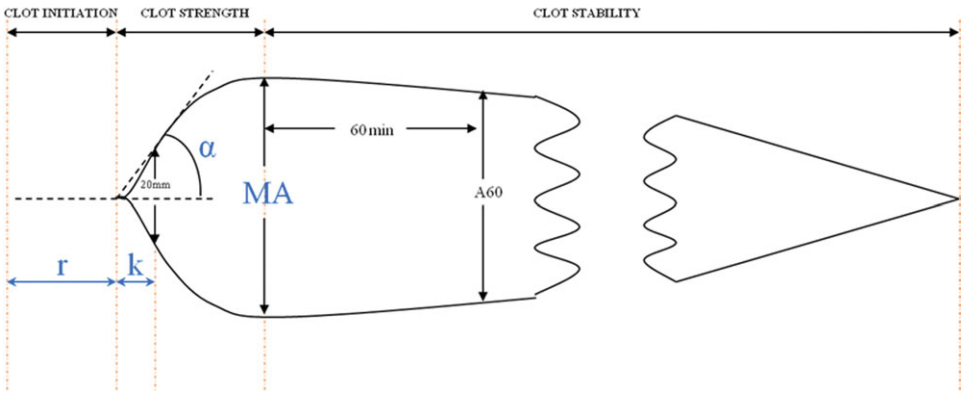

Figure 1. Schematic diagram of TEG® trace. TEG® parameters illustrate the functional activity of clot initiation, kinetics, maximal strength, and clot stability. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

fibrinogen which is biologically active) by utilizing an additional reagent.

The aim of this study was to determine if the ratio of functional fibrinogen to platelets, as measured by TEG® could be reliably utilized as a predictor of intraoperative and postoperative thrombotic complications following free tissue transfer surgery.

MATERIALS AND METHODS

A retrospective review of patients undergoing surgery for head and neck pathology with free-flap reconstruction, performed by the senior author, between April 2006 and June 2007 was conducted.

Functional fibrinogen to platelet ratio was determined at the induction of anesthesia and this baseline result used for subsequent analysis. All patients, as per local routine practice, had regular TEG® analyses (without the additional functional fibrinogen to platelet ratio) performed throughout the perioperative period in addition to routine hematology and biochemistry investigations (including a coagulation screen).

Calculation of Functional Fibrinogen to Platelet Ratio

TEG® analysis was completed using the TEG® 5000 hemostasis analyzer (Hemoscope Corp, Niles, IL). This measures the viscoelastic properties of blood, and the resulting hemostasis profile is a measure of the time it takes for the first fibrin strand to be formed, the kinetics of clot formation and the strength and dissolution of the clot (Fig. 1). Approximately 80–90% of the strength of the maximum amplitude (MA) is related to platelet numbers and function.

A "Clauss correlated" functional fibrinogen level (TEG-Fib) achieved through the addition of the monoclonal antibody c7E3 [abciximab (ReoPro®, Eli Lilly, IN)], which binds the glycoprotein IIb/IIIa receptor on the platelet surface, was used to remove the platelet component of the clot to measure the fibrinogen contribution to clot strength, expressed as MA_R.

With the concurrent use of an unmodified TEG® sample, the independent contribution of fibrinogen and platelets to the overall clot strength could be determined. For standard TEG® analysis, a 1 ml sample of whole blood was added to a kaolin activator vial. After inverting the vial to ensure adequate mixing, 360 μg of kaolin activated whole blood was transferred to the analyzer. To test the functional fibrinogen level, 355 μg of the remaining kaolin activated whole blood was added to a second cup which contained 5 μg abciximab (Fig. 2). Analytical software within the TEG® software (version 4.2.3) was used to calculate the functional fibrinogen level (FLEV) through the transformation of the MA value.

As the maximal amplitude (MA) of thromboelastography using whole blood (MA_W) measures clot strength and represents the collective contribution of both fibrinogen and platelets we were first able to inhibit the platelet function, and subsequently calculate the functional fibrinogen to platelet ratio using the equation:

$$\text{Functional fibrinogen to platelet ratio} = \frac{MA_R}{MA_W} \times 100$$

In total, 29 patients (male: $n = 17$; female: $n = 12$), with a mean age of 58 years (32–83 years) had functional fibrinogen to platelet ratios available (Table 1). Preoperative anticoagulation in line with local protocol at the time of the study was not used.

The functional fibrinogen to platelet results were compared to data previously obtained from a healthy adult control group ($n = 42$). Participants in this group were freely consenting laboratory staff, who each donated 1 ml of blood for baseline modified functional fibrinogen and standard TEG® testing. Data were collected to permit familiarity with the methodology and as such no demographic data were stored.

Table 1. Patient Demographics, Baseline Functional Fibrinogen to Platelet Ratio (FF:Plt) and Thrombotic Complications

Patient	Sex	Age	Site of resection	Pathology	Flap(s)	Baseline FF:Plt	Thrombotic complications
1	M	83	Mandible	Osteosarcoma	Latissimus Dorsi, and Radial	55	Intraoperative anastomotic thrombus
2	M	43	Mandible	SCC Recurrence	Fibula and Latissimus Dorsi	55	Arterial anastomotic thrombus
3	M	34	Mandible	Ameloblastoma*	Fibula	39	
4	M	59	Mandible	SCC (pT4, pN1)	Fibula and Radial	36	
5	M	83	Mandible	SCC (pT4, pN2b)	Fibula and Radial	50	Intra-operative IJV thrombus
6	F	61	Mandible	SCC (pT4, pN0)	Fibula and Radial	34	Arterial anastomotic thrombus
7	M	32	Maxilla	Ewings sarcoma	Radial	26	
8	F	63	Mandible	SCC recurrence	Radial and Scapular	45	Venous anastomotic thrombus
9	M	75	Floor of Mouth	SCC (pT3, pN0)	Radial	35	
10	M	57	Floor of Mouth	SCC (pT4, pN2b)	Radial	50	Intraoperative IJV thrombus
11	F	52	Tongue	SCC (pT1, pN0)	Radial	46	
12	F	57	Mandible	Ameloblastoma*	Fibula	35	
13	M	48	Floor of Mouth	SCC (pT1, pN0)	Radial	44	Intraoperative IJV thrombus
14	F	55	Mandible	SCC (pT4, pN0)	Radial	39	
15	F	32	Right cheek	Malignant ameloblastoma	Groin	37	
16	M	69	Pharynx	SCC (pT4, pN2c)	Radial	42	
17	M	53	Mandible	SCC (pT4, pN2b)	Fibula	32	
18	F	79	Mandible	SCC (pT4, pN0)	Fibula	30	
19	F	73	Maxilla	SCC (pT4, pN0)	Radial	32	
20	M	75	Mandible	SCC (pT1, pN0)	Radial	44	
21	M	45	Mandible	Odontogenic keratocyst with pathological fracture*	Fibula	39	
22	M	50	Floor of mouth	SCC (pT1, pN0)	Radial	41	
23	F	77	Mandible	SCC (pT4, pN0)	Fibula	49	Arterial anastomotic thrombus
24	M	49	Lateral tongue	SCC (pT2, pN0)	Radial	38	
25	F	76	Tonsillar fossa	SCC (pT2, pN0)	Radial	36	
26	M	55	Lateral tongue	SCC (pT1, pN0)	Radial	51	
27	F	54	Lateral tongue	SCC (pT2, pN2b)	Radial	42	
28	M	50	Lateral tongue	SCC (pT2, pN0)	Radial	39	
29	F	46	Lateral tongue	SCC (pT2, pN2b)	Radial	42	Venous anastomotic thrombus

** signifies benign pathology.*

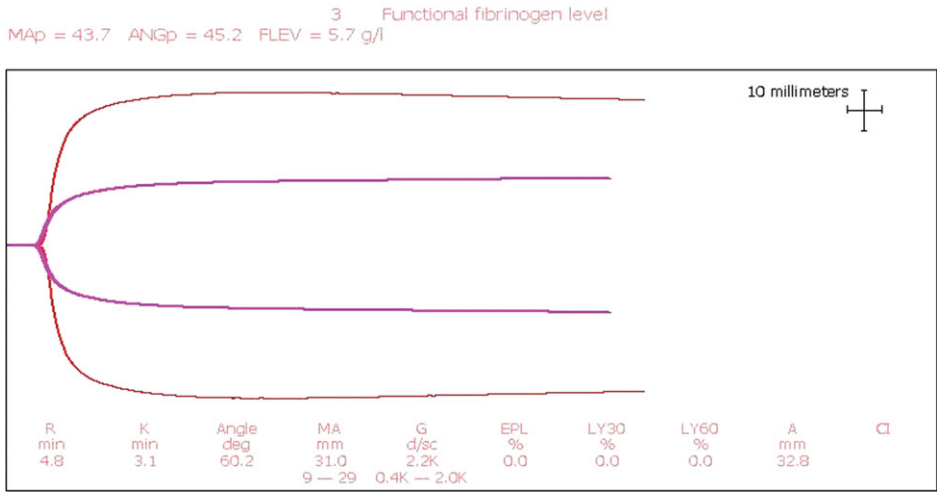

Figure 2. Schematic diagram to show: Large trace (red) = the MA as a function of fibrinogen and platelet activity on whole blood (MA_W); small trace (pink) = the MA as a function of fibrinogen contribution alone, after exposure to Reopro (MA_R). Allowing for the determination of the independent contributions of fibrinogen and platelets to overall clot strength. $MA_R/MA_W \times 100$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 2. Comparison of Thrombotic and Flap Complications, With Age and Body Mass Index (BMI) for the Two Subgroups of Functional Fibrinogen to Platelet Ratios [Mean (Range)]

Group	*A*	*B*
Functional fibrinogen to platelet ratio	<42% $n = 16$	≥42.0 $n = 13$
Age (years)	55 ± 15	62 ± 14
BMI (kg m^{-2})	27 ± 6	23 ± 5
Thrombotic events	$n = 1$	$n = 8$
Flap loss	$n = 1$	$n = 3$

Because blood analysis utilizing TEG® constitutes routine patient care (with no additional blood samples required), and the control group were laboratory staff, ethical approval was not required in the United Kingdom.

Statistical analysis was performed with an Independent samples Mann Whitney U test and Fishers Exact Test on SPSS version 17 (Statistical Package for the Social Sciences, IBM Corp, Somers, NY), with results displayed as mean ± SD.

RESULTS

The functional fibrinogen to platelet ratio results were significantly higher in the surgery group (40.8 ± 7.4) compared to healthy controls (32.4 ± 6.1), ($P < 0.05$; Independent samples Mann-Whitney U test). Within the surgery group, patients with malignancy ($n = 26$) had higher ratios compared to those with benign pathologies ($n = 3$), with mean functional fibrinogen to platelet ratios of 41% ± 7% and 38% ± 2%, respectively (Table 1).

Of the 29 patients studied, 31% ($n = 9$) had some form of thrombotic event (Table 1). One patient had an early venous anastomotic thrombotic event, which was detected prior to wound closure, with no postoperative flap complications following thrombus removal and repeat anastomosis. Five patients experienced flap complications, necessitating return to the operating theatre where anastomotic thrombosis was identified as the cause. Of these, three were arterial thromoboses, with successful salvage in one case; two were venous thrombosis, with both flaps ultimately lost. In the remaining three cases thrombosis within the internal jugular vein (IJV) was noted and removed at the time of primary surgery, with no further complication. There were no incidents of deep vein thrombosis or pulmonary emboli.

The functional fibrinogen to platelet ratio results were stratified into two groups, based upon the apparent clustering of thrombotic complications in those with ratios above 42% (Table 2). In group A (ratio < 42%), one patient experienced flap complications (ratio 34%), with ultimate loss of both fibula and radial flaps on postoperative day 11 (Fig. 3).

In group B (ratio ≥42%), eight patients experienced thrombotic complications; with three flap failures on days 1, 5, and 9, respectively. In the first case (ratio 45%), repeat surgery was complicated with further anastomotic thrombosis, but salvage successful. In the second patient (ratio 55%), both free flaps (fibula and latissimus dorsi) were lost, with subsequent failure of a repeat free flap. In the final patient (ratio 42%), repeat surgery was uneventful. The incidence of all thrombotic complications was statistically higher in group B ($P = 0.003$; Fishers Exact Test), (Fig. 4).

The groups were similar for both age and BMI (Table 2). Only one patient had a previous history of VTE

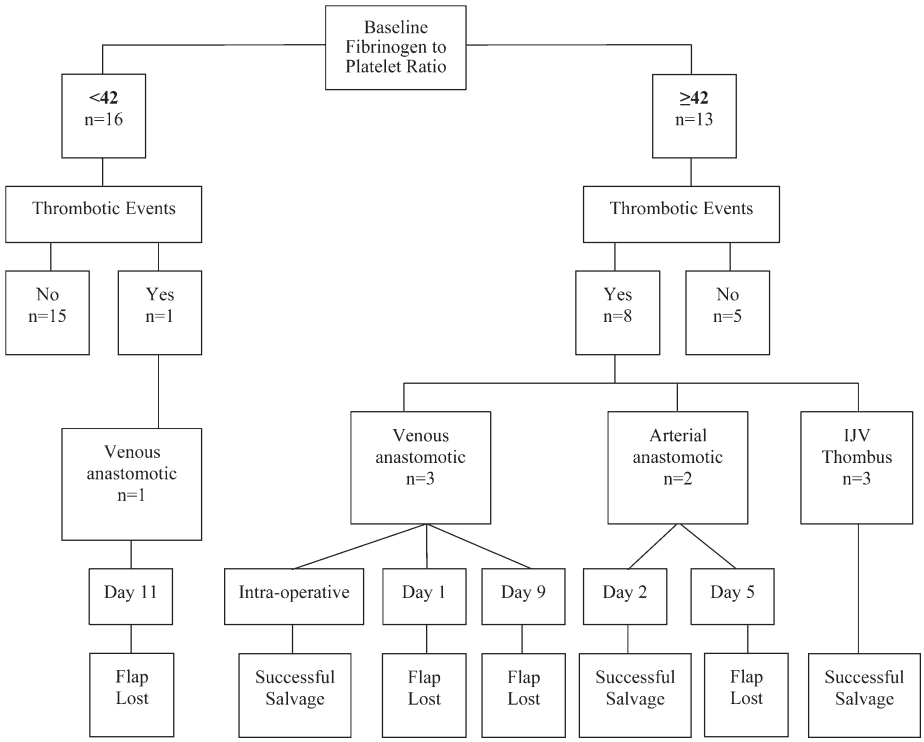

Figure 3. Flow diagram correlating flap outcomes with functional fibrinogen to platelet ratio.

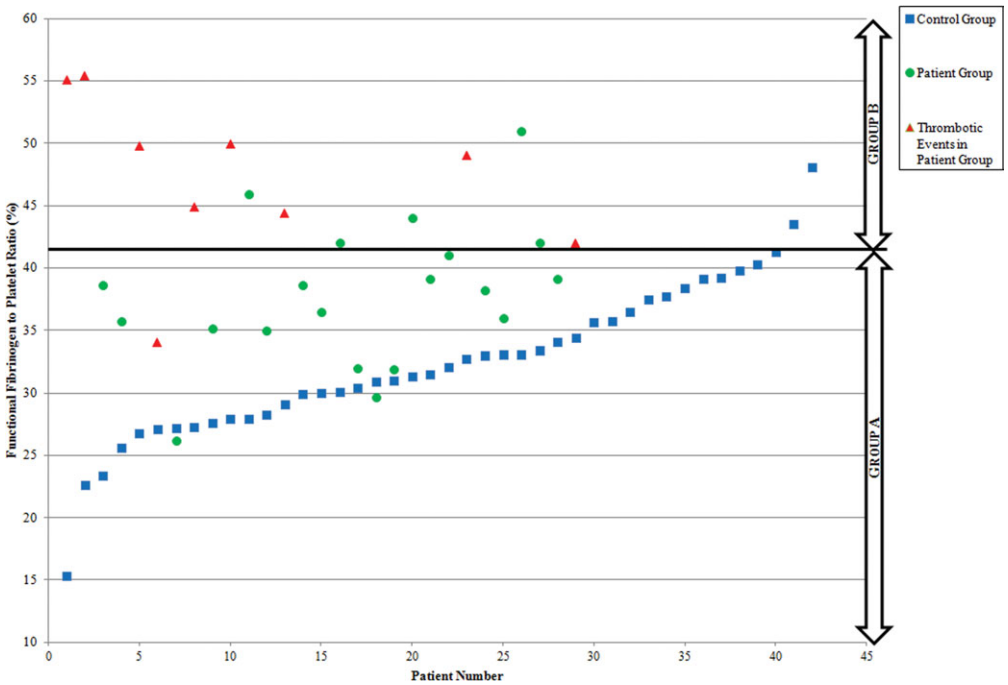

Figure 4. Graph showing the functional fibrinogen contributions of the patient group (green) compared to healthy controls (blue) as measured by TEG® analysis. Patients who experienced thrombotic events are highlighted (▲). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(deep vein thrombosis), and there were no prior incidences of anastomotic complications for any of the patients studied. The patient with a past history of DVT had a functional fibrinogen to platelet ratio of 46% at induction of anesthesia for flap surgery, but did not experience any thrombotic complications at or following surgery.

A functional fibrinogen to platelet ratio of ≥42% results in a sensitivity of 89% and specificity of 75% for predicting thrombotic events.

DISCUSSION

This preliminary study has demonstrated that functional fibrinogen to platelet ratio performed at induction of anesthesia may be a useful preoperative predictor of patients likely to experience thrombotic complications.

Patients undergoing surgery had significantly higher ratios compared to normal controls consistent with the increased risk of VTE in malignant disease states.

During the study period, a further 19 free flaps were completed, resulting in 48 flap procedures by the senior author. In this group one patient underwent successful flap salvage for anastomotic venous occlusion. The overall free-flap success rate for the study period was 92%. However, a free-flap survival rate of 86% was achieved in the 29 patients studied, lower than would be expected. This discrepancy is likely to represent a combination of chance, and an increased request rate for a functional fibrinogen to platelet ratio in patients who may have been clinically perceived to be at increased risk of flap thrombosis.

The number of patients included in this study was small, making further validation with a prospective study necessary. However, in the majority of cases thrombotic complications may have been predicted preoperatively with high functional fibrinogen to platelet ratios. One of the 16 patients (6%) in group A (ratio <42%), and 8 of the 13 patients (62%) patients in group B (ratio ≥42%) experienced thrombotic flap complications.

There are numerous scoring methods to identify patients at high risk for VTE; however none specifically identify those patients likely to have free-flap thrombotic events leading to flap failure. The use of the Caprini score in our patient cohort would result in the majority of our patients being deemed high risk—since they are mostly over the age of 60 years (two points), have malignancy (two points), are having major surgery (two points), and depending upon the donor site, will have an immobilizing plaster (two points).[17] In view of smoking and alcohol use, many will also score additional points for comorbidity. However, not all experienced thrombotic complications. In the NHS, in view of financial constraints, it is necessary to target therapy to those most in need. Using unfractionated heparin needs to be fully justified, and the use of devices such as implantable dopplers are expensive, and are a luxury which cannot be afforded to every patient. By identifying those in a cohort of patients all deemed "high risk" that are more likely to develop thrombotic flap complications additional measures to prevent or identify early flap failure can be instituted. These additional measures may include additional chemical thromboprophylaxis such as unfractionated heparin (particularly intraoperatively), or monitoring devices such as Doppler probes or microdialysis.[18]

Patients included in this study had the functional fibrinogen to platelet ratio measured at the time of induction of anesthesia (when the first routine TEG® is ordinarily performed) to avoid the need for an additional blood sample. As a result, high risk patients were not identified at a sufficiently early time to institute preoperative additional anticoagulation. It would be interesting to see the effect of performing the test on the day prior to surgery, so that preventative measures could be implemented. In a recent amendment of the hospital protocol on the preoperative management of surgical patients it has been decided that all patients should now receive a dose of 2,500 U of dalteparin the night prior to surgery. The benefit of this small additional dose is questionable.

No demographic data were available for the healthy control group. Age, sex, and ethnicity have been demonstrated to impact upon TEG® results,[19,20] and it is likely that the age distribution of the control group was lower than the study group. However, it is the correlation of a high ratio with thrombotic complications, rather than comparison to healthy controls which is of most importance. Although all patients undergoing free tissue transfer under the care of the senior author, have standard TEG® analysis, functional fibrinogen to platelet ratios (which is an additional test) were not routinely obtained. Full preoperative screening for hereditary thrombophilia is not routinely undertaken, and often the first indication of problems is a failing flap. The short time to obtain a functional fibrinogen to platelet ratio at the induction of anesthesia is one of the key benefits of the test.

Whilst included as a thrombotic complication, the significance of thrombosis within the internal jugular vein seen at primary surgery is unclear. This was found in three patients, at the time of surgery, without subsequent flap complication. Where IJV thrombus was removed, additional anticoagulation measures, including intraoperative unfractionated heparin, were instigated with close clinical surveillance. This is likely to have reduced potential adverse sequelae in these patients. We have noted an increased incidence of IJV thrombosis detected at primary surgery than is alluded to in the literature.[21,22]

A number of factors for flap failure have been discussed in the literature, including extrinsic compression of the pedicle, the use of interpositional vein grafts, and technical error.[2] Despite sound surgical technique, a hypercoaguable state may still predispose a patient to thrombotic events that may ultimately jeopardize the microvascular anastomosis.[23] It has been reported that 96% of microsurgeons routinely use anticoagulants in an attempt to minimize postoperative thrombotic complications.[24]

Without a mechanism to detect high risk patients, targeted therapy is not possible, subjecting all patients to the potential adverse effects of these measures.

The recognized risk factors for thrombosis are related to one or more elements of Virchow's triad—stasis, vessel injury, and hypercoagulability; factors frequently encountered in oncology patients undergoing free tissue transfer. High plasma fibrinogen levels have been correlated with increased thromboembolic risk in patients with cancer or cardiovascular disease.[23] Kuo et al.[23] investigated the impact of hyperfibrinogenemia on patency of microvascular anastomoses. Using a rodent model, they performed femoral artery and vein anastomosis with and without intraveneous administration of fibrinogen. Laser Doppler flowmetry was used to assess the patency of the anastomosis preoperatively and 2 h postoperatively. Vascular patency was assessed 7 days postoperatively. They found that there was no statistical difference in patency of the femoral vessels after vessel division and reanastomosis. This experimental data did not support their clinical findings of 20% of patients with hyperfibrinogenemia suffering postoperative thrombotic events resulting in flap failure. The increased functional fibrinogen to platelet ratio seen in those patients experiencing thrombotic complications in this study is consistent with the finding of microvasular complications associated with hyperfibrinogenemia; elevated fibrinogen being a recognized finding in patients with malignancy.[25]

Wang et al.[26] reviewed the outcome of 58 flaps in patients with recognized hypercoaguability. They reported an increased flap thrombosis rate of 20.7% compared to the average for all flap cases of 4.2%. In their patient cohort, none of the failing flaps were salvageable. The authors discussed the potential of flap complications being amenable to mechanical thrombolytics, systemic anticoagulation, and change of the target donor vessels, making preoperative identification of at-risk patients of key importance. In our cohort, the only successful postoperative successful salvage was in the case of an arterial thrombus on postoperative day 2, in whom the baseline functional fibrinogen to platelet ratio was 49%.

Whilst TEG® is increasingly being utilized in postoperative surgical management, the current study is the first to highlight the potential predictive benefit of the technique in free-flap surgery.

CONCLUSION

Functional fibrinogen to platelet ratio levels may be a useful tool to identify patients likely to experience postoperative thrombotic events. Further prospective validation is required, however, the results of this preliminary study suggest that this method may aid clinicians in targeting additional anticoagulation methods and close surveillance to those patients most at risk, reducing patient morbidity.

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REFERENCES

1. Chien W, Varvares MA, Hadlock T, Cheney M, Deschler DG. Effects of aspirin and low-dose heparin in head and neck reconstruction using microvascular free flaps. Laryngoscope 2005;115:973–976.
2. Novakovic D, Patel RS, Goldstein DP, Gullane PJ. Salvage of failed free flaps used in head and neck reconstruction. Head Neck Oncol 2009;1:1–5.
3. Kruse AL, Luebbers HT, Gratz KW, Obwegeser JA. Factors influencing survival of free-flap in reconstruction for cancer of the head and neck: A literature review. Microsurgery 2010;30:242–248.
4. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ. Predictors of recurrence after deep vein thrombosis and pulmonary embolism. A population-based cohort study. Arch Intern Med 2000;160:809–815.
5. Heit JA. The epidemiology of venous thromboembolism in the community. Arterioscler Thrombos Vasc Biol 2008;28:370–372.
6. Gordon SG, Mielicki WP. Cancer procoagulant: A factor X activator, tumor marker and growth factor from malignant tissue. Blood Coagul Fibrinolysis 1997;8:73–86.
7. ten Cate H, Falanga A. Overview of the postulated mechanisms linking cancer and thrombosis. Pathophysiol Haemost Thromb 2008;36:122–130.
8. Rickles FR, Falanga A. Molecular basis for the relationship between thrombosis and cancer. Thrombos Res 2001;102:215–224.
9. Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. Lancet Oncol 2005;6:401–410.
10. Kesting MR, Holzle F, Wales C, Steinstraesser L, Wagenpfeil S, Mucke T, Rohleder NH, Wolff KD, Hasler RJ. Microsurgical reconstruction of the oral cavity with free flaps from the anterolateral thigh and the radial forearm: A comparison of perioperative data from 161 cases. Ann Surg Oncol 2011;18:1988–1994.
11. Kruse AL, Bredell MG, Lubbers HT, Jacobsen C, Gratz KW, Obwegeser JA. Clinical reliability of radial forearm free-flap procedure in reconstructive head and neck surgery. J Craniofac Surg 2011;22:822–825.
12. Townley WA, Nguyen DQ, Rooker JC, Dickson JK, Goroszeniuk DZ, Khan MS, Camp D. Management of open tibial fractures—A regional experience. Ann R Coll Surg Engl 2010;92:693–696.
13. Ducic I, Brown BJ, Rao SS. Lower extremity free flap reconstruction outcomes using venous coupler. Microsurgery 2011;31:360–364.
14. Samama CM. Thromboelastography: The next step. Anesthesia Analgesia 2001;92:563–564.
15. Falanga A, Marchetti M, Vignoli A, Balducci D. Clotting mechanisms and cancer: Implications in thrombus formation and tumor progression. Clin Adv Hematol Oncol 2003;1:673–678.
16. Ganter MT, Hofer CK. Coagulation monitoring: Current techniques and clinical use of viscoelastic point-of-care coagulation devices. Anesthesia Analgesia 2008;106:1366–1375.
17. Pannucci CJ, Bailey SH, Dreszer G, Fisher Wachtman C, Zumsteg JW, Jaber RM, Hamill JB, Hume KM, Rubin JP, Neligan PC, Kalliainen LK, Hoxworth RE, Pusic AL, Wilkins EG. Validation of the Caprini risk assessment model in plastic and reconstructive surgery patients. J Am Coll Surg 2011;212:105–112.
18. Smit JM, Zeebregts CJ, Acosta R, Werker PM. Advancements in free flap monitoring in the last decade: A critical review. Plast Reconstr Surg 2010;125:177–185.
19. Roeloffzen WW, Kluin-Nelemans HC, Mulder AB, Veeger NJ, Bosman L, de Wolf JT. In normal controls, both age and gender affect coagulability as measured by thrombelastography. Anesth Analg 2010;110:987–994.

20. Singhal D, Smorodinsky E, Guo L. Differences in coagulation among Asians and Caucasians and the implication for reconstructive microsurgery. J Reconstr Microsurg 2011;27:57–62.
21. Eley KA, Watt-Smith SR. Coagulopathies and the use of LIDCO plus rapid monitoring in patients following head and neck resection and reconstruction. Br J Oral Maxillofac Surg 2010;48:189–191.
22. Felstead AM, Perkins CS. Thrombosis of the internal jugular vein: A rare but important operative finding. Br J Oral Maxillofac Surg 2010;48:195–196.
23. Kuo Y-R, Jeng S-F, Wu W-S, Lin C-J, Sacks JM, Yang KD. Hyperfibrinogenemia alone does not affect the patency of microvascular anastomosis. Clinical experience and animal study. Ann Plast Surg 2005;54:435–441.
24. Askari M, Fisher C, Weniger FG, Bidic S, Lee WP. Anticoagulation therapy in microsurgery: A review. J Hand Surg Am 2006;31:836–846.
25. Olsson E, Svartling N, Asko-Seljavaara S, Lassila R. Activation of coagulation and fibrinolysis during reconstructive microsurgery in patients with cancer. Microsurgery 2001;21:208–213.
26. Wang TY, Serletti JM, Cuker A, McGrath J, Low DW, Kovach SJ, Wu LC. Free tissue transfer in the hypercoagulable patient: A review of 58 flaps. Plast Reconstr Surg 2011;129:443–453.

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Low molecular weight heparin in patients undergoing free tissue transfer following head and neck ablative surgery: review of efficacy and associated complications

Karen A. Eley [a,*], Rachel J. Parker [b], Stephen R. Watt-Smith [a]

[a] *Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, United Kingdom*
[b] *Blood Safety and Conservation Team, Oxford University Hospitals NHS Trust, Headley Way, Oxford OX3 9DU, United Kingdom*

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Abstract

Most microsurgeons report the use of anticoagulants in their routine practice. Anti-Xa concentrations are preferentially used to monitor treatment with low molecular weight heparin (LMWH). The aim of this retrospective study was to measure the therapeutic response to standard dosing with LMWH (using anti-Xa) in patients after ablative and reconstructive surgery for head and neck cancer, and to review the associated risk of bleeding. We retrospectively reviewed 153 patients who had undergone resection of primary or recurrent tumours of the head and neck with free flap reconstruction. In total, 173 free flap procedures were completed. Medical records were reviewed to find the anticoagulation regimen used, anti-Xa result, patients' weight, and any associated complications. Fourteen patients returned to theatre because of bleeding; of these no cause was identified in 6 and a haematoma was evacuated. The distribution of unexplained haematoma was similar for all dose regimens of dalteparin. Anti-Xa results were available in 47 cases, and of these, 22 (47%) were within the prophylactic range (0.2 IU/ml or more). Our results highlight the high incidence of inadequate response to standard prophylactic doses of LMWH in patients with head and neck cancer. Increasing the dose of dalteparin does not seem to increase the risk of bleeding or formation of a haematoma. These findings may be transferable to other surgical specialties.

Keywords: Anti Xa; Free flap; Anticoagulation; Complication; Haematoma; LMWH; Heparin; Dalteparin; Head and neck malignancy

Introduction

Microvascular free tissue transfer is a reliable technique for reconstruction of the head and neck, with a reported success of 90–99%.[1] However, despite improvements in technical expertise there remains an appreciable risk of anastomotic thrombosis, most notable within the first 48 hours, with resultant disastrous consequences.[2] The use of anticoagulants after free tissue transfer is controversial and practices vary,[3,4] but in an international survey of the management of free flaps in 1989, Salemark[5] reported that prophylactic antithrombotic agents were used in 91% of centres. Today, the most commonly used agents seem to be aspirin and low molecular weight heparin (LMWH). These are used to minimise the risk of anastomotic thrombosis and as prophylaxis against venous thromboembolism (VTE) in patients who are typically immobile after prolonged operations. However, these agents are not without risk, which include bleeding, haematoma, thrombocytopenia, and gastric irritation. LMWH has broadly replaced unfractionated heparin (UFH) because it has better pharmacokinetic properties and an improved safety profile.[6] With only a moderate prolonging of the activated partial thromboplastic time, measurement of anti-Xa concentrations are preferentially used to monitor LMWH therapy.[7] For dalteparin the recommended peak anti-Xa concentration is 0.5–1.0 IU/ml or 1.0–2.0 IU/ml for full anticoagulation with twice daily and once daily dosing,

* Corresponding author.
E-mail addresses: Karen.a.eley@gmail.com (K.A. Eley), Rachel.parker@ouh.nhs.uk (R.J. Parker), Steve.watt-smith@ndm.ox.ac.uk (S.R. Watt-Smith).

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respectively; and 0.2–0.4 IU/ml for prophylactic anticoagulation for VTE.[7,8] The same regimen for prophylaxis is routinely used for all patients post-operatively, irrespective of their body mass index. The aim of this retrospective study was to measure the therapeutic response to standard doses of LMWH in patients (using anti-Xa concentrations) after ablative and reconstructive surgery for head and neck cancer, and to review the associated risk of haematoma for the varying dose regimens.

Patients and methods

Between 2006 and 2009 we retrospectively reviewed all patients at our unit who had ablative surgery for head and neck cancer with free tissue transfer. Patients' medical records and the departmental database were used to obtain information relating to prescription of anticoagulants, pre-operative weight, comorbidity, and post-operative morbidity. Comorbidity was assessed using the Adult Comorbidity Evaluation-27 (ACE-27) scoring system, which has four grades of decompensation: none, mild, moderate, and severe.[9] The presenting tumour was not included in this scoring process. At the time of the study routine prophylaxis included dalteparin 5000 IU once daily with or without aspirin 75 mg once daily post-operatively. We recorded the anti-Xa results and incidence of bleeding that required a return to the operating theatre. Since the end of 2008 we have requested anti-Xa concentrations 4 hours after the initial dose of dalteparin with subsequent adjustment of dose, to ensure optimal treatment with LMWH. Only those results of anti-Xa tests which could be confidently confirmed as being done at the correct time interval were included for data analysis. The prophylactic range (at 4 hours) was considered to be 0.2–0.4 IU/ml. For the purpose of this study, we considered that post-operative haematoma and bleeding for which no cause was found were related to the anticoagulant given. Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS version 18.0, IBM, USA). Descriptive analysis was first completed using histograms, box plots, and scatter plots. Statistical comparison was done using paired Student's *t*-tests and Chi square tests. Probabilities of 0.05 were considered significant.

Results

Of the 153 patients, 18 underwent more than one free flap procedure (16 had 2 procedures; 2 had 3 procedures) as a result of recurrence ($n=3$), a second primary tumour ($n=3$), to aid function ($n=7$), or due to flap failure ($n=7$) (Table 1). Three further flaps failed, and patients subsequently had delayed or pedicled reconstruction. In 5 cases the flap was successfully salvaged (including treatment with leeches, $n=1$), and a further 2 patients lost an area of skin paddle.

Fourteen patients required a return to theatre because of bleeding. In 8 of these an active bleed was identified secondary to loose Ligaclips (Ethicon) ($n=1$), bleeding from the anastomosis ($n=1$), erosion of a vessel by a drain ($n=1$), or another identified bleed from a vessel ($n=5$). However, in 6 no active bleeding was identified and a haematoma was evacuated. Table 1 shows the ACE-27 score, age, and weight for the three groups. The distribution of unexplained haematoma, was similar for all dalteparin regimens (Table 2, Fig. 1), and the difference between groups was not significant ($p=0.71$).

Most patients had dalteparin with or without aspirin (Table 3). Nine patients were managed post-operatively with

Table 1
Patients' details, comorbidities, and free-flap reconstruction by bleeding complications.

	Return to theatre for bleeding ($n=14$)		No bleeding complications ($n=159$)
	Cause identified ($n=8$)	Cause not identified ($n=6$)	
Sex			
Male	5	3	93
Female	3	3	66
Mean (SD) age (years)	54 (16)	66 (16)	61 (14)
Mean (SD) weight (kg)	82 (14)	60 (7)	71 (18)
ACE-27			
0	3	2	55
1	4	4	89
2	1	0	15
Free flap			
Radial	4	4	93
ALT	1	1	18
Fibula	2		21
Latissimus dorsi	–	1	9
Fibula and radial	1	–	8
Fibula and ALT	–	–	5
Fibula and latissimus dorsi	–	–	1
Other	–	–	4

ALT: anterolateral thigh flap.

Table 2
Dalteparin prescription in patients with no bleeding or haematoma and in those with unexplained post-operative haematoma. Data are number (%).

Dalteparin dose (IU)	No bleeding complications ($n = 159$)	Active bleeding identified at return to theatre ($n = 8$)	Unexplained haematoma ($n = 6$)
2500 once a day	7 (5)	0	0
5000 once a day	100 (63)	5	4
5000 twice a day	34 (21)	1	2
7500 or more once a day	18 (11)	2	0

Table 3
Anticoagulation regimen and number of associated bleeding complications.

	Dalteparin dose (IU)								
	2500 once a day		5000 once a day		5000 twice a day		7500 or more once a day		Total
	Aspirin	No aspirin	Aspirin	No aspirin	Aspirin	No aspirin	Aspirin	No aspirin	
No complications	5	2	71	29	19	15	13	5	159
Identified bleed	0	0	4	1	1	0	2	0	8
Haematoma	0	0	3	1	2	0	0	0	6
Total	5	2	78	31	22	15	15	5	173

UFH, and 5 were ultimately started on warfarin because of thrombosis within the internal jugular vein or problematic flap salvage, or both. There were no complications identified in those managed with UFH.

Anti-Xa results were available in 47 cases, and a further test done in three patients after the dose of dalteparin had been adjusted (Fig. 2). Of these, 22 (44%) were within the prophylactic range (0.2 IU/ml or more) (Table 4). The mean (SD) weight of patients with anti-Xa concentrations of less than 0.2 IU/ml was 84 (24) kg (range 48.5–157), and for those with a concentration of 0.2 IU/ml or more it was 65 (12) kg (range 45–86). There was a strong negative correlation ($p = 0.01$) with the anti-Xa result with increasing weight. The anti-Xa concentration improved in 2 of the 3 patients who had the dose adjusted. Of the 47 cases with anti-Xa results there were six flap complications. One was successfully salvaged, but 5 were ultimately lost. All but two anti-Xa results were below 0.2 IU/ml, with patients receiving a dalteparin dose of 5000 IU every day.

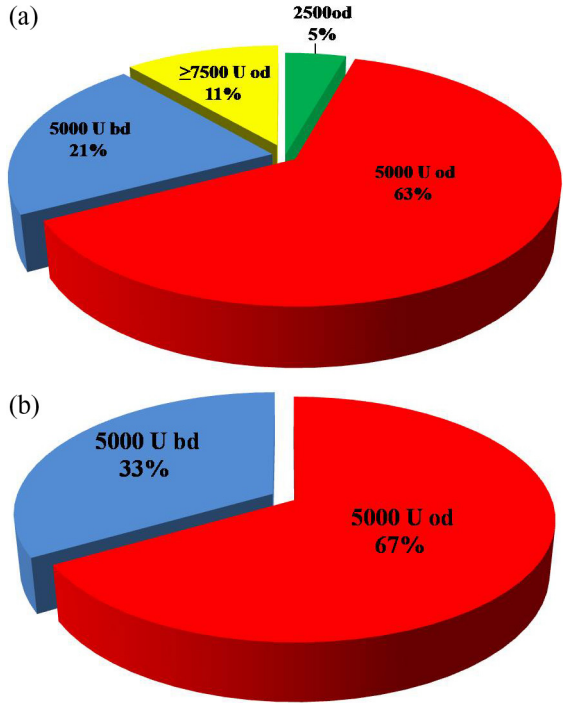

Fig. 1. Distribution of dalteparin prescription in patients with no bleeding/haematoma complications (a) and those experiencing unexplained haematoma (b).

Anti-Xa results were available in 8 of 14 patients who required a return to theatre because of bleeding or haematoma. Of these 5 had identified vessel bleeding in whom only 2 had anti-Xa concentrations within the prophylactic range (mean 0.13; range 0.01–0.24). Of the remaining three patients with a haematoma, two had anti-Xa concentrations within the prophylactic range (mean 0.26; range 0.1–0.47).

One patient, an 82-year-old man, was treated for suspected post-operative pulmonary embolism, although there was some doubt associated with the diagnosis. He weighed 70 kg and had a mandibulectomy and reconstruction with a fibula free flap. He had been prescribed dalteparin 5000 IU twice daily with no adjuvant aspirin. Anti-Xa concentration was not measured.

Table 4
Result of anti-Xa tests in 47 cases with varying doses of dalteparin (three patients had repeat tests).

Dalteparin dose (IU)	Anti-Xa concentration (U/ml)	
	Less than 0.2	0.2 or more
2500 once a day	6	0
5000 once a day	18	14
5000 twice a day	2	5
7500 or more once a day	2	3

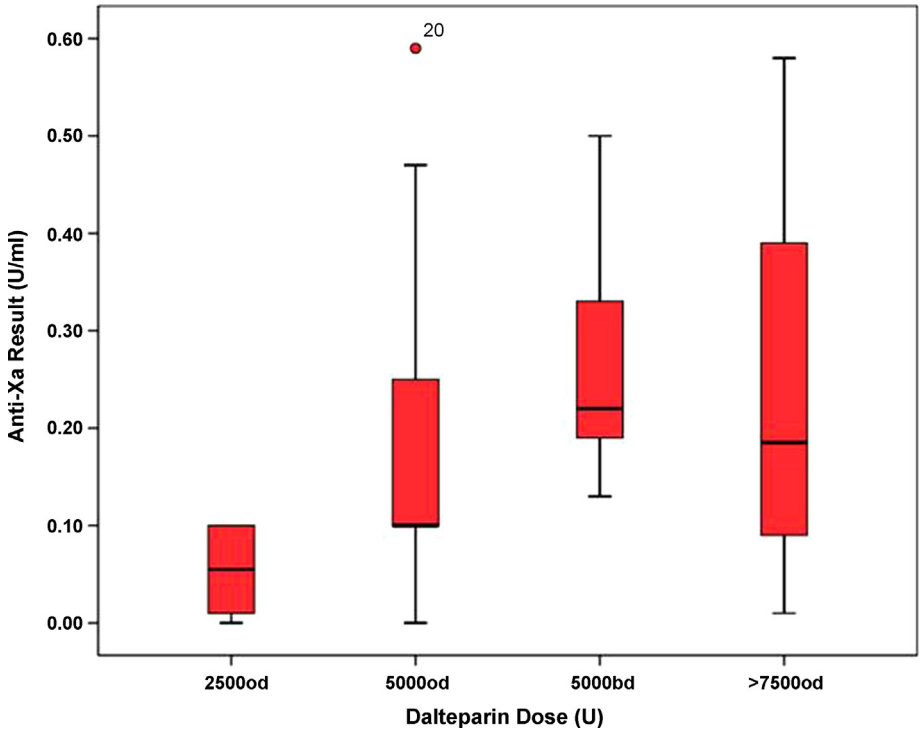

Fig. 2. Box plot of anti-Xa results with varying dalteparin dose.

Discussion

It has been shown that anti-Xa results strongly correlate with mean patient weight, which is consistent with studies on the anti-Xa response to dalteparin in those who are obese.[10] It implies that standard dose regimens are not suitable for all patients. However, despite a variable anti-Xa response to prophylactic regimens in routine clinical practice, prescription is rarely adjusted according to a patient's weight. The results available from the manufacturer state that mean (SD) peak (4 hour) concentrations of anti-Xa in trials after single doses of 2500, 5000, and 10,000 IU of dalteparin were 0.19 (0.04), 0.41 (0.07), and 0.82 (0.10) IU/ml, respectively.[11] However, in our study, a dose of 2500 IU was rarely enough to bring the anti-Xa concentration into the prophylactic range.

Measuring anti-Xa concentrations in patients and adjusting the dose of dalteparin seems to be a safe and reliable way to ensure efficacy. In our group 56% had an anti-Xa concentration below 0.2 IU/ml, which is not deemed sufficient for prophylaxis. Although the dose was adjusted, few had a repeat test to find out the resultant effect. Of the three patients who did, the result in one was still not in the prophylactic range.

Our results are limited by the retrospective nature of the study. The accuracy of the anti-Xa results rely on clear documentation of the time that dalteparin was given and venepuncture done. While most patients were cared for in the intensive care unit, which uses electronic administration records, it is anticipated that some blood tests for anti-Xa concentrations were not perfectly timed. Patients with head and neck malignancy are typically advanced in age and have multiple comorbidities. This can prolong recovery, reduce mobility, and increase the risk of VTE, which is further heightened by the procoagulant effects associated with malignant disease. Despite a high proportion of patients having anti-Xa concentrations below the prophylactic range, the incidence of VTE in our group was low with only one case identified. However, since the anti-Xa concentration was not measured in this patient, it is impossible to know whether the dose of dalteparin was appropriate. It is possible that the incidence of VTE was under-reported as a result of patients being treated at peripheral hospitals after discharge, although it would be expected that such treatment would be reported to the operating surgeon and documented in the medical records. Further contributing factors that reduced the incidence of VTE in this group include the intraoperative and early post-operative use of pneumatic compression devices, antithrombotic stockings, and where possible, early mobilisation.

The adverse outcomes in patients with acute coronary syndrome and anti-Xa concentrations below the therapeutic range have been reported,[12] but we know of no such relation reported after flap surgery. A number of factors may interfere with the effectiveness of LMWH given subcutaneously in patients with head and neck cancer including low cardiac output, reduced peripheral blood flow, or subcutaneous oedema during the early post-operative period.[13] This further highlights the benefit of routine monitoring of anti-Xa.

While LMWH reduces the risk of VTE, the benefits for free flaps remain uncertain. Animal studies have shown that dalteparin prevents arterial thrombosis as effectively as

UFH.[14,15] Reported success rates for free tissue transfer in head and neck malignancy are 90%–96%,[16–19] which are consistent with our findings. Of the 10 flaps lost, anti-Xa results were available in 5, and only 2 of these were in the therapeutic prophylactic range. In most cases flaps failed after the critical 48-hour post-operative period. Potential contributing factors leading to failure include pregnancy, diabetes mellitus, and cardiorespiratory diseases. Olsson et al.[20] noted that of two patients with anastomotic thromboses, both had anti-Xa concentrations below 0.3 IU/ml, and that pre-operative anticoagulation with 2500–5000 IU was not reliable.

The ideal anticoagulant for free flap surgery would not only effectively reduce thrombosis in the pedicle, but would do so with minimal adverse side effects. Statins, in view of their vasoprotective action, anticoagulation, and anti-inflammatory properties, are potential alternatives to traditional anticoagulants, but currently no intravenous preparations are available. In our group, 35 patients (20%) were on statins at the time of surgery, and of these, 5 had flap or haematological complications, or both (lost flap $n = 2$; identified bleed $n = 2$; haematoma $n = 1$). In view of the small numbers the data fail to yield any significant correlations, but there is certainly scope for future research. The risk, in terms of bleeding or formation of a haematoma, did not seem to be influenced by the dose of dalteparin, or prescription of aspirin. Since all patients were given heparin in some form, and only a very small number were managed with UFH, it is not possible to compare these findings with those encountered with UFH or in the absence of anticoagulation. Previous studies have reported that LMWH has a substantially reduced risk of adverse side effects, including formation of a haematoma when compared with UFH.[21] However small, the use of LMWH carries risk, but this seems to be outweighed by the prophylactic benefits. Our results highlight the high incidence of inadequate response to standard prophylactic doses of LMWH in patients with head and neck cancer. These findings may be transferable to other oncological surgical specialties.

Conflict of interest

The authors have no conflicts of interest.

References

1. Kruse AL, Luebbers HT, Gratz KW, et al. Factors influencing survival of free-flap in reconstruction for cancer of the head and neck: a literature review. *Microsurgery* 2010;**30**:242–8.
2. Ashjian P, Chen CM, Pusic A, et al. The effect of postoperative anticoagulation on microvascular thrombosis. *Ann Plast Surg* 2007;**59**:36–40.
3. Fosnot J, Jandali S, Low DW, et al. Closer to an understanding of fate – the role of vascular complications in free flap breast reconstruction. *Plast Reconstr Surg* 2011. Epub ahead of print June 15.
4. Chen CM, Ashjian P, Disa JJ, et al. Is the use of intraoperative heparin safe? *Plast Reconstr Surg* 2008;**121**:49e–53e.
5. Salemark L. International survey of current microvascular practices in free tissue transfer and replantation surgery. *Microsurgery* 1991;**12**:308–11.
6. Hammerstingl C. Monitoring therapeutic anticoagulation with low molecular weight heparins: is it useful or misleading? *Cardiovasc Hematol Agents Med Chem* 2008;**6**:282–6.
7. Wilson SJ, Wilbur K, Burton E, et al. Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low-molecular-weight heparin for the treatment of venous thromboembolism. *Haemostasis* 2001;**31**:42–8.
8. Lim W, Dentali F, Eikelboom JW, et al. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med* 2006;**144**:673–84.
9. Piccirillo JF, Tierney RM, Costas I, et al. Prognostic importance of comorbidity in a hospital-based cancer registry. *J Am Med Assoc* 2004;**291**:2441–7.
10. Smith J, Canton EM. Weight-based administration of dalteparin in obese patients. *Am J Health System Pharm* 2003;**60**:683–7.
11. Pfizer. *Fragmin dalteparin sodium injection*. Available from: http://www.pfizer.com/files/products/uspi_fragmin.pdf, 2007.
12. Montalescot G, Collet J, Tanguy M, et al. Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin. *Circulation* 2004;**110**:392–8.
13. Rommers M, Van Der Lely N, Egberts T, et al. Anti-Xa activity after subcutanous administration of dalteparin in ICU patients with and without subcutaneous oedema: a pilot study. *Crit Care* 2006;**10**(3):R93. Epub 21 June 2006.
14. Karsenti G, Le Manach Y, Bouvier S, et al. Statins: a new pharmacological agent for free flap surgery? *J Plast Reconstr Aesthet Surg* 2010;**63**:870–4.
15. Malm K, Dahiback B, Arnlijots B. Low-molecular-weight heparin (dalteparin) effectively prevents thrombosis in a rat model of deep arterial injury. *Plast Reconstr Surg* 2003;**111**:1659–66.
16. Eckardt A, Meyer A, Laas U, et al. Reconstruction of defects in the head and neck with free flaps: 20 years experience. *Br J Oral Maxillofac Surg* 2007;**45**:11–5.
17. Chen CM, Lin GT, Fu YC, et al. Complications of free radial forearm flap transfers for head and neck reconstruction. *Oral Surg Oral Med Oral Path Oral Radiol Endod* 2005;**99**:671–6.
18. Wolff KD, Hölzle F, Wysluch A, et al. Incidence and time of intraoperative vascular complications in head and neck malignancy. *Microsurgery* 2008;**28**:143–6.
19. Bianchi B, Copelli C, Ferrari S, et al. Free flaps: outcomes and complications in head and neck reconstructions. *J Cranio-Maxillo-Facial Surg* 2009;**37**:438–42.
20. Olsson E, Svartling N, Asko-Seljavaara S, et al. Activation of coagulation and fibrinolysis during reconstructive microsurgery in patients with cancer. *Microsurgery* 2001;**21**:208–13.
21. De A, Roy P, Garg VK, et al. Low-molecular-weight heparin and unfractionated heparin in prophylaxis against deep vein thrombosis in critically ill patients undergoing major surgery. *Blood Coagul Fibrinolysis* 2010;**21**:57–61.

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Letters to the Editor

Coagulopathies and the use of LiDCO *Plus* Rapid monitoring in patients following head and neck cancer resection and reconstruction

Sir,

We read with interest the short communication by Abdel-Galil et al.[1] regarding the intraoperative use of the LiDCO™ *Plus* Rapid monitoring device (LiDCO Ltd, Cambridge, UK). As described in our letter of 2009,[2] and at the BAOMS Annual Conference in 2009, we can attest to its benefits.

We have been using LiDCO™ *Plus* Rapid for patients undergoing major head and neck surgery for the past 3 years - introduced as part of an ongoing research study on the effects of pressors on free tissue transfer.

We reported the ease of use of this system in our patients in whom invasive arterial pressure monitoring is frequently employed. Optimising fluid balance is paramount to minimise post-operative morbidity and flap survival. The results of our 3 year retrospective review of patients undergoing head and neck cancer resection and reconstruction prior to and following introduction of LiDCO™ *Plus* Rapid monitoring (146 free flap procedures), demonstrated that the key benefits were a reduction in intra-operative fluid administration, (when taking urine output and operative procedure length into account the LiDCO™ group received less fluid per hour ($p < 0.04$)) and decreased post-operative hospital stay ($p < 0.02$).

Unlike Abdel-Galil et al.[1] we do not routinely use a strict protocol for fluid bolusing, but we have noted that during operation colloids are used more than crystalloids when using LiDCO™ *Plus* Rapid. In view of this, attention needs to be paid to the potential adverse effects of induced coagulation abnormalities associated with artificial colloids.

Patients with cancers of the head and neck are commonly susceptible to coagulopathies, and we encounter prothrombotic complications in roughly 5% of our patients. We therefore disagree with the statement of Felstead and Perkins[3] that thrombosis within the internal jugular vein is rare. The key to successful management of these patients is the appropriate selection of anticoagulation treatment, and we reported in Shanghai that standard prescription, low molecular weight heparin is frequently insufficient. We use thromboelastography (TEG)[4] to monitor our patients perioperatively, and we monitor the dalteparin response by measuring anti-Xa. This is another aspect to our ongoing research.

We continue to investigate the use of the LiDCO™ Plus *Rapid* system in monitoring our patients, and welcome the results of a prospective randomised controlled trial by Abdel-Galil et al.

References

1. Abdel-Galil K, Craske D, McCaul J. Optimisation of intraoperative haemodynamics: early experience of its use in major head and neck surgery. *Br J Oral Maxillofac Surg* 2010;**48**:189–91.
2. Eley KA, Watt-Smith SR. Re: Postoperative fluid balance in patients having operations on the head and neck. *Br J Oral Maxillofac Surg* 2009;**47**:249.
3. Felstead AM, Perkins CS. Thrombosis of the internal jugular vein: a rare but important operative finding. *Br J Oral Maxillofac Surg* 2010;**48**:195–6.
4. Mitchell DA, Gorton H. Thromboelastographic study of the effect of manipulation of central veins on coagulability of venous blood. *Br J Oral Maxillofac Surg* 2005;**43**:215–8.

Karen A. Eley *
Stephen R. Watt-Smith
Department of Oral & Maxillofacial Surgery, Oxford Radcliffe Hospitals NHS Trust, Headley Way, Oxford OX3 9DU, United Kingdom

* Corresponding author. Tel.: +44 01865 743103.
E-mail addresses: Karen.a.eley@gmail.com (K.A. Eley), Steve.watt-smith@ndm.ox.ac.uk (S.R. Watt-Smith)

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Wire loop technique for retrieval and reduction of the displaced condylar fragment

Sir,

I have read the paper by Jones SD, et al.[1] with interest, and would like to mention several technical matters that I think are important.

The screw technique described necessitates the use of a rotary instrument deep in the infratemporal fossa, which

production will be presented. The implants were produced for a particular patient individually with high accuracy in order to achieve not only fully functional, but also aesthetic defect replacements.
Conclusion: Individual implants compensate the loosed function and repair patient's aesthetic visage, reduce time necessary for surgery and are comfortable for surgeons during the surgery.

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P180
Suction drainage of odontogenic keratocysts of the mandible

B. Liu*, **Y.F. Zhao**, **W.F. Zhang**
Department of Oral and Maxillofacial Surgery, School of Stomatology, Wuhan University, Wuhan, Hubei Province, China

Background and Objectives: The aim of this study was to evaluate the effects of suction drainage on odontogenic keratocysts (OKCs) of the mandible and its role in conjunction with curettage. To analyse the effect of suction drainage on Ki-67 and IPO-38 labelling indices of odontogenic keratocysts before and after suction drainage.
Methods: Biopsy and suction drainage were performed simultaneously in 39 cases of OKC of the mandible. Clinical and radiological examinations of these patients were carried out regularly. The curettage via intraoral incision was completed until the extent of disease significantly shrunk. The volume of the cavity and area of the cyst on a panoramic radiograph were measured preoperatively and postoperatively. The labelling index (LI), employing two cell proliferation markers IPO-38 and Ki-67, was studied by the immunohistochemical technique. From preoperative and postoperative specimens of each case were stained with monoclonal antibodies for IPO-38 and Ki-67 respectively. The labelling indices for Ki-67 and IPO-38 were recorded and compared between fields. Comparison was made between preoperative and postoperative labelling indices.
Results: After a mean duration of suction drainage of 5.5 months, the size of OKCs had shrunk by a mean of 62.4% based on the panoramic radiographs findings. A parakeratinised epithelium was transformed into a hyperplastic, stratified, non-keratinising squamous epithelium after suction drainage in 37 cases (94.9%), and higher inflammatory density was found postoperatively than preoperatively. Postoperatively, there was higher inflammatory density in metaplastic epithelium than in classic OKC epithelium. The radiolucent area of cyst on a panoramic radiograph was linearly related to the volume in the cavity. The average LIs for Ki-67 and IPO-38 were lower postoperatively than preoperatively, and with LI for Ki-67 significantly lower ($P = 0.021$). When postoperative LI for Ki-67 in metaplastic epithelium was compared with that in classic parakeratinised epithelium, there was a decreased LI in the former ($P = 0.033$). No complication occurred after curettage and no recurrence appeared with an average follow-up of 4 years.
Conclusions: It appears that suction drainage resulted in the classic parakeratinised epithelium of OKC transformed histologically to metaplastic squamous epithelium and induced new bone formation surrounding the cyst. It preserved anatomical structures and reduced recurrence after secondary curettage.

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P181
Clinical and patient subjective evaluation of different reconstruction methods in mandibular defects

Q. Wan
Department of Oral and Maxillofacial Surgery, School of Stomatology, Wuhan University, Wuhan, Hubei Province, China

Background and Objectives: To evaluate retrospectively the clinical and patient subjective outcomes of different reconstruction methods in mandibular defects.
Methods: A retrospective analysis of 254 patients undergoing reconstruction of mandibular defects over the past 15 years was performed. The patients were divided into four groups according to the reconstruction methods: free bone grafts (FBG group; n = 122); particulate bone cancellous marrow grafts (PBCM group; n = 91); reconstruction plates (RP group; n = 22); microvascular free flaps (MFF group; n = 19). The clinical history review, clinical and radiological examination, and questionnaires were performed to compare the survival rates, complication rates, functional and aesthetic results among four groups. Sample characteristics were described with descriptive statistics and comparisons of results among the groups were made with Fisher exact tests (alpha = 0.05).
Results: The mean follow-up was 58.7 months (range, 3–176 months), lost 31 patients. 9 patients died, survival rate was lowest in RP group ($P = 0.02$). 14 patients had complications, complication rates were no significant different among four groups ($P = 0.45$). The functional and aesthetic comparison showed that mastication, diet, satisfaction of facial appearance, oral continence, social activities, and speech were no significant different among four groups ($P > 0.05$ respectively). The bite force was lowest in RP group ($P = 0.012$).
Conclusions: This study demonstrates that clinically and patient subjectively evaluated results of the four reconstruction methods were no significant different. According patient's etiopathogenesis, diseased region, treatment planning, age, sexuality, and occupation, etc., to choose the optimal method for each patient is the key factor to get the best prognosis.

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P182
Are routine prophylactic dalteparin doses appropriate in patients undergoing head and neck cancer resection and reconstruction?

S.E. Bond
Department of Maxillofacial Surgery, The John Radcliffe Hospital, Headington, Oxford, United Kingdom

The use of free flap surgery for reconstruction following head and neck cancer has become routine practise. Intra- or postoperative anastomotic thrombosis is the leading cause of flap failure occurring most frequently during the first two postoperative days. In an attempt to address this, approximately 96% of microsurgeons report to routinely use anticoagulants. Additionally, this group of patients are at increased risk of postoperative venous thromboembolism (VTE), and the need for adequate prophylaxis critical. Low molecular weight heparins (LMWH) have broadly replaced unfractionated heparin due to more preferable pharmacokinetics and a better safety profile. With only a moderate prolonging effect on the activated partial thromboplastic time, anti-Xa levels are preferentially used to monitor LMWH therapy. For dalteparin the manufacturer recommends the peak anti-Xa level to be 0.5–1.0 U/mL and the trough > 0.1 U/mL. The adverse outcomes in patients with acute coronary syndrome with subtherapeutic anti-Xa levels have been reported. The aim of this study was to review the anti-Xa response to standard dalteparin prophylaxis in patients following free flap surgery for head and neck

cancer. We retrospectively reviewed 50 patients undergoing head and neck cancer surgery at our unit between January and December 2008. Following complications secondary to anastomotic thrombosis, we recently introduced close anticoagulant monitoring in our patients to include routine thromboelastogram, and anti-Xa levels following dalteparin administration in patients deemed to be at increased risk. Current postoperative prophylaxis in use includes aspirin 75 mg (following a 300 mg loading dose on day 1 postoperative), and dalteparin 5000 units once daily. Anti-Xa results were available in 17 patients. Review of these results revealed that all but one patient had levels identifying subtherapeutic levels of anticoagulation, necessitating increased dosages of dalteparin. With close attention to adequate anticoagulation, none of these 17 patients experienced flap failure or VTE. Certainly the potential non-response to standard dalteparin dosing may have been predicted in those patients with high body mass index, although data evaluating the safety of using weight-based doses of LMWH in obese patients are limited. A number of factors might interfere with the effectiveness of subcutaneous administrated LMWHs in head and neck cancer patients, including low cardiac output, decreased peripheral blood flow, or subcutaneous oedema during the early postoperative period. These preliminary results highlight the high frequency of inadequate response to standard prophylactic LMWH dosing in patients with head and neck cancer, warranting further investigation.

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P183
Is the ratio of functional fibrinogen to platelets as measured by thromboelastography a predictive parameter for thrombotic complications in free tissue transfer surgery?

R. Parker, **K.A. Eley**, **S.E. Bond***, **S.R. Watt-Smith**
Department of Maxillofacial Surgery, The John Radcliffe Hospital, Headington, Oxford, United Kingdom

The risk of total flap loss after free microvascular tissue transfer is estimated to be between 2 and 6%. Flap failure is most frequently due to anastomotic thrombosis, occurring in the early postoperative period. The exact causes of events leading to thrombotic occlusion still are not clearly elucidated, although authors have observed detrimental effects of increased platelet counts, platelets aggregation, and elevation of fibrinogen levels on flap survival. In patients with hyperfibinogenemia related to oral cancer, the safety of performing a successful microsurgical procedure for complex tissue defects has been debated, and the correlation between hyperfibrinogenemia and vascular thrombosis in microsurgery remains unclear. Rodent research suggests no significant difference in the platelet counts associated with hyperfibrinogenemia, yet increased plasma fibrinogen levels are associated with increases in platelet aggregability. Observation of our patients undergoing free tissue transfer in the head and neck subjectively revealed increased flap failure associated with both elevations in fibrinogen and platelet levels. We retrospectively reviewed 42 patients undergoing free tissue transfer following head and neck cancer resection. The ratio of preoperative fibrinogen to platelet was calculated for each patient preoperatively. A control group of normal fibrinogen to platelet ratio results were obtained from 49 healthy volunteers. Fibrinogen to platelet ratios in patients with head and neck cancer preoperatively were significantly higher ($P < 0.001$) than this control group. In total, seven patients (17%) experienced major graft failure secondary to thrombotic events. Two of these patients had intraoperative thrombotic events. The preoperative fibrinogen to platelet ratio was above 50% in six patients, correctly identifying their increased thrombotic tendency. In the one patient with a preoperative ratio of 34%, postoperative results demonstrated continuing elevating ratios, which may have highlighted forthcoming flap failure. These preliminary results suggest that the use of preoperative fibrinogen to platelet ratios may aid in identifying patients at increased risk of anastomotic thrombosis.

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P184
Structural characteristics of the asymmetric mandible revealed by three-dimensional computed tomography

W. Park*, **J.Y. Kim**, **J.W. Choi**, **B.C. Kim**, **S.H. Lee**
Department Advanced General Dentistry and Department of Oral and Maxillofacial Surgery, Dental Hospital, Yonsei University, Seodaemungu, Seoul, Korea

Background and Objectives: Facial asymmetry is one of the most complex dentofacial deformity. To achieve good postoperative results, accurate diagnosis and proper treatment planning is mandatory. To analyse three-dimensional bony architecture and structure, 3D computed tomography (CT) is very effective method. Although 3D CT image can show exact 3D image in virtual space, there is no definite protocol for analysing complex craniofacial structures. In this study, we tried to compare the 3D characteristics of mandible between symmetric and asymmetric patients in 3D CT.
Methods: 40 dataset of deformity patients were used in this study. 20 patients were facial asymmetry and 20 patients were mandibular prognathism without facial asymmetry. After setting proper midsagittal plane, reference points which can represent facial growth and development. With these highly reproducible reference points, 3D structural analysis was performed and compared with both groups.
Results: Condylar length showed remarkable difference in asymmetric group than symmetric group. However, not only the condylar length but also angular components showed difference in asymmetric group. This result means that facial asymmetry is complex linear, angular difference in affected and non-affected site.
Conclusions: 3D evaluation of asymmetric mandible gives much information to understand asymmetric dentofacial deformity. This information will be very useful knowledge in treatment planning facial asymmetry.
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P185
Instant reconstruction of defect of oral cancer with composite flaps

H. Zhu*, **J. He**
Department of Oral and Maxillofacial Surgery, Shanghai Ninth People's Hospital, Shanghai, China

Background and Objectives: Large area defect will be remained for radical resection of cranial-maxillofacial region in some of the advanced oral cancer. It seriously affects the masticatory and linguistic function and the appearance of the patients. Composite flaps were designed to accomplish one-stage repair large defect after oral cancer operation.
Methods: From June 1998 to June 2006, 8 composite flaps were designed to repair

Are routine prophylactic Dalteparin doses appropriate in patients undergoing head and neck cancer resection and reconstruction?

Miss Karen A Eley[1], Ms Rachel Parker[2],
Mr Stephen E Bond[3], Mr Stephen R Watt-Smith[3]
Department of Oral & Maxillofacial Surgery, Oxford Radcliffe Hospitals NHS Trust, Headley Way, Oxford OX3 9DU, UK

INTRODUCTION:

The use of free flap surgery for reconstruction following head and neck cancer has become routine practise. Intra-or post-operative anastomotic thrombosis is the leading cause of flap failure[1,2] occurring most frequently during the first two postoperative days[1]. Additionally, this group of patients are at increased risk of post-operative venous thromboembolism[3], and the need for adequate prophylaxis critical. In an attempt to address this, approximately 96% of microsurgeons report to routinely use anticoagulants[1].

Low molecular weight heparins (LMWH) have broadly replaced unfractionated heparin due to more preferable pharmacokinetics and improved safety profile[4]. With only a moderate prolonging effect on the activated partial thromboplastic time, anti-Xa levels are preferentially used to monitor LMWH therapy[5]. For Dalteparin the manufacturer recommends the peak anti-Xa level to be 0.5-1.0U/ml and the trough >0.1 U/ml[5,6]. The adverse outcomes in patients with acute coronary syndrome with subtherapeutic anti-Xa levels have been reported[7].

AIMS:

To determine the anti-Xa response to standard Dalteparin doses in patients following free flap surgery for head and neck cancer.

METHODS:

We retrospectively reviewed all patients undergoing free tissue transfer for head and neck cancer at our unit with respect to low molecular weight heparin dose and anti-Xa results. Standard Venous Thromboembolism (VTE) prophylaxis in our unit includes Aspirin 75mg, and Dalteparin 5000 IU/od. Between 2006 and 2009, the authors (SWS & SB) completed 150 free tissue transfer procedures spanning 133 surgical sessions and 114 patients for head and neck cancer or associated complications. The patient notes were unavailable for 7 patients. In total, Anti Xa results were available following 41 surgical procedures (35 patients).

RESULTS:

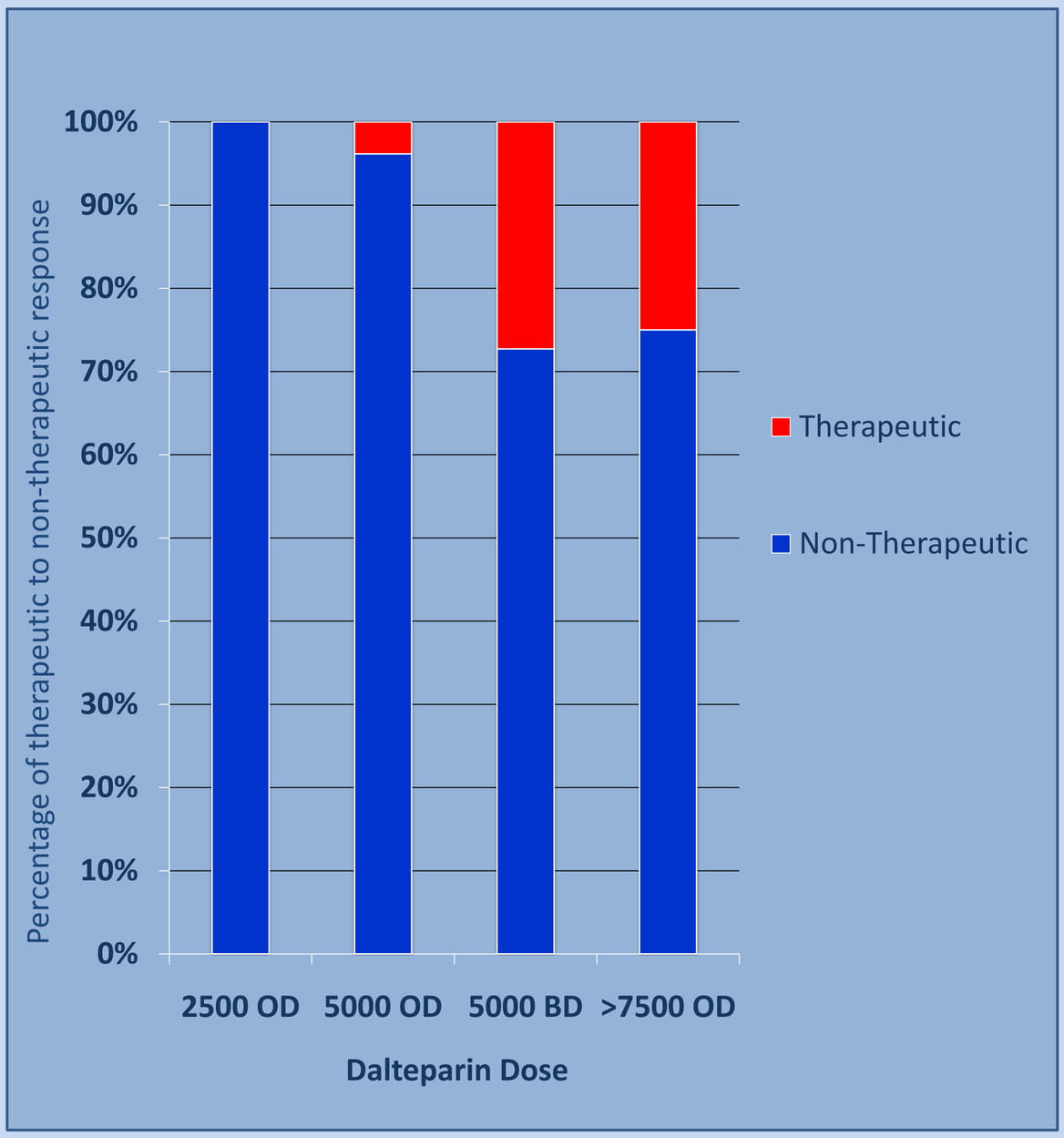
Therapeutic Dalteparin Dose

Dalteparin Dose	Therapeutic	Age (Years)	Weight (Kg)	Flap Failure
2500 OD	0	-	-	0
5000 OD	1	74	57	0
5000 BD	3	53 7	56.4 4	1
>7500 OD	1	88	84	0

Non-Therapeutic Dalteparin Dose

Dalteparin Dose	Non-Therapeutic	Age (Years)	Weight (Kg)	Flap Failure
2500 OD	5	63 12	82 16	0
5000 OD	25	59 12	77 24	4
5000 BD	8	54 12	88 35	0
>7500 OD	3	55 12	88 21	1

6 Patients were managed with IV Heparin, 4 of these were ultimately warfarinised



Day of Flap Failure in Non-Therapeutic Dalteparin Patients

	Day	Flap
5000 OD		
1	23	Fibula
2	8	Radial
3	35	Fibula
4	2	Fibula
>7500 OD		
1	22	Radial (partial loss)

Post-operative Day of Flap Failure in Therapeutic Dalteparin Patients

	Day	Flap
5000 od	13	Radial

DISCUSSION:

In total, only five patients had anti Xa results within the therapeutic range, only one of whom was on the standard dosage of 5000 units/od. There was significant flap morbidity associated with this dose regimen, with a flap loss rate of 16%. (n=4); with increased anticoagulation, two of these patients underwent successful free tissue transfer, and two had successful pedicled flaps. Of the 102 free flap procedures in which an anti Xa was not performed, 60 patients were given 5000 IU/od, with one flap requiring salvage, and two flaps lost; 32 patients were given 5000 IU/bd, with three flaps salvaged and four flaps lost; and five patients were given 7500 IU/od, with one flap salvaged, and one flap lost. The flap failure rate for this group was 7%.

Overall, one patient developed post-operative pulmonary embolism, whilst on 5000 units/bd (anti-Xa not performed), and the flap failure rate 9%.

Anti-Xa is more likely to be conducted on patients with concern regarding clotting, contributing to the higher incidence of flap failure in this group.

Studies suggest that standard prophylactic Dalteparin doses of 5000 units od are appropriate in hospitalised patients in preventing VTE.[9] Whilst prophylactic doses prevented VTE in all but one of our patients, the number of patients with anti-Xa results in the therapeutic range is small, potentially reflecting the prothrombotic potential of patients with head and neck malignancy.

CONCLUSIONS:

Standard prophylactic doses of Dalteparin, may not be suitable doses for use in patients with head and neck cancer undergoing free flap surgery, and anti-Xa monitoring is advocated.

REFERENCES:

1.Askari, M, et al. *Anticoagulation therapy in microsurgery: A review.* J Hand surgery, 2006, 31: 836-846.
2.Chen, CM, et al. *Is the use of intra-operative heparin safe?* Plast Rec surg, 2008
3.Linkins, LA. *Management of venous thromboembolism in patients with cancer: role of dalteparin.* Vascular health and risk management, 2008, 4: 279
4.Hammerstingl C**.** *Monitoring therapeutic anticoagulation with low molecular weight heparins: is it useful or misleading?* Cardagen med chem, 2008, 6: 282
5.Wilson, SJA, et al. *Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low-molecular-weight heparin for the treatment of venous thromboembolism.* Haemostasis, 2001, 31: 42-48.
6.Lim W et al. *Meta-analysis: Low-molecular-weight heparin and bleeding in patients with severe renal insufficiency.* Annals internal medicine, 2006, 144
7.Montalescot, G, et al. *Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin.* Circulation, 2004, 110
8.Rommers, MK, et al. *Anti-Xa activity after subcutanous administration of dalteparin in ICU patients with and without subcutanous oedema: a pilot study.* Crit Care, 2006
9.Kucher N et al. *Efficacy and safety of low dose dalteparin in preventing VTE among obese or elderly hospitalised patients* Arch Int Med 2005; 165: 341

[1]Miss Karen A Eley, MBChB, MRCS(Ed), is a Surgical Trainee & DPhil Student, Oxford
[2]Ms Rachel Parker, SOPD, is a Haemostasis Specialist , Oxford
[3] Mr Stephen E Bond, MBBS, BDS, FDS RCS, FRCS(Ed) (OMFS) & Mr Stephen R Watt-Smith, MBBS, BDS, FDSRCS, MD, are Consultants in Oral & Maxillofacial Surgery, Oxford

19th International Conference on Oral and Maxillofacial Surgery, Shanghai, May 2009

Is the ratio of functional fibrinogen to platelets as measured by thromboelastography a predictive parameter for thrombotic complications in free tissue transfer surgery?

Miss Karen A Eley, Miss Rachel Parker,
Mr Oliver Pearson, Mr Stephen E Bond, Mr Stephen R Watt-Smith

Department of Oral & Maxillofacial Surgery, Oxford Radcliffe Hospitals NHS Trust, Headley Way, Oxford OX3 9DU, UK

Introduction:

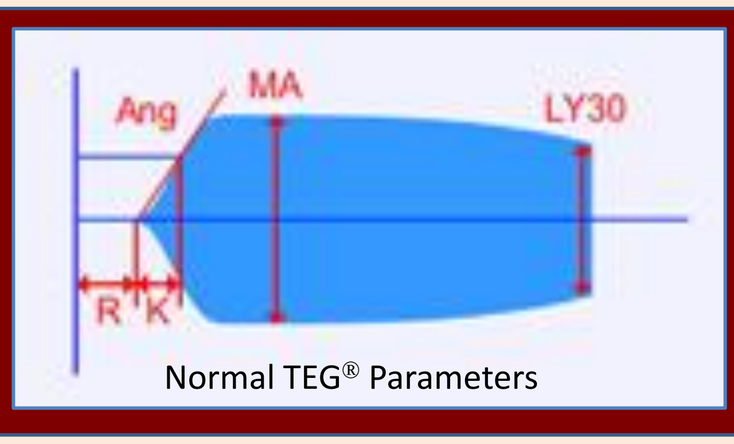
The risk of total flap loss after free microvascular tissue transfer is estimated to be between 2 and 6%[1], most frequently as a result of anastomotic thrombosis in the early postoperative period. The exact cause of thrombotic occlusion are unknown,[2] although authors have observed detrimental effects of increased platelet counts, platelet aggregation, and elevation of fibrinogen levels on flap survival.[3-5]

Rodent research suggests no significant difference in the platelet counts associated with hyperfibrinogenemia,[2] yet increased plasma fibrinogen levels are associated with increases in platelet aggregability. [6]

Thromboelastography (TEG®) is a method of measuring the viscoelastic properties of a blood clot, developed in Germany in 1948.

Aims:

To determine if the ratio of functional fibrinogen to platelets is a predictor for thrombotic failure of free tissue transfer following head and neck cancer resection.



Normal TEG® Parameters

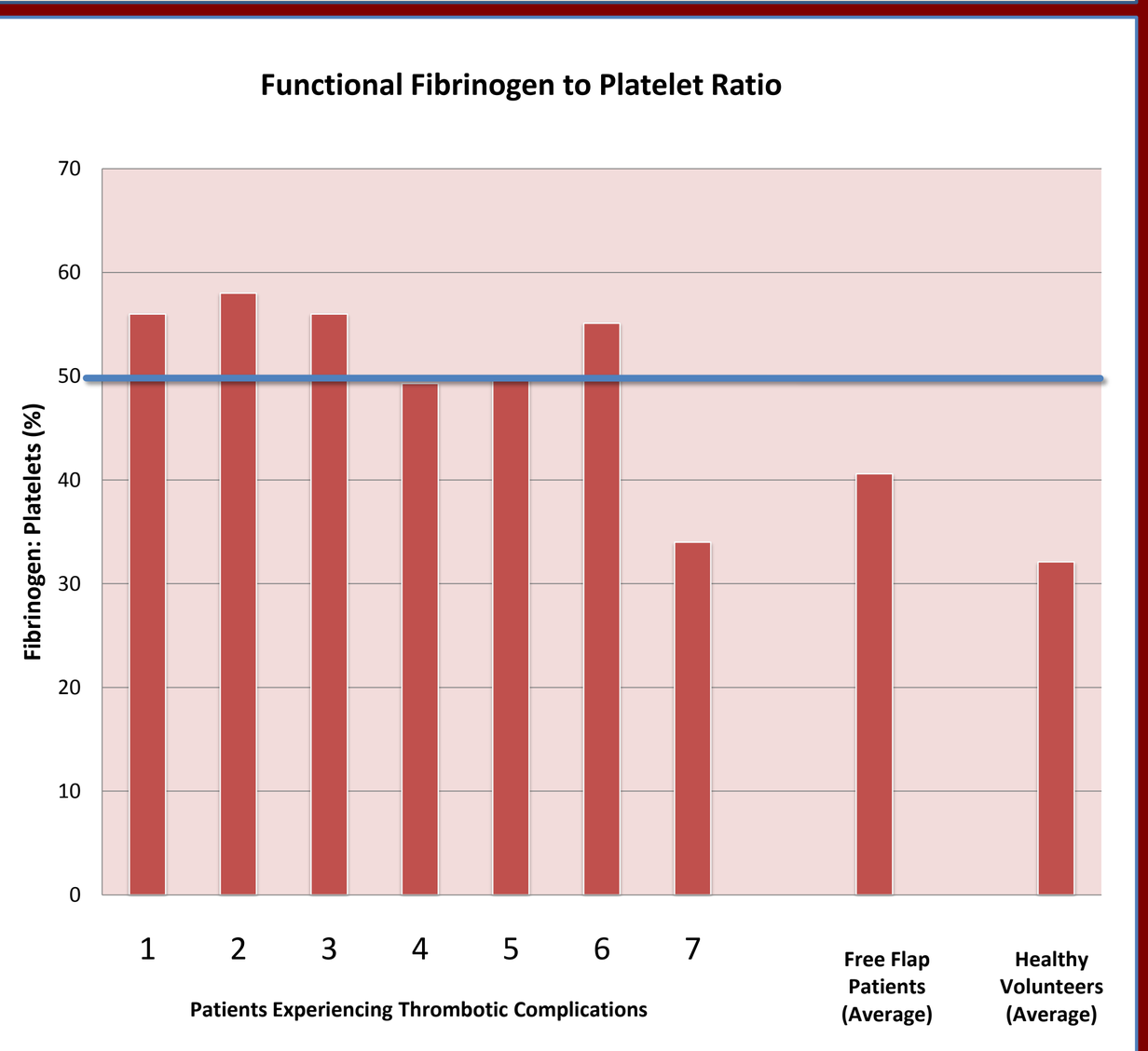
Methods:

The ratio of functional fibrinogen to platelets was determined pre-operatively in 42 patients undergoing free tissue transfer for head and neck malignancy. The results were compared to those obtained from 49 healthy volunteers. Modified thromboelastography was performed on the TEG® 5000 Haemoscope, which utilises the addition of monoclonal antibody fragment c7E3, binding to the platelet surface fibrinogen receptor glycoprotein GP11a/IIIb[7]. The independent contribution of fibrinogen and platelets to clot strength could thus be determined, and a ratio of fibrinogen to platelets calculated.

Results:

Fibrinogen to platelet ratios in patients with head and neck cancer preoperatively were significantly higher ($p<0.001$) than the control group.

Overall there was a 16.6% (n=7) thrombotic complication rate. This resulted in an overall graft failure rate of 11.9% (n=5). Two patients had intra-operative thrombotic events. The pre-operative fibrinogen to platelet ratio was above 50% in six patients (graph), correctly identifying their increased thrombotic tendency. In the one patient with a pre-operative ratio of 34%, post-operative results demonstrated continuing elevating ratios, that may have highlighted forthcoming flap failure.



Discussion:

The ratio of functional fibrinogen to platelet contribution is significantly higher in patients with head and neck cancer compared to the normal population. The hypercoaguable state of cancer patients is well recognised. This increased clotting tendency is of high significance in this group in view of the necessity for microvascular free tissue transfer.

In most patients the ratio of functional fibrinogen to platelets accurately predicted thrombotic events.

This study identifies a potential pre-operative predictor of patients in whom thrombotic events may be anticipated and suitable anticoagulation could therefore be instituted.

This study included only a small number of patients, and further study is required to further examine these findings.

Conclusions:

These preliminary results suggest that the use of pre-operative fibrinogen to platelet ratios may aid in identifying patients at increased risk of anastomotic thrombosis.

References:

1. Durnig P, Meier M, et al. *Monitoring of free flaps and replantations. Status quo in German-speaking microsurgery units.* Handchi Mikrochir Plast Chir, 2008, Dec 8
2. Kuo, YR, et al. *Hyperfibrinogenemia alone does not affect the patency of microvascular anastomosis.* Annals of Plastic Surgery, 2005, Vol. 54(4): 435-441.
3. Khouri, R. *Free flap surgery.* Clini Plast Surg, 1992, Vol. 19. 757-761.
4. Suominem S, Asko-Seljavaara S. *Free flap failures.* Microsurgery, 1995, Vol. 16. 396-399.
5. Johnson PC. *Platelet-mediated thrombosis in microvascular surgery: new knowledge and strategies.* Plast Reconstr Surg, 1990, Vol. 86. 359-367.
6. Feng, D, et al.*Platelet glycoprotein IIIa P1A polymorphism, fibrinogen, and platelet aggregability: the framingham heart study.* Circulation, 2001, Vol. 104. 104
7. Greilich PE, Alving BM, et al. *A modified thromboelastographic method for monitoring c7E3 Fab in heparinized patients.* Anaesth Analg 1997; 84:31

Miss Karen A Eley, MBChB, MRCS(Ed), is a Surgical Trainee and DPhil Student, Oxford
Miss Rachel Parker, SOPD, is a Haemostasis Specialist, Oxford
Mr Oliver Pearson, is a Blood Management Coordinator, Oxford
Mr Stephen E Bond, MBBS, BDS, FDS RCS, FRCS(Ed) (OMFS), is a Consultant in Oral & Maxillofacial Surgery, Oxford
Mr Stephen R Watt-Smith, MBBS, BDS, FDSRCS, MD, is a Consultant in Oral & Maxillofacial Surgery, Oxford

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A review of post-operative feeding in patients undergoing resection and reconstruction for oral malignancy and presentation of a pre-operative scoring system☆

Karen A. Eley[a,*], Rupali Shah[b], Stephen E. Bond[c], Stephen R. Watt-Smith[c]

[a] *Nuffield Department of Surgical Sciences, University of Oxford, Oxford University Hospitals NHS Trust, Headley Way, Oxford OX3 9DU, United Kingdom*

[b] *Department of Nutrition & Dietetics, Oxford University Hospitals NHS Trust, Old Road, Headington, Oxford, OX3 7LJ, United Kingdom*

[c] *Department of Oral and Maxillofacial Surgery, Oxford University Hospitals NHS Trust, Headley Way, Oxford OX3 9DU, United Kingdom*

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Abstract

Percutaneous endoscopic gastrostomy (PEG) and nasogastric tubes (NGT) are routine after resection and reconstruction of oral cancer. The selection of the most appropriate method of feeding can be challenging, as both methods carry morbidity. This makes correct selection paramount. The objectives of this retrospective review were to identify the benefits and complications of feeding with PEG and NGT in patients with oral malignancy. We retrospectively reviewed 144 patients who had undergone oral cancer resection and reconstruction, to compare PEG and NGT feeding and to identify the key factors that aid selection of the most appropriate feeding method. We used these factors to develop the Key to Appropriate Replacement Enteral Nutrition (KAREN) scoring system. One hundred and twenty of the 144 patients were managed with PEG, and of these, 9 used it for less than 28 days. The mean (range) duration of use was 13 (5–63) days, and 1.9 (1–5) tubes/patient were used. The KAREN scoring system assigned the correct method of feeding in 92% of cases. The scoring system requires prospective validation but could provide clinicians with a tool to assist in a sometimes difficult decision.

Keywords: PEG; Gastrostomy; Nasogastric feeding; NGT; Head and neck cancer; Oral cancer; Free flap

Introduction

The incidence of head and neck cancer continues to rise, with oral cancer increasingly affecting younger patient groups. Typically, patients have a history of smoking tobacco, or alcohol misuse, or both, with concurrent illnesses and occasionally concurrent malignancies.[1] Between 35% and 60% of patients with head and neck malignancy are malnourished, and optimised nutritional support is vital for their postoperative recovery.[1,2] Patients frequently require enteral feeding to bypass the oral cavity and pharyx to permit healing of the surgical site, and recovery of a safe swallow mechanism. In certain cases patients will become reliant upon long-term enteral nutritional support. In the early 1990s percutaneous endoscopic gastrostomy (PEG) tubes became the preferred method of feeding such patients.[3] Despite their popularity, PEG tubes are associated with both morbidity and mortality, and they should be restricted to those patients who require longer term nutritional support. However, tube

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* Corresponding author. Tel.: +44 01865 743103.
E-mail addresses: Karen.a.eley@gmail.com (K.A. Eley), Rupali.shah@ouh.nhs.uk (R. Shah), Steve.bond@ouh.nhs.uk (S.E. Bond), Steve.watt-smith@ndm.ox.ac.uk (S.R. Watt-Smith).

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selection can be difficult. Available guidance[4–7] suggests that PEG tubes should be considered if it is anticipated that nutritional intake is likely to be inadequate for a period of longer than 2–4 weeks.

The potential benefits of insertion of a PEG tube at the time of resection have previously been reported.[8] The aim of this study was to review the benefits and complications of PEG and nasogastric (NG) feeding in patients managed in our unit, and develop a scoring system that has the potential to aid selection of the most appropriate tube.

Materials and methods

We retrospectively reviewed all patients who had primary or secondary head and neck cancers resected with immediate free flap reconstruction between January 2006 and 2010. A total of 144 patients were identified, and their medical records, and the electronic reporting systems (Centricity PACS and CaseNotes©) were reviewed to obtain details of type of tumour, operation, method of postoperative feeding, duration of feeding, and associated complications.

We routinely obtain consent from patients for the use of medical records for audit and research purposes as part of the consent process for operations. Ethical approval for a retrospective review of casenotes as part of an audit of clinical practice was not required.

Routine practice at the time of the study included (where required) the insertion of a PEG by the upper gastrointestinal surgeons using the pull technique (which provides direct endoscopic visualisation of the upper gastrointestinal tract) immediately preoperatively. PEG tubes were placed once the anaesthetist had secured the airway. For patients to be managed with NGT, these were placed at the end of the operation with the aid of a flexible endoscope, with post-operative radiological confirmation of the position. Patients were ventilated for the first post-operative night on the Critical Care Unit, with typically fewer elective tracheostomies performed.[9] All patients were given standard postoperative antibiotic prophylaxis, and gastric protection. Typically, a PEG was selected when nutritional support was likely for 4 weeks or more, with consideration given to the volume of the tumour, its site, and whether the patient was to have postoperative adjuvant treatment.

Statistical analysis was aided by the Statistical Package for the Social Sciences (version 18, SPSS Inc, Chicago, IL, USA) and comprised binary logistic regression. After the data had been analysed and the decision-making processes had been reviewed, the Key to Appropriate Replacement Enteral Nutrition (KAREN) scoring system was developed to assist in identifying those patients most likely to require prolonged nutritional support and therefore should receive a PEG tube. Though it was created retrospectively, this scoring system provides a basis for future prospective analysis. Data are expressed as mean (range) or number of patients.

Results

The 144 patients (male $n = 88$, and female $n = 56$) had a mean age of 62 (29–88) years. The diagnosis in all but 4 patients was squamous cell carcinoma (SCC); 3 had sarcomas, and 1 had a malignant ossifying fibromyxoid tumour. A primary tumour was resected in 126 cases, a second primary tumour in 9, and recurrent tumours in 9. The site of excision and method of reconstruction are shown in Table 1.

Nasogastric tube feeding

Twenty-four patients were managed postoperatively with NGT, and of these, 3 ultimately required a PEG tube; 2 because of postoperative complications unrelated to the NGT that prolonged their need for nutritional support (hypoxic brain injury after a respiratory arrest, and postoperative pneumonia, $n = 1$ each). These were inserted at 21 and 30 days, respectively. The final patient had a PEG tube placed as a separate outpatient procedure after discharge and before starting a course of radiotherapy to the pharynx.

The duration of use of the NGT was 13 (5–63) days. In addition to the two patients ultimately progressing to PEG, 2 further patients were reliant upon NGT for longer than 28 days (33 and 63 days respectively). In the first case this was the result of a perforated colonic diverticulum unrelated to the primary resection. The second patient had an NGT for 63 days after resection of a commisure and tumour of the cheek with reconstruction using a radial forearm free flap and local rotation flap. Early return to oral nutrition was anticipated, but post-operative recovery was eventful with return to the critical care unit due to respiratory failure. The use of NG feeding was discontinuous with times of full oral nutrition before succumbing to further complication.

Patients required the insertion of a mean of 1.9 NGT (1–5 tubes/patient), as a result of accidental removal or dislodgement. Two patients developed complications directly related to their NGT, which resulted in prolonged stay in hospital (aspiration pneumonia in both cases).

Percutaneous endoscopic gastrostomy (PEG)

The remaining 120 patients were given PEG tubes. Five were inserted preoperatively in the endoscopy suite a mean of 14 (2–26) days preoperatively, and the remainder ($n = 115$) at the time of operation. This group included one patient who required open jejunostomy because of coexisting pancreatic disease.

There were no serious PEG-related complications in the 5 who had had the PEG preoperatively. One patient developed complex feeding problems (diabetic gastroparesis as a result of autonomic neuropathy), and ultimately required supplemental Total Parental Nutrition (for one month) in addition to jejunal gastrostomy extension.

Postoperative imaging of the abdomen was required in 10 patients (computed tomography (CT), $n = 7$, and fluoroscopy,

Table 1
Site of excision and type of free flap used.

Site	ALT ($n=14$)	Radial ($n=96$)	Fibula ($n=12$)	LD ($n=7$)	Scapular ($n=1$)	ALT + fibula ($n=4$)	Radial + fibula ($n=10$)	Total ($n=144$)
Alveolus, mandible, retromolar trigone	2	11	12	2	1	3	10	41
Maxilla	0	1	0	1	0	1	0	3
Floor of mouth, ventral tongue	1	18	0	0	0	0	0	19
Lateral/posterior tongue	6	48	0	3	0	0	0	57
Buccal mucosa/cheek/lip	5	13	0	1	0	0	0	19
Tonsillar fossa, pharynx, soft palate	0	5	0	0	0	0	0	5

ALT = anterolateral thigh; LD = latissimus dorsi.

$n=3$) who had PEG or jejunostomy tubes inserted at the time of operation. The indications for imaging included significant abdominal pain, early sepsis, and confusion, raising concern of a PEG leak. This occurred on an average of 6.3 days post insertion (3–12 days). In one case CT showed a colonic injury secondary to insertion of the PEG tube, which required laparotomy and removal of the PEG. A leak from the PEG was found on imaging in one patient, who also had a laparotomy. In both cases subsequent recovery was uneventful. In a further 3 patients imaging identified an abdominal cause for their symptoms that was unrelated to the gastrostomy (ischaemic bowel, acute pancreatitis, and perforated colonic diverticulum). In the remaining 5 patients imaging was within normal limits.

Of the 120 patients managed with PEG, 19 developed minor complications (16%). These included abdominal pain that did not warrant investigation ($n=4$), problems associated with the feed ($n=3$), leakage of feed around the stoma ($n=2$), overgranulation of the stoma ($n=7$), infection of the skin at the site ($n=2$), and accidental removal of the tube (which did not require replacement or further intervention) ($n=1$).

To date, 13 patients continue to use the PEG tube and their mean duration of use is 795 (310–1344) days at the time of writing. Thirty patients died with their PEG tubes still in use, resulting in a mean duration of use at the time of death of 186 (2–654) days. The remaining 77 patients had their PEG tubes removed as a separate outpatient endoscopic procedure or at the time of further operation. The mean duration of use from insertion to request for removal was 141 (13–636) days, and to the date of actual removal 212 (27–733) days.

Selection of postoperative feeding route

In those patients managed with a PEG tube, 9 patients used it for less than 28 days, and in these patients NGT may have been more appropriate. All nine patients had minimal coexisting medical problems with ASA grade I or II, and were treated by partial glossectomy with a radial forearm free flap up to 6 cm × 4 cm in size.

In the NGT group, the four patients who required prolonged nutritional support had unpredictable postoperative complications. The combination of comorbidity and excision site was not sufficient to predict these events preoperatively.

Development of a preoperative scoring system

The scoring system (Table 2) was devised from a combination of statistical analysis of the retrospective review, and additional information from the medical records. Not every patient required feeding for the whole period before radiotherapy was started. Binary logistic regression between the NG and PEG groups, using only those patients who were deemed appropriately managed, showed no significant difference between the groups for age or sex. ASA grade (grouped for I–II, and III–IV), alcohol intake, and type of free flap all met or approached 95% significance ($p=0.06$, $p=0.012$, and $p=0.09$, respectively).

Table 2
Key to appropriate replacement enteral nutrition (KAREN) score.

	Definition	Score
K	**Known clinical tumour stage T3 or T4**	3
A	**ASA Grade:** III–V	3
	Alcohol consumption: >40 units/week	3
R	**Reconstruction:**	
	Fibula/ALT/Latissimus dorsi	2
	≥ 2 simultaneous free flaps	3
	Radiotherapy: More than one field following surgery planned	2
E	**Excision of tumour:**	
	Anterior 2/3 of tongue+/− Floor of mouth	1
	Posterior 1/3 tongue	2
	Total glossectomy	4
	Mandibulectomy	2
	Tonsillar fossa/ pharyngeal/ soft palate	2
N	**Number of regular medications:** >3	2

Method of nutritional support	Total score
Nasogastric Tube	0–3
PEG Tube	4 or more

Table 3
Scoring system used retrospectively in 142 patients.

Type of feeding	Correctly predicted ($n = 131$)	Incorrectly predicted ($n = 11$)	Total ($n = 142$)
Nasogastric tube	21	1	22
Percutaneous endoscopic gastrostomy	110	10	120

ASA grade, alcohol intake, and type of free flap were insufficient in isolation to select the method of feeding accurately. Further factors typically used in decision-making, including clinical stage of tumour, site of tumour, and planned radiotherapy (together with number of sites) were therefore included to improve the scoring system. Patients who were prescribed many drugs orally often remain reliant on their PEG tube for these despite almost full return to oral nutrition. The number of drugs was therefore considered to be a further contributing factor in selection.

Using this method, all 9 patients who had the PEG tube in place for less than 28 days would have been identified as more suitable for an NGT than a PEG. For the NGT group, the KAREN score would have identified only 1 of the 4 patients who required prolonged nutrition. However, two patients developed unpredictable postoperative complications (perforated colonic diverticulum, and hypoxic brain injury). Taking these two patients into consideration, and applying the scoring system to the remaining 142 patients (Table 3), resulted in a prediction rate of 92%.

Discussion

The risks associated with placement of a PEG include bleeding, injury to the bowel, compromise of the airway, and possible seeding of malignant cells. Tumours of the oral cavity may result in obstruction of the upper airway, and in these cases a secure endotracheal tube is advocated during placement of a PEG. Failure to do so has resulted in deaths.[10] Placement of a PEG at the time of operation minimises demands of time on endoscopy lists and eliminates the risks of local anaesthesia or sedation. The upper gastrointestinal tract can be examined for any coexisting conditions, and appropriate management of gastrooesophageal reflux disease may be instigated to minimise postoperative morbidity. The seeding of malignant cells as a result of upper gastrointestinal endoscopy before resection of oral cancer is a potential risk, but was not seen in any of the patients studied.

The main problem associated with NGT is displacement. Patients required a mean of 1.9 tubes each postoperatively, a finding similar to those of previous studies.[3] Reinsertion of an NGT in patients after resection of head and neck cancer and reconstruction can be challenging. The swallow mechanism is often inhibited, the tissues may be insensate, and postoperative swelling may obstruct the passage of the tube. Other reported problems include nasal irritation and mucosal ulceration.[2] Two of the patients in this study developed aspiration pneumonia, probably secondary to dislodgement of the NGT during feeding, despite confirmation of its position before feeding was started. The diameter of the NGT is relatively small, which makes giving drugs through it difficult.[11] This is particularly problematic in patients with cancer of the head and neck who have several coexisting conditions that require multiple drugs.

The complication rate was higher in the PEG tube group, with two major complications directly related to the PEG tube (2%). Iatrogenic injury to the colon at the time of PEG insertion is particularly rare, and in reported cases may not present for many weeks after insertion of the PEG.[12] Imaging was requested in 10 patients (8%), but was within normal limits in 5.

Major complications contributed to this high investigation rate. The minor complication rate was 16%, which resulted in an overall complication rate of 18%. This is lower than previously reported.[3,13] It is likely that there are a number of contributory factors to this. Insertion of a PEG is completed only by a senior member of the surgical team, and only after the airway has been secured. The nursing staff follow a protocol of flushing out a tube before use, and patients are taught how to manage the PEG as soon as they are able. Patients are closely followed up in the outpatient department after discharge, with support from the dieticians and clinical nurse specialists. This ensures that the site of the stoma is inspected often, and preventive mechanisms put in place to avoid complications.

The mean duration of use of a PEG until request for removal was 141 days, and to actual removal 212 days. This indicates a mean of 71 days from the point of referral to removal – an appreciable delay. Subsequent changes have been instigated, with a resultant reduction in waiting times for endoscopic removal of a PEG. In addition, the requirement for endoscopic removal may be reduced with the use of "cut and push" tubes, which are currently being evaluated. All patients are assessed and followed up by the dietician and speech and language teams. The decision to remove the PEG is multifactorial, and while discussion of removal may have taken place earlier during the follow-up, the date of referral for removal was considered to be more accurately documented.

Further concern about the use of PEG is a delay in return to normal feeding, which may result from protracted disuse of the muscles of deglutition.[2,14] Rogers et al.[15] reported decreased quality of life scores in patients who continued to use their PEG compared with those who had had it removed or had not used a PEG tube at all. However, those who continued to use the PEG tube were also more likely to have had adjuvant treatment and to have more advanced disease, both of which are important contributors to quality of life scores. The impact on quality of life of a delay in re-establishing oral nutrition is difficult to quantify. It is difficult to compare patients' satisfaction accurately between

NGT and PEG tubes, as this would entail randomisation of feeding tubes, which would be inappropriate in many cases.

In the group of patients studied, the KAREN scoring method seemed reliable, with selection of the correct tube in 92% of patients. The system uses the key factors that are likely to result in prolonged nutritional support including the size and site of the tumour, the method of reconstruction, and the extent of planned postoperative radiotherapy. However, the results should be interpreted within the limits of a retrospective review. By the nature of the study only those patients who had free tissue transfers were included, and so the volume of the tumour was much greater than in patients treated by local resection and local flaps/mucosal grafts. As we work in a tertiary referral centre, we often see larger tumours, which contributes to our greater use of PEG. The scoring system was developed and assessed only on retrospective data at one centre in a group of patients with perioral malignancies. However, these data should be available prospectively, and the study provides the basis for prospective review to permit refinement and the creation of a highly accurate and reliable tool.

Conflict of interest

None declared.

Acknowledgements

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References

1. Arosarena O. Perioperative management of the head and neck cancer patient. *J Oral Maxillofac Surg* 2007;**65**:305–13.
2. Mekhail T, Adelstein D, Rybicki L, Larto M, Saxton J, Lavertu P. Enteral nutrition during the treatment of head and neck carcinoma: is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube? *Cancer* 2000;**91**:1785–90.
3. Corry J, Poon W, McPhee N, Milner A, Cruickshank D, Porceddu S, et al. Prospective study of percutaneous endoscopic gastrostomy tubes versus nasogastric tubes for enteral feeding in patients with head and neck cancer undergoing (chemo)radiation. *Head Neck* 2009;**31**: 867–76.
4. National Institute for Health and Clinical Excellence (NICE). *Guidance on cancer services: improving outcomes in head and neck cancers. The manual*; 2004. Available from: www.nice.org.uk.
5. National Institute for Health and Clinical Excellence (NICE). *Nutritional support for adults. Oral nutrition support, enteral tube feeding and parenteral nutrition*; 2006 [cited 16 May 2010]; Available from: http://guidance.nice.org.uk/CG32/Guidance/pdf/English.
6. Loser C, Aschl G, Hebuterne X, Mathus-Vliegen EMH, Muscaritoli M, Niv Y, et al. ESPEN guidelines on artificial enteral nutrition—percutaneous endoscopic gastrostomy (PEG). *Clin Nutr* 2005;**24**:848–61.
7. Scottish Intercollegiate Guidelines Network (SIGN). *Diagnosis and management of head and neck cancer. A national clinical guideline*; 2006. Available from: www.sign.ac.uk.
8. Cunliffe DR, Swanton C, White C, Watt-Smith SR, Cook TA, George BD. Percutaneous endoscopic gastrostomy at the time of tumour resection in advanced oral cancer. *Oral Oncol* 2000;**36**:471–3.
9. Marsh M, Elliott S, Anand R, Brennan PA. Early postoperative care for free flap head and neck reconstructive surgery—a national survey of practice. *Br J Oral Maxillofac Surg* 2009;**47**:182–5.
10. Oakley R, Donnelly R, Freeman L, Wong T, McCarthy M, Calman F, et al. An audit of percutaneous endoscopic gastrostomy insertion in patients undergoing treatment for head and neck cancer: reducing the incidence of peri-operative airway events by the introduction of a tumour assessment protocol. *Ann R Coll Surg Engl* 2009;**91**:249–54.
11. Hujala K, Sipilä J, Pulkkinen J, Grenman R. Early percutaneous endoscopic gastrostomy nutrition in head and neck cancer patients. *Acta Otolaryngol* 2004;**124**:847–50.
12. Friedmann R, Feldman H, Sonnenblick M. Misplacement of percutaneously inserted gastrostomy tube into the colon: report of 6 cases and review of the literature. *J Parenter Enteral Nutr* 2007;**31**:469–76.
13. Chandu A, Smith AC, Douglas M. Percutaneous endoscopic gastrostomy in patients undergoing resection for oral tumors: a retrospective review of complications and outcomes. *J Oral Maxillofac Surg* 2003;**61**: 1279–84.
14. Murphy BA. Advances in quality of life and symptom management for head and neck cancer patients. *Curr Opin Oncol* 2009;**21**:242–7.
15. Rogers SN, Thomson R, O'Toole PO, Lowe D. Patients experience with long-term percutaneous endoscopic gastrostomy feeding following primary surgery for oral and oropharyngeal cancer. *Oral Oncol* 2007;**43**:499–507.

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Cervico-facial infections following dental extraction

D.W. Anchassi, M.K. George, K. Fan. *Kings College Hospital NHS Foundation Trust, UK*

Introduction: Tooth extraction is the definitive treatment for resolution of dental infections and pathology. Some patients require hospital admission for management of subsequent post extraction sepsis with its associated morbidity. The objective of the study was to evaluate the incidence, risk factors and impact associated with cervico-facial infection post routine dental extractions.
Method: A retrospective study was carried out of all patients admitted with cervico-facial infection following dental extraction over 17 months. Clinical records were analysed for demographic data, type, number and nature of tooth extraction along with circumstances prior to admissions.
Results: Of 201 patients admitted with loco-regional infection 43 met the criteria. 44% of these patients had no medical history of note. Extractions were most commonly of wisdom teeth (47%), with 35% multiple and 53% surgical extractions. 67% of patients had oral antibiotics before admission. Sixty percent of patients presented via A&E although 51% of patients had prior dental review. Seventy-nine percent of patients required incision and drainage under GA. Six patients (14%) spent between them 34 days in Intensive Care Unit. 54% of patients had resultant scarring and one suffered antibiotic anaphylaxis.
Conclusion: Post extraction sepsis can be associated with morbidity and mortality. This may be reduced by identification of those at risk along with more aggressive initial management at post extraction reviews. Medical history was not as strongly linked as expected. Multiple and/or more complex extractions of wisdom teeth are associated with a high risk.

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Routine use of percutaneous endoscopic gastrostomy (PEG) in head and neck oncology: benefits and pitfalls

K.A. Eley, S.R. Watt-Smith. *Oxford Radcliffe Hospitals NHS Trust, UK*

Introduction: The risks of PEG feeding have been recently debated within the literature. Whilst the majority of authors report the insertion of a PEG tube prior to the commencement of radiotherapy, it has become our routine practice for insertion to take place at the time of primary cancer resection.
Aims: The aim of this retrospective review was to determine the complication rate with routine use of PEG tube in comparison to those patients where a nasogastric feeding tube is utilised in the post-operative period.
Methods: We retrospectively reviewed all patients undergoing head and neck cancer resection and reconstruction performed in the Department of Oral & Maxillofacial Surgery over a 4 year period, during which time over 170 surgical procedures were performed.
Results: In total, 70% of patients undergoing free flap surgery for head and neck malignancy received a PEG tube at the time of their surgery. In those where a nasogastric tube was used in preference to a PEG tube the majority of patients required re-insertion of their NG tube at least once, and in some cases up to six times during the recovery period. The risks and benefits of the PEG will be discussed, including one mortality directly associated with a PEG leak.
Conclusions: Insertion of PEG tubes at the time of primary surgery is not risk free, but should be considered in patients where it is anticipated that oral re-feeding will be delayed or where radiotherapy is likely to be required.

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Mucous plugs as a cause of benign salivary gland obstruction: are they underdiagnosed? A restrospective study

M. Warner, M. Brennand Roper, S. Gowrishanker, J. Makdissi, S. Whitley. *St Bartholomews's and the Royal London Hospitals NHS Trust, UK*

Introduction and Aims: Mucous plugs may cause identical symptoms to those of stones and strictures. We highlight their incidence and the importance of Digital Subtraction Sialography (DSS) to identify and treat a pathology that is seldom considered and under-diagnosed via other imaging techniques.
Material and Methods: We present a 4-year retrospective study of 328 patients referred for parotid and submandibular DSS.
Results and Statistics: DSS identified mucous plugs in 113 (34.5%) of our 328 cases. Of the mucous plugs identified, 74 (65.5%) occurred as a single entity. 20 (17.7%) were associated with a stricture, 16 (14.2%) associated with a stone, whilst 2 (1.8%) occurred with both a stone and stricture.
Mucous plugs were more common in the submandibular salivary gland (59.3%, n = 67) than the parotid (40.1%, n = 46).
41 (36%) of our patients diagnosed with mucous plugs via DSS, underwent primary investigation with an ultrasound scan. None of these ultrasounds identified mucous plugs.
Conclusions and Clinical relevance: This study demonstrates that DSS is the essential tool for the diagnosis of mucous plugs when a ductal obstruction is clinically suspected. Ultrasonography is inadequate.
The benefits of DSS in this situation are two fold. By excluding stones and strictures as a differential diagnosis, more invasive treatment is avoided. Secondly, in the case of mucous plugs, DSS can be therapeutic. Further analysis is currently being undertaken.
This study identifies mucous plugs as a cause of symptomatic salivary gland pathology in their own right, and their incidence is higher than reported in the literature.

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Predictive biomarkers for malignant transformation to carcinoma ex-pleomorphic adenoma

A. Schache, R. Shaw, J. Risk, T. Liloglou, A. Triantafyllou, D. Lowe, G. Hall. *University of Liverpool, UK*

Introduction and Aims: The diagnostic criteria for Carcinoma Ex-Pleomorphic Adenoma (CXPA) are varied and histopathology interpretation is subjective. A diagnostic biomarker for malignancy would aid histological diagnosis and may be a predictive tool in the benign precursor for CXPA, Pleomorphic Adenoma (PA).
Material and Methods: We analysed a series of 59 salivary neoplasms, 28 PA (47%) and 31 CXPE (53%), for quantitative promoter methylation using two methylation analysis techniques.
DNA was extracted by micro-dissection from FFPE samples and bisulphite treated. Quantitative methylation data for 7 gene promoters was obtained. p16, TIMP3 and MLH1 promoter methylation was determined using pyrosequencing whilst RASSF1, RARβ, TMF and CYGB promoter methylation was assessed using quantitative real-time polymerase chain reaction (RT-PCR).
Results and Statistics: The MLH1 gene promoter was essentially unmethylated in all cases. TIMP3 and p16 showed correlation between methylation and malignancy. In particular, significant methylation of p16 was shown in 8/28 (29%) CXPA samples compared with 0/27 (0%) in Pleomorphic adenoma samples (sensitivity 0.29, specificity 1.00).
qMSP results showed correlation between promoter methylation and tumour type for both RARβ and RASSF1 (sensitivity and

Reference

1. Amernik K, Kabacińska A, Tarnowska C, Paradowska-Opałka B. Acute ear trauma caused by failure of mobile phone/cellular phone. *(In Polish) Otolaryngol Pol* 2007;**61**:484–6.

S. Sharma *
A. Majumdar
Maxillofacial Unit, Luton and Dunstable Hospital NHS Foundation Trust, Lewsey Road, Luton, LU4 0DZ, United Kingdom
* Corresponding author.
E-mail address: sujatasharma@hotmail.co.uk (S. Sharma)

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Free microvascular transfer of segmental corticocancellous femur for reconstruction of the alveolar ridge

Sir,

We read the article "Free microvascular transfer of segmental corticocancellous femur for reconstruction of the alveolar ridge" by Gaggl et al with great interest and we congratulate them on obtaining good results with this new method of bony reconstruction.[1] The femur has been the source of bone for management of non-union of the lower limbs but the bone is normally taken from the medial condyle and not the femoral shaft. The vascular pedicle for these is also based on the genicular artery and associated venae comitantes.[2,3]

As mentioned in the paper, the reconstruction of the bony facial defect can be achieved by using free flaps such as scapula, fibula, and iliac crest. Another source of bone is the distal radius, which has given promising results for smaller bony defects involving the alveolus and atrophic mandibles. Harvesting a composite radial free flap carries the risk of postoperative fracture of the radius, which can be minimised by taking less than 40% of the radial circumference and prophylactic plating of the radius. This paper does not deal with these key issues with the femoral flap. The consequences of femoral fracture would be devastating. A study by Chowaniec et al (Presented at Bioengineering Conference, Proceedings of the IEEE 31st North Eastern Annual Conference, 2005) on human cadavers showed that if you take more than 35% of the circumference of the femur, the mean (SD) maximal load tolerated by the femur drops from 840 (297) pounds to 810 (235) pounds. As this flap weakens the femur slightly and also it changes structural integrity, fixation of the femur may well be prudent.

References

1. Gaggl AJ, Burger HK, Chiari FM. Free microvascular transfer of segmental corticocancellous femur for reconstruction of the alveolar ridge. *Br J Oral Maxillofac Surg* 2008;**46**:211–7.
2. Choudry UH, Bakri K, Moran SL, Karacor Z, Shin AY. The vascularized medial femoral condyle periosteal bone flap for the treatment of recalcitrant bony non-union. *Ann Plast Surg* 2008;**60**(2):174–80.
3. Cavadas PC, Landin L. The treatment of recalcitrant distal tibial nonunion using the descending genicular corticoperiosteal free flap. *J Trauma* 2008;**64**(1):144–50.

Khaleeq-Ur Rehman [1]
Department of Oral and Maxillofacial Surgery, University Hospital Birmingham, Birmingham, B15 2TT, United Kingdom
E-mail address: khaleeq@doctors.org.uk
[1] Present address: 15 Chapel Street, Lye, Stourbridge, West Midlands, DY9 8BT, United Kingdom.

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Myocardial infarction diagnosed by troponin concentration in postoperative patients with head and neck cancer admitted on the day of operation

Sir,

Theatre direct admission (TDA), whereby patients for elective operations attend a holding bay on the day of operation, and are admitted to a ward postoperatively, has been introduced in hospitals throughout the UK, including our own. This way of increasing throughput was introduced to them maxillofacial department in 2007.

Initial reports about same day surgical admissions in vascular and colorectal surgery have been favourable.[1,2]

Though TDA has been a success for most of our patients, we noted appreciable morbidity in those admitted by this route for resection and reconstruction of cancers of the head and neck.

Patients are assessed preoperatively to exclude those with coexisting conditions for which preoperative admission to a ward is required. As a consequence, preselected "low risk" patients for TDA should have little postoperative morbidity.

We reviewed all patients who underwent major operations for head and neck cancer in our department from 2003 to 2007, to find out the incidence of troponin-positive myocardial infarction.

Of the 131 patients admitted to the ward preoperatively, troponin concentrations were requested for 33 patients, and were significant in nine (7% of the total patients). In the 15 patients admitted by TDA, troponin concentrations were requested in seven patients, and were positive in three (20% of the total patients).

The high incidence of myocardial infarction may reflect a cluster that would have occurred at this time irrespective of the route of admission. Despite this, these results raised sufficient concern for us to instigate a return to preoperative admission to a ward for all our patients who were having major operations for cancer of the head and neck. Subsequent repeat audit of 49 patients admitted preoperatively to the ward, showed significant improvement in postoperative cardiac morbidity, with troponins being

requested in 12 patients, and positive in only one (2% of total patients).

The surgical stress response is a systemic reaction to injury that includes endocrine, immunological, and haematological effects, with a magnitude and duration proportional to the injury.[3,4] The combination of a patient's anxiety associated with admission to hospital, and the serious stress response from an extensive operation, are probable contributory factors to postoperative complications such as myocardial infarction.[5] TDA may therefore not be appropriate for all patients having major operations.

References

1. Rothwell LA, Bokey EL, Keshava A, Chapuis PH, Dent OF. Outcomes after admission on the day of elective resection for colorectal cancer. *ANZ J Surg* 2006;**76**:14–9.
2. Calligaro KD, Dandura R, Dougherty MJ, DeLaurentis DA, Raviola CA. Same-day admissions and other cost-saving strategies for elective aortoiliac surgery. *J Vasc Surg* 1997;**25**:141–4.
3. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000;**85**:109–17.
4. Wilmore DW. From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. *Ann Surg* 2002;**236**:643–8.
5. Kehlet H. The surgical stress response: should it be prevented? *Can J Surg* 1991;**34**:565–7.

Karen A. Eley *
S.R. Watt-Smith
Department of Oral & Maxillofacial Surgery, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, United Kingdom

* Corresponding author.
E-mail addresses: Karen.eley@orh.nhs.uk (K.A. Eley), Steve.watt-smith@ndm.ox.ac.uk (S.R. Watt-Smith)

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Use of uterine dilators to create a safe tunnel for a microvascular pedicle in the radiated neck

Sir,

Microvascular free tissue transfer is a standard method for the reconstruction of complex surgical defects in the head and neck region, and its use has resulted in advanced and technically difficult cases being accepted for operation. Adjuvant chemoradiation has improved disease-free survival, but recurrence and second primary tumours still cause problems. Repeated operations with neck dissection and radiation can make the neck difficult to operate on when further reconstruction is needed.[1,2] Microvascular anastomosis must be perfectly constructed if a free flap is to be successful; external compression, twisting or kinking of the pedicle, or tension on the site of anastomosis must be avoided.[3] These can be difficult to achieve in the previously operated or radiated neck. The creation of a tunnel from the neck to the oral cavity can cause undesirable bleeding or damage to vital structures in the neck such as the hypoglossal and lingual nerves.

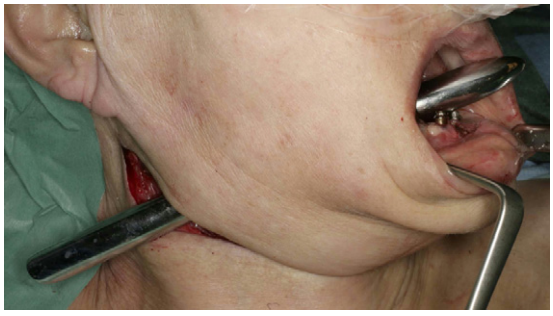

Fig. 1. The tunnel for the pedicle is made with uterine dilatators.

We present a new and safe technique that creates a tunnel from the neck to the intraoral space. We used standard uterine dilators (Aesculap®, Tuttlingen, Germany) to create a tunnel for a vascular pedicle in 12 patients who had had previous head and neck operations and radiotherapy. Care must be taken to ensure that immediately surrounding tissues are not at risk during the first insertion of the chosen size of dilator. Dilatation is done using increasing sizes of calibre. At the end of dilatation the largest dilator (26 mm) is left in place for 20 minutes to allow the vascular pedicle to be tunnelled. There were no complications, and use of these dilators is simple and fast (Fig. 1).

References

1. Schusterman MA, Miller MJ, Reece GP, Kroll SS, Marchi M, Goepfert H. A single center's experience with 308 free flaps for repair of head and neck cancer defects. *Plast Reconstr Surg* 1994;**93**:472–80.
2. Singh B, Cordeiro PG, Santamaria E, Shaha AR, Pfister DG, Shah JP. Factors associated with complications in microvascular reconstruction of head and neck defects. *Plast Reconstr Surg* 1999;**103**:403–11.
3. Urken ML, Vickery C, Weinberg H, Buchbinder D, Biller HF. Geometry of the vascular pedicle in free tissue transfers to the head and neck. *Arch Otolaryngol Head Neck Surg* 1989;**115**:954–60.

Jyrki Törnwall *
J. Snäll
H. Thoren
S. Yli-Petäys
P. Lassus
Department of Oral and Maxillofacial Surgery, Helsinki University Central Hospital, Kasarmikatu 11-13, PO Box 263, 00029 HUS, Helsinki, Finland

* Corresponding author. Tel.: +358504272853.
E-mail address: jyrki.tornwall@hus.fi (J. Törnwall)

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E-mail address: slaverick@nhs.net

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Re: Postoperative fluid balance in patients having operations on the head and neck

Sir,

Bryniarska et al.[1] highlighted important concerns in the management of patients after head and neck surgery. We identified similar problems with postoperative fluid overload in our patients after reconstruction with free flaps. After resection of head and neck cancers and reconstruction our patients remain intubated and ventilated for the first postoperative night. Hypotensive episodes are common as a consequence of anaesthesia maintained with propofol and morphine. Potential consequences of this are inadequate flap perfusion and fluid overload secondary to boluses of fluid given in an attempt to normalise blood pressure.

Complications resulting from inappropriate fluid management are thought to develop in as many as 50% of perioperative patients, and their adverse outcomes are well documented.[2,3]

The unresolved dilemma is the relation between flap perfusion, systemic blood pressure, cardiac output, and which drugs have the most influence on flap perfusion. We are currently evaluating various alpha-agonists and inotropes to identify the optimal treatment for flap perfusion.

As part of this ongoing research we introduced continuous monitoring of cardiac output perioperatively. Measurement of cardiac output or stroke volume is a necessary facet of caring for critically ill patients.[4] Previously only possible using invasive pulmonary artery catheters, the LiDCO™ Plus system is one method of minimally invasive monitoring that is now available to us.[5] This system calculates the variations in pulse pressure, systolic pressure, and stroke volume that occur through the respiratory cycle, providing reliable information regarding the patient's response to fluids.[5] As it is routine practise to obtain central venous access and monitor arterial pressure in patients with head and neck cancer, LiDCO™ *plus* could be used, with the potential to optimise perioperative fluid balance.

Declaration

The authors have no affiliation with LiDCO Ltd.

References

1. Bryniarska E, Srinivasan D, MacBean A, Oloyede D. Postoperative fluid balance in patients undergoing head and neck surgery. *Br J Oral Maxillofac Surg* 2008;**46**:611.
2. Wei S, Tian J, Song X, Chen Y. Association of perioperative fluid balance and adverse surgical outcomes in esophageal cancer and esophagogastic junction cancer. *Ann Thorac Surg* 2008;**86**:266–72.
3. Walsh SR, Cook EJ, Bentley R, et al. Perioperative fluid management: prospective audit. *Int J Clin Pract* 2008;**62**:492–7.
4. Rhodes A, Sunderland R. Arterial pulse power analysis: The LiDCO™ plus system. In: Pinsky MR, Payen D, editors. Functional haemodynamic monitoring. Update Intens Care Emerg Med 2005;42: 183–92.
5. Pearse RM, Ikram K, Barry J. Equipment review: an appraisal of the LiDCO plus method of measuring cardiac output. *Crit Care* 2004;**8**:190–5.

Karen A. Eley *
S.R. Watt-Smith
Oxford Radcliffe Hospitals NHS Trust, Headley Way, Oxford OX3 9DU, United Kingdom

* Corresponding author.
E-mail address: Karen.eley@nds.ox.ac.uk (K.A. Eley)

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Re: Allergy to metal caused by materials used for intermaxillary fixation: Case report

Sir,

The patient's eczema disappeared after 2 days[1] but the other symptoms persisted for 11 days. The recovery struck us as fast, but we do not understand why the symptoms disappeared so quickly.

Reference

1. Hashitana S, Maeda T, Okui S, Takaoka K, Honda K, Urade M. Allergy to metal caused by materials used for intermaxillary fixation: Case report. *Br J Oral Maxillofac Surg* 2008;**46**:315–6.

Susumu Hashitani *
Department of Dentistry and Oral Surgery, Hyogo College of Medicine, Japan
* Tel.: +81 798 45 6677; fax: +81 798 45 6679.
E-mail address: susumu@hyo-med.ac.jp

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Re: Letter to the Editor: Will any wire do?

Sir,

I share the problem faced by Walker and McCann.[1] I work in a busy trauma referral centre and we usually keep one wiring set for temporary wiring on patients with avulsed teeth, or fractures.

tion from artefacts caused by the internal or external fixation. Transcutaneous ultrasound can detect early evidence of healing of long bones [Joseph et al., 1999]. The effectiveness of ultrasound evaluation of mandibular osteotomy sites with non-union has been assessed.

Materials and methods: Two patients developed non-union of composite DCIA free flap reconstructions of the mandible following post-operative radiotherapy and chemotherapy. Infective episodes were complicated by neutropenia in one case. Treatment included hyperbaric oxygen therapy, surgical debridement, removal of failed internal fixation,and external fixation.

The progress of bony healing was monitored with serial orthopantomographs and ultrasound scans of the osteotomy gaps with the external fixation in-situ. The detection of echogenic foci was the criterion for initial calcification as this has been histologically shown to correlate with callus maturation [Moed et al., 1998].

Results: Transcutaneous ultrasound scanning detected early callus formation that preceded the radiographic changes by several weeks.*Clinical relevance*: Trancutaneous ultrasound provides early objective evidence of progressive bony healing and is reassuring for both the patient and surgeon.

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P 42

A comparison of skin graft success in the head and neck with and without the use of a pressure dressing

Christopher Carter*, J. Morrison, G. Markose, W.S. Hislop, W.J.R. Currie

Crosshouse Hospital, Kilmarnock, United Kingdom

Introduction/aims: There was a perception within the Maxillofacial Unit that there was a higher infection rate of skin grafts in the head and neck where a pressure dressing was applied. The infection usually led to a variable loss of the skin graft and subsequent morbidity.

The aim of this study was to compare the healing of skin grafts in the head and neck with and without the use of pressure dressings. This would then be compared to published data.

Materials/methods: A retrospective analysis was undertaken of patients who had undergone excision of a skin lesion on the head or neck and reconstruction with a skin graft between 2005 and 2008. Success was determined by the percentage take of the graft and the absence of infection. The demographics, site of skin graft harvest and recipient site of each group were also analysed for significant differences.

Results/conclusions: The results of the study are discussed and the use of pressure dressings debated. Given the significant morbidity associated with skin graft loss, recommendations for future practice will be discussed.

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P 44

Intra-operative use of LiDCO—is there an effect on the volume of intravenous fluids used by anaesthetists during free flap surgery for head and neck cancer?

Karen Ann Eley*, S.R. Watt-Smith

Oxford Radcliffe Hospitals NHS Trust, United Kingdom

The deleterious effects of inappropriate fluid prescription have been well documented, and include prolonged hospital stay. Patients with head and neck cancer have multiple co-morbidities and optimal fluid administration is paramount. Previously only possible using pulmonary artery catheters, the LiDCOTM plus system calculates the variations in pulse pressure, systolic pressure, and stroke volume that occur through the respiratory cycle, providing reliable information regarding the patient's response to fluids.

LiDCO Plus monitoring was introduced as part of a clinical research trial, and has become routinely used during all free flap procedures in our department.

The aim of this study was to determine if LiDCO Plus had an impact upon intra-operative fluids in this cohort of patients.

We retrospectively reviewed the clinical notes of all patients in whom the LiDCO Plus system had been used intra-operatively. These were case matched to patients prior to the introduction of LiDCO Plus, to determine the volume and type of fluids prescribed, and post-operative patient course.

Statistical analysis is currently been undertaken, but subjectively it appears that the use of LiDCO Plus has reduced the volume of intra-operative fluid administration, and decreased post-operative morbidity and in-patient hospital stay.

The LiDCO Plus system is suitable for use in patients undergoing head and neck cancer surgery since it is routine practice to obtain arterial and central venous access. This system provides the anaesthetist with another indicator of patient filling status, which is more reliable than central venous pressure, since it is unaffected by change in patient positioning.

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Use of desflurane to maximise teaching in busy day case oral and maxillofacial surgical operating theatre

Leo Cheng*, Alastair Mulcahy, John Meads, Helen Drewery

Barts and the London NHS Trust, United Kingdom

Introduction: Training time is pressurised because of the imposition of the European Working Time Directives. In order to maximise the training time in day case theatres without prolonging the patients' recovery time, less turn round time between patients is crucial. We investigated the feasi-

Intra-operative use of LiDCO™ *Plus* – Is there an effect on the volume of intravenous fluids used by anaesthetists during free flap surgery for head and neck cancer?

Miss Karen A Eley, Mr Stephen R Watt-Smith

Department of Oral & Maxillofacial Surgery, Oxford Radcliffe Hospitals NHS Trust, Headley Way, Oxford OX3 9DU

Introduction

Complications resulting from inappropriate fluid management are thought to occur in as many as 50% of perioperative patients, and their adverse outcome well documented.[1,2]

We have recently introduced continuous cardiac output monitoring for our patients perioperatively as part of an ongoing research project. Measurement of cardiac output or stroke volume has been regarded as a necessary facet of caring for critically ill patients [3]. Previously only possible using invasive pulmonary artery catheters, the LiDCO™ *plus* system is one method of minimally invasive monitoring that is now available to us [4]. The Stroke Volume Variance (SVV) is derived directly from the arterial pressure waveform. This system is appropriate in head and neck cancer patients since it is routine practise to obtain central venous access and arterial monitoring. This method provides reliable information regarding the filling status of the patient avoiding inappropriate fluid administration.

Aim:

To determine if the intra-operative use of LiDCO™ has an impact upon the volume of fluid used intra-operatively by anaesthetists, and subsequent post-operative morbidity and hospital stay.

Methods:

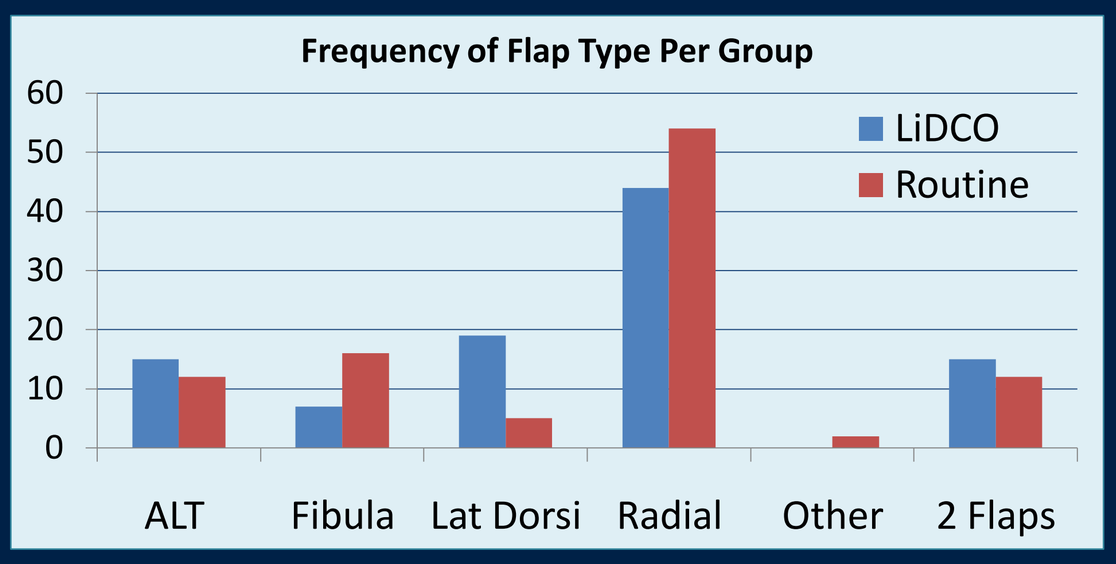
A retrospective review of all patients undergoing free flap procedures for head and neck cancer to determine intra-operative fluid prescrbing, and post-operative recovery in those patients in which LiDCO™ *Plus* monitoring was used compared to those prior to its induction.

Between January 2006 and April 2009, 157 free flap procedures were completed during 140 surgical sessions in our department. The notes for 7 patients were unavailable for review, the anaesthetic chart missing in the notes of a further patient, and the LiDCO™ data corrupt in a further two patients. These patients were therefore excluded from the study. In total, 146 free flaps were completed during 130 surgical sessions on 111 patients for primary head and neck cancer resection or reconstruction of associated problems. LiDCO ™ monitoring was used for 27 free flap sessions (24 patients; 3 patients undergoing two separate surgical procedures).

Results:

- Both groups were similar for:
  - Flap Type
  - Age
  - Sex
  - Weight
  - Intra-operative fluid administration
- Colloids were more frequently used in the LiDCO™ group ($p<0.03$)
- When urine output and procedure length were taken into account, the LiDCO™ group received less fluid per hour than the routine group ($p<0.04$)
- Post-operative morbidity and mortality was decreased in the LiDCO™ group
  - 7 post-operative deaths occurred in the routine group
- Post-operative hospital stay was significantly less in the LiDCO™ group ($p<0.02$)

	LiDCO™	Routine
Male	52%	52%
Female	48%	48%
Age (years)	58 ± 9	62 ± 15
Weight (Kg)	76 ± 24	69 ± 14
Operation Length (Hours)	8 ± 1.3	7 ± 1.8



Fluid Input/Output	*LiDCO*™	*Routine*
Crystalloid (Litres)	6.0 ± 1.5	6.4 ± 1.9
Colloid (Litres)	0.7 ± 0.7	0.4 ± 0.8
Blood (Units)	0.7 ± 1	0.8 ± 1
Total Fluid In (Litres)	7.0 ±1.7	7.0 ± 2.1
Urine Output (Litres)	1.1 ± 0.7	1.2 ± 1.0
Balance (Litres)	5.9 ± 1.7	5.9 ± 1.8
Balance/procedure length (ml/hr)	728 ± 169	814 ± 250

Average Hospital Stay (Days)	
LiDCO™	13.6 ± 5
Routine	21.7 ± 18

Discussion:

Peri-operative monitoring of cardiac output allows early recognition of occult hemodynamic abnormalities and can guide resuscitation [5]. Studies have clearly identified a reduction in post-operative morbidity associated with targetted fluid administration [6]. The results of our study on a small patient population suggest that the intra-operative use of LiDCO™ *Plus* monitoring results in an increased tendency for colloid filling, and a decreased fluid balance per hour. Post-operative in hospital stay was significantly reduced in the LiDCO™ group, with an associated fall in post-operative complications. Further investigations are currently being conducted to determine and optimise peri-operative filling status.

Conclusion:

LiDCO™ *Plus* is an additional source of patient monitoring suitable for patients undergoing free flap surgery, permitting goal directed therapy, and resulting in decreased post-operative morbidity.

References:

1. Wei S, Tian J, Song X, Chen Y. *Association of perioperative fluid balance and adverse surgical outcomes in esophageal cancer and esophagogastic junction cancer*. Ann Thorac Surg. 2008 Jul; 86(1): 266-72
2. Walsh SR, Cook EJ, Bentley R, Farooq N, Gardnet-Thorpe J, Gaunt ME, Coveney EC. *Perioperative fluid management: prospective audit.* Int J Clin Pract. 2008; 62(3):492-7
3. Rhodes A, Sunderland R. *Arterial pulse power analysis: The LiDCO™ plus system. Functional harmodynamic monitoring Update in Intensive care and emergency medicine* 2005; 42: 183-192
4. Pearse RM, Ikram K, Barry J. *Equipment review: An appraisal of the LiDCO ™ plus method of measuring cardiac output*. Crit Care. 2004; 8(3): 190-195
5. Pittman J, Bar-Yosef S, et al. *Continuous cardiac output monitoring with pulse contour analysis: A comparison with lithium indicator dilution cardiac output measurement*. Crit Care Med 2005; 33(9)
6. Jonas M, Fennell J et al. *Haemodynamic optimisation of the surgical patient revisited.* Anasthes Int 2008; 2(1)

Miss Karen A Eley, MBChB, MRCS(Ed), is a surgical trainee & DPhil Student, Oxford
Mr SR Watt-Smith, MBBS, BDS, FDSRCS, MD, is a Consultant in Oral & Maxillofacial Surgery, Oxford

The authors have no affiliation with LiDCO ™

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in terms of survival benefit, partly because of the more unpredictable nature of clinical presentation of lymphatic metastases in melanoma. We examine the reasoning behind advice for different patterns of lymph node resection following different cutaneous malignancies.

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The value of PET/CT in head and neck oncology diagnostic dilemmas

Liviu Marius Hanu-Cernat*, P. Nankivell, G. James

Worcestershire Royal Hospital, Worcester, United Kingdom

PET/CT is currently restricted to specific clinical circumstances such as an unknown primary with neck nodal disease and suspicion of recurrence in previously treated areas when CT and MRI failed to provide a diagnosis.

An audit of 24 head and neck oncology patients who benefited from PET/CT was carried out analysing clinical situations and organisational settings leading to a request for PET/CT, the timeframe from request to scan, reasons for requesting the scan, significant diagnostic findings and evaluation of treatment related implications.

The waiting time ranged from 2 to 30 days with a median of 13 days.

There were 10 cases of carcimoma of unknown primary and 12 patients who received treatment previously, 9 with surgery and chemoradiotherapy and 3 with chemoradiotherapy alone.

In the previously treated group presentation was with suspected recurrent/residual local disease in 8 cases, regional in 11 cases, loco-regional in 2 cases, metastases in 2 cases and widespread disease in 1 case.

Reasons for requesting PET/CT were an unknown primary, suspected recurrent/residual disease, suspected metastases and suspected malignancy, with one or more reasons per request.

PET/CT identified 8 primary tumours, recurrent/residual disease or absence of disease in 10 cases, confirmed metastases in 6 cases and clarified the extent of tumour in 12 cases.

The reasons for requesting PET/CT were matched by corresponding significant diagnostic findings in 23 cases and extra significant diagnostic findings in 3 cases with treatment related implications in 15 cases.

The results are analysed statistically and discussed in the context of available literature.

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Changes in inferior alveolar nerve following mandibular distraction in dogs

Mohamed Bahaa Khidr*, Aly Abdul Haleem, Mohamed Foda

Oral and Maxillofacial Surgery Department, Al-Minia University, Egypt

Introduction: DO represents a last time point in the historical evolution of reconstructive surgery through inductive surgery. It is well known fact that the mechanical or physical potentialities can influence the biological tissue behavior.

Aims: The evaluation of the biological tissue response of inferior alveolar nerve through mandibular bone distraction.

Materials/methods: This study was performed on 20 dogs divided to two groups. The first group included 10 animals subjected to corticotomy at the mandibular angle then distracted on either side of the corticotomy line by external distractor for 10 mm length using two different rates of distraction. Half of this group (5 dogs) underwent distraction rate of 1.0 mm/day for 10 days, while for the rest of the group the distraction rate was 2.0 mm/day for 5 days. The second group included 10 animals subjected to the same procedures but the distraction was performed for 20 mm distance. In each subgroup of the two main groups one animal was subjected to bilateral corticotomy but distracted only at one side. The non-distracted side was taken as a control. The consolidation period was 6 weeks.

Results: Results indicated inferior alveolar nerve changes; comprising signs of severe degeneration, marked separation of the perineural sheath, decrease in number of axons and intervening areas of edema were seen in animals subjected for increased length with higher rate of distraction.

Conclusions: DO must be done at lower rate to avoid the deleterious effect on the inferior alveolar nerve.

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Post-operative troponin positive cardiac events in patients undergoing head and neck cancer resection admitted on the day of surgery

Karen Ann Eley*, S.R. Watt-Smith

Oxford Radcliffe Hospitals NHS Trust, United Kingdom

Theatre direct admission (TDA), whereby patients for elective operations attend a holding bay on the day of operation, and are admitted to a ward postoperatively, has been introduced in hospitals throughout the UK, including our own. Initial reports about same day surgical admissions in vascular and colorectal surgery have been favourable.

Patients are assessed preoperatively to exclude those with coexisting conditions for which preoperative admission to a ward is required. As a consequence, pre-selected "low risk" patients for TDA should have little postoperative morbidity.

We reviewed all patients who underwent major surgery for head and neck cancer in our department from 2003 to 2008, to determine the incidence of troponin positive myocardial infarction.

Prior to the introduction of TDA admissions, 7% of 131 patients had troponin positive cardiac events during the post-operative recovery phase. This increased to 20% during the seven month period of TDA admissions, and subsequently returned to 2% following re-introduction of pre-operative ward admission.

The surgical stress response is a systemic reaction to injury that includes endocrine, immunological, and haematological effects, with a magnitude and duration proportional to the injury. The combination of a patient's anxiety associated with admission to hospital, and the serious stress response from an extensive operation, are probable contributory factors to postoperative complications such as myocardial infarction. TDA may therefore not be appropriate for all patients having major operations.

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Three-dimensional imaging and characterisation of bone using a novel omnidirectional ultrasound array: proof of concept

Duncan F. Campbell [a,*], David K. Smythe [a,b]

[a] *Monklands District General Hospital, Airdrie, Scotland, United Kingdom*
[b] *University of Glasgow, United Kingdom*

Introduction/aims: Fundamental to bone surgery is our inability to assess the progression of bone healing. Currently we have to wait for rigid union. Ideally, when is the best time to remove fixation? How successful are bone morphogenic proteins and other advanced techniques? In short, we need better ways to see healing bone.

Materials/methods: We have built and tested a novel prototype 2D ultrasound array in association with the Universities of Strathclyde and Bristol, employing principles derived from seismic reflection imaging. The 550 elements in our planar array are omnidirectional. Each is activated in turn as a point source illuminating the whole volume beneath the array, while all 550 simultaneously receive the backscattered echoes. The conversion of the resulting dataset into a true 3D volumetric image is done using standard geophysical industry software. The full image is obtained within an inverted pyramid about 60 mm below the 48 mm × 42 mm array. Resolution is 1 mm horizontally and about 0.3 mm vertically, but in contrast to conventional ultrasound methods does not degrade with depth.

Results: Imaged inorganic phantoms and cut samples of bovine bone show that the technology transfer of 3D imaging from the seismological to the medical ultrasound domain is successful, even though the elements at present have limited omnidirectionality and a frequency of only 2 MHz.

Conclusions/clinical relevance: The image makes allowance for the widely different sound velocities of bone/tissue: the elastic properties (and hence strength) of bone can be estimated directly from the data.

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Ultrasound guided interstitial photodynamic therapy of deep seated lesions

Sorcha MacKay *, Waseem Jerjes, Tahwinder Upile, Zaid Hamdoon, Syedda Abbas, Farai Nhembe, Shinali Patel, Simon Morley, Colin Hopper

UCLH Head & Neck Centre, London, United Kingdom

Introduction: Photodynamic therapy is a minimally invasive therapy that results from the interaction between a photosensitiser, oxygen and light. The delivery of light can by either by surface illumination or interstitial application.

We describe the intraoperative application of ultrasound in guiding light delivery in photodynamic therapy.

Method and materials: A total of 60 patients with various deep seated pathologies in the head and neck, upper and lower limbs were treated with mTHPC-photodynamic therapy. 2D Ultrasound was used to guide the needle insertion in the diseased area.

Results: It was possible to clearly identify the needles during insertion in all treatments and it was possible to guide parallel needle insertions using ultrasound. Although the resolution of ultrasound is not as good as other imaging modalities (i.e. CT, MRI) it was satisfactory in identifying the centre and the peripheries of the pathological lesions.

Ultrasound is very easy to perform, non-invasive, relatively inexpensive, quick and convenient, suited to imaging soft tissues and does not cause any discomfort.

Conclusion: Ultrasound can be used to guide 'real-time' photodynamic therapy of deep seated tumours and other malformations and can augment the information from other imaging modalities without affecting the patient's treatment outcome.

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Binge drinking amongst 8845 13–14-year-old English pupils and the harms they suffered

Sharon Cheung *, Fran Ridout, Allan Hackshaw, Stephen Sutton, Ken Gannon, Iain Hutchison

Barts and The London NHS Trust, United Kingdom

Introduction: The aim of the research was to find out about attitudes to drinking and the drinking habits of young people in order to inform intervention programmes to discourage binge drinking.

Post-operative troponin positive cardiac events in patients undergoing head and neck cancer resection admitted on the day of surgery

Miss Karen A Eley, Mr Stephen R Watt-Smith

Department of Oral & Maxillofacial Surgery, Oxford Radcliffe Hospitals NHS Trust, Headley Way, Oxford OX3 9DU, UK

INTRODUCTION:

Theatre Direct Admissions (TDA) is a method of increasing throughput of patients introduced in hospitals across the UK. Patients attend a holding bay pre-operatively, in close proximity to theatres, and are transferred to the ward post-operatively. Initial reports about same day surgical admissions in vascular and colorectal surgery have been favourable.[1,2] Patients are assessed preoperatively to exclude those with coexisting conditions for which preoperative admission to a ward is required. As a consequence, pre-selected "low risk" patients for TDA should have little postoperative morbidity.

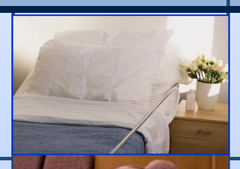
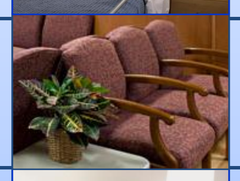
AIMS:

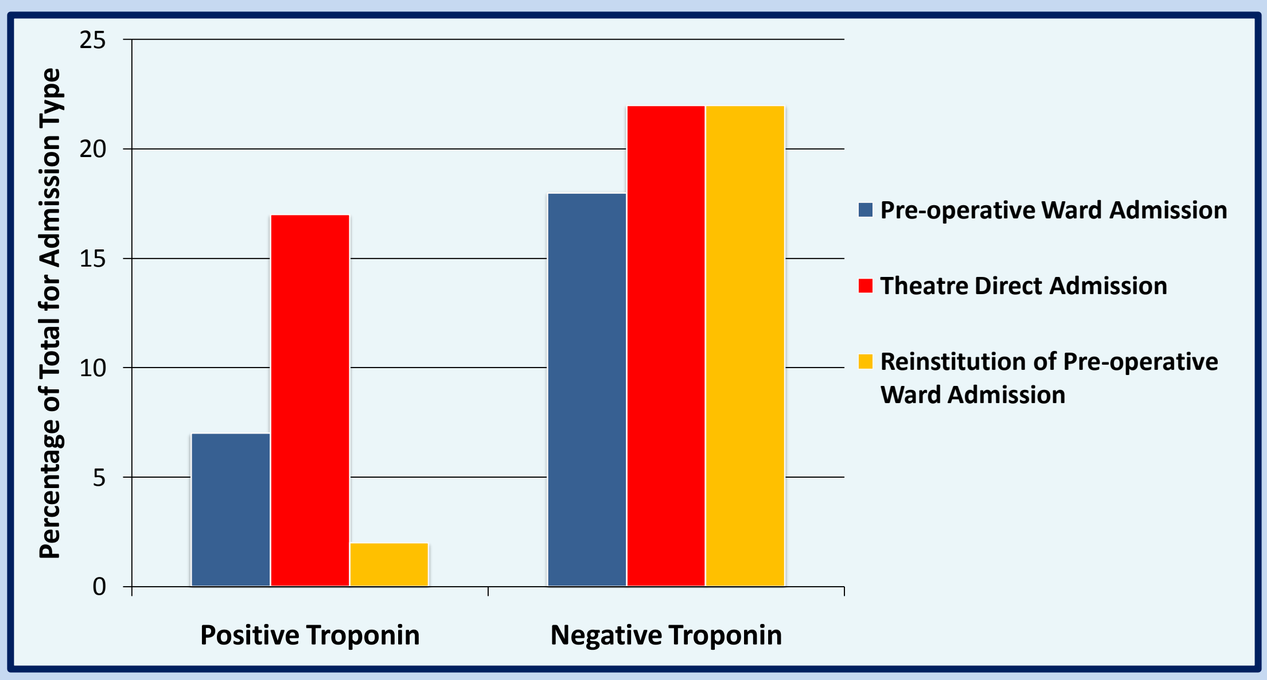
To determine the incidence of post-operative troponin positive Myocardial Infarction (MI) rate in patients following head and neck cancer resection and reconstruction patients admitted pre-operatively to the ward compared to those via TDA.

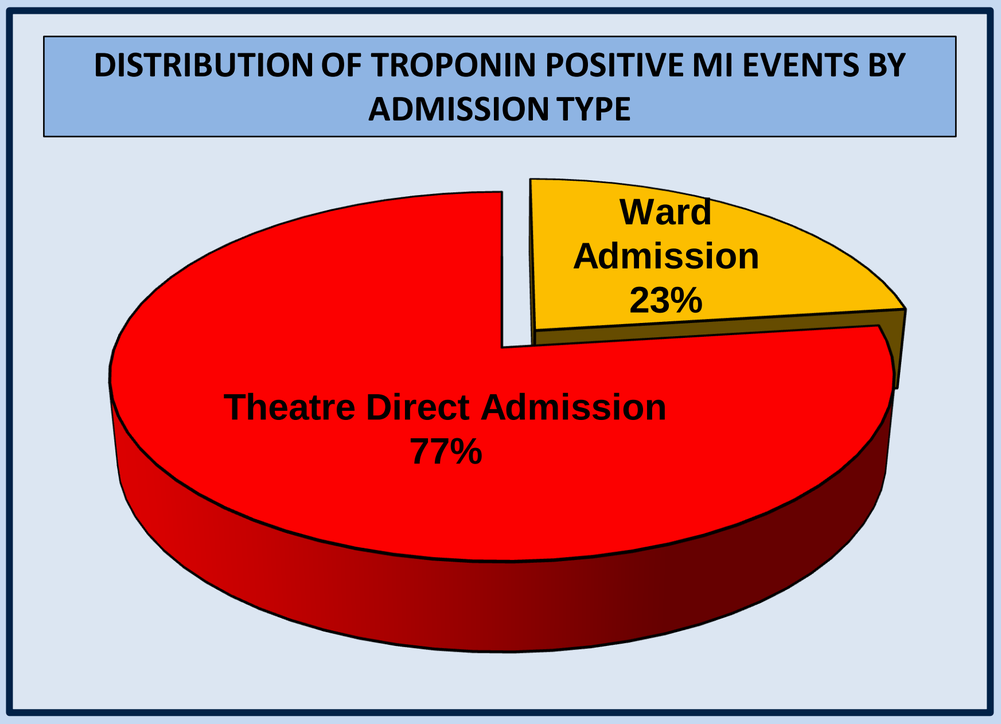
METHODS:

Retrospective review of all patients undergoing resection and reconstruction for head and neck cancer between 2003-2008 (n=195), in the department of Oral & Maxillofacial Surgery, Oxford, to determine incidence of troponin positive MI rate.

RESULTS:

Cohort	Admission Type	Troponin				Total
		Positive	Negative	Total Requests	Total Not Requested	
1	Ward Admission 	9 (7%)	24	33 (25%)	98	*131*
2	Theatre Direct Admission 	3 (20%)	4	7 (47%)	8	*15*
3	Reinstitution of Ward Admission 	1 (2%)	11	12 (24%)	37	*49*





DISCUSSION:

The surgical stress response is a systemic reaction to injury that includes endocrine, immunological, and haematological effects, with a magnitude and duration proportional to the injury.[3,4] The combination of a patient's anxiety associated with admission to hospital, and the serious stress response from an extensive operation, are probable contributory factors to postoperative complications such as myocardial infarction.[5]

Chiang et al [6] reported an incidence of 3.6% among patients undergoing microvascular head and neck reconstruction. Our patient cohort was of more advanced age in comparison, with increased co-morbidity.

The increased incidence of MI in patients admitted via TDA may reflect a cluster that occurred at this time, irrespective of admission method.

In response to these findings, our unit continues to use pre-operative ward admission for all patients undergoing resection and reconstruction for head and neck cancer.

The pre-operative night spent on the ward provides an opportunity to become accustomed to hospital stay, and the opportunity to further discuss the surgical plan thereby allaying any residual concern.

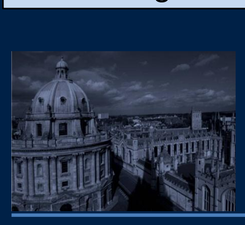
Further research is warranted on the optimised therapy for patients undergoing this type of surgery, and we are currently investigating the benefit of perioperative monitoring of stoke volume variance to optimise fluid balance.

CONCLUSIONS:

TDA may not be appropriate for all patients having major operations, in view of the compounding stress associated with this method of hospital admission.

REFERENCES:

1. Rothwell LA, Bokey EL, Keshava A, Chapuis PH, Dent OF. Outcomes after admission on the day of elective resection for colorectal cancer. ANZ J Surg 2006; 76: 14-19.
2. Calligaro KD, Dandura R, Dougherty MJ, DeLaurentis DA, Raviola CA. Same-day admissions and other cost-saving strategies for elective aortoiliac surgery. J Vasc Surg 1997; 25:141-4.
3. Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000; 85: 109-17.
4. Wilmore DW. From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. Ann Surg 2002; 236: 643-8.
5. Kehlet H. The surgical stress response: should it be prevented? Can J Surg 1991; 34: 565-7
6. Chiang S, Cohen B, Blackwell K. Myocardial infarction after microvascular head and neck reconstruction. The Larynoscope; 2002; 112: 1849-52



Miss Karen A Eley, MBChB, MRCS(Ed), is a Surgical Trainee & DPhil Student, Oxford
Mr Stephen R Watt-Smith, MBBS, BDS, FDSRCS, MD, is a Consultant in Oral & Maxillofacial Surgery, Oxford

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