COARCTATION OF THE AORTA: MANAGEMENT IN A NON-SURGICAL CENTRE AND EVALUATION OF AORTIC STIFFNESS & CARDIAC FUNCTION

Isma Rafiq

Submitted for Doctor of Medicine (MD) Research Degree

University of East Anglia

Student number 100084010

14 December 2021

Approximately 46,000 words

Norwich Medical School, University of East Anglia,

Norfolk and Norwich University Hospital (Cardiology Department)

Guys and St Thomas's Hospital

(Division of Imaging and Biomedical Engineering)

DECLARATION

I confirm that I have prepared and written this MD Thesis independently by myself with support from my supervisors. All contributions are clearly stated in the "Contributions" section. All information taken from various sources and reproduced in this thesis are clearly and properly referenced and attributed.

Isma Rafiq

CONTRIBUTIONS

Part 1: Observational dataset on congenital heart disease

The student was responsible for study design, data management (identifying relevant data fields, checking for completeness and consistency, obtaining additional data from original medical records and long term follow up data on clinical events and deaths), preparing a spreadsheet of data for analysis, performing descriptive statistics (frequency and distribution, means, medians, tables and figures), literature searches and writing the thesis report. The clinical database had been set up and maintained by Dr Freeman. Supervisors provided regular meetings and critical input. Statistical analyses were also carried out by Mr Ian Nunney a qualified statistician from University of East Anglia.

Part 2: Cardiac MRI assessment of coarctation of the Aorta

The student was responsible for study design, preparing the protocol, ensuring that all relevant ethical and institutional approvals were in place, recruiting patients including obtaining informed consent, carrying out the clinical and research aspects of the Cardiac MRI studies, and interpreting and reporting the results. The student prepared the database for analysis and carried out descriptive statistical analysis. The main supervisor Dr Tarique Hussain provided input into the study design and protocol, supervised the student's progress through the project, assisted with statistical analysis and provided critical input to the thesis. Dr Kostas Dimopoulos assisted with additional statistical analyses for this section.

Funding

The study was supported by the Adult Congenital Heart Disease charitable fund at Norfolk and Norwich University Hospital.

ACKNOWLEDGEMENTS

There are a very large number of people who have assisted with this thesis: I am indebted to each and every one of them. In particular

- My Educational, Academic and Clinical supervisor Dr Leisa Freeman for mentoring, encouraging and being the force of nature during my research period
- My Primary Supervisor, Dr Marcus Flather for his guidance throughout my research period
- My Second Supervisor, Dr Tarique Hussain for his enthusiasm, overseeing my progress guidance and supervising my Cardiac MRI training throughout my research period
- Dr Catherine Head and Christoph Kiesewetter for providing me with support during recruitment and running the Cardiac MRI on their list.
- Dr Kostas Dimopoulos for advice and support during thesis revisions
- Mr Ian Nunney for statistical support
- Dr Tim Gilbert as clinical director of the department to balance my clinical commitments.
- All the study participants without whom this work would not have been done.

DEDICATION

I dedicate this thesis to my parents, Mohammed Rafiq and Bushra Rafiq, my husband Adeel and daughter Ayra. Most Importantly, the role model I had throughout my career, Dr Leisa Freeman, who has never let me fall.

ABSTRACT

Background: Adult Congenital Heart Disease (ACHD) is growing rapidly as patients with corrected congenital heart disease are living longer. Coarctation of the aorta is a common congenital heart disease characterised by stenosis of the proximal descending aorta. Despite advances in management, long-term complications remain common.

Methods: The first part analyses data from a prospective clinical register of ACHD patients conducted in the only non-surgical specialist centre with a focus on coarctation patients using cross sectional and longitudinal observational methods. Second part consists of a prospective observational study using cardiac magnetic resonance (CMR) imaging to evaluate the associations of pulse wave velocity (PWV, a measure of arterial stiffness), systemic vascular resistance (SVR) and cardiac function in patients with corrected coarctation.

Results: The NORPAP database was set up in 1993 and in January 2015, had 2322 ACHD patients (mean age 42 years, 52% female, 62%). Coarctation (n=223, 9.6%), 90% had a corrective procedure and a third required additional procedures during follow-up. Older patients at registration and those diagnosed after age 1 year had a greater likelihood of hypertension, death and recoarctation. Forty-five repaired patients were included in the CMR study: mean age 33 years left ventricular ejection fraction 64%, baseline PWV 5.8m/s and SVR 1345 dynes.cm^{-5}. There were significant univariate associations between PWV and SVR with advancing age, female gender and hypertension, although only age was retained in the multivariate model.

Conclusions: Coarctation of the aorta comprised approximately 10% of the ACHD population, with a low risk of long-term adverse outcomes. Patients who were not diagnosed in the 1st year of life had higher risk of hypertension, death and recoarctation. Abnormalities in vascular function were found in CMR in patients with corrected coarctation, and arteriolar resistance may adversely influence myocardial function. These observations could help coarctation patients at risk of future complications.

Access Condition and Agreement

Each deposit in UEA Digital Repository is protected by copyright and other intellectual property rights, and duplication or sale of all or part of any of the Data Collections is not permitted, except that material may be duplicated by you for your research use or for educational purposes in electronic or print form. You must obtain permission from the copyright holder, usually the author, for any other use. Exceptions only apply where a deposit may be explicitly provided under a stated licence, such as a Creative Commons licence or Open Government licence.

Electronic or print copies may not be offered, whether for sale or otherwise to anyone, unless explicitly stated under a Creative Commons or Open Government license. Unauthorised reproduction, editing or reformatting for resale purposes is explicitly prohibited (except where approved by the copyright holder themselves) and UEA reserves the right to take immediate ‘take down’ action on behalf of the copyright and/or rights holder if this Access condition of the UEA Digital Repository is breached. Any material in this database has been supplied on the understanding that it is copyright material and that no quotation from the material may be published without proper acknowledgement.

Contents

LIST OF FIGURES

LIST OF TABLES

Abbreviations

Abbreviation	Meaning
ACHD	Adult Congenital Heart disease
Ao	Aorta
AoS	Aortic stenosis
AoV	Aortic valve
ASD	Atrial Septal Defect
AV	AV canal defects
BA	Balloon angioplasty
BPM	Beats per minute
ccTGA	Congenitally corrected Transposition of Great Arteries
CoHD	Congenital Heart Disease
CMR	Cardiac Magnetic Resonance
CO	Cardiac out put
CoA	Coarctation of the Aorta
COALA	Coarctation Long-term Assessment
CoHD	Congenital Heart Disease
Complex CHD	Complex Congenital heart disease
DoH	Department of Health
EDS	Ehler Danlos Syndome
FT	Feature Tracking
GUCH	Grown up Congenital Heart disease
LD	Loey Dietz Syndome
LV	Left ventricle
LVOT	Left ventricular outflow tract
MVD	Mitral valve

NNUH	Norfolk and Norwich University Hospital
NORPAP	Norwich and Papworth
PAPVD	Partial anomalous pulmonary venous drainage
PDA	Patent ductus Arteriosus
PS	Pulmonary Stenosis
PWV	Pulse valve velocity
Rt, Lt	Right, Left
RVOT	Right ventricular outflow tract
SV	Stroke Volume
SVR	Systemic vascular resistance
TAPVD	Total anomalous pulmonary venous drainage
TGA	Transposition of Great arteries
ToF	Tetralogy of Fallot
ULG	Upper to lower limb gradient
VSD	Ventricular septal defect

1. Introduction: Incidence of Congenital Heart Disease (CoHD) and Prevalence of Adult Congenital Heart Disease (ACHD)

This thesis aims to investigate risk factors associated with adverse outcomes in adult patients with coarctation of the aorta (CoA) using a clinical registry database set up in the only accredited non-surgical centre managing these patients in the UK. A prospective cardiac magnetic resonance investigation in patients with CoA was also set up to determine associations between pulse wave velocity (a surrogate for aortic stiffness) and peripheral vascular resistance with measures of left ventricular function to see if any of these could assist in identifying higher risk patients.

1.1 Definitions and classification of congenital/adult congenital heart disease

ACHD lesions are divided into three levels of severity: simple, moderate and complex as shown in Table 1.1.

Table 1.1 Classification of Adult Congenital Heart Disease complexity (Baumgartner, De Backer et al. 2021)

MILD:
Isolated congenital aortic valve disease and bicuspid aortic disease
Isolated congenital mitral valve disease (except parachute valve, cleft leaflet)
Mild isolated pulmonary stenosis (infundibular, valvular, supravalvular)
Isolated small ASD, VSD, or PDA
Repaired secundum ASD, sinus venosus defect, VSD, or PDA without residuae or sequellae, such as chamber enlargement, ventricular dysfunction, or elevated PAP.
MODERATE: (Repaired or unrepaired where not specified; alphabetical order)
Anomalous pulmonary venous connection (partial or total)
Anomalous coronary artery arising from the PA
Anomalous coronary artery arising from the opposite sinus
Aortic stenosis - subvalvular or supravalvular
AVSD, partial or complete, including primum ASD (excluding pulmonary vascular disease)
ASD secundum, moderate or large unrepaired (excluding pulmonary vascular

disease)
Coarctation of the aorta
Double chambered right ventricle
Ebstein anomaly
Marfan syndrome and related HTAD, Turner Syndrome
PDA, moderate or large unrepaired (excluding pulmonary vascular disease)
Peripheral pulmonary stenosis
Pulmonary stenosis (infundibular, valvular, supravalvular), moderate or severe
Sinus of Valsalva aneurysm/fistula
Sinus venosus defect
Tetralogy of Fallot – repaired
Transposition of the great arteries after arterial switch operation
VSD with associated abnormalities (excluding pulmonary vascular disease) and/or moderate or greater shunt.
SEVERE: (Repaired or unrepaired where not specified; alphabetical order)
Any CHD (repaired or unrepaired) associated with pulmonary vascular disease (including Eisenmenger syndrome)
Any cyanotic CHD (unoperated or palliated)
Double-outlet ventricle
Fontan circulation
Interrupted aortic arch
Pulmonary atresia (all forms)
Transposition of the great arteries (except for patients with arterial switch operation)
Univentricular heart (including double inlet left/right ventricle, tricuspid/mitral atresia, hypoplastic left heart syndrome, any other anatomic abnormality with a functionally single ventricle)
Truncus arteriosus
Other complex abnormalities of AV and ventriculoarterial connection (i.e. crisscross heart, heterotaxy syndromes, ventricular inversion

ASD = atrial septal defect; AV = atrioventricular; AVSD = atrioventricular septa defect; CHD = congenital heart disease; HTAD = heritable thoracic aortic disease; LV = left

ventricle/ventricular; PA = pulmonary artery; PAP = pulmonary artery pressure; PDA = patent ductus arteriosus; VSD = ventricular septal defect."

1.2 Overview of Congenital Heart disease and Adult Congenital Heart disease

Congenital heart disease (CoHD) is the most common congenital defect in new-borns. The incidence of congenital heart disease is reported to be 6-13 per 1000 live births(Wren, Reinhardt et al. 2008, Ishikawa, Iwashima et al. 2011, Khoshnood, Lelong et al. 2012, Wren, Irving et al. 2012, Jensen, Brown et al. 2014). The difference in incidence is due to different methods of collection and prevalence of disease. Studies in the United Kingdom have highlighted an incidence of congenital heart disease 6.5/1000 live birth(Wren, Reinhardt et al. 2008, Wren, Irving et al. 2012). A Norwegian registry has recently quoted an incidence of 3.4/1000 live births from 1994 -2009, and they have mentioned a decline in the number due to early recognition and termination of pregnancy(Leirgul, Fomina et al. 2014). A population-based study of live births from the Danish population from 1977 to 2005 has shown a prevalence of 10.5/1000 live births(Oyen, Poulsen et al. 2009). Similarly, another European study from greater Paris has shown an incidence of 9/1000 live births. Most diagnoses were made prenatally, and VSD was excluded(Khoshnood, Lelong et al. 2012). A population-based study from Atlanta has shown an incidence of 8.3/1000 live births. The majority of patients in this cohort had ventricular septal defect and secundum ASD ~~and~~ followed by tetralogy of Fallot (Reller, Strickland et al. 2008). A population-based study in Taiwan from 2000 -2006 has shown an incidence of congenital heart disease at 13.08/1000live births. The most common defects were ventricular septal defect, secundum atrial septal defect, and patent ductus arteriosus(Wu, Chen et al. 2010). Most Asian countries have been unable show an actual incidence or prevalence of congenital heart disease due to lack of an infrastructure allowing development of population-based databases for registration of congenital heart disease and development of associated services. Some reports from India have shown that the prevalence of congenital heart disease may be as high as in western countries. Reports from different regions of India are shown in the table 1.2 below.

Table 1.2 Description of Congenital Heart Disease (Gupta, Gupta et al. 1992, Khalil, Aggarwal et al. 1994, Thakur, Negi et al. 1995, Chadha, Singh et al. 2001)

Table shows reports of congenital heart disease prevalence in different regions of India and in different age groups. Studies did not use standardized methods to sample or detect congenital

heart disease which may partly explain the different frequencies, which may also reflect genuine differences.

Authors	**Total Patients studied**	**Age group**	**No of CHD per 1000**
Khalil et al	10,964	Live births	3.9
Gupta et al	10,263	6-16 years	0.8
Chadha et al	11,833	< 15 years	4.2
Thakur et al	15,080	5-16 years	2.25

Van der Linda et al. performed a systematic review and Meta-analysis on all the available published articles to establish the incidence of congenital heart disease Fig 1.1. The report showed the following geographical distribution of congenital heart disease(van der Linde, Konings et al. 2011).

*FIGURE 1.1 SYSTEMIC REVIEW AND META-ANALYSIS OF INCIDENCE OF CONGENITAL HEART DISEASE IN THE WORLD (14) The figure shows total CoHD birth prevalence per continent (upper panel) and World Bank income group since 1970 (lower panel). The overall prevalence was found to be higher in Asia followed by Europe but prevalence was also significantly higher in the higher earning income countries(*van der Linde, Konings et al. 2011*). No data were available for low-income countries. Symbols indicate significant differences from comparators.*

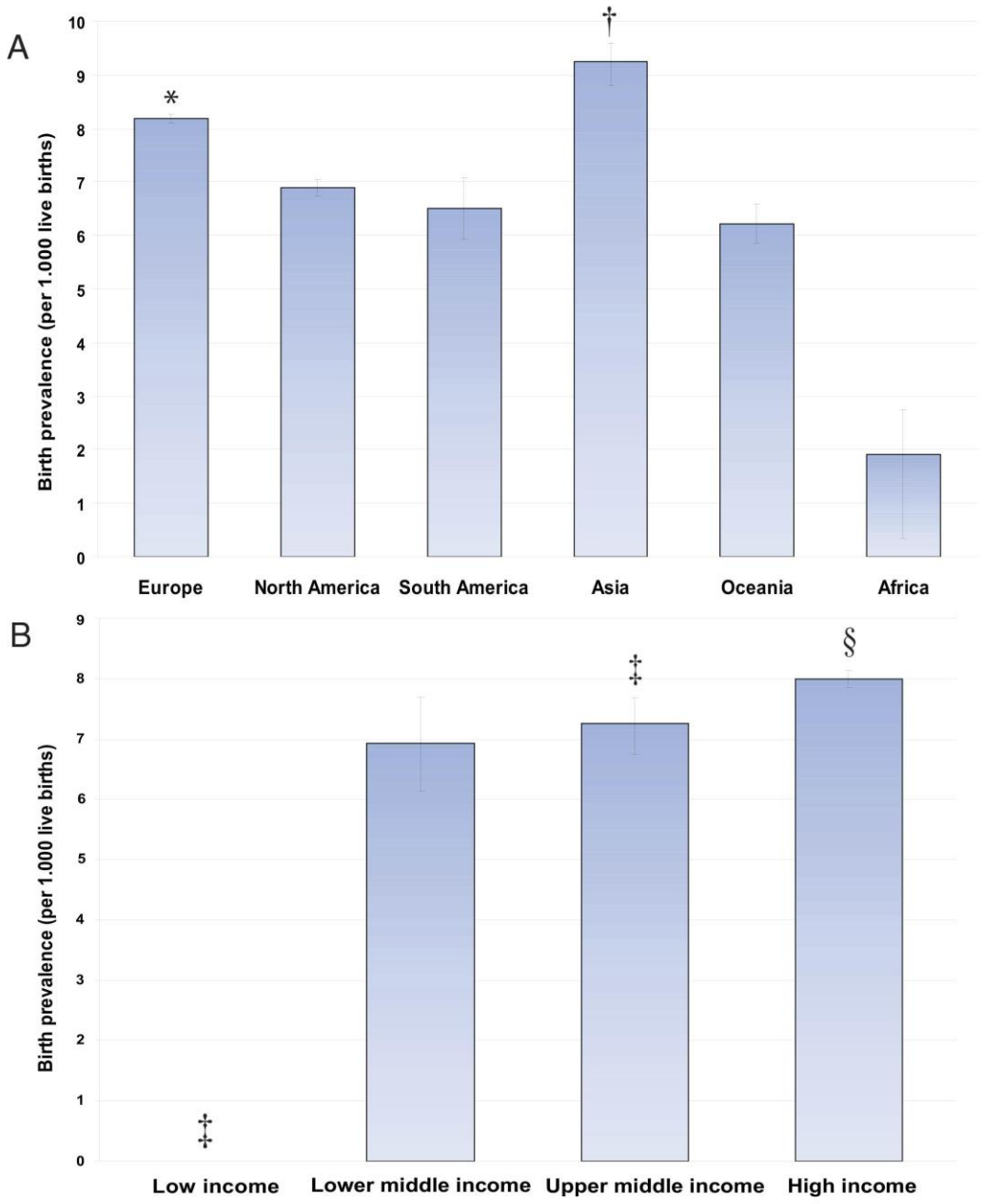
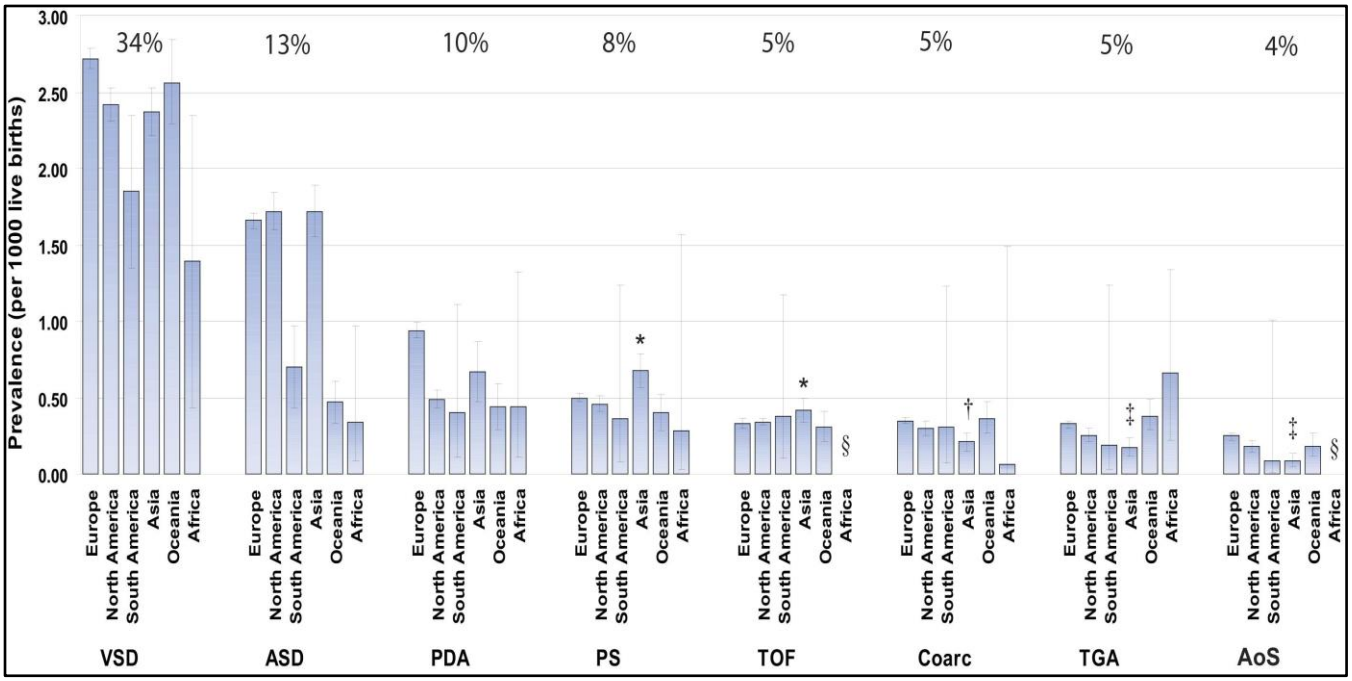


*FIGURE 1.2 DISTRIBUTION OF TYPE CONGENITAL HEART DEFECTS OVER THE GLOBE higher prevalence of ToF and PS as compared with Europe and North America, while Europe and America showed a higher prevalence of aortic valve disease and coarctation. There were no data available on the incidence of AoS and ToF from Africa(*van der Linde, Konings et al. 2011*). Abbreviations: VSD (ventricular septal defect), ASD (atrial septal defect), PDA (patent ductus arteriosus, PS (pulmonary stenosis), TOF (tetralogy of Fallot), Coarc (coarctation of the Aorta), TGA (transposition of the great arteries), AoS (aortic stenosis).*



Twenty five percent of the infants born with CoHD have critical heart disease, which is defined as a patient requiring catheter intervention or surgery. Before the cardiac surgical era, one-fifth of these children survived beyond childhood apart from the natural survivors or patients with mild congenital lesions(Macmahon, McKeown et al. 1953). Since 1985 due improvement in the diagnosis, management and refinement of surgical techniques the pattern of survival for children with congenital heart disease has changed leading to a steep increase in a number of survivors beyond adulthood(Connelly, Webb et al. 1998). This has resulted in the development of a new subspecialty – Adult Congenital Heart Disease (ACHD) (Perloff 1991). As a new specialty, there is a need to demonstrate safety and outcomes of the service(Celermajer and Deanfield 1991).

1.3 Prevalence of Adult Congenital Heart Disease with Classification

Before the 1980's the paediatric population with CoHD was larger than those of ACHD and only one-fifth of the paediatric population survived to adulthood. Advances in diagnostic, interventional and surgical techniques have allowed a greater proportion of paediatric congenital heart patients to survive to adulthood. As birth prevalence estimates of congenital heart disease vary widely over the globe with no systemic reporting of deaths, it is hard to estimate an exact figure for the prevalence but is likely to be 3000 per million live birth(van der Bom, Bouma et al. 2012). Prevalence and survival of CoHD are shown in Table 1.3

Table 1.3 Reported Birth Prevalence and Survival of congenital heart disease to Adulthood(van der Linde, Konings et al. 2011)

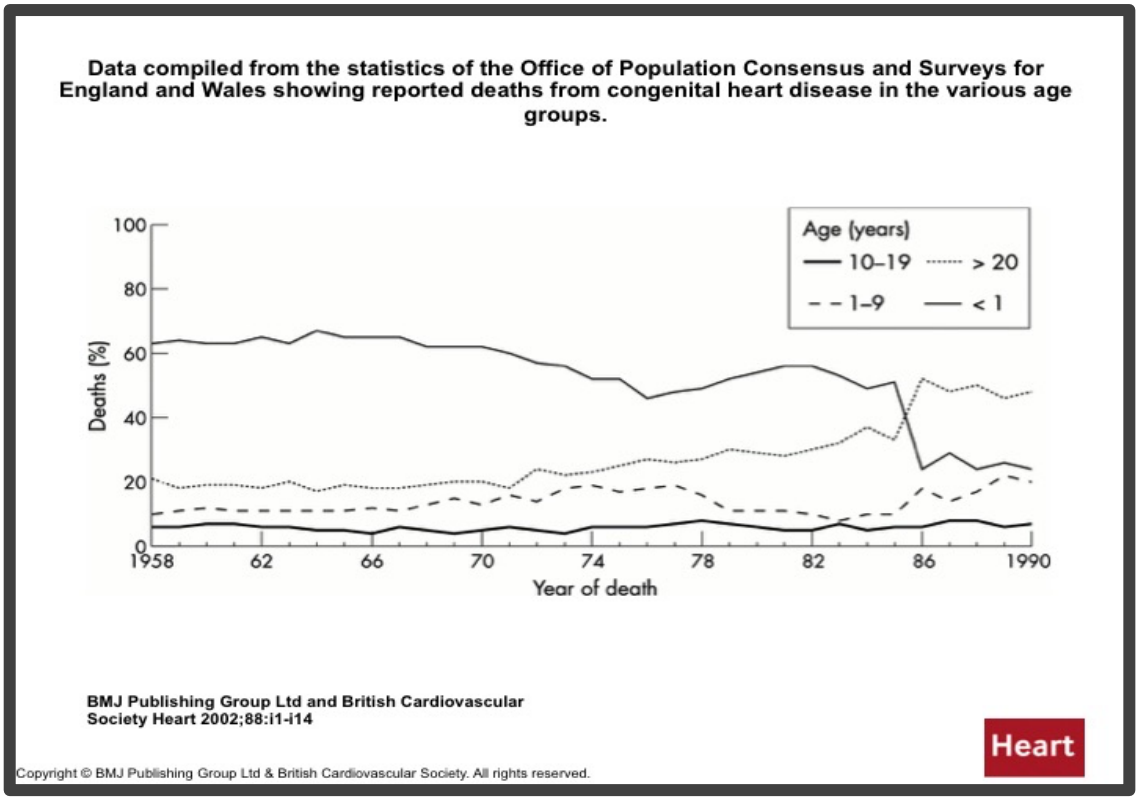
Heart defect	Birth prevalence*	Survival to adulthood					
		1940-1959		1960-1979		1980-1989	
Severe		%	Ref	%	Ref	%	Ref
Double-outlet RV or LV	157	0	Samánek[32]	38	Kirklin et al[33]	43	Samánek and Voríšková[31]
Single ventricle	106	5	Moodie et al[34]	30	Moons et al[15]	50	Moons et al[15]
Tricuspid atresia	79	27	Samánek[32]	20	Dick et al[35]	36	Samánek and Voríšková[31]
Pulmonary atresia	132	0	Samánek[32]	25	Coles et al[36]	44	Leonard et al[37]
Transposition of the great arteries	315	0	Campbell[13]	27	Gilljam[38]	75	Moons et al[15]
Truncus arteriosus	107	0	Campbell[13]	20	Moons et al[15]	40	Moons et al[15]
Ventricular inversion	45	30	Rutledge et al[39]	50	Rutledge et al[39]	73	Rutledge et al[39]
Hypoplastic left heart syndrome	266	0	Hoshino et al[40]	0	Osiovich et al[41]	10	Moons et al[15]
All severe	1207	3		22		45	
Moderate							
PAPVC and TAPVC	94	0	Samánek[32]	60	Moons et al[15]	79	Moons et al[15]
AVSD, ostium primum	348	49	Samánek[32]	55	Miller et al[42]	79	Moons et al[15]
Coarctation of the aorta	409	40	Hoffman[12]	60	Hesslein et al[43]	65	Samánek and Voríšková[31]
Ebstein anomaly	61	20	Celermaijer et al[44]	40	Celermaijer et al[44]	64	Samánek and Voríšková[31]
Moderate/severe PS	218	80	Hoffman[11]	95	Hayes et al[45]	95	Hayes et al[45]
Sinus venosus type ASD	66	40	Campbell[13]	79	Luciani et al[46]	96	Moons et al[15]
Subvalvular and supravalvular aortic stenosis	120	60	Kitchiner et al[47]	83	Brown et al[48]	96	Scott et al[49]
Tetralogy of Fallot	421	20	Bertranou et al[50]	64	Samánek and Voríšková[31]	79	Moons et al[15]
Complex VSD†	1071	25	Campbell[13]	80	Frontera-Izquierdo and Cabezuelo-Huerta[51]	95	Frontera-Izquierdo and Cabezuelo-Huerta[51]
All moderate	2808	35		71		85	
Mild							
Congenital AS	281	60	Kitchiner et al[47]	73	Elkins et al[52]	97	Moons et al[15]
Mild PS	510	80	Hoffman[11]	95	Hayes[45]	97	Moons[15]
PDA	799	70	Samánek[32]	95	Mavroudis et al[53]	95	Mavroudis et al[53]
Mild ASD	875	95	Garne[8]	98	Garne[8]	99	Garne[8]
Mild VSD	2499	95	Garne[8]	98	Garne[8]	99	Garne[8]
All mild	4964	87		96		98	
All ACHD	8979	60		78		87	

Abbreviations: *RV*, Right ventricle; *LV*, left ventricle; *PAPVC*, partial anomalous pulmonary venous connection; *TAPVS*, total anomalous pulmonary venous connection.
*Birth prevalence per million live births.
† Complex VSD comprises ventricual septal defect in combination with absent pulmonary valve, aortic regurgitation or coarctation, mitral disease, right ventricular outflow tract stenosis, or straddling tricuspid of mitral valve.

Although CoHD patients are living longer, they do experience complications such as recurrent lesions, arrhythmias, heart failure, and interventional and surgical procedures. An expansion of services is required to accommodate needs of this growing population(Perloff 1991, Report of the British Cardiac Society Working 2002) The prevalence of ACHD has increased in the UK, and Somerville emphasized the need for further training of medical staff and expansion of services to fulfil expanding clinical needs (Webb and Williams 2001, Report of the British

Cardiac Society Working 2002). The pattern of change in survival and death is shown in Figure 1.3.

Figure 1.3 Reported deaths from CoHD in the Various Age Groups (20)



Data compiled from the Office of Population Census highlighted the higher incidence of death in congenital heart disease patients in infancy in 1958, and after 1986 the incidence of death increases in the adolescent and adult group.(Somerville 1997, Report of the British Cardiac Society Working 2002). The data were compiled to streamline services as well as training for expanding congenital heart disease patients. The UK Department of Health (DoH) documented the number of CoHD patients to be 133,190 in 2000, rising to 158,990 in 2010, with 90% of patients of these patients in adolescence and older(Freeman 2008). The DoH used a statistical model derived from the Bethesda conference 2001 based on the birth rate and historical survival data to predict the size of the future ACHD population. Stuart et al. used Marelli's model based on a study from Quebec where a prevalence of congenital heart disease was reviewed over four sequential time periods 1985. 1990. 1995 and 2000 including 45,960 patients. The study showed a relatively constant number in the paediatric group but increased prevalence in the adult group (estimated at 4 per 1000 adults with a slight predominance of the

disease in females and 9% with complex congenital heart defects (Marelli, Mackie et al. 2007). Marelli and colleagues extrapolated the same model and estimated a population 847,876 and 83.275 in USA and Canada (Marelli, Therrien et al. 2009, Stuart 2012). Using the same model the prevalence in the United Kingdom was potentially underestimated by 10%(Stuart 2012).

Table 1.4 Estimated Prevalence of ADULT Congenital Heart Disease(Marelli, Ionescu-Ittu et al. 2014)

Table 1. Estimated prevalence of congenital heart disease in the adult (>18 years) in England.

2000	2010	2000	2010	2000	2010	2000	2010
Complex		***Moderate***		***Simple***		***Total***	
Department of Health							
16,870	21,030	50,680	61,390	63,640	76,570	133,190	158,990
Estimated change							
	+20%		+17%		+14%		+19%
Marelli prevalence							
						156,052†	176,196†

†*Predicted on basis of prevalence of 4.1 per 1000 adults taken from Quebec population database 2000.*
Projected population of adults (>16 years) for 2001 and 2011 were used for the Marelli prevalence data projections as estimated population projections for England 2000 and 2010 >18 years were not available from the Office of National Statistics.
Data taken from [102].

In 2006 the English department of health used a model based on birth rates and survival rates presented in Bethesda conference in 2001(Webb and Williams 2001). Marelli model is for the same dataset, demonstrated the ACHD population was underestimated by 10%. Provision of care has been challenging for ACHD patients due to increase in numbers and complexity together with a need for regular monitoring. Arrhythmias are a particular problem of survivors and their ~~management~~ requirement for electrophysiology procedures and devices is high (Kumar, Tedrow et al. 2015, Hessling 2016, McLeod and Warnes 2016). Heart failure is common and acquired clinical conditions such as ischaemic heart disease increase as the population ages(Engelings, Helm et al. 2016). Inheritance, genetics, contraception together with counselling and monitoring in pregnancy and delivery are also important aspects of care (Kovacs, Silversides et al. 2006). Psychosocial support is required and psychological services are under resourced.

1.4 Management patterns for ACHD in the UK

Congenital heart disease care for the paediatric group has a strong infrastructure, which has led to excellent care and survival for these patients. As a result, there is a huge population, which has transitioned to the adulthood with congenital heart disease ranging from simple to complex congenital heart disease. Although the care provision at a tertiary level is excellent, there have been no structure or system to follow up these patients at local services with a specialist interest in congenital heart disease.

In 2002, Jane Somerville provided an executive report advising the expansion of services for ACHD. She highlighted that 20 to 25% of patients had complex CoHD requiring specialist care while 40 to 45 % of patients had simple needs and can be cured and discharged from the services. There is also an intermediate group requiring long-term follow-up. The report also recommended integrated care for ACHD patients preferably at tertiary centres with interventional and surgical facilities. Somerville et al. also highlighted that there should be a nationally integrated specialist centres in cardiology. ESC guidelines have developed over the years and provided the paradigm for management of congenital heart disease patients.

In 2007, the UK National Specialist Commissioning Group (NSCG) agreed to a review for the designation of Specialist Surgical Centres (SSC Level 1) for Grown Up Congenital Heart (GUCH) or ACHD To ensure accreditation of the whole patient pathway, Specialist Commissioners would also designate Local GUCH/ACHD (Level 3) centres where local adult cardiologists with an interest in GUCH/ACHD would have the benefit of visiting Level 1 or Level 2 GUCH/ACHD cardiologists – thus creating a Hub and Spoke model as part of a congenital cardiac network. [26] The process of designation including Standard setting and information review has led to the new CHD review (2015). In the most recent iteration an intermediate level was also described – the Specialist Cardiology Centre (SCC Level 2) which would manage and investigate CoHD patients as though SSC/Level 1 but without congenital cardiac surgery. 1.5WTE trained adult congenital cardiologists would staff this. The Standards against which prospective SSC (Level1) and SCC (Level 2) hospitals are currently being evaluated by NHS England with a view to commissioning of services. The required link of SSC (under Safe and Sustainable, *NHS England Commission guidelines*) with congenital surgeons (who operate on both children and adults (with 125 cases per surgeon per year with 4 surgeons on the rota) will challenge some existing centres to fulfil SSC status.

Despite some progress, it is likely that large group of patients may not even be identified, may be lost to follow-up (usually at Transition) or are followed-up inappropriately in their local general adult cardiology clinics(Wren and O'Sullivan 2013). It has been proposed that all centres should keep a contemporary ACHD database to ensure that all patients are kept under review. In a database analysis of Tetralogy of Fallot at Great Ormond Street, Wray et al. found that 25% of patients with repaired congenital heart disease were not followed up and suggested there could be 15000 patients in England and Wales without adequate care (Wray, Frigiola et al. 2013).

The provision of care by trained ACHD cardiologists is slowly becoming a reality. The Standards for that care have been set and commissioning of service (be it Level 1, Level 2 or Level 3) will eventually cover England and Wales. Historical geographical location may still mean that certain areas are under-provided in the medium term. NHS England have assessed Level 1 and Level 2 against prospective Standards. Level 1 centres currently will be GSTT, BARTS, Southampton, Bristol, Birmingham, Liverpool, Leeds and Newcastle. As only NNUH complied with all the Standards, they will definitely be commissioned as a level 2 centre; Brighton & Sussex and Oxford are likely to achieve compliance for Level 2.

1.5 Coarctation Of The Aorta

1.5.1 Introduction

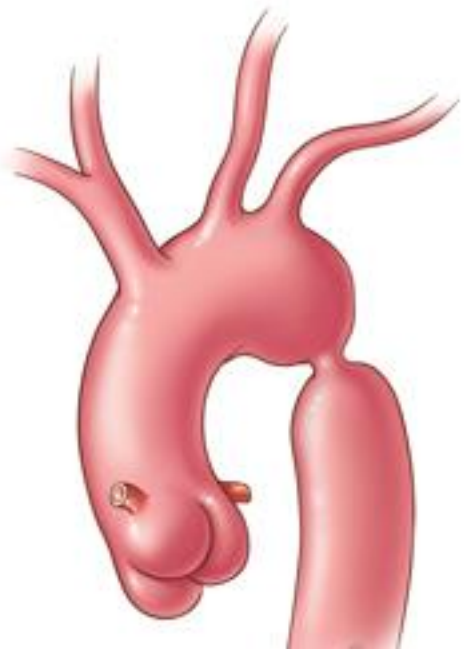
Coarctation of the aorta (CoA) is a narrowing of the descending aorta, typically located at the site of insertion of the ductus arteriosus, distal to the left subclavian artery as shown in Figure 1.4. CoA is a complex congenital cardiovascular disorder, which requires careful assessment and potentially life-long monitoring. Morgagni et al first described it in 1760, after performing an autopsy in a monk and further descriptions came from Jordan and Reynaud in 1827 and 1828 respectively but it was not clinically recognised until 1933(Jenkins and Ward 1999).

1.5.2 Isolated CoA or simple coarctation.

Classification is guided by the site of narrowing as shown below

- Preductal
- Juxtaductal
- Post-ductal

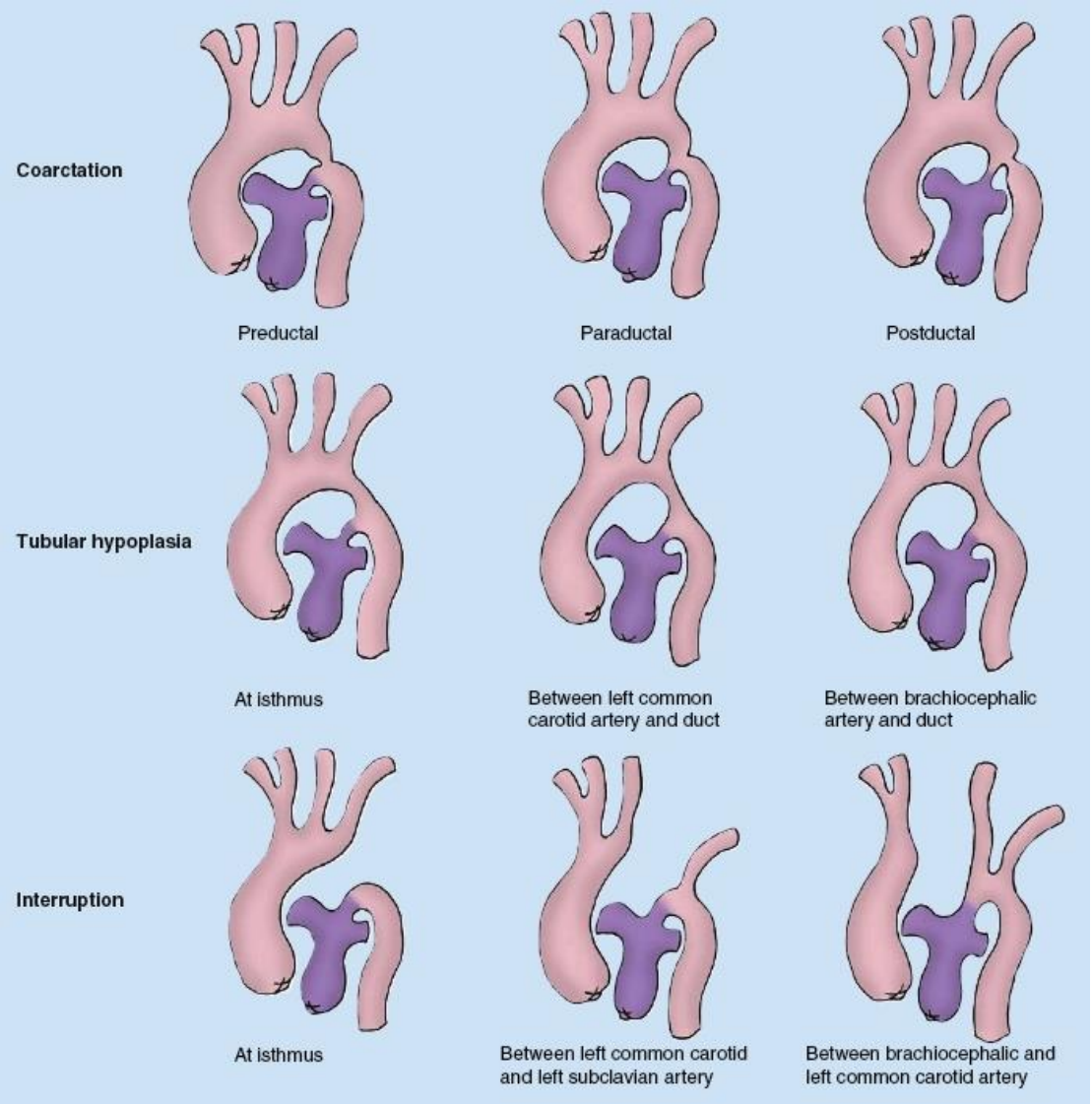
Figure 1.4 showing isolated Coarctation of Aorta.



Source Illustration Cleveland Clinic

It is useful to understand the difference between coarctation of the aorta, tubular hypoplasia and interruption of the arch as all three anatomical pathologies are treated with different approaches Figure 1.5.

Figure 1.5 DIFFERENT TYPES OF CONGENITAL ABNORMALITIES OF THE AORTA INCLUDING COA



Source: Expert Rev of Obstetric Gynaecol @ 2008 Expert Reviews Ltd.

Complex CoA includes association with a bicuspid aortic valve in 50% of the cases(Warnes 2003), ventricular septal defect, mitral valve disease and aneurysm of Circle of Willis (3-5% of the cases)(Becker, Becker et al. 1970). CoA can also occur with transposition of great arteries, Taussig-Bing anomaly (transposition of the great arteries to the right ventricle and malposition of the pulmonary artery with subpulmonary VSD), double inlet left ventricle,

tricuspid atresia, hypoplastic left heart syndrome and rarely with right ventricular outflow tract obstruction. Coarctation of the aorta is associated with genetic and chromosomal conditions like Turner, William and Noonan syndrome.

1.5.3 Epidemiology,

CoA makes up about 5% of all congenital heart disease and is the fifth most common congenital defect. The prevalence is about 4 per 10,000 live births(Hoffman and Kaplan 2002, Reller, Strickland et al. 2008). Prevalence in males is 59% versus 49% in females (1980) although Jenkins et al. described it to be three times more common in males(Jenkins and Ward 1999).The incidence was noted to be higher in the European population(Van der Horst and Gotsman 1972).

1.5.4 Pathogenesis & Pathophysiology

The precise pathogenesis of aortic coarctation is unknown, but there are two popular theories for the development of this disorder.

1. Migration of ductal tissue into the wall of the foetal aortic arch(Ho and Anderson 1979, Russell, Berry et al. 1991)
2. Reduction of antegrade intrauterine flow can cause underdevelopment of the left ventricular outflow tract and the aortic arch leading to the development of Coarctation(Rudolph, Heymann et al. 1972).

Congenital CoA shows medial thickening and intimal hyperplasia at the coarctation site forming a posterolateral ridge, which encircles the aorta. Post-mortem studies in foetuses and neonates have shown abnormal aortic wall properties, Niwa et al. have shown an increase in elastic tissue and decrease in the smooth muscle in the pre-stenotic area compared to the post-stenotic aorta. Despite these findings, we are not clear if these findings are acquired or inherited(Niwa, Perloff et al. 2001). Vogt et al. described increased aortic stiffness even with successful repair in the coarctation patients in comparison to healthy neonates suggesting abnormal properties of the aortic vessel wall (Vogt, Kuhn et al. 2005). Cystic medial necrosis is associated with adverse events in patients with CoA. Isner et al. studied tissue taken from 31 patients and autopsy in 2 patients in demonstrating depletion and disarray of elastic tissue which is a consistent feature of aneurysm formation (Isner, Donaldson et al. 1987). The role of genetics has been identified and is a major contributory factor for CoA such as Turner

syndrome, Mosaic Trisomy 16, Trisomy 21, 22q11 and Noonan syndrome. A number of compensatory mechanisms in CoA occur in response to elevated left ventricular pressure including left ventricular hypertrophy and development of collaterals (internal mammary, intercostal, and scapular vessels). Coarctation of the aorta also increases left ventricular pressure and afterload leading to myocardial hypertrophy and systemic hypertension. CoA with a large ventricular septal defect, patent ductus arteriosus, or mitral regurgitation leads to an increase in left ventricular end-diastolic pressure and pulmonary artery hypertension which is ~~frequently~~ associated with complex CoHD.

1.5.5 Clinical Presentation

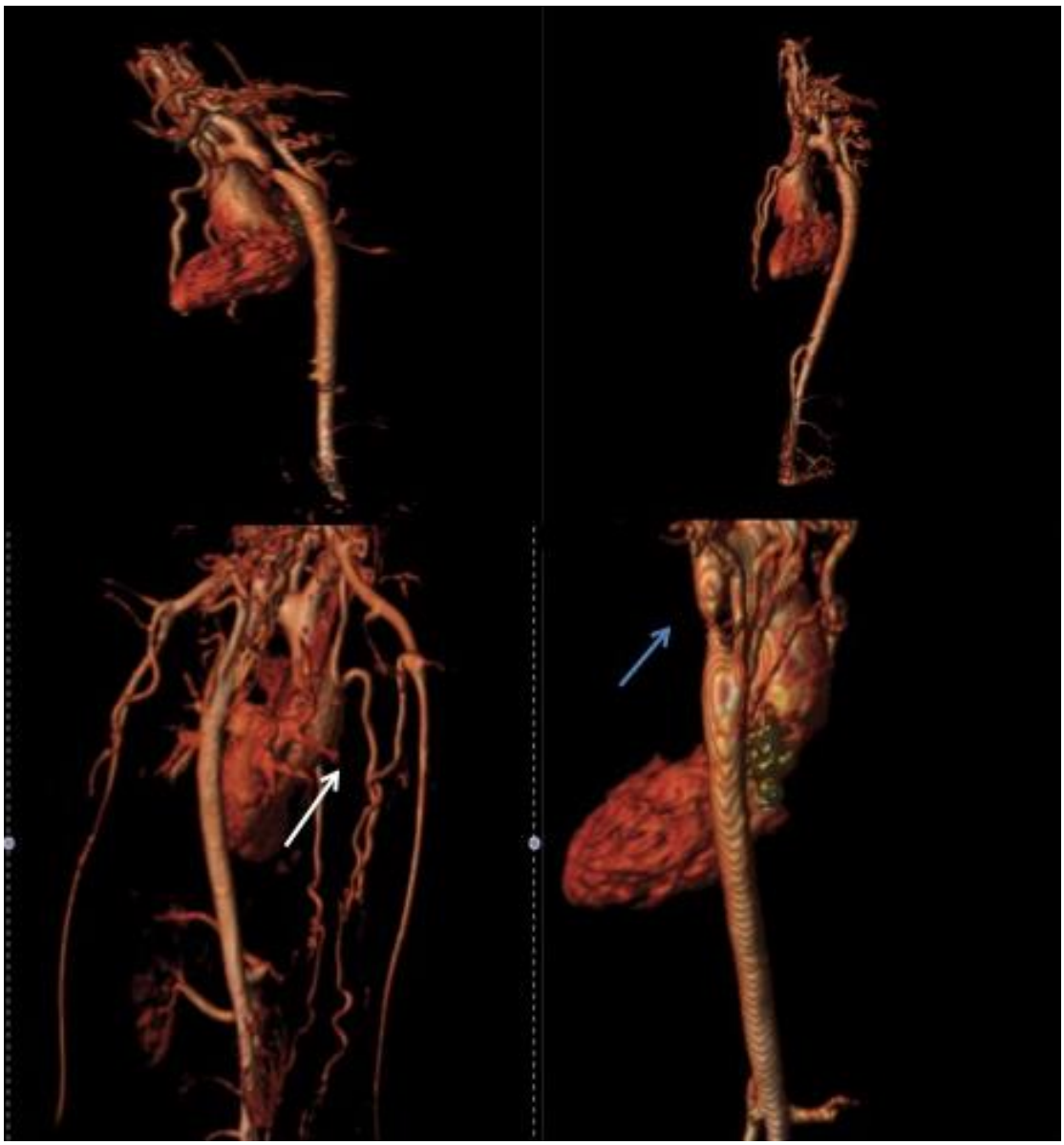
The natural history of CoA is predominantly derived from hospital post mortem series before the era of surgery, 1933. The average age of survival was 35 years, with 75% death rate by 46 years (Jenkins and Ward 1999, Warnes, Williams et al. 2008). The first CoA dataset was presented in 1945. Unoperated patients or the ones operated upon later in life had a high burden of complications such as systemic systolic hypertension, accelerated coronary artery disease, stroke, aortic dissection and heart failure. Bicuspid aortic valve associated stenosis or regurgitation was a well-recognised complication leading to early death. Death was caused by heart failure, myocardial infarction, aortic dissection, rupture, endocarditis, endarteritis and intracerebral haemorrhage(Jenkins and Ward 1999, Warnes, Williams et al. 2008). Variations of presentation with collaterals are shown in Figure 1.6.

Historical data has focused on the degree of stenosis in CoA and associated cardiovascular abnormalities. 60% of untreated patients with severe coarctation and 90% with complex congenital heart disease die in the first year of life. In untreated patients who survive beyond the first two years, 25% die before the age of 20, 50% before the age of 32 and 75% before the age of 46years and 92% before the age of 60(Campbell 1970). There have been anecdotal reports that patients have survived into late 70's, 80's and even up to the age of 92(Connelly, Webb et al. 1998). In essence survival of patients with coarctation of the aorta is dependent on the degree of narrowing. Patients surviving to adulthood usually have mild post-ductal CoA. As a result, they can remain asymptomatic for a long period. Arterial hypertension is not detected early in life. Hence, the diagnosis may be delayed until adolescence or later. Depending upon the severity (45-50), patients may also present with hypertension, headache, epistaxis, dizziness, tinnitus, cold extremities, claudication, abdominal angina and also

intracranial haemorrhage. Thus, the presentation of CoA may be bimodal with symptoms in childhood but then a potentially long quiescent period after correction followed by further symptoms in adult life.

FIGURE 1.6 SEVERE COARCTATION OF AORTA WITH COLLATERALS

3D volume rendered CMR image showing - native severe coarctation with collaterals. White arrow points at the collaterals and the blue arrow shows the severe narrowing of the descending aorta – the native coarctation.



1.5.6 Management. Clinical Outcomes and Comparison between Surgery and Percutaneous intervention

Management of CoA can be conservative or surgical or catheter based. Surgery or catheter intervention depends upon the type of coarctation and associated cardiac anomalies. There are number of professional guidelines available summarizing available evidence and experience although the evidence-base for treating CoA is limited.

1.6 Guidelines and evidence for intervention in non- critical CoA

The 2020 European guidelines recommended the following indications for intervening on patients with non-critical CoA (Baumgartner, Bonhoeffer et al. 2010)

- All patients with non-invasive blood pressure difference of more than 20mmhg between upper limb and lower limb, regardless of symptoms if they have systemic blood pressure > than 140/90 and there is evidence of pathological hypertension on exercise or left ventricular hypertrophy, (Class 1 evidence)
- Independent of the pressure difference, patients with systemic hypertension with greater than 50% narrowing of the aorta in relation to the aorta at the diaphragm on CMR, CT or invasive angiography (Class IIa).
- Independent of pressure difference and systemic hypertension, patients with > 50% narrowing of the aorta in relation to the aorta at diaphragm on CMR, CT or on invasive angiography (Class IIb).

In 2018 ACC/AHA also published guidelines for management of adult congenital heart disease patients and recommendations for intervention is as follow(Warnes, Williams et al. 2008).

- Peak to peak coarctation gradient of greater or equal to 20mmHg requires intervention.
- Peak to peak gradient of less than 20mmhg with evidence of severe coarctation on anatomic imaging and radiological evidence of collateral follow warrants intervention.

In children indication for intervention includes a peak-to-peak gradient of greater than 20mmHg or radiological evidence of collaterals and heart failure(Yetman, Nykanen et al. 1997, Attenhofer Jost, Schaff et al. 2002). In the presence of collaterals, the gradient across the coarctation site may be inaccurate due to shunting of blood through the collateral(Attenhofer Jost, Schaff et al. 2002).

1.7 Type of Intervention in Coarctation – Surgery

Surgery for aortic coarctation was introduced in 1945. There are number of techniques which have been used to treat aortic coarctation and they all are used or combined depending upon the underlying anatomy of the patient(Lacour-Gayet, Bruniaux et al. 1990, Jurcut, Daraban et al. 2011).

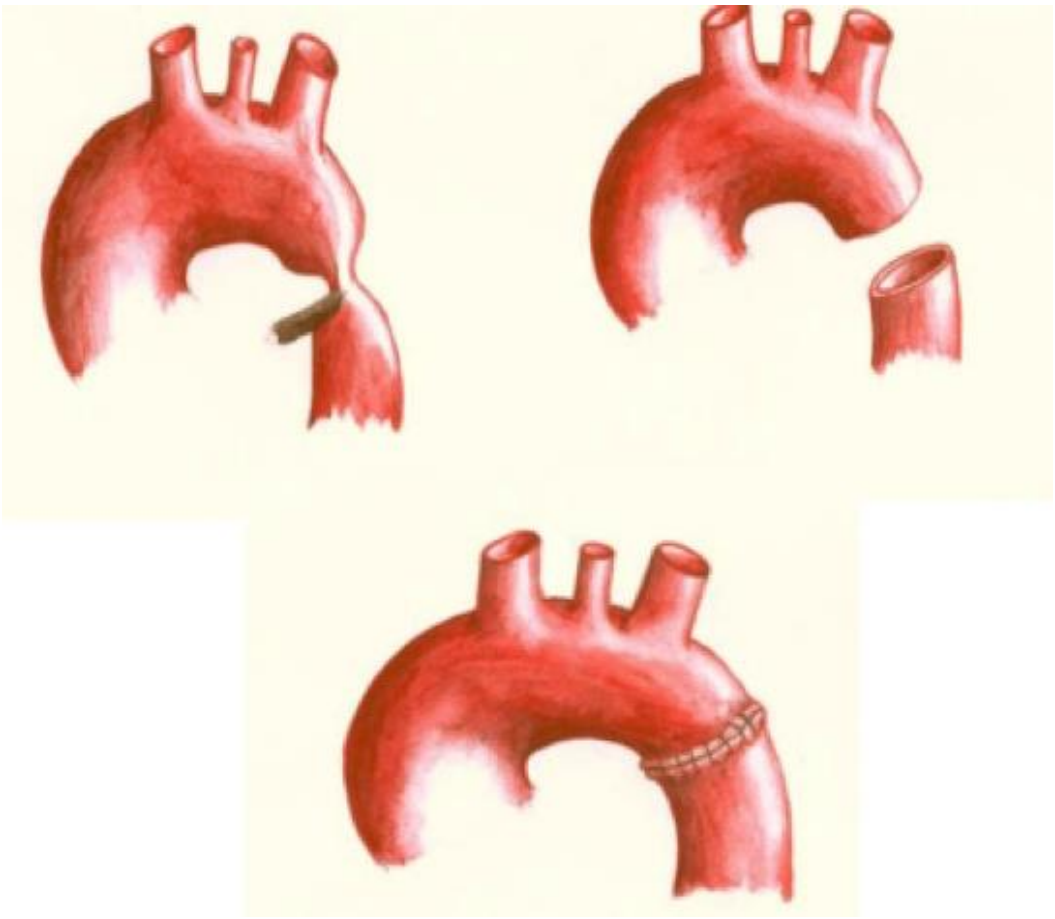
The main techniques are as follow.

1. End to end anastomosis
2. Subclavian flap repair
3. Patch aortoplasty
4. Interposition grafts.
5. By-pass Graft.

End-to-End Anastomosis

Resection of the stenotic part of the aorta is performed, and both ends are joined (Figure 1.7). This type of repair is reserved for infants and children, as the segment of narrowing is short with no collaterals. On the contrary, it is difficult to perform in adults due to a longer part of narrowing requiring resection. As a result, it is hard to perform a direct anastomosis. Benefits of the procedure include a total relief of coarctation of the aorta, potential for growth at the site of anastomosis, avoidance of prosthetic material, complete resection of ductal tissue and preservation of the left subclavian artery.

Figure 1.7 END TO END TO ANASTOMOSIS REPAIR

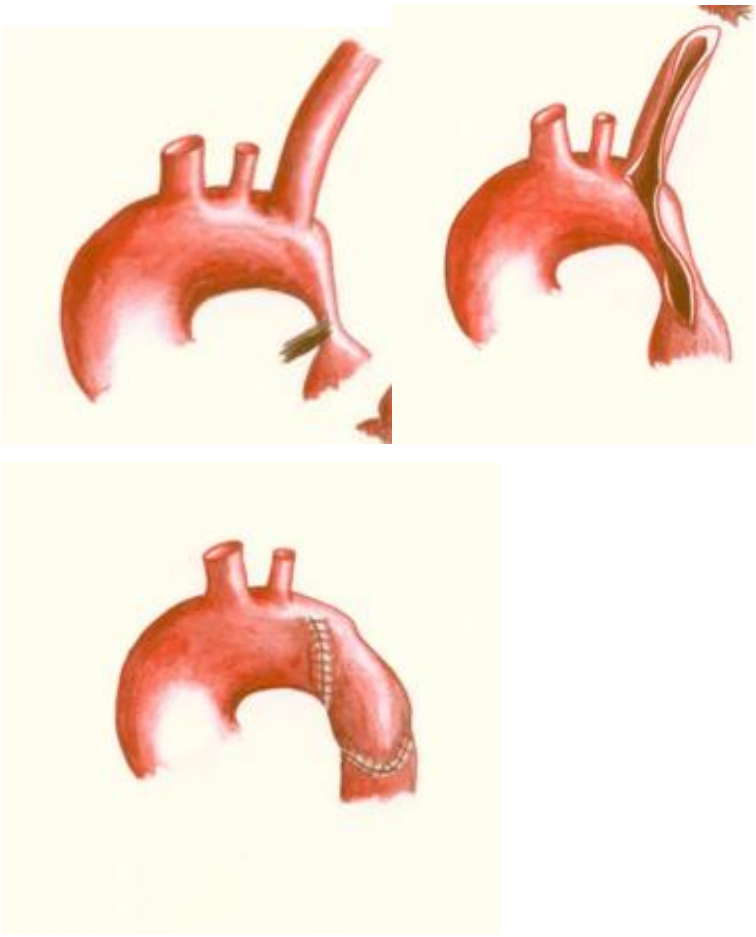


Source: Hans Hammers Illustrations.

Subclavian Aortoplasty

Subclavian arterial repair is the second most common procedure performed in the children. In adults, subclavian repair is performed in cases of isolated aortic coarctation with a shorter segment of hypoplasia. The main benefit of the procedure is total relief of the obstruction; potential normal growth of the repaired site and no requirement for prosthetic material. Figure 1.8 shows the operative sequence for satisfactory subclavian flap repair.

Figure 1.8 SUBCLAVIAN ARTERY REPAIR

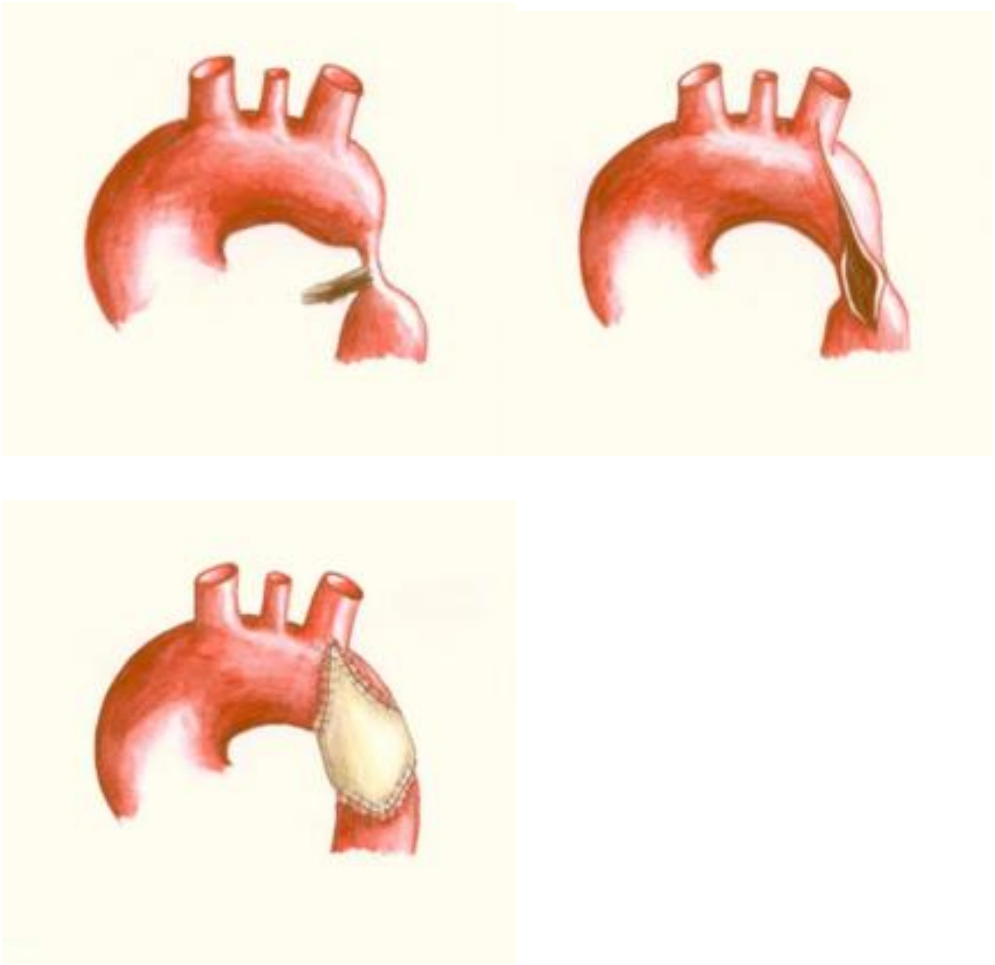


Source: Hans Hammers Illustrations

Patch Aortoplasty

In 1957 the first Dacron patch was used to repair CoA and was commonly used, but the procedure has fallen out of favour due to aneurysm formation and rupture(Rheuban, Carpenter et al. 1985, Parikh, Hurwitz et al. 1991, Aebert, Laas et al. 1993). Dacron material is a prosthetic material, which has tendency to form aneurysms (Figure 1.8).

Figure 1.9 SCHEMATIC PRESENTATION OF PATCH AORTOPLASTY

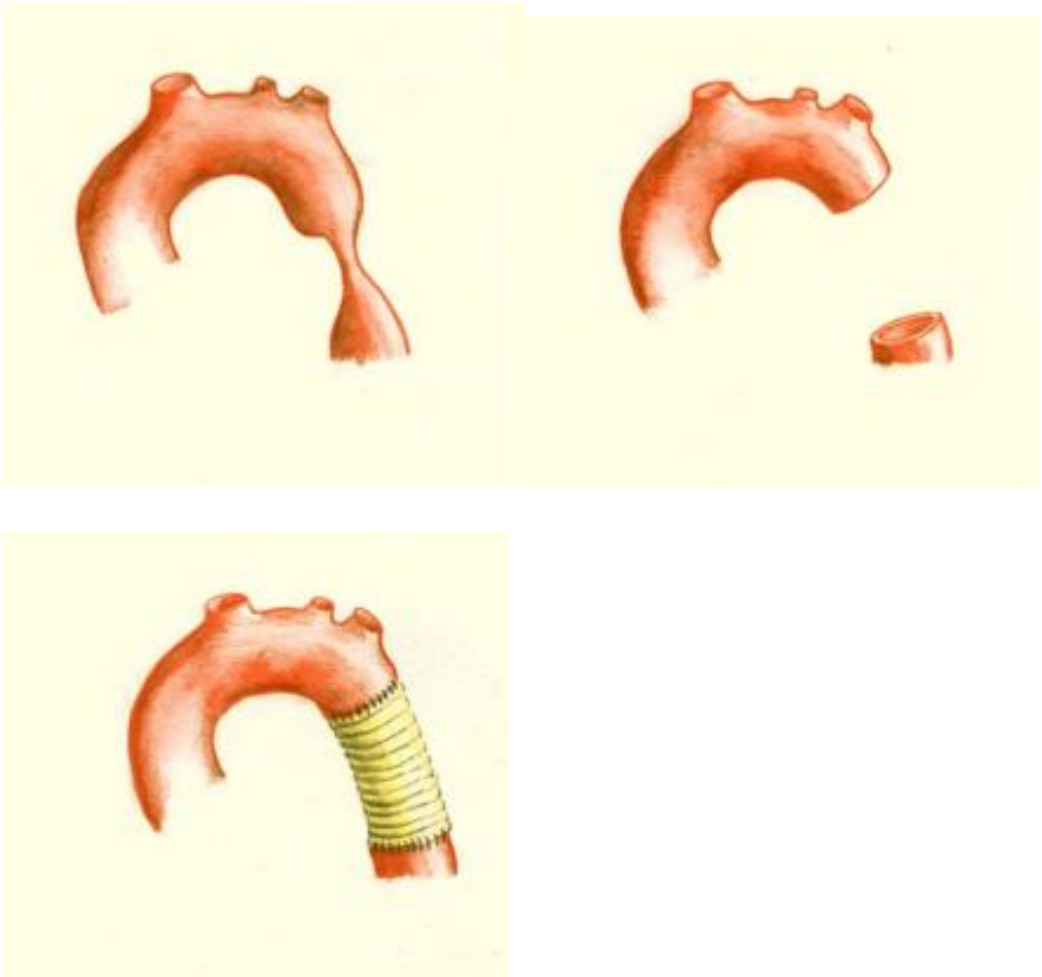


Source: Hans Hammers Illustrations

Interposition Graft

Interposition grafts are indicated in adults where growth has been completed and can also be used in cases of long tubular narrowing. It was first performed in 1951, and studies have shown it be a favourable surgical technique with no evidence of dilatation and aneurysm formation(Aebert, Laas et al. 1993), Figure 1.10.

Figure 1.10 INTERPOSITION GRAFT

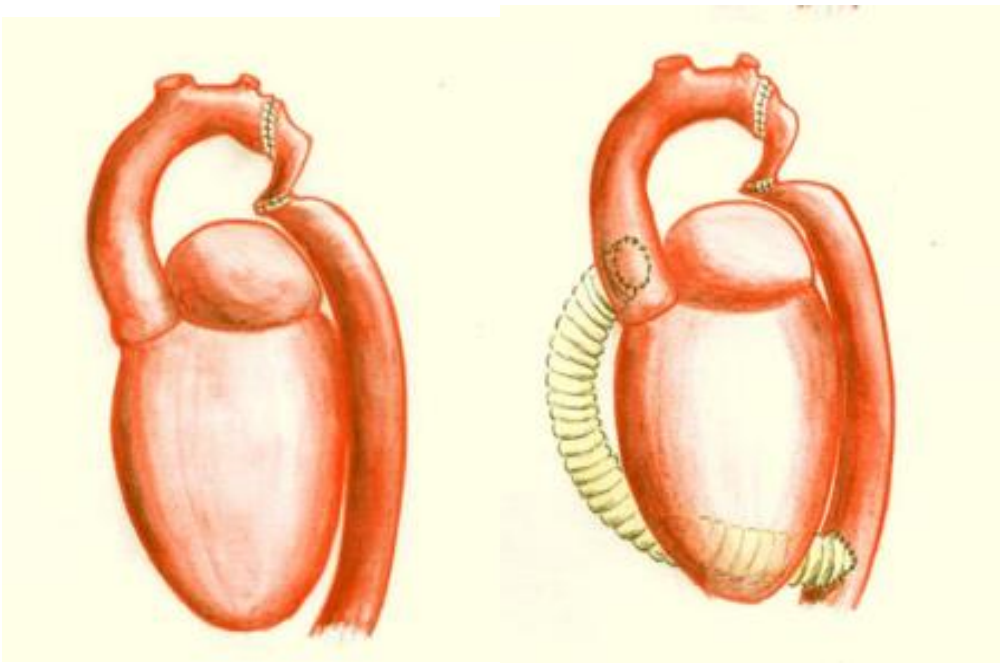


Source: Hans Hammers Illustrations

Bypass Grafts.

Bypass graft is used for patients with severe aortic coarctation and less developed collaterals, and also for patients with recoarctation. The procedure connects the ascending aorta to the descending aorta, and the narrowing is completely bypassed(Heinemann, Ziemer et al. 1997, Almeida de Oliveira, Lisboa et al. 2003) Figure 1.11. The main benefit of this technique is a negligible risk of causing spinal cord ischaemia that can lead to paraplegia.

Figure 1.11 BY PASS GRAFT



Source: Hans Hammers Illustrations

In summary, the end-to-end anastomosis remains the treatment of choice and should be considered first-line management in suitable patients. In children, subclavian repair is the second procedure of choice but not preferred in adults due to a higher incidence of arm ischaemia. Patch aortoplasty can be performed in children and adults with ease but has been abandoned due to an increased risk of aneurysm formation (Mendelsohn, Crowley et al. 1992, Parks, Ngo et al. 1995, Knyshov, Sitar et al. 1996). Interposition grafts and extra-anatomic bypass grafts are reserved for adults with good long-term outcome. Outcome following coarctation has been interesting. A series published by Nortan et al. reviewed 1337 patients undergoing CoA repair. Subclavian flap repair was used in 763 patients (57%), end to end 406 patients (30%) and patch aortoplasty 133 patients (9.9%). Only 20 patients had interposition graft.Mortality was high in neonates in whom surgery was performed in the first week of life, only eight patients out of 279 patients died at the age of 3 months to the age of one. The presence of an extra cardiac lesion (ventricular septal defect) increases the mortality from 0.9% to 6.8%. In cases of complex coarctation, the mortality rate was as high as 16.6% and up to 45% when surgery was performed as an emergency (Nortan 1984-1995)

1.8 Type of Intervention in Coarctation – Percutaneous interventions

Balloon angioplasty – In a case of native discrete aortic coarctation, balloon angioplasty is a procedure of choice in infants greater than an age of 4 months(Warnes, Williams et al. 2008, Silversides, Kiess et al. 2010, Feltes, Bacha et al. 2011). It is also considered a palliative procedure in critically ill patients with heart failure with severe left ventricular dysfunction, with systemic disease such as Turner syndrome. In this scenario, there is no formal age limit(Feltes, Bacha et al. 2011).

Aortic Coarctation Stents

In the last decade, stent implantation has become an alternative for a surgical procedure in adolescents and adults. It's effectively used to treat native coarctation as well recoarctation. It is a successful technique in 90% of the cases(Krieger and Stout 2010). Balloon angioplasty is considered to be an excellent method with quick results and low procedural complications but at the same time due to damage to the intimal layer of the aorta leads to a higher incidence of recoarctation, aneurysm formation and aortic rupture(Tyagi, Arora et al. 1992, Krieger and Stout 2010). The major advantage of the stent is that it provided radial support to the aortic wall and helped to oppose the torn intimal wall to the medial wall. This provides better healing and gives the opportunity to resize the stent at a different age or in the need of recoarctation without causing a transmural tear (Rosenthal 2005, Golden and Hellenbrand 2007). The success of the procedure depends on the segment of the coarctation covered by the stent without causing protrusion into the left subclavian artery. The diameter of the stent is chosen on the basis of the diameter of the proximal aorta. Stent procedure is successful if the gradient drops to less than 10mmHg and the diameter of the stented vessel improve by 90% comparison to the surrounding normal aorta(Zabal, Attie et al. 2003, Forbes, Garekar et al. 2007, Holzer, Chisolm et al. 2008). Like other procedures, stenting is not free of complications. There is a high risk of aortic rupture at the time of deployment(Mahadevan, Vondermuhll et al. 2006). The high risk of intimal tear or intramural tear is due to pre-dilatation of the coarctation segment(Forbes, Garekar et al. 2007). The most common complication is aneurysm formation(Suarez de Lezo, Pan et al. 1995, Harrison, McLaughlin et al. 2001). Despite these observations stent implantation is considered the treatment of choice in adolescent and adult patients with growing evidence of potential greater safety and efficacy of covered stents compared to bare stents.(Erben, Oderich et al. 2019)

1.9 Comparison of Surgery and Percutaneous techniques.

Forbes et al presented an overview of comparison between the surgical, balloon angioplasty (BA) and stent implantation group(Forbes, Kim et al. 2011). 350 patients were recruited for this study, from 36 institutions. 217 underwent stent implantation, 61 underwent balloon angioplasty, and 72 patients underwent surgery. All three interventions showed a steep decline in resting blood pressure in each group. ~~A stent was superior to balloon angioplasty.~~ Stent and surgery both were superior to balloon angioplasty in lowering the upper to lower extremity systolic blood pressure. The stent has shorter hospitalisation as compared to the surgery and less immediate complications. Surgical intervention and stent patients had a better haemodynamic response in a short and immediate review in comparison to the balloon angioplasty. Imaging has also confirmed better outcome in the stent and surgical group as compared to balloon angioplasty alone(Forbes, Kim et al. 2011)

Table 1.5 COMPARISON OF SURGERY, BALLOON ANGIOPLASTY OR STENT PLACEMENT FOR COARCTATION OF AORTA (adapted from (*Forbes, Kim et al. 2011*)

Data shows decrease in SBP and ULG in all groups after the procedure with lowest ULG and length of stay associated with stent procedures. SBP = systolic blood pressure; ULG = upper to lower extremity systolic blood pressure gradient.

Before Intervention	Surgery (n=72)	Balloon (n= 61)	Stent (n=217)	P-Value
Rt arm SBP mmHg	137±19	138±23	143±21	0.061
Pre- ULG	37±21	43±23	40±24	0.399
After Intervention				
Rt arm SBP mmHg	123±13	118±15	125±15	0.002
Discharge ULG	7.7±18.2	10.3±12.9	4.9±12.9	0.0032
Length of Stay (mean days)	6.4	3.6	2.4	0.001

Complications – Acute aortic wall injury was observed in the BA and the stent group, predominantly in the elderly. A higher incidence of aortic wall rupture and dissection was seen(Varma, Benson et al. 2003, Tan and Mullen 2005). A study by Congenital

cardiovascular Interventional Study Consortium (CCISC) have shown that balloon angioplasty and surgery had higher incidence of aneurysm formation which was 43.8% and 12.5% respectively while the incidence was low in the stent group 5.4% (Fletcher, Cheatham et al. 1998, Forbes, Kim et al. 2011).

1.10 Comorbidities and complications associated with aortic coarctation

1.10.1 Hypertension

Recurrent hypertension is a common morbidity; it is a major factor in postoperative cerebrovascular events, aortic rupture, and heart failure as well as accelerated coronary artery disease. Cohen et al. reported a prevalence of 8% in his study (BP > 150mmhg and diastolic more than 90mmHg(Cohen, Fuster et al. 1989). Prevalence of hypertension was dependent upon the age of repair; Koller et al. in his cohort of 362 patients demonstrated that patients who underwent surgery between the ages of 2 to 9 years hypertension were prevalence was the same as in the normal population. The study also showed that late hypertension was indication of recoarctation(Koller, Rothlin et al. 1987). A number of theories have been postulated. The occurrence of late hypertension occurs due to abnormal baroreceptor response(Simsolo, Grunfeld et al. 1988), increased aortic stiffness(Rees, Somerville et al. 1989) or neuroendocrine activation(Ross, Clapp et al. 1992). Ambulatory blood pressure measurements have been raised with reduced diurnal variation and also exercise induced hypertension is very common in this group. A large long term registry from Finland has shown that 13% of patients with repaired coarctation had persistent hypertension into adulthood (Raissadati, Haukka et al. 2020)

1.10.2 Coronary Artery Disease

Coronary artery disease has been associated with coarctation of the aorta. Accelerated hypertension and genetic predisposition may lead to coronary events and death later in life(Lawrie, DeBakey et al. 1981). Incidence ranges between 37% (77) to 21% (83,84). Hypertension and hypercholesterolemia may also accelerate coronary artery disease. A recent study – compared the incidence of coronary artery disease in the coarctation group compared with those with ventricular septal defects - found a higher incidence of coronary artery disease in coarctation patients, and yet, coarctation per se, is not a risk factor if corrected for other risk factors such as hypertension, hypercholesterolemia and diabetes mellitus(Roifman, Therrien et al. 2012).

1.10.3 Cerebrovascular Events

Two types of cerebrovascular events are encountered in coarctation patients, prothrombotic which is a hypercoagulable state or thrombotic events in the preoperative and postoperative period due to accelerated hypertension. Haemorrhages usually occur in the presence of Berry aneurysms; the incidence of which is low as 0-7%(Bobby, Emami et al. 1991).Thromboembolic events appear likely to be related to high burden of plaque in the carotid artery(Bobby, Emami et al. 1991).

1.10.4 Aortic Complications

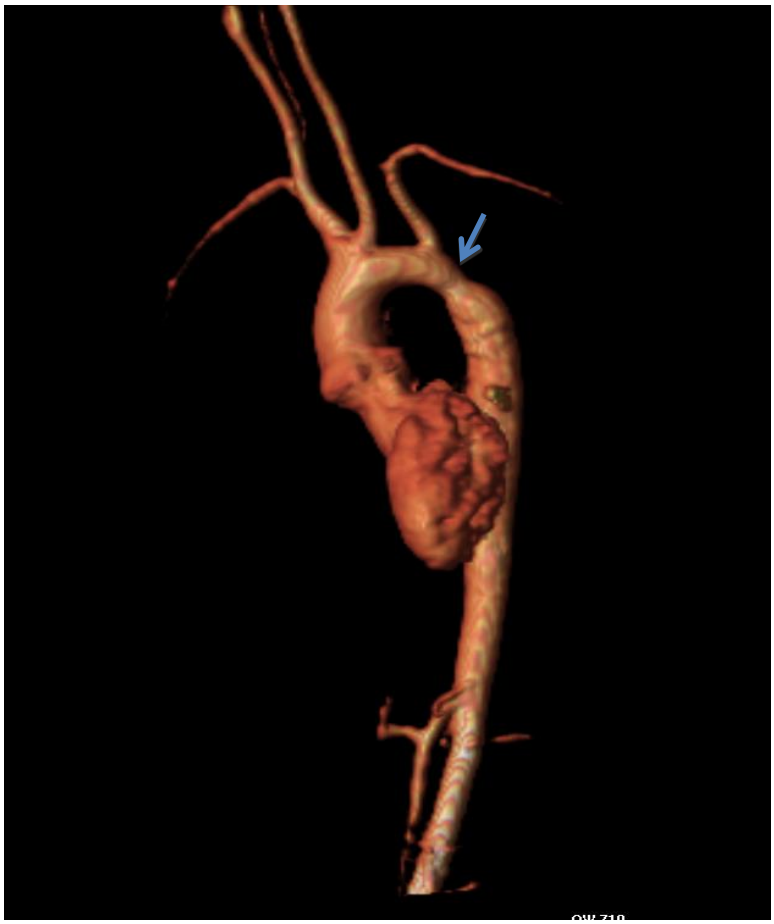
Despite inventions of different techniques and reconstruction by surgery and stent placements, patients suffer from a number of complications such as recoarctation, aortic aneurysm and infective endarteritis(Jenkins and Ward 1999, Rosenthal 2005, Vriend and Mulder 2005).

1.10.5 Aortic Recoarctation

Recoarctation is a common complication that is experienced by this group of patients (Figure 1.12). Recoarctation is clinically diagnosed if there is a blood pressure difference of more than 20mmHg between the upper lower limbs or on angiography the peak-to-peak gradient is 20mmHg. Age at repair is considered to be a major factor involved in the incidence of recoarctation. In a series by Koller et al, he reviewed 362 cases 10 years post surgery and found that recoarctation incidence was high as 10% in patients who had a repair done before the age of 2 years as compared to older children where the incidence was only 3.5%(Koller, Rothlin et al. 1987). While other series which have also suggested a higher incidence of recoarctation in older age at surgery the infants weight at the time of surgery also predicts the risk of recoarctation(Brouwer, Kuntze et al. 1991). The type of repair is a major risk factor in predicting the risk of recoarctation. Certain studies also suggest that subclavian flap repair has a higher incidence of recoarctation than an end to end anastomosis (Clarkson, Nicholson et al. 1983, Presbitero, Demarie et al. 1987, Dietl, Torres et al. 1992). Presbitero et al reported in a series of 226 patients a risk of only 8% of recoarctation in end-to-end anastomosis as compared to other types of repairs – where the incidence was as high as 25%(Presbitero, Demarie et al. 1987). Similarly, in another study, there was reported an incidence of 17.5% in those patients who were not suitable for an end to end anastomosis(Clarkson, Nicholson et al. 1983). Balloon angioplasty has a higher incidence of recoarctation; a randomised trial of 36 patients has shown an incidence of 25% of recoarctation in the balloon angioplasty (n=16) as compared to 6% in the surgical group (n=20) (Shaddy, Boucek et al. 1993). It is impossible to predict the time frame for development of recoarctation it appears(Simon and Zloto 1974, Brouwer, Kuntze et al. 1991).

FIGURE 1.12 RECOARCTATION IN END TO END ANASTOMOSIS REPAIR.

The blue arrow shows the site of repair with mild narrowing



Aneurysm Formation and rupture

Aneurysm formation is a common complication, which occurs at the site of repair, or proximal aorta, which can lead to aortic rupture. Aneurysm formation is dependent upon the type of repair and the literature has shown that the incidence is high (20%) in patch aortoplasty cohort(Bergdahl and Ljungqvist 1980). Knyshov et al. published a series of 891 patients with repaired coarctation of the aorta, of which 48(5.4%) patients were found to have an aneurysm and 18 patients out of the 48 died due to aortic rupture and endarteritis over a 20-year follow-up.43% of the patient who developed aneurysm had a patch repair.(Knyshov, Sitar et al. 1996) Aneurysm formation is also common in patients who underwent balloon angioplasty, a study reported an incidence of 5% at the median age of 14 months(Rao, Galal et al. 1996). There are other series, which have shown that remains of abnormal tissue may also lead to development

of aneurysms(Isner, Donaldson et al. 1987, Moodie 1990). Two decades ago it was hard to detect an aortic aneurysm but, with the availability of cardiac MRI, it is easier to have interval surveillance to detect and monitor the rate of progression to allow timing of intervention. All patients who have a documented aneurysm should be followed up on a yearly basis to assess the progression of aneurysm and to decide on the timing of intervention(Baumgartner, Bonhoeffer et al. 2010). Proximal aortic rupture is higher in patients with bicuspid aortic valve and Turner syndrome. Repair is advocated depending upon the progression or development of clot at the site of the aneurysm. The following image Figure 1.13 shows an aneurysm following patch angioplasty.

Figure 1.13 Aneurysm formation in Subclavian Repair

1.10.6 Infective Endarteritis

Infective endocarditis is rarely seen in contemporary practice but was more common in the pre-surgical era when high-velocity jets were responsible for the injured surface where microbes attached to form an infective lesion usually below the site of repair(Presbitero, Demarie et al. 1987). Nevertheless, interposition graft endocarditis does occur.

1.10.7 Bicuspid Aortic Valve

Bicuspid Aortic valve (BAV) disease is found in 80% of cases, significant stenosis and regurgitation develop in up to two third of cases out of which 10% require aortic valve replacement(Simon and Zloto 1974, Stewart, Ahmed et al. 1993). BAV is associated with ascending aorta dilatation with a higher risk of dissection independent of coarctation.

1.10.8 Long-term Survival

Overall long-term survival is good in repaired isolated coarctation reaching up to the age of 60 years(Bhatt and Defaria Yeh 2015), but reduced as compared to the normal population. The largest series, from a single centre published the long-term outcome of coarctation in 819 patients from 1946-2005; the primary outcome shows a low mortality post-surgery, but long-term survival is reduced as compared with the normal age-matched population. They showed in their series the actuarial survival were 93.3%, 86.3%, 73.5% at 10, 20 and 30 years. The incidence of reintervention was high(Brown, Burkhart et al. 2013). The Northern congenital abnormality survey of children born between 1985 and 2003 in the United Kingdom, reported survival of 89.6% of the patients with coarctation of aorta at 20 years of follow-up (Tennant, Pearce et al. 2010). Similarly, the observational European Heart Survey described 551 patients with coarctation with a reported mortality at 0.7 per cent at five years (Engelfriet, Boersma et al. 2005). Primary repair at a younger age has always been favoured and has a better outcome. The Mayo series highlighted older age at repair had higher long-term mortality(Cohen, Fuster et al. 1989, Brickner, Hillis et al. 2000, Brown, Burkhart et al. 2013).

1.11 Other Issues

Pregnancy

As the population is surviving beyond the paediatric age, the risks and management in pregnancy of women with coarctation of the aorta is important. The range of complications is different in repaired as compared with unrepaired coarctation.

The review data is limited in unrepaired coarctation; one series highlighted that, although major cardiovascular events are not common, they can be fatal.

a. Unrepaired Coarctation

There is a high risk of dissection at the site of narrowing or aortic rupture especially in the presence of bicuspid aortic valve. Hypertension is common(Deal and Wooley 1973, Beauchesne, Connolly et al. 2001). If hypertension remains uncontrolled with medication surgery or stent placement is advised to relieve the obstruction. Stent placement can safely occur in the second trimester with low risk of teratogenic effects of radiation.

b. Repaired Coarctation

Despite an ideal that pregnancy is planned after careful assessment and investigation the incidence of hypertension during pregnancy remains high. There is also a high incidence of miscarriages (Beauchesne, Connolly et al. 2001, Vriend, Drenthen et al. 2005).

1.12 Overall Outcome

Drenthen et al, reviewed studies published between 1985 to 2007 which reviewed 244 pregnancies with Coarctation of Aorta and described the incidence of preeclampsia to be 4.9% with expected rate of 2-3% in normal population, pregnancy induced hypertension was 11.1 per cent as compared with expected rate of 5% in the normal population. There was no incidence of arrhythmias and risk of cardiovascular events was low. There is a higher incidence of premature delivery in this group (Drenthen, Pieper et al. 2007).

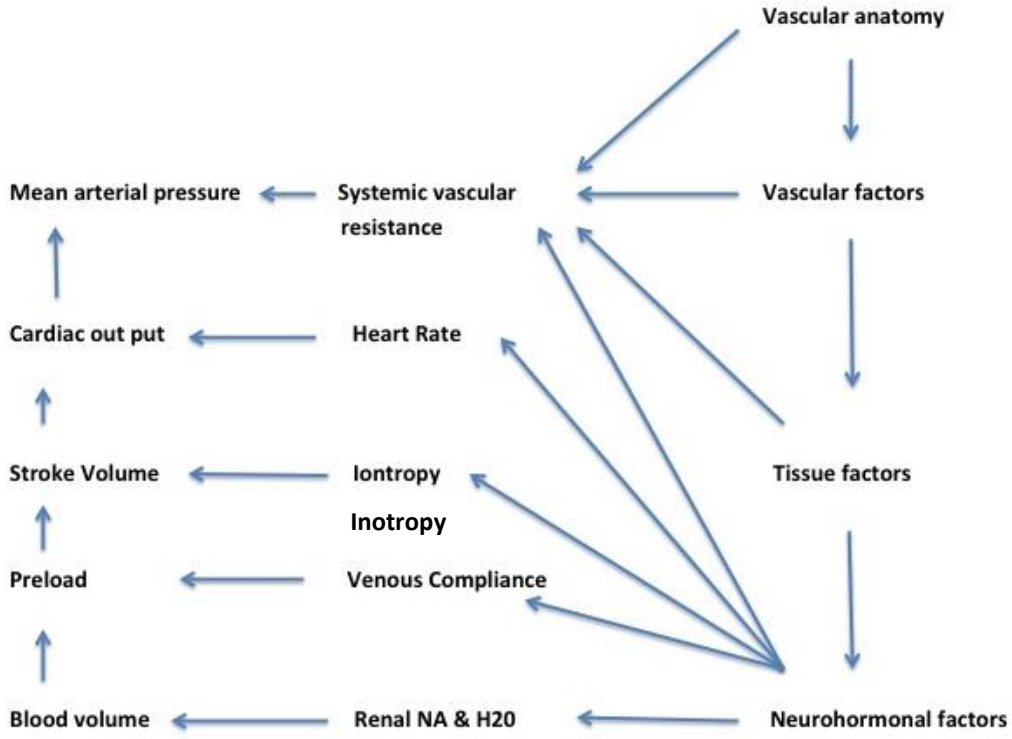
Beauchesne et al. highlighted that serious complications were uncommon in women, even with a gradient of > than 20mmhg and in all series the main concern was hypertension(Beauchesne, Connolly et al. 2001). Perinatal mortality was approximately twice in mothers with hypertension compared to those without hypertension in a population based study of 15 million pregnancies, although there was no clear excess of complications in patients with pregnancy and CoA (Ramlakhan, Tobler et al. 2020, Grover, Brandt et al. 2021)

1.13 Coarctation review of cardiovascular haemodynamics – what do we know already

Stroke volume ranges between 50 -100ml from each ventricle. The product of heart rate and stroke volume is known as cardiac output, which is 5.0l/minute. Stroke volume itself is dependent upon preload, afterload and contractility. Preload is the volume in the ventricle, and depends upon the venous return. Preload can be measured in three different ways – as left ventricular end diastolic pressure, left atrial pressure or as pulmonary end diastolic pressure. Right-sided preload can be measured as central venous pressure (Figure 1.14). Afterload is the resistance in the ventricle that has to overcome the force to open the valves and circulate the blood in the body. Contractility is the heart contraction. Afterload is inversely related to stroke volume and cardiac output, for the left heart it is measured as systemic vascular resistance SVR (Normal 800 – 1200 dynes); for the right heart it is measured as pulmonary vascular resistance PVR (Normal value is 120 -200 dynes). Mean arterial pressure is the perfusion pressure created as a result of cardiac activity as described above. A pressure of 60mmhg is considered to be sufficient to perfuse the organs. Mean arterial pressure is calculated as follows:

Mean arterial pressure = 2 x diastolic + systolic / 3.

Figure 1.14 Different factors involved in generating arterial pressure



1.14 Aortic Haemodynamic and Aortic Stiffness

Stiffness in the aorta increases with ageing, a likely aetiological factor is systemic hypertension, though genetic predisposition is probable. Aortic stiffness, or decreased arterial compliance, occurs as a result of structural and functional changes in the vessel wall. Arterial stiffness is considered to be an independent predictor of adverse outcome with all-cause cardiovascular morbidity and mortality. Different types of arterial processes occurs in the arterial vessel wall -, arteriosclerosis and atherosclerosis. The former is a degenerative change in the vessel wall whilst in atherosclerosis there is plaque formation due to lipid and platelet deposition on the intimal surface. Both are responsible for increasing aortic stiffness with age(Izzo 2004).

1.14.1 Aortic Haemodynamic: Mechanism and principles for the development of Aortic stiffness

The aorta is a 3D structure and has complex haemodynamic properties Figures 1.15 and 1.16 (Lee and Kamm 1994, O'Rourke, Staessen et al. 2002).

1. The aorta works according to the Windkessel principle, in which it acts as both a conductive and reservoir system. As a conductive system the aorta provides blood to peripheral vessels against the total peripheral resistance, but at the same time, it provides a buffering system for each ventricular contraction through arterial and ventricular coupling. As a result, the histological structure of the wall varies through the aorta to accommodate this function. The proximal aorta is high in elastin so it can adjust to the systolic pulse and the stroke volume. The thoracic aorta and immediate vessels are rich in elastin but more distally, the stiffness increases and the content of collagen is higher than the elastin.
2. Different factors are involved in aortic haemodynamics. Stress is the force, which is applied to a particular area, and it can be applied in any direction such as longitudinal, radial and circumferential. Laplace's law defines circumferential force on a vessel wall and is directly proportional to the vessel, pressure and radius and is inversely proportional to the vessel thickness. Strain (ε) is the force, which is deformation and is measured as any change across a length of an object, which subjected to force.

$$(\varepsilon) = L1\text{-}L0/L0$$

(ε) The strain and L1 is the final length and L0 is the given length

The elastic locus is stress/strain ratio that's equally important in the haemodynamic

$$E = \text{stress/compliance}$$

3. Stiffness is resistance to deformation. Measurement of arterial stiffness is reliant on three factors E the elastic modulus, and H is the thickness of the wall and r is the radius.
4. Arterial compliance is an absolute change in the area ΔD for a pressure step ΔP at a given fixed length. Its reciprocal of stiffness

$$C = \Delta D/\Delta P$$

5. Pulsatility causes stretching of the long bearing elastin lamella if the arterial vessel and mechanical stress on the wall causing structural changes and hence increases stiffness (Khoshdel, Thakkinstian et al. 2006).

6. Genetic factors also play a critical role in the development of aortic stiffness. Polymorphism of metalloproteinase 9 is also an independent predictor of aortic stiffness(Yasmin, McEniery et al. 2006).

Figure 1.15 Normal Haemodynamics of the Aorta(Cavalcante, Lima et al. 2011)

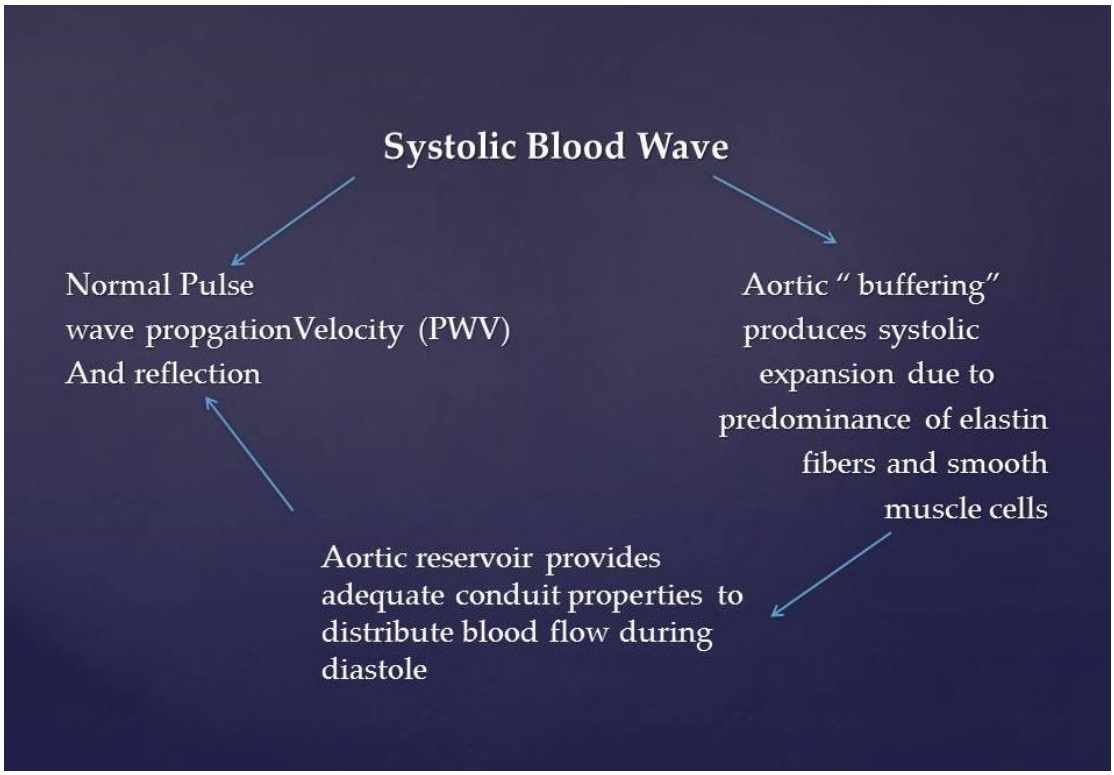
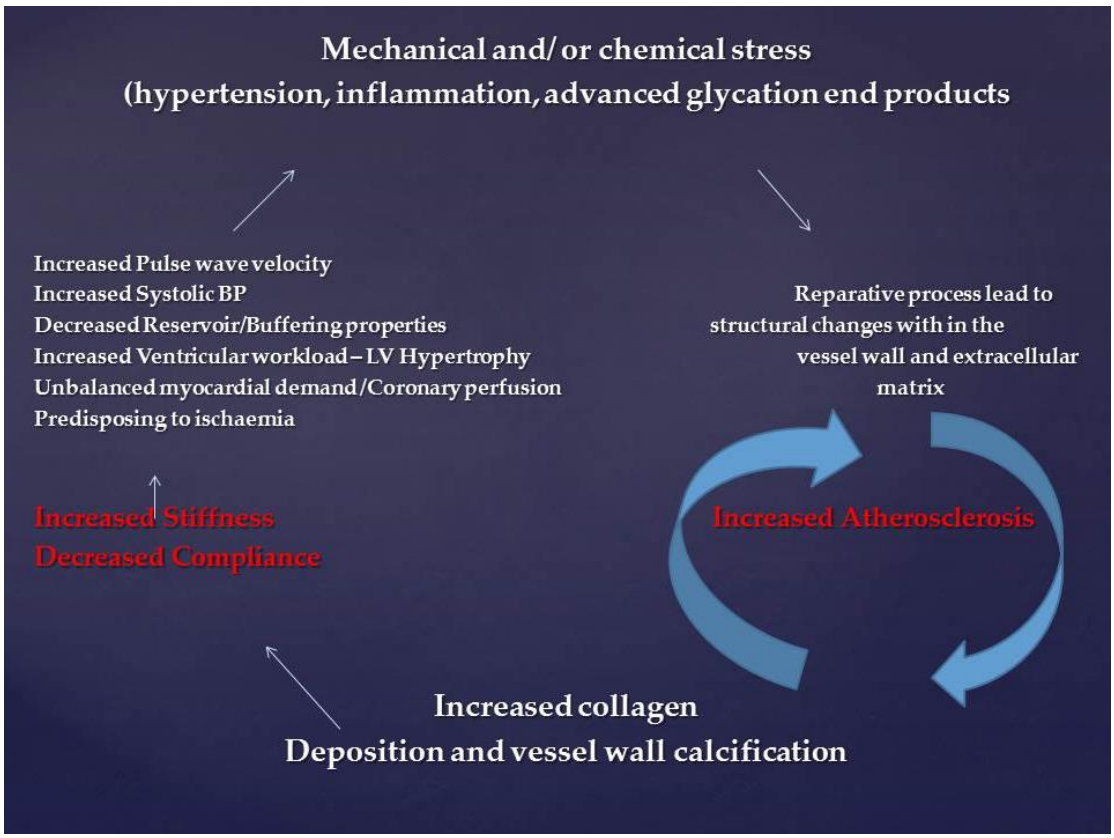


Figure 1.16 - Different factors responsible for increasing aortic stiffness(Cavalcante, Lima et al. 2011).



Several mechanisms are responsible for affecting the structure and function of the vessel wall, which are responsible for increasing aortic stiffness(Cavalcante, Lima et al. 2011).

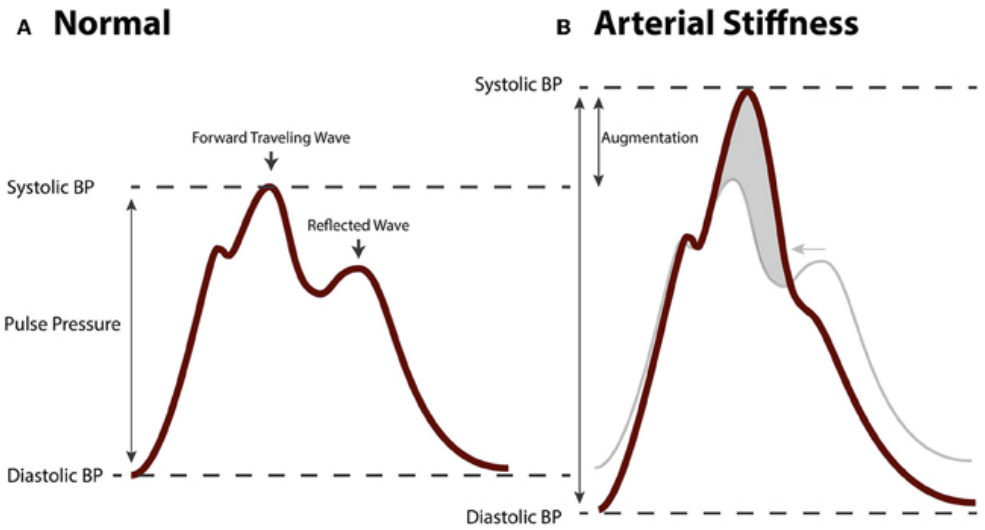
1.15 Measurement of Aortic Stiffness

1.15.1 Pulse Wave Velocity

Pulse wave velocity is the most validated method for measuring aortic stiffness. It's a simple non-invasive method, which is measured with accuracy and reproducibility, and most importantly literature has shown a direct relationship with adverse outcome(Lehmann, Parker et al. 1993, Asmar, Benetos et al. 1995, Asmar, Topouchian et al. 1997). Pulse velocity is inversely related to arterial compliance, e.g., the stiffer is the vessel the pulse will be transmitted quicker as compared to a compliant and distensible vessel. PWV is a measure of aortic stiffness over a certain length of a vessel while compliance, distensibility and strain are a local marker of arterial elasticity. PWV can be measured as a transit time from two pulse waveforms between two points on a vascular vessel. The distance L is divided by the wave foot-to-foot time for that foot wave to reach the end point on that vessel. The following diagram

shows a normal aortic waveform one the other in the context of arterial stiffness (figure 1.17, 1.18).

Figure 1.17 Arterial wave forms in Normal aorta and with increased Aortic Stiffness(van Varik, Rennenberg et al. 2012).

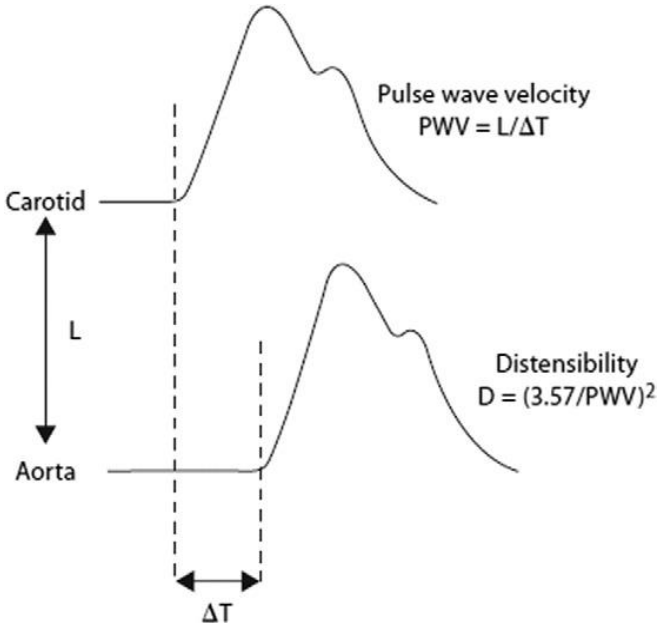


Aortic stiffness has been measured by different techniques

1. Carotid Doppler
2. Advanced echocardiography techniques
3. Cardiac MRI

1. Carotid-Femoral Pulse wave velocity method.

Figure 1.18- Measurement of Aortic Stiffness by Carotids(Cavalcante, Lima et al. 2011).

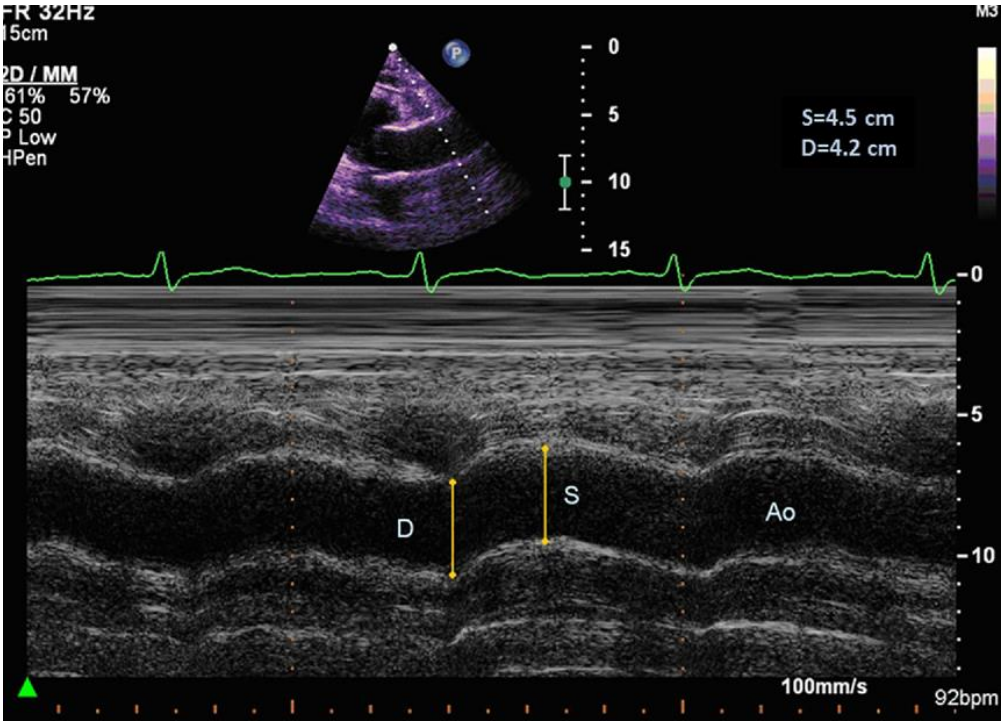


In this method, the pulse velocity is measured from the carotid artery to the proximal artery. L is the measured distance; T presents the time delay between the feet of two waveforms. PWV is calculated as ΔT/L. The normal value for a middle-aged man is 4m/s in the ascending aorta, 5m/s in abdominal aorta and carotids, 7m/s in the brachial artery and 8m/s in the terminal iliac.

1.15.2 Echocardiography.

Pulse wave velocity can be assessed by echocardiography with pulse wave Doppler although it's not frequently used, its give a good indication of regional aortic stiffness(Baguet, Kingwell et al. 2003, Vitarelli, Giordano et al. 2010). Transthoracic and transoesophageal echocardiography accurately predicts aortic stiffness.On Transthoracic echocardiogram, the first point is taken 3cm above the aortic valve by using M Mode as shown in the Figure 1.19.

Figure 1:19-Echocardiography - Flow seen in carotid artery(Cavalcante, Lima et al. 2011).



The second point is taken just below branching of the left subclavian artery and the PWV is calculated by a validated formula by Stefanadis et al(Stefanadis, Stratos et al. 1990).

Aortic distensibility (in cm2 dyne) = 2 x systolic diameter - diastolic diameter/diastolic diameter –brachial pulse pressure.

1.15.3 Cardiac MRI

Aortic stiffness is measurable by Cardiac MRI using validated methods as described in the second part of this thesis. Different methods have been used in cardiac MRI to aortic stiffness.

a. Steady state free precession state imaging with electrocardiographic gating is used for measuring aortic cross-sectional area with contouring with a temporal resolution of less the 40ms. Gradient echo phase contrast velocity acquisition can also be used for aortic diameter measured by aortic contouring. The maximum and minimum diameter can be used to measure the aortic stiffness(Herment, Lefort et al. 2011).

b. Velocity encoded MRI with phase contrast sequences gives an accurate measure of blood flow velocity to study the propagation of aortic pulse. This method has been validated against invasive method and has an excellent co-relation.

   This method was used in our study to analyse pulse velocity.

1.16 Clinical Value and Prognostic relationship of Cardiac and Non- Cardiac Conditions with Aortic Stiffness

1.16.1 Cardiac Atherosclerotic Disease and Congenital Heart Disease

1. Atherosclerosis and calcification

As the vessel wall gets damaged by a process of shear stress on the vessel, to protect the vessel atherosclerosis develops which leads to calcification as well which leads to further aortic stiffness.

a. Coronary artery calcification is related to aortic stiffness(Ahmadi, Nabavi et al. 2011).

b. Thoracic aorta calcification is inversely related to increased thoracic aortic stiffness(Al-Mallah, Nasir et al. 2014).

2. Bicuspid aortic

Bicuspid aortic valve disease has been extensively studied. It has been reported in cases of FBN1 gene mutation there have been high levels of metalloproteinase leading to abnormal elastic properties(Bunton, Biery et al. 2001, Fedak, de Sa et al. 2003). Abnormal aortic stiffness and distensibility are present in 40% of the cases(Nistri, Grande-Allen et al. 2008). Increased aortic stiffness leads to worsening of aortic regurgitation and LV function. Aortic regurgitation worsens quickly in patients with increased aortic stiffness as increased distensibility required to accommodate a large volume of blood which is not possible in cases with increased stiffness hence the cardiac function worsens quickly leading to patient deterioration(Wilson, McDonald et al. 1992, Kopel, Tarasoutchi et al. 2001).

3. Tetralogy of Fallot

Aortic dilatation is related to increased pulse velocity across the aorta inversely related to increased aortic stiffness(Chong, Wong et al. 2006).

1.16.3 Vasculopathies

4.Marfan, Ehler Danlos syndrome

Marfan syndrome has an FBN-1 genetic mutation, which leads to abnormal intima of the vessel wall and increased aortic stiffness leading to aortic dilatation and dissections. A number of studies have shown that aortic stiffness starts to increase early in childhood and progresses with age. Serial studies of such patients had led to detail study of aortic mechanics and help to predict progression of aortic dilatation and dissection(Vitarelli, Conde et al. 2006, Yasmin, McEniery et al. 2006).

5.Aortic Coarctation

Ou, p et al. (Ou, Celermajer et al. 2008), has shown in his study despite successful repair of the coarctation, increased aortic stiffness has been observed in the proximal segment of the repaired aorta as compared to the post repaired descending aorta. This may lead to the development of aortic aneurysm which has been observed regardless of successful repair of the aorta, and 20 -40% of the patients also develop hypertension. Aortic coarctation is an important congenital pathology and accounts for 10% of the adult congenital heart disease

defects. In the setting of bicuspid aortic valve as well as coarctation increased aortic stiffness has been noted resulting in development post repair aortic dilatation, aneurysms, hypertension, coronary artery disease.

Further studies have shown that aortic stiffness can be altered pharmacologically, and early intervention may help to prevent these comorbidities as described in Table 1.6.

TABLE 1.6 EFFECT OF DIFFERENT MEDICATIONS ON AORTIC STIFFNESS

Drug	Trial	Effects
Angiotensin converting enzyme inhibitors	None	Small studies have shown reduced pulse wave velocity at 3hr and 15 hrs. of administration. The mechanism is related to reduction of augmentation index subsequently lowering systolic blood pressure(Benetos, Vasmant et al. 1991, Heesen, Beltman et al. 2001)
Angiotensin receptor blockers (ARB)	None	There is not much data available to study the effect the ARB on aortic stiffness hence it is difficult to comment on the outcome.
Beta-Blocker	Reason Trial	The trial compared atenolol with combination perindopril/indapamide in a randomised trial. Reduction of systolic blood pressure by either strategy was associated with reduction in pulse wave velocity. There was a modest decrease in the augmentation index. A reduction in heart rate was associated with a reduction of central aortic pressure and systolic blood pressure (Protogerou, Blacher et al. 2009)
Ca-Channel Blocker	Café	This is the largest study, which randomised 2703 patients to atenolol+thiazide or perindopril+amlodipine. The amlodipine regimen was found to have a significantly greater reduction of central aortic pressure compared to the atenolol combination although systolic blood pressures were not different between the randomised groups(Cameron, Meredith et al. 2006).
Statin		The role of statin remains controversial. Some studies have shown a decrease in aortic stiffness(Shige, Dart et al. 2001, Williams, Lacy et al. 2009). Rosuvastatin has been demonstrated to reduce three nitrotyrosine levels, which reduce aortic stiffness (Pirro, Schillaci et al. 2007). Interestingly it has been noted that reduction in cholesterol has been an independent marker in reducing aortic stiffness.

6.Hypertrophic Cardiomyopathy

Patients with increased cardiac mass have increased aortic stiffness as compared to healthy subjects in hypertrophic cardiomyopathy. Patients with positive late gadolinium enhancement on MRI are found to have even high aortic stiffness. It is unclear at this stage whether aortic stiffness can be used as a risk stratification factor in this group of patients(Boonyasirinant, Rajiah et al. 2009).

1.16.3 Role of aortic stiffness in non-cardiac conditions

1.Diabetes Mellitus

Cardiac MRI studies in patients with diabetes have generally shown increased aortic stiffness. A large multicohort study has shown that there is altered vasculature in the young cohort with increased aortic stiffness(Stacey, Bertoni et al. 2010). Aortic stiffness is also considered to be an independent risk predictor for mortality in diabetic and abnormal glucose tolerance test patients(Cruickshank, Riste et al. 2002).

2.Chronic Renal failure

Increased global aortic stiffness has independently been associated with decreased creatinine clearance regardless of the mean arterial pressure. Due to decreased aortic distensibility and abnormal diastolic pressure in these group coronary artery perfusion is affected(Doyle, Mark et al. 2008).

Conclusion

Aortic stiffness is an important manifestation of aortic haemodynamic and plays a significant role in increasing the LV load and has effects on cardiovascular morbidity and there are a number of medications that have an effect on aortic stiffness including beta blockers and calcium antagonists. Adult Congenital heart disease patients are a unique group of patients and observational data has shown aortic dilatation post-surgery in the arterial switch group, tetralogy of Fallot, and most importantly in coarctation of the aorta.

Future Work

The second part of this thesis studies the effect of aortic stiffness and cardiac function using myocardial strain and mitral flow in patients with CoA. If a direct association was established,

further clinical research would be required to determine the effect of medication and other interventions on aortic stiffness cardiovascular morbidity.

2 Chapter 2 – Methods NORPAP DATASET

2.1 Aims and hypotheses to be tested in NORPAP dataset

Part A: NORPAP Adult Congenital Heart Disease database

Main aims:

A. **Describe the main clinical characteristics, treatments and outcomes of patients treated for Coarctation of the Aorta in a specialised centre without surgical facilities in the UK**
B. **Assess the quality of care in the non-surgical centre through indirect comparisons with existing datasets from other adult congenital heart disease centres**
C. **Identify the main contributing clinical factors (age, gender, aortic valve pathology, age at corrective surgery) associated with hypertension and key clinical outcomes like death and ischaemic heart disease in univariate and, if appropriate, multivariate statistical models**

Hypotheses to be tested

A. **Patients treated in a non-surgical Adult Congenital Heart Disease centre will have similar characteristics, treatments and clinical outcomes to those attending a conventional surgical centre**
B. **Patients with corrected Coarctation at older ages are more likely to develop hypertension**
C. **Patients who are older, have corrected Coarctation at older ages and have a bicuspid aortic valve are more likely to have worse clinical outcomes and risk of recoarctation**

2.2 Methods NORPAP DATASET

Background to the NORPAP database

The Adult Congenital Heart Disease (ACHD) Service at Norfolk and Norwich University Hospital was set up in 1991. There are 11 centres providing recognized ACHD services in the UK with 10 of these providing surgical and interventional services and only one without on-site ACHD surgery, which is Norfolk and Norwich. Due to the novel paradigm of providing ACHD services in a relatively remote city in the UK, a database recording key baseline, treatment and outcome information on all registered patients was established for quality and audit purposes, as well as to monitor service requirements for example number of investigations and procedures related to the service as well as trends or increasing needs over time. The service was started at NNUH and it was only in 2008 that clinics occurred at Papworth and the dataset from that cohort added to the NNUH existing database. The amalgamated database has been given the name Norwich Papworth ACHD database or NORPAP for short. An initial report from the database in 2002 showed that 340 adult patients (186 male and 154 female patients with average age of 36 years old were seen in a dedicated congenital heart disease clinic. At that time 55% of patient had had a first intervention, 13.3% had a second intervention and 3.2% had a third intervention. The table below from the paper shows the diagnoses at Norfolk and Norwich in 2002 (Freeman, Wood et al. 2002)

Table 2.1 SUMMARY OF ADULT CONGENITAL HEART DISEASE DIAGNOSIS AT NORFOLK AND NORWICH IN 2002 (Freeman, Wood et al. 2002)

Table 1. Summary of GUCH patient diagnoses in a district general hospital

	Total number of patients	Male	Female
	340	**186**	**154**
Septal defects (28.2%)	**96**		
VSD	44	28	16
1°ASD/partial AV canal	2	16	15
2°ASD*	31	10	21
Aortic pathology (27.7%)	**94**		
Bicuspid aortic valve*	38	25	13
SubAS	13	7	6
SupraAS	2	2	
AR 2° con abn valve	2	1	1
Coarctation of aorta	39	26	13
Marfan/HOCM(15%)	**51**		
Marfan's syndrome*	41	29	12
HOCM*	10	5	5
Fallot's tetralogy (10.6%)	**36**	**19**	**17**
Other congenital valvular abnormalities (7.9%)	**27**		
Pulmonary stenosis	17	8	9
Mitral valve lesions	9	2	7
Ebstein's anomaly	1		1
Transposition types (5.3%)	**18**		
TGA	15	10	5
CCTGA	3	3	
Complex congenital heart disease (5.3%)	**18**		
Single ventricle	9	2	7
Complex pul atresia	5	2	3
Pulmonary atresia/intact VS	2	1	1
Tricuspid atresia	2		2

Key: * patients also seen in general cardiology clinics
1°ASD = primum atrial septal defect; 2°ASD = secundum ASD; AR = aortic regurgitation; AV = atrioventricular; CCTGA = congenitally corrected transposition of great arteries; complex pul atresia = complex pulmonary atresia with multiple aorto-pulmonary collaterals; con abn = congenital abnormality; HOCM = hypertrophic cardiomyopathy; subAS = subaortic stenosis; supraAS = supra-aortic stenosis; TGA = transposition of great arteries; VS = ventricular septum; VSD = ventricular septal defect;

2.3 Database structure and set up

The NORPAP Access database was exported to an Excel spread sheet with a single-entry line per patient with fields for principle diagnosis, medical history, treatments and clinical events.

Patients were entered as a new entry on the database at their first clinic visit and information for subsequent clinic visits or events were entered into the same row on the database using additional fields. A list of the core fields and additional fields are provided in Table 1 in results chapter 2 for NORPAP dataset. Data was entered by one person (LJF).

2.4 Quality assurance

Quality assurance for the database was carried out in the following ways:

- Cross checking of entries against electronic letters in real time (to ensure that patient data was entered for all new patients)
- Searching for duplicates based on last name, hospital number and data of birth
- Random checking of specific entered data including the correct diagnosis associated concomitant lesions, type of interventions, number of procedures and associated comorbidities. Mainly large cohorts such as ventricular septal defects, tetralogy of Fallot, pulmonary stenosis, transposition of great arteries, atrioventricular canal defects and coarctation of the aorta. against source data (from, investigation reports and electronic records).
- Identification and completion of missing key baseline data. Certain fields (Table ACHD) were considered mandatory to describe patients and attempts to complete these fields were made using all available methods including the medical record and electronic systems.
- Within the database, deaths (and other outcome events) are recorded, along with dates of death together with likely cause of death. A search for additional deaths was made to ensure that all deaths were recorded as far as possible by checking the last correspondence and clinic letter.

- The group with coarctation of the aorta was the focus of this investigation and therefore further quality assurance checks were carried out by checking each patient's dataset against medical and electronic records with specific focus on their last visit in clinic.
- The NORPAP database had items of missing data including date of registration (first visit), baseline blood pressure and information on follow up medication. Using hospital records, key data were identified and in some cases date of registration had to be imputed using the best available information. The data were entered by a single clinical practitioner and not formally validated during the evolution of the database apart from during the analysis for this thesis. For the purpose of the thesis all critical data for patients with Coarctation of the Aorta used in the analyses for this thesis was quality assured as far as possible by cross checking with hospital records including gender, age and diagnosis. For example the diagnosis of bicuspid aortic valve was validated by reviewing echocardiography reports for each patient. The analysis is mostly cross sectional and retrospective in nature but the ascertainment of deaths and knowledge of the approximate length of follow up for each patient allows for some longitudinal analyses to understand the influence of key baseline characteristics on outcomes including mortality.

2.5 Rationale to Analyse the NORPAP Dataset

In 1993, there were no concrete guidelines or infrastructure for Adult congenital heart disease patients. Dr Leisa Freeman had a view and a foresight for the need of a dataset to monitor patients and clinical outcomes, hence the database was established before the guidelines were implemented. It was also felt at the time, as it was a single-handed practice and a newly emerging speciality, it would guide future treatment. Hence for the last decade it has significantly contributed to the European database and also became the basis for my MD thesis. Keeping the UK National Specialist Commissioning Group review in 2014 in focus and anticipation of new changes from *NHS, England's* review, we decided to analyse the

dataset to determine how standards of care in current dataset compared with accepted guidelines and standards (2014)

Dr Freeman and I decided to analyse the main dataset and then focus on the CoA subgroup. One important reason to study CoA patients was an observation that despite adequate repair patients are still often hypertensive. This observation also led to development of a prospective study at Guys and St' Thomas' described in part 2. While I was carrying out the thesis, the *NHS England review* assessed level 1 and level 2 centres against prospective Standards. Level 1 centres currently will be GSTT, Barts, Southampton, Bristol, Birmingham, Liverpool, Leeds, and Newcastle. Only NNUH complied with all the Standards and has been commissioned as a Level 2 centre; Brighton & Sussex and Oxford are likely to achieve compliance for level 2. Not only has the database benchmarked ACHD clinical outcomes, it has provided metrics to support service provision and development. It also highlights a clinical service, set up by a single-handed practitioner for the 21 of the last 23 years who has invested a lifetime, to provide good clinical care to patients nearer to home. This sets a standard and model for other centres to follow and establish services for ACHD patients. Research is an important aspect of clinical care and ACHD is a speciality where the majority of patients require lifelong follow-up, hence establishing the clinical outcomes and identifying comorbidities will help us to address the issues by designing prospective studies.

2.6 Analysis plan – coarctation of the aorta subset

1. Descriptive data were presented for numbers (n) and proportions (%) of patients, age (mean/standard deviation), gender (n/%), principle diagnosis (n/%), main treatments (n/%) and outcomes (n/%) for the whole group and for the CoA subgroup.
2. Further analyses were carried out for the coarctation of the aorta subgroup:

- Comparison of the main baseline characteristics of the coarctation subgroup (age, gender, comorbidities) with the main group using the t-test for continuous variable and the chi squared test for proportions
- Outcomes of patients associated cardiac defects, comorbidities, complications such as recoarctation and aneurysm formation, pregnancy and death were recorded during the duration of follow up in the database
- Stratified analysis exploring the association between age and gender for key baseline characteristics and outcomes using regression analysis.

- Association of baseline factors including age, gender, age at first corrective surgery, number of procedures, aortic valve anatomy were explored with occurrence of hypertension at registration in a univariate and multivariable logistic regression models. Associations are expressed as odds ratios and 95% confidence intervals. A similar analysis was carried out exploring associations of these variables (including hypertension) with death.

3. A qualitative comparison was also made against established reference datasets (published literature) in terms of baseline characteristics, treatments and outcomes to see if our results were broadly in line with these and accepted clinical guidelines for management of coarctation of the aorta.
4. All data relating to patient characteristics, diagnoses and treatments refer to the initial visit unless otherwise stated
5. Deaths were confirmed from documentation in the database and through information from NHS Digital which links patient NHS number with the National Death Registry via the Office of National Statistics. This method has shown a high degree of reliability although we were not able to obtain information on causes of death.

Genotyping

For genotyping, patients were referred to Addenbrookes Hospital. In previous years, genetic testing was not readily available and only patients who had dysmorphic features, or learning disabilities were referred to confirm a suspected diagnosis, especially when this had implication for treatment. 22q11, Turner syndrome, Williams and Marfan syndrome were tested. Turner and Down syndrome were diagnosed by karyotyping, while for 22q11, Williams, and Noonan syndromes, fluorescence in situ hybridization was used. Nowadays, with growing recognition of the importance of achieving a genetic diagnosis in cardiac congenital anomalies, most patients are screened for genetic disorders in childhood in tertiary paediatric centres. Advances in genetic screening and technology have made these tests easily accessible, with great benefit to congenital patients. In 2013, a dedicated monthly genetic clinic was set up in Norwich, which runs in conjunction with Addenbrookes.

All adult congenital patients are counselled in clinic with regards to the risk of transmitting congenital heart disease to their offspring, currently estimated as an average 3-5% in comparison to the risk in the normal population (1%).

2.6.2 Detection of hypertension

Patients had a minimum of at least three blood pressure readings at registration. In some patients the GP was asked to keep patient under observation and to start therapy if found to be hypertensive. Hypertension in untreated patients was based on World Health Organisation criteria of persistent office reading (average of minimum two readings) right arm systolic blood pressure ≥140mmHg or diastolic blood pressure≥ 90mmHg. Patients already on hypertensive medication were considered to be hypertensive.

Chapter 3 RESULTS – NORPAP DATASET

3.1Baseline Characteristics

A total of 2322 patients were included in the overall dataset at the time of analysis (2017). A flow diagram of patient inclusion is shown in Figure 3.1. About half of patients were female and about three quarters were followed up at Norfolk and Norwich University hospital as compared to Papworth. Baseline characteristics including age, gender, diagnosis and other relevant medical data are shown in Table 3.1 and Figure 3.2 show the distribution of congenital heart defects. Left ventricular outflow tract (LVOT) defects were the commonest congenital pathology followed by ventricular and atrial septal defect while coarctation of the aorta made up 10% of those included in the registry.

Table 3-2 shows the distribution of congenital heart disease by gender. Inspection of the larger subgroups showed that males were more likely to have LVOT, Marfan's and CoA while females were more likely to have secundum ASD and pulmonary stenosis.

Figure 3.1 Flow Chart

Numbers of patients included in the overall ACHD dataset and the CoA subset and reasons why patients were excluded from inclusion in the analysis

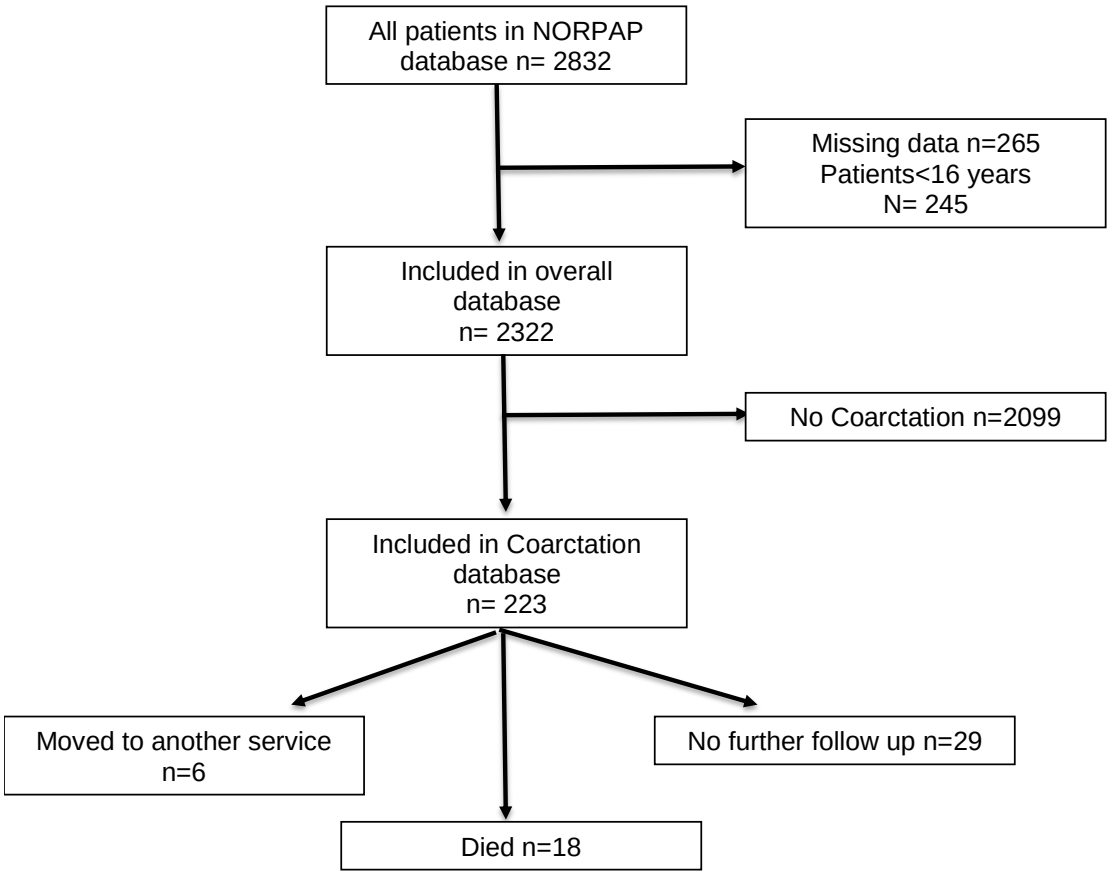


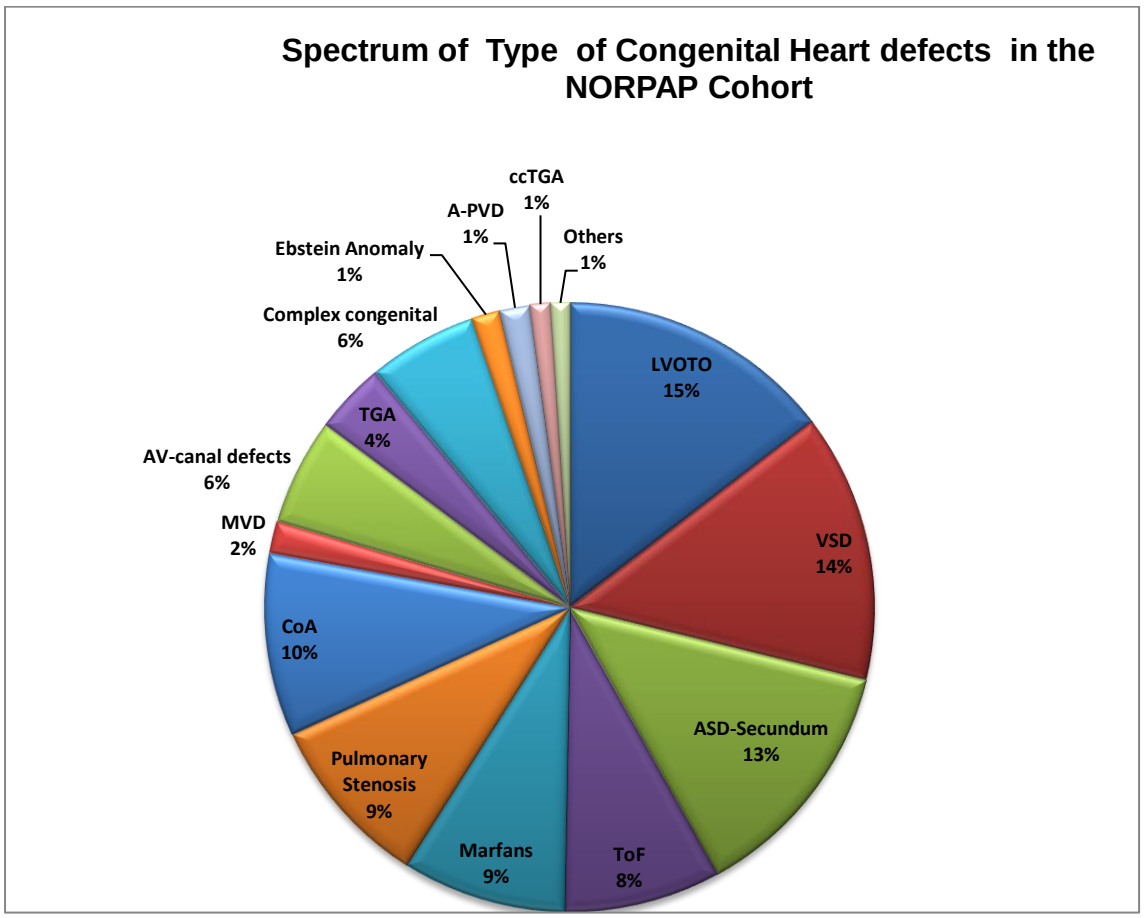
Table 3.1 DEMOGRAPHICS OF WHOLE NORPAP DATABASE AND COA SUBGROUP

Characteristic	**Whole dataset**	**Coarctation subgroup**
Number included	2322	223 (10%)
N at Papworth	595	47
N at NNUH	1727	176
Age at registration (mean years and standard deviation)	42 (8)	40 (12)
Gender Male	1105 (48%)	146 (65%)
Gender Female	1217 (52%)	77 (35%)
Diagnosis at baseline		
LVOTO	337(13%)	
VSD	328(14%)	
ASD – Secundum	302(13%)	
Tetralogy of Fallot	192(8%)	
Marfans	201(9%)	
Pulmonary Stenosis	212(9%)	
Coartation of Aorta	223(10%)	
MVD	46(3%)	
AV –canal defect	131(6%)	
TGA	87(4%)	
Ebstein Anomaly	35(2%)	
Anomalous pulmonary venous drainage	23(1%)	
ccTGA	25(1%)	
Complex CHD	134(5%)	
Others	23(1%)	
Medical history		

Previous surgery/Intervention	1432(62%)	203(91%)
Maximum number of surgical interventions	4	4

LVOTO = Left ventricular outflow tract obstruction, VSD = Ventricular Septal Defect, ASD= Atrial Septal Defect, Fallots = Tetralogy of Fallot, MVD = Mitral Valve Disease, AV Canal Defect= Atrioventricular canal defect, TGA = Transposition of Great Arteries, ccTGA = Congenitally corrected transposition of arteries, Complex CHD = Complex congenital heart disease.

Figure 3.2 PIE CHART showing THE DISTRIBUTION OF ADULT CONGENITAL PATIENTS IN THE NORPAP COHORT



See Footnote Table 1 and Glossary for Abbreviations

Table 3.2 TYPE OF CONGENITAL DEFECTS BY GENDER

Diagnosis &Number Total no =2322	**Male N=1217**	**Female N=1105**	**P value (male versus female)**
LVOT N= 337 (15%) (Valvular= 275, Supravalvular = 16, Subvalvular = 46)	226(67%)	111(33%)	<0.01
VSD N=328(14%)	149(44%)	186(56%)	0.04
ASD- Secundum N=302(13%)	110(36%)	193(64%)	<0.01

Fallot N=192(8%)	104(54%)	88(46%)	NS
Marfans N=201(9%)	137(68%)	64(32%)	<0.01
Pulmonary Stenosis N=212(9%)	87(41%)	125(59%)	0.04
Coarctation of the Aorta N=223(10%)	181(71%)	74(29%)	<0.01
Mitral valve disease N=46 (3%)	28(61%)	18(39%)	NS
AV- Canal Defect N=131(6%)	63(48%)	67(52%)	NS
Transposition Of Great arteries N=87 (4%)	60(69%)	27(31%)	0.03
Complex Congenital Heart Disease N=134 (5%)	68(51%)	66(49%)	NS
Ebstein Anomaly N=35 (2%)	18(50%)	18(50%)	NS
Anomalous Pulmonary venous drainage N=37 (1%)	25(68%)	12(32%)	NS
Congenitally Corrected Transposition of Great Arteries N=25 (1%)	17(68%)	8(32%)	NS
Others N=23(1%)	8(35%)	15(65%)	NS

Two hundred and sixty-four patients with phenotypic appearances were genotyped in the NORPAP cohort and findings are shown in Table 3-3. Two hundred and twenty-four patients were found to be genotype positive and 40 genotype negative. Positive genotype distribution is shown in Figure 3-3. Downs syndrome was the commonest presentation followed by Noonan, Turner, 22q11 and Williams syndromes. Only 10 per cent of the NORPAP dataset was genotyped due to lack of availability of genetic testing at the time of diagnosis.

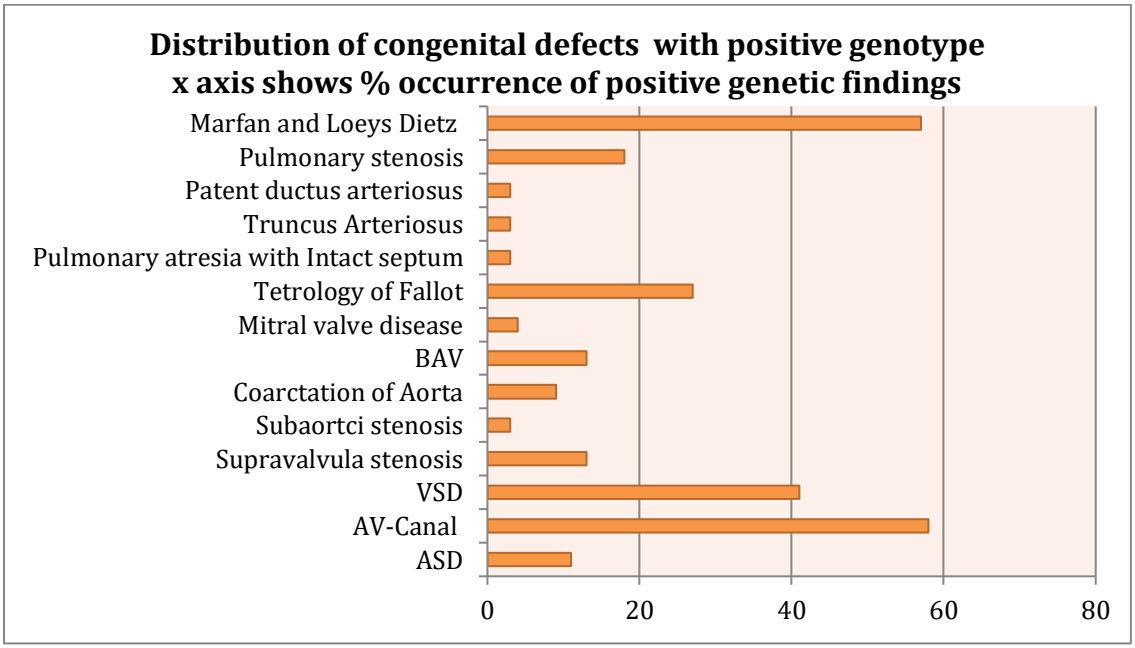
Table 3.3 INCIDENCE OF GENETIC SYNDROME IN THE NORPAP COHORT

Syndromes	**Main Diagnosis for Cardiac Defects**
Downs Syndrome N = 106 (4%) M= 58 F = 48	ASD, Atrioventricular canal defects, Tetralogy of Fallot, Ventricular septal defect, Single ventricle, Patent ductus arteriosus, Coarctation and Bicuspid aortic valve
Noonan Syndrome N= 7 (<0.1%) M= 9 F= 8	ASD, Atrioventricular canal defects, Pulmonary stenosis, Branch PA stenosis, subaortic stenosis, HOCM
Turner Syndrome N=13 (1%) All females	Coarctation of aorta and bicuspid valve, Partial anomalous venous drainage, Patent ductus arteriosus and Ventricular septal defect
DiGeorge Syndrome 22q11 del N=18(1%) M=9 F=9	Tetralogy of Fallot, Pulmonary atresia with intact ventricular septum, Ventricular septal defect, Truncus arteriosus, Aneurysm of sinus of valsalva, Bicuspid aortic valve and coarctation
Williams Syndrome N 15(1%) M = 11 F= 4	Supravalvular stenosis, Bicuspid aortic valve, Mitral Valve disease
Holt-Oram Syndrome N=6(<0.1%) F=1 M=5	Atrial septum defect secundum, VSD, BAV
Alagille's Syndrome N=5(<0.1%) F=4 M=1	Tetralogy of Fallot, Pulmonary stenosis, Bicuspid aortic valve
Goldenhar Syndrome N= 1(<0.05) M=1	Atrioventricular- canal, Ventricular septal defect
Russell Silver Syndrome N=1(<0.05%) F=1	Ventricular septal defect
Klippel Feil Syndrome N= 2(,0.05%) F=1 M=1	Pulmonary stenosis, VSD

Marfan Syndrome N=37 (2%) F=11 M=25	Mitral valve prolapse
Loeys Dietz Syndrome N=4(<0.05%) F=2 M=2	Dilated Aorta
Others N= 17(1%) F= 9 M= 8	Tetralogy of Fallot, VSD, Sub aortic stenosis, Pulmonary atresia

FIGURE 3.3 FREQUENCY OF GENETIC CHANGES BY DIAGNOSIS CATEGORY

AV canal defects and Marfan syndrome showed the highest frequencies of genotype associations. BAV=bicuspid aortic valve; VSD= ventricular septal defect; AV canal= aorto-ventricular canal; ASD= atrial septal defect



3.2 Treatments in NORPAP dataset

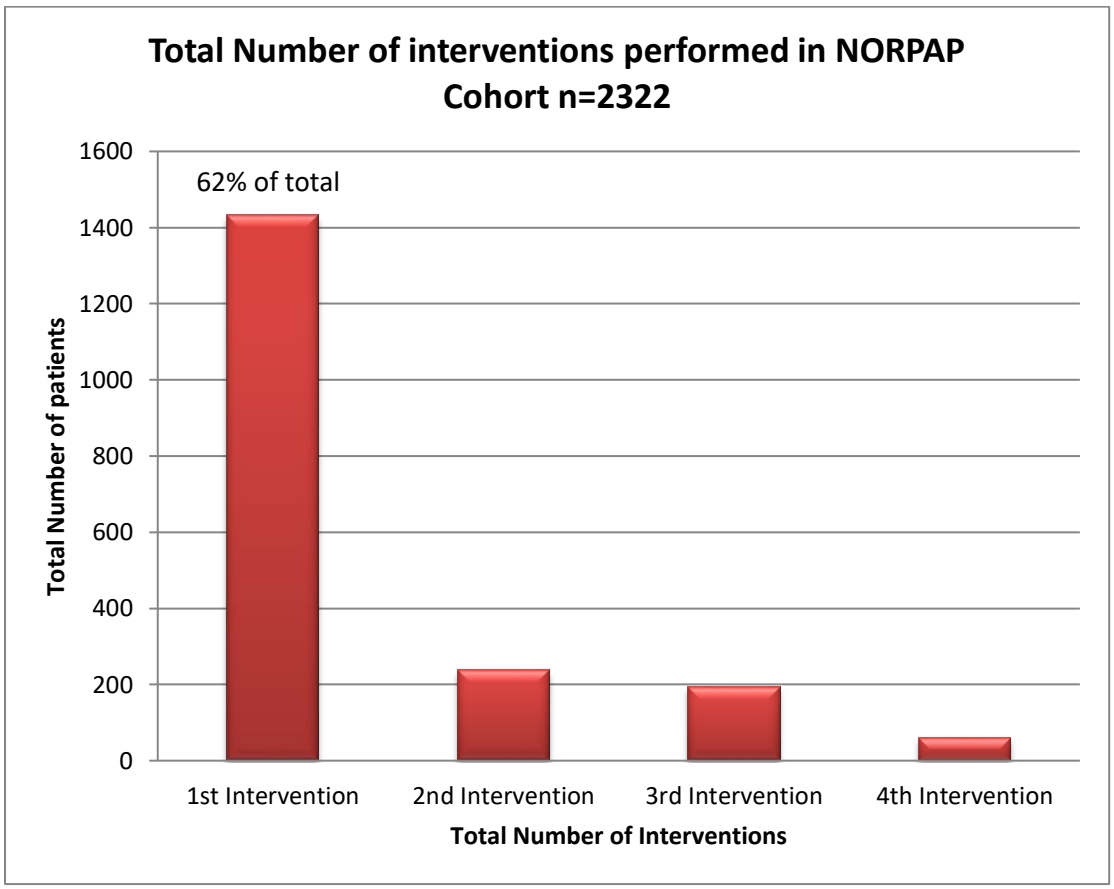
Overall 62% of patients with any congenital heart disease had undergone a corrective procedure compared to 91% of the CoA patients with the majority having surgical procedures rather than percutaneous interventions (Table 3-5 and Figure 3-4). About one third of patients overall needed a repeat procedure while in the CoA subgroup the need for at least one repeat corrective procedure was about 50%. Medical treatments were given to about half of the group overall but 80% in the CoA subgroup ($P<0.01$ compared to the group overall) with ACE inhibitors, beta-blockers and calcium channel blockers being the most commonly prescribed (Table 3-4).

TABLE 3.4 MEDICAL AND SURGICAL TREATMENTS IN NORPAP DATASET.

Treatment	**Whole dataset**	**Coarctation subgroup**	**P value***
Number included	2322	223 (10% of total)	
Surgical treatments, number and type	1432(62%)	203(91%)	P<0.01
2nd Intervention	237(10%)	77(35%)	
3rd Intervention	193(8%)	21(9%)	
4th Intervention	61 (3%)	10(5%)	
Surgery	1279 (55%)	176(79%)	P<0.01
Percutaneous	154 (7%)	27 (12%)	
Other interventions (EP pacemakers etc.)			
EP Studies	342(15%)		
PPM	118(5%)		
Medical Treatments	1087(47%)	188(84%)	P<0.01
ACE inhibitor	295 (13%)	71 (32%)	
Beta blocker	235 (10%)	36(15%)	
Ca-channel	120 (5%)	36(15%)	
Warfarin	142 (6%)	6 (3%)	
Aspirin	71 (3%)	1(1%)	
Others	102 (4%)	8 (4%)	

* Comparison is made between all ACHD diagnoses without CoA versus CoA alone patients

Figure 3.4 NUMBER AND FREQUENCY OF INTERVENTIONS IN THE NORPAP COHORT.



3.3Clinical Outcomes in the NORPAP dataset

Overall complication in terms of adverse clinical outcomes appeared low in the dataset overall and in the CoA subgroup (Table 3-5). There were 162 (7%) deaths amongst the whole ACHD cohort (2322 patients) followed up to the end of December 2016 over a mean of 12 years (standard deviation 4 years) follow up and causes of death are available in a subset (Table 3-6). Tachyarrhythmias were documented in 13% overall and 9% in the CoA subgroup. Device therapy was required in about 5% and 6% of patients had pulmonary arterial hypertension. Infective endocarditis was observed in just 2% over the observation period. In the CoA subgroup the incidence of stroke was 2% and psychosocial issues which included anxiety, depression, manic-depressive disorder occurred in 11%.

TABLE 3.5 CLINICAL OUTCOMES OF WHOLE NORPAP DATASET AND COA SUBSET.

No significant differences detected between non-CoA and CoA subgroups

Outcome measure	**Whole dataset**	**Coarctation subgroup**
Number included	2322	223
Deaths recorded	162 (7%)	18 (8.1%)
Comorbidities	57(2%)	2(0.5%)
IHD	42 (2%)	14(6%)
Tachyarrhythmia	342(13%)	20(9%)
Bradyarrhythmia's	118(5%)	9(4%)
Pulmonary hypertension	142(6%)	0
Infective endocarditis	48 (2%)	4(2%)
Stroke	Not known	4(2%)
Psychosocial	Not known	27(11%)
Procedures		
Electrophysiology ablation	100(4%)	0
Device therapy	118(5%)	9(4%)
Percutaneous Coronary Intervention	7(0.5%)	5(2%)

Causes of death and the main congenital heart disease diagnosis are documented in Table 6. Of the 57 deaths that had some documentation about possible cause, about one third were related to heart failure and another third to arrhythmias (Table 3.6). Endocarditis (10%), pulmonary arterial hypertension (5%) and ischaemic heart disease (3%) were much less commonly associated with death.

TABLE 3.6 INCIDENCE OF DEATH AND MAJOR CAUSE.

Cause of Death Total number =57*	**Main diagnosis**
Heart Failure N=19 (35%)	ASD, VSD, PDA, TAPVD, Partial AV canal Eisenmenger, Single ventricle, Pulmonary atresia with intact septum, Ebstein anomaly, TGA
Arrhythmias N=15 (27%)	Partial AV canal defect, Atrial septal defect, TGA, Ebstein anomaly, Complex congenital Heart disease,
Ischaemic Heart disease N=2 (3%)	Bicuspid AV, Congenitally abnormal aortic valve, Atrial septal defect with pulmonary arterial hypertension. Marfans syndrome. Monocusp aortic stenosis
Endocarditis N=6 (10%)	Tetralogy of Fallot, Double outlet RV, Ebstein anomaly, TGA, PAPVD, VSD, Pulmonary atresia with intact septum
PAH N=5(9%)	Partial AV canal defects, PDA Eisenmenger, Ebstein anomaly with coarctation, Double outlet RV.
Cardiac surgery related mortality N=4 (6%)	Single ventricle, Ventricular septal defect with aortic regurgitation, Ebstein anomaly with coarctation
Non-cardiac Surgery N= 1(2%)	Closed Atrial septal defect.
Renal failure N=2(3%)	Double outlet Right ventricle, late repair, Tetralogy of Fallot
Cystic fibrosis N=1 (2%)	Secundum ASD
Pneumonia N=2 (3%)	Pulmonary stenosis, AV canal Eisenmenger's syndrome
Hepatic Ca N=1 (2%)	Pulmonary atresia and VSD
Ca Lung N= 1(2%)	Ventricular septal defect
Stroke N= 2 (3%)	Partial AV canal defect, ASD, VSD and TAPVD. Downs syndrome
Suicide N=1(2%)	Marfan syndrome
Unknown N= 1(2%)	Partial AV canal defect

*Causes of death were only available for a subset of the 162 deaths

3.3.1 Incidence of tachy- and brady-arrhythmias in NORPAP database

Clinical tachyarrhythmia occurred in 15% of all patients included in the database. Patients with atrial septal defect presented with the highest absolute number and proportion of arrhythmias and received the most ablation procedures (Table 3.7). Tetralogy of Fallot had the next highest rate at 10% and other categories had 6% or less. Ablation procedures were carried out in one third of all patients presenting with clinical tachyarrhythmias.

Table 3.7 INCIDENCE OF TACHYARRHYTHMIAS AND ASSOCIATION WITH CONGENITAL HEART DISEASE.

Type of Defects	**Arrhythmias Total number=342**	**Ablation Total Number = 118**
Atrial Septal Defect (Secundum) N=303	85(25%)	23 (25%)
Atrioventricular canal defect N=130	21(6%)	3(3%)
Ventricular septal defect N=328	29(6%)	7(6%)
Transposition of great arteries N=87	21(6%)	7(9%)
Congenitally corrected transposition of great arteries N=25	14(4%)	4(3%)
Bicuspid Aortic Valve N=275	19(5%)	4(3%)
Subaortic stenosis N=46	5(1%)	1(1%)
Coarctation of the Aorta N=223	22(6%)	7(9%)
Single Ventricle N=40	20(6%)	7(9%)
Tetralogy of Fallot N=192	40(10%)	1(1%)
Pulmonary Atresia With intact septum N=15 Pulmonary Atresia with VSD N=21	8(2%)	1(1%)
Pulmonary Stenosis N=212	11(3%)	2(3%)
Ebstein Anomaly N=35	21(6%)	11(14%)
Anomalous pulmonary venous drainage N=37	7(2%)	2(3%)
Patent ductus arteriosus N=23	3(1%)	0(0%)
Truncus arteriosus N=8	2(1%)	0(0%)

Clinical bradyarrhythmias requiring pacing devices occurred in about 5% of all patients in the dataset. Half of all devices used were dual chamber pacemakers and there were no clear gender differences (Table 3-8).

Table 3.8 INCIDENCE OF BRADYARRHYTHMIAS AND DEVICE IMPLANTS.

Total No	**Bradyarrhythmia's**	**Devices**
2322	118	118
Incidence	Male to female ratio	Type of devices
5% of total population	M = 65 (55%) F = 53 (45%)	AAI = 3 (3%) VVI = 14 (12%) DDD = 55 (47%) ICD = 23 (19%) CRT-D = 6 (5%) CRT-P =17 (14%)

3.4 Analysis of Coarctation of the Aorta subgroup

Coarctation of the aorta made up about 10% of the whole dataset, mean age was 40 years, 35% female, 55% bicuspid valve, 90% had a prior corrective intervention (and 85% of these were surgical procedures) and half had hypertension (Table 3-9). End to end anastomosis was the commonest surgical approach practiced in the NORPAP cohort, followed by patch angioplasty, subclavian flap repair and interposition or bypass grafts (Table 3-9). In 3% of the cases it was not clear what type of repair was undertaken. About half of all patients who had a first corrective procedure went on to have repeat procedures and about half of repeat procedures were percutaneous. About 5% of patients had 4 procedures (Table 3-9 and Figures 3-5 and 3-6). Coarctation related complications include recoarctation (23%), aneurysm formation (3%), Hypertension (50%), strokes (2%). Incidence of death was 8% compared to 7% for the overall dataset (P=NS Table 3-6). A total of 37 (48%) women had 61 pregnancies with 51 live births (84%) with normal neonatal outcome. 10 miscarriages were documented (16%).

Table 3.9 DEMOGRAPHICS AND CLINICAL OUTCOME OF COARCTATION OF AORTA.

Characteristic	**Coarctation subgroup**
Number included	223
Age at registration	40
Gender female	77(35%)
Gender Male	146(65%)
Mean age at diagnosis*	9 years
Associated cardiac lesions at baseline	
VSD	28(13%)
PDA	12(5%)
Subaortic ridge	8(4%)
Mitral valve disease	6(3%)
Atrial septal defect	3(1%)
Partial anomalous pulmonary venous drainage	1(0.5%)
Double inlet LV	1(0.05%)
Double Aortic Arch	1(0.05%)
Pulmonary Stenosis	2(1%)
Ebstein anomaly	1(0.05%)
Associated valve disease	
Bicuspid	121(55%)
Monocusp	4(2%)
Unknown	13(6%)
Interventions	
1st Intervention Surgery Percutaneous	203 (91%) 176(79%) 27 (12%)
2nd Intervention Surgery Percutaneous	77(35%) 50 (22%) 27(12%)
3rd Intervention Surgery Percutaneous	21(10%) 14(6%) 7(4%)
4th Intervention Surgery Percutaneous	10(5%) 6 (3%) 4 (2%)
Surgery to correct coarctation	185 (87%)
Surgery not related to coarctation	27 (13%)
Cardiac comorbidities	
Arrhythmias	20(9%)
Conduction defects	9(4%)
Ischaemic heart disease	14(6%)

Endocarditis	4(2%)
Syndromes	9(4%)
PHTN	4(2%)
Coarctation related complications	
Recoarctation	65(23%)
Aneurysm formation	8(3%)
Hypertension	114(51%)
Strokes/berry aneurysm	4(2%)
Death	2(1%)
Psychosocial	27(11%)
Other issues	N= 77 (female)
Total pregnancies Live Births Miscarriages	61(80%) 51(66%) 10(13%)

*Age at diagnosis estimated from age at intervention data

Figure 3.5 SURGICAL AND PERCUTANEOUS TREATMENT OF PATIENTS WITH COA.

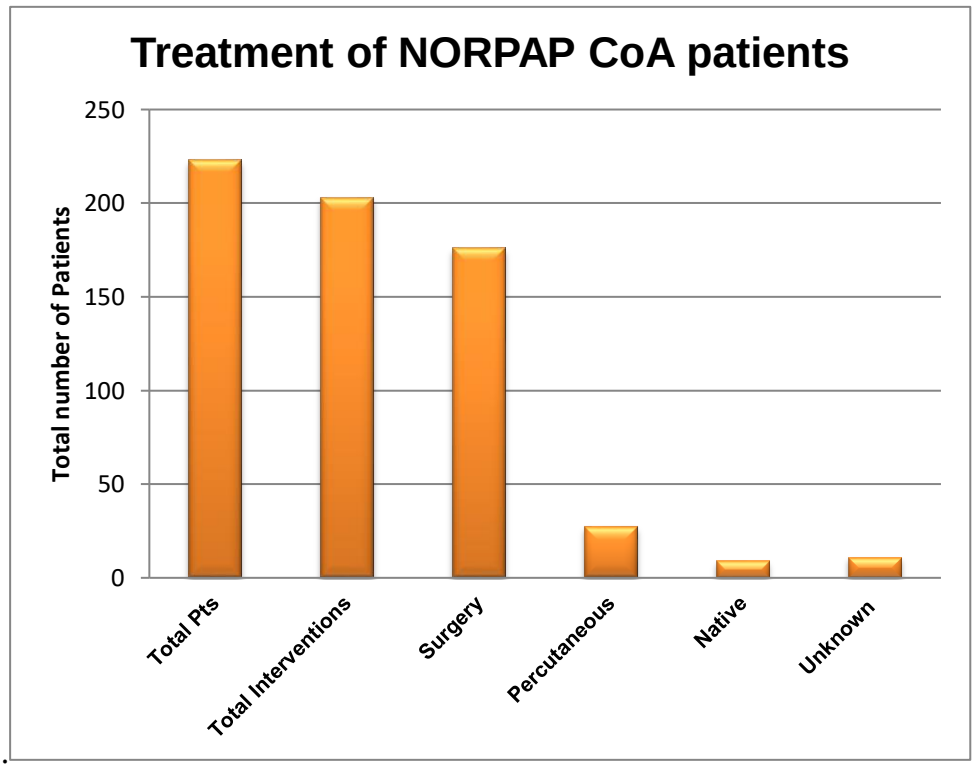
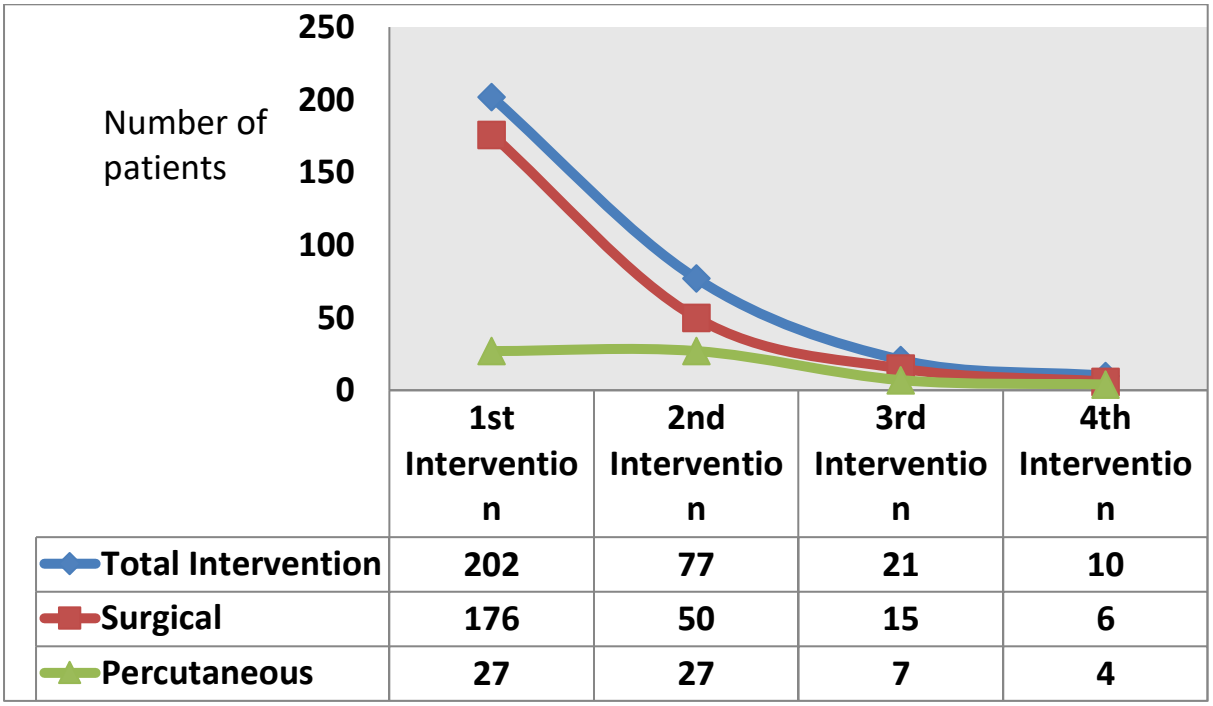


Figure 3.6 PATTERNS OF INTERVENTION FOR PATIENTS WITH COA.



	1st Intervention	2nd Intervention	3rd Intervention	4th Intervention
Total Intervention	202	77	21	10
Surgical	176	50	15	6
Percutaneous	27	27	7	4

End to end anastomosis was the most common type of repair in patients with hypertension (Table 10).

Table 3.10 TYPE OF INTERVENTION AND RELATION TO HYPERTENSION.

Type of Intervention	Total number N=203	%
End to end Anastomosis	106	52%
Subclavian flap repair	23	11%
Patch angioplasty	25	12%
Interposition or bypass grafts	15	7%
Unknown	7	3%
Percutaneous	26	15
Hypertension patients n=110	Type of Surgical Repair	%
End to end anastomosis	60	64%
Subclavian Flap Repair	9	10%
Interposition Graft	10	11%
Dacron	14	15%
Unknown	1	1%

The total number of patients who had surgical correction of coarctation was 169 and of these 27 patients had additional surgical procedures. Of these 27, 56% had aortic valve replacement (AVR), 22% AVR and root repair, 7% mitral valve replacement and 15% coronary artery bypass graft. End to end anastomosis was the commonest surgical approach practiced in the NORPAP cohort, followed by patch angioplasty, subclavian flap repair and interposition or bypass grafts. In 3% of the cases it was not clear what type of repair was undertaken. Incidence of hypertension was low in patients with stent implantation. In the surgical group, incidence of hypertension was higher in the end to end anastomosis group.

3.5 Subgroup analysis of CoA patients by age at intervention.

Information on surgical and percutaneous procedures was available for 185 patients and these were included in a stratified analysis based on age less than 1 year (group 1) or more than 1 year (group 2) at the time of diagnosis (Table 11). Diagnosis was made at age <1 year in 69% of patients and their mean age at intervention was 4 years, while in the 31% for whom diagnosis was made at age ≥1, intervention was carried out at a mean age of 25 years (Table 11). Gender distribution was similar in both groups with about one third being female. The association of VSD with coarctation in the younger age group was significantly higher than the older age group (17% versus 4% p=0.02) otherwise there was no difference in patterns of associated congenital heart lesions and both groups has 60% incidence of bicuspid aortic valves. The type of interventional procedure (surgery or percutaneous) and the rate of repeat intervention rates were similar between the two groups with about 10% in both groups having up to 4 procedures including the index corrective procedure (Table 11).

There was no apparent difference in incidence of arrhythmias or conduction defects and the prevalence of ischaemic heart disease and hypertension was significantly higher in the age ≥1 year at diagnosis group which may be also be a reflection of their older age in the database. The incidence of recoarctation and aneurysm formation was significantly higher in age ≥1 year at diagnosis group although stroke, endocarditis and death rates were all low at 1-2% and not different between the two groups. Pregnancy was documented in 86% of women in both groups but the rate of live births was 100% in the ≥1 year at diagnosis group, which was significantly higher than the 86% of live births for the age <1 year at diagnosis group. (Table 3.11).

Table 3.11 SUBGROUP ANALYSIS BASED ON AGE AT DIAGNOSIS.

Variable	**Age at diagnosis < 1 year**	**Age at diagnosis ≥ 1 year**
Number included (total n=185)	127(69%)	58(31%)
Baseline characteristics		
Mean age at intervention	3.9yrs	25yrs
Mean age at analysis	35.6yrs	53yrs
Gender female	42 (33%)	22 (37%)
Gender Male	85 (67%)	36 (63%)
Associated Cardiac lesions at baseline		
VSD	22 (17%)	2 (4%)*
PDA	2 (2%)	1 (2%)
Subaortic Ridge	4 (3%)	1 (2%)
Mitral Valve Disease	5 (3%)	1 (2%)
Atrial Septal Defect	1 (1%)	1 (1%)
Partial anomalous pulmonary venous drainage	1 (1%)	0
Double inlet LV	1(1%)	0
Double Aortic Arch	1(1%)	0
Pulmonary stenosis	2(2%)	0
Ebstein	0	1(1%)
Associated Valve Disease		
Bicuspid	75 (59%)	35(60%)
Monocusp	1 (1%)	0
Unknown	5 (3%)	1(2%)
Intervention		
1st Intervention	127 (100%)	58 (100%)
Surgery	126(99%)	57(98%)
Percutaneous	1(1%)	1(2%)
2nd Intervention	55(43%)	26(52%)

Surgery	32(25%)	16(27%)
Percutaneous	22(17%)	10(17%)
3rd Intervention	15(12%)	7(11%)
Surgery	8(6%)	6(10%)
Percutaneous	6(5%)	1(2%)
4th Intervention	7(6%)	2(4%)
Surgery	4(2%)	2(4)%
Percutaneous	4(2%)	0
Cardiac –Comorbidities		
Arrhythmias	11(9%)	9(16%)
Conduction defect	4(3%)	5(8%)
Ischaemic heart disease	1(0.5%)	9(16%)*
Endocarditis	2(1%)	2(4%)
Syndromes	5(3%)	2(4%)
Turners	4(3%)	1(2%)
Williams	0	1(2%)
22q11	1(0.05%)	0
PHTN	1(0.05%)	2(4%)
Coarctation related complications		
Recoarctation	28(24%)	37(64%)**
Aneurysm	2(1%)	6(12%)**
Hypertension	63(50%)	44(76%)**
Stroke/berry aneurysm	2(1%)	1(2%)
Death	0	2(4%)
Other issues	N= 42 (female)	N= 22 (female)
Total pregnancies	36(86%)	19(86%)
Live births (% of pregnancies)	31(86%)	19(100%)**
Miscarriages	5(4%)	0
Psychosocial problems	14(12%)	13(22%)

***p<0.05; **p<0.01**

3.6 Analysis of Coarctation of the Aorta subgroup by gender

The full CoA subgroup with complete data (n=223) were included in an analysis by gender with about one third being female (table 12). Mean age at the time of review in both males and females was 40 years, mean age at diagnosis was 9 years in both groups and incidence rates of associated aortic valve abnormalities and other congenital cardiac defects were also similar (Table 3-12). The rate of first intervention was similar in both groups however males had a significantly higher rate of surgical intervention than females. The rate of second intervention was also higher in males although this was not significant and this may have been driven by the significantly higher rate of recoarctation in males versus females. Cardiac comorbidities including hypertension, arrhythmias were similar between the two groups however males were significantly more likely to receive drug therapy including ACE-inhibitors than females. Endocarditis, stroke and death were not significantly different (Table 11). Arrhythmias, conduction defects were common in the female group. Ischaemic heart disease had a higher incidence in the male cohort. Syndromes were common in the female cohort (8% versus 1%) as expected as patients with Turners syndrome classically present with coarctation of the aorta.

Table 3.12 COARCTATION SUBGROUP ANALYSIS BY GENDER.

Variable	**Gender female**	**Gender male**
Number included (total n=223)	77(32%)	146(65%)
Baseline characteristics		
Age Years (mean)	41±6	40±6
Age at Intervention	Median 9	Median 9
Sinus Rhythm	74 (96%)	141 (97%)
Other rhythms if relevant	Atrial Flutter Complete heart block	Complete heart block, ventricular tachycardia
Aortic valve pathology		
Tricuspid Valve	29(38%)	53(36%)
Bicuspid Valve	41(53%)	80(55%)
Monocusp	1(1%)	3(2%)
Abnormal valves	1(1%)	1(0.05%)
Unknown	5(5%)	9(6%)
Other associated cardiac anomalies		
VSD	7(9%)	21(14%)
Subaortic Ridge	5(6%)	3(2%)
Mitral valve disease	1(1%)	5(3%)
Atrial Septal defect	1(1%)	2(1%)
Partial anomalous pulmonary venous drainage	1(1%)	0
Double inlet LV	0	1
Double Aortic Arch	0	1 (0.05%)
Pulmonary Stenosis	0	2 (1%)
Outcomes		
1st Intervention	68 (88%)	135(93%)

Surgery	55(71%)	121(83%)*
Percutaneous	13(17%)	14(10%)
2nd Intervention	19(25%)	59(38%)
Surgery	12(16%)	32(22%)
Percutaneous	7(8%)	27(18%)
3rd Intervention	6(8%)	15(10%)
Surgery	2(3%)	10(6%)
Percutaneous	4(6%)	5 (3%)
4th Intervention	4(6%)	6 (4%)
Surgery	1(1%)	2(1%)
Percutaneous	2(2%)	4(3%)
Comorbidities/ outcomes		
Arrhythmias	8/77 (9%)	12/146(8%)
Ischaemic heart disease	2/77(3%)	12/146(8%)
Endocarditis	1/77*(1*%)	3/146(2%)
Stroke/berry aneurysm	1/77(1%)	3/146(2%)
Death	1(1%)	1(0.5%)
Genetic Syndromes	7/77(8%)	2/146(1%)
Turner	7/77(8%)	0
Williams syndrome	0	1/146(0.05%)
22q11	0	1/146(0.05%)
Pulmonary HTN	4/77(5%)	0
Complications		
Recoarctation	11(14%)	55(38%)**
Aneurysm	3(4%)	5(3%)
Repaired	2(1%)	3(2%)
Non –Repaired	1(1%)	2(1%)
Hypertension	39/77(34%)	75/146(34%)

One drug therapy	5(6%)	38(26%)**
Two drug therapy	4(5%)	28(17%)*
Three drug therapy	3(4%)	8(5%)
Fourth drug therapy	0	2(1%)
Beta –blocker	16(21%)	21(14%)
ACE	17(23%)	55(38%)*
CA- Channel Blocker	8(11%)	29(20%)
Alpha Blocker	1(1%)	3(2%)
Diuretic	8(11%)	10(7%)

*P<0.05, **P<0.01

4 3.5 Analysis of factors associated with hypertension

Older Age at registration and older age at corrective surgery were found to be significantly associated with hypertension in univariate and multivariate analysis but other factors were not associated Tables 3.13 and 3.14).

Table 3.13 PROPORTION WITH HYPERTENSION

	Hypertension	**N**	**Mean**	**SD**	**95% CI**
Age at 1st registration	No	107	27.1	15.6	(24.2,30.1)
	Yes	110	35.4	17.4	(32.1,38.7)

TABLE 3.14 : UNIVARIATE ASSOCIATIONS WITH HYPERTENSION

Variable	Value	No (N)	% No	Yes (N)	%Yes	Total	Total %	P-value
Gender	F	42	54.5	35	45.5	77	34.5	0.4009
	M	71	48.6	75	51.4	146	65.5	
Age Band*	< 25	70	65.4	37	34.6	107	48.0	0.0001
	25-50	31	39.2	48	60.8	79	35.4	
	>50	12	32.4	25	67.6	37	16.6	
corrective surgery	< 1 year	65	62.5	39	37.5	104	46.6	0.0010
	> I year	48	40.3	71	59.7	119	53.4	
Number procedures	1	75	52.4	68	47.6	143	64.1	0.4785
	2+	38	47.5	42	52.5	80	35.9	
aortic valve anatomy	Bicuspid	61	49.2	63	50.8	124	55.6	0.0841
	Tricuspid	39	47.6	43	52.4	82	36.8	
	Unknown	13	76.5	4	23.5	17	7.6	

**Age at time of analysis*

TABLE 3.15 ODDS RATIOS FOR ASSOCIATIONS WITH HYPERTENSION (UNADJUSTED)

	Odds Ratio	Lower Limit	Upper Limit	P Value
Sex M vs F	1.268	0.729	2.205	0.40
Age	1.031	1.014	1.049	<0.01
Age band 25 to 50 vs < 25	2.929	1.604	5.349	<0.01
Age band > 50 vs < 25	3.941	1.779	8.728	
corrective surgery > 1 year vs < 1year	2.465	1.436	4.231	<0.01
Aortic valve anatomy Bicuspid vs Tricuspid	0.937	0.536	1.637	0.09

Aortic valve anatomy Unknown vs Tricuspid	0.279	0.084	0.928	
N procedures 2+ vs 1	1.219	0.705	2.108	0.4785

TABLE 3.16 ODDS RATIOS FOR ASSOCIATIONS WITH HYPERTENSION (ADJUSTED)

Adjusted Odds Ratio	**Odds Ratio**	**95% Confidence Limits**		**P value**
Sex M vs F	1.476	0.812	2.684	0.23
Age at analysis	1.027	1.008	1.047	<0.01
Age band 25 to 50 vs < 25	2.812	1.487	5.316	<0.01
Age band > 50 vs < 25	3.298	1.399	7.774	
N procedures 2+ vs 1	1.025	0.552	1.902	0.98
corrective surgery at age > 1 year vs < 1year	1.706	0.946	3.076	0.04
Aortic valve anatomy Bicuspid vs Tricuspid	0.773	0.417	1.434	0.10
Aortic valve anatomy Unknown vs Tricuspid	0.313	0.086	1.137	

3.7 Analysis of mortality Coarctation of the Aorta subgroup

Two hundred and five patients contributed to an analysis of factors affecting mortality as 18 patients had incomplete baseline data. There were 18 deaths in the coarctation cohort (8%). The average age at death was (68.7 years+-19.9 table 3.17). Patients who died were mainly diagnosed in the second decade of life (26.67+-13.9). Unfortunately we were not able to establish causes of death. In univariate analysis (multivariate analysis was not possible due to the small number of deaths) older age at registration and corrective surgery carried out at age> 1 year were associated with a higher risk of mortality (Table 3.18).

TABLE 3.17 PROPORTION OF DEATHS AND AGE IN THE COARCTATION COHORT

	Dead	N	Mean age	SD	95% CI
age	No	199	40	16.0	(37.6,42.1)
	Yes	18	69	19.9	(58.8,77.2)

TABLE 3.18 UNIVARIATE ASSOCIATION WITH MORTALITY

	Death						
Variable	No		Yes				
	N	%	N	%	Total	%	p
Female	70	90.9	7	9.1	77	34.5	0.6849
Male	135	92.5	11	7.5	146	65.5	
age< 25 yrs	38	97.4	1	2.6	39	17.5	<.0001
25-50	118	98.3	2	1.7	120	53.8	
>50	49	76.6	15	23.4	64	28.7	
Surgery < 1 year	101	97.1	3	2.9	104	46.6	0.0079
> I year	104	87.4	15	12.6	119	53.4	
Bicuspid AV	114	91.9	10	8.1	124	55.6	0.2821
Tricuspid AV	77	93.9	5	6.1	82	36.8	
Unknown AV	14	82.4	3	17.6	17	7.6	
1 procedure	132	92.3	11	7.7	143	64.1	0.7809
2+ procedures	73	91.3	7	8.8	80	35.9	
Hypertension No	106	93.8	7	6.2	113	50.7	0.297
Hypertension Yes	99	90.0	11	10.0	110	49.3	

4 Discussion – NORPAP Outcomes

4.1Outcome of NORPAP Adult Congenital Heart Disease Dataset

The distribution of adult congenital heart disease is in keeping with that published in the literature(Report of the British Cardiac Society Working 2002, Marelli, Mackie et al. 2007, Freeman 2008, Wren and O'Sullivan 2013). In 2002, Jane Somerville highlighted that 20-25% of the patients with ACHD had complex needs requiring lifelong specialist care, 40-45% had simpler conditions unlikely to cause future problems, and an intermediate group that will require lifelong follow-up (Report of the British Cardiac Society Working 2002). In NORPAP 10% had Complex congenital heart disease, 53% of the patients had simpler lesions and 37% had intermediate lesions. At the time of the Executive Report lesions that were considered simple and 'curable' were considered by many clinicians not so 'simple', since the late natural or palliated conditions still carried risk of complications, mandating lifelong follow up. Examples include VSD, which may develop a double chamber RV causing right ventricular outflow tract obstruction or a bicuspid aortic valve with associated ascending aortopathy. In comparison with the data presented in 2002 (incidence of Adult Congenital Heart Disease) from the Norwich and Norwich service, the incidence of complex congenital heart disease has only increased by about 5%.

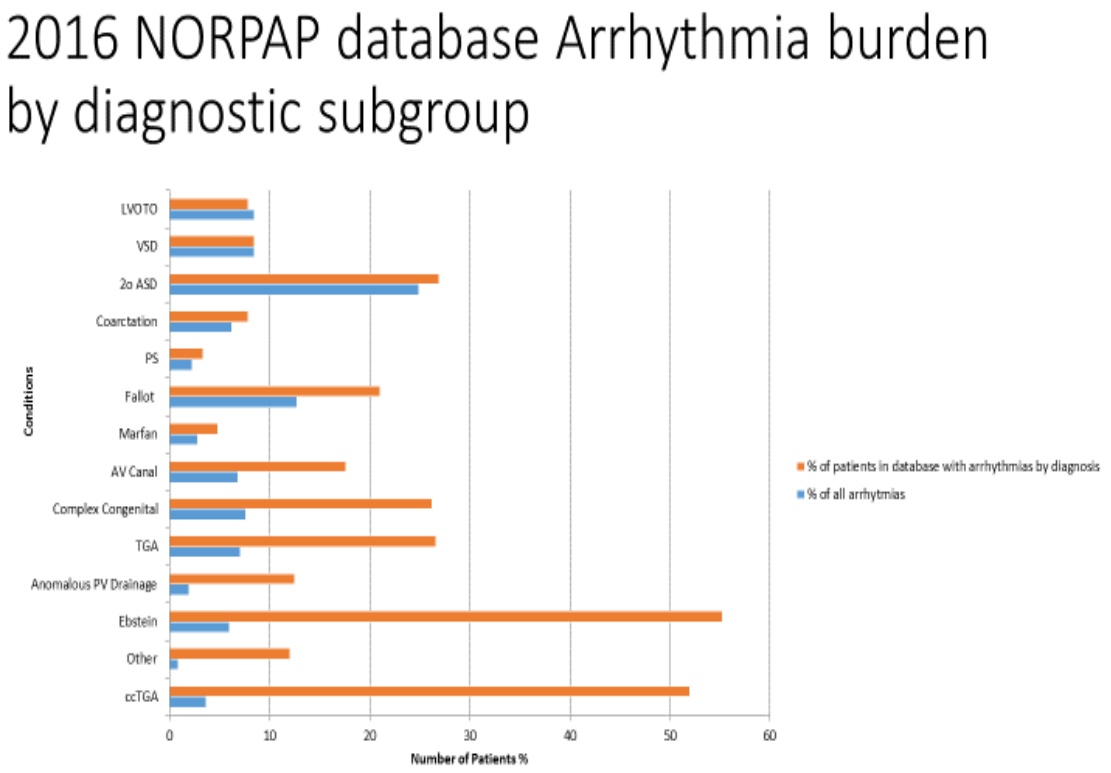
In NORPAP, VSD was the most common lesion (14%), followed by ASD (13%), LVOTO (13%), Coarctation of Aorta (10%), Pulmonary stenosis (9%), Marfan Syndrome (9%) and Tetralogy of Fallot (8%) respectively. Other lesions in small numbers included atrioventricular canal defects (6%), Complex congenital heart disease (5%), Transposition of the Great arteries (4%), Mitral valve disease (3%), Ebstein anomaly (2%) and anomalous pulmonary venous drainage and other small congenital defects that made the remaining 1% of the cohort (Chapter 3, Table 3.1). These findings are is in keeping with the worldwide high incidence of VSDs, ASDs and LVOTOs as documented in the literature, but the rest of the NORPAP dataset differs as the incidence varies according to geographical distribution, e.g. A study from Atlanta showed a higher incidence of ASD, VSD and TOF while a population based study from Taiwan showed a higher incidence of VSD, ASD and PDA (Hoffman 1990, Hoffman and Kaplan 2002, Reller, Strickland et al. 2008, Wu, Chen et al. 2010, van der Linde, Konings et al. 2011, van der Bom, Bouma et al. 2012). About 40% of NORPAP patients required intervention from birth although it is difficult to compare the number of expected interventions with world or

national figures as each centre has a different population and spectrum of congenital heart disease and access to health care resources.

Syndromes associated with an underlying identified gene are frequently seen with congenital heart defects. Only 10% of NORPAP has been genotyped and this is consistent with the relatively low incidence of the genetic testing at the time of setting up the database although this has changed now as all patients are tested in the paediatric service. Consistent with previous reports, the commonest syndromes with congenital heart disease are those such as Downs, Turners, Noonans, etc. (See Table 1b in Chapter 3). It has been an exciting decade for genomic medicine, where specific genes have been identified for aortopathy, channelopathy and cardiomyopathy. Similarly, genomics has progressed in congenital heart disease. In contemporary practice, all patients with congenital heart disease are tested as neonates for currently recognised genetic abnormalities. There remain a large cohort of patients who transition to the adult service who were either not tested as neonates due to the unavailability of the test (Rafiq and Freeman 2015), or because the phenotype-genotype or association of conditions had not been recognised at that time. We have advocated the close collaboration of the congenital cardiologist and geneticist in the adult congenital clinic to guide not only inheritance risk, but cascade screening and perhaps predict future risks(Rafiq and Freeman 2015). At NNUH for example, the genetics clinic is held within the cardiology department and cases discussed at the monthly genetics MDT.

The commonest comorbidity in NORPAP apart from hypertension was tachyarrhythmia's (13%). A recent study analysed in a large USA centre, 52,725,227 admissions of which 109,168 (0.02%) had congenital heart disease(Loomba, Buelow et al. 2016). Out of the 0.02% congenital patients 25% of the patients had arrhythmias at some stage of their life requiring admissions. In NORPAP, the most frequent presenting arrhythmias was atrial fibrillation which is in keeping with that documented in literature(Teuwen, Ramdjan et al. 2015), but not consistent with data presented by Loomba et al(Loomba, Buelow et al. 2016). In NORPAP, the main underlying structural abnormalities were atrial septal defects while in the Loomba cohort tricuspid atresia was the most common followed by Ebstein anomaly. Although NORPAP shows the incidence of arrhythmias in ASD is highest by condition, the prevalence of arrhythmias is similar to Loomba's with the highest incidence in Ebstein, ccTGA, complex congenital heart conditions such as tricuspid atresia as shown in Figure 4.1. 5% of the patients had bradyarrhythmias requiring pacing(Triedman 2002).

Figure 4.1 ARRHYTHMIA BURDEN.



Only 6% of the NORPAP patients have pulmonary arterial hypertension (PAH). 10% of adult congenital patients either transition with established PAH but others continue to be identified with new PAH during follow up. (Kaemmerer, Gorenflo et al. 2013, Roth and Aboulhosn 2016). Targeted medical therapy has improved functional capacity and within the Eisenmenger population may improve survival but does not provide cure(Diller and Gatzoulis 2007, Diller, Alonso-Gonzalez et al. 2013). Those patients, who fail medical therapy, may be considered for heart and lung transplantation(Stoica, McNeil et al. 2001, Waddell, Bennett et al. 2002) though the UK numbers per year are low and survival is substantially below that of heart transplant alone. About 7% of NORPAP patients died since the service was established. It appears that main causes of death are heart failure, arrhythmias, endocarditis, pulmonary arterial hypertension and ischaemic heart disease. The mortality figures highlight those comorbidities most likely to require admission for management within the various designated specialist ACHD services and allow estimates of inpatient beds to be predicted per 1000 ACHD patients under follow up.

Six per cent of patients died at the time of cardiac surgery (Single ventricle, Ventricular septal defect with aortic regurgitation, Ebstein anomaly with coarctation) while 2% died at the time of non-cardiac surgery. Other causes included renal failure, cystic fibrosis, and pneumonia. 4% of the patients died of cancer, this in keeping with the data published by the Brompton group(Diller, Kempny et al. 2015). One patient committed suicide. Psychosocial issues were not well documented in NORPAP but there has been no documentation of suicide in literature while anxiety and mood disorders are common in this population (Kovacs and Utens 2015, Ferguson and Kovacs 2016).

Survival to 18 years of age in the majority of CHD conditions is now expected (Somerville 1997) Thus the number of ACHD patients exceeds that within paediatrics - and will continue to rise. Modelling such growth in numbers is the remit of NHS England to allow planning for the provision (and workforce) of the congenital network services (at Level 1 – Specialist Surgical Centres, Level 2 – Specialist Cardiology Centres and local Level 3 (with interest) hospitals). The requirement within the Standards is for unit related databases (such as NORPAP) to be maintained which will allow better estimates of the numbers currently under surveillance as well as the numbers transitioning from paediatrics. Not surprisingly, mortality remains higher than the general population with the commonest cause of death being heart failure – as found in NORPAP(Verheugt, Uiterwaal et al. 2010, Diller, Kempny et al. 2015, Engelings, Helm et al. 2016). This too is important since such patients have frequent bed days and increasingly require both palliative care and the community heart failure service(Verheugt, Uiterwaal et al. 2010, Zomer, Uiterwaal et al. 2011, Greutmann, Tobler et al. 2015, Engelings, Helm et al. 2016).

4.2 Outcome of NORPAP Coarctation of Aorta Dataset

This study of NORPAP found a 9% prevalence of coarctation of the aorta, a male to female ratio of 2:1. A prevalence of 4-6% is documented in the literature, thus the NORPAP incidence was slightly higher which could be related to the fact that coarctation repairs were carried out in Norwich up to the late 1970's. I have compared our findings with an Australian paper published in 2015, by Choudhary et al.(Choudhary, Canniffe et al. 2015). They included 151 patients with a mean age 35±15 years. Choudhary et al have shown improved survival of 89% at the age of 60 years. Seven deaths were reported in the Sydney cohort. Two deaths were

related to fatal intracranial haemorrhage, one at an age of 24 and second at the age of 67 years while the latter had mild coarctation. The third death was a 30-year-old lady with subclavian flap repair and Turner syndrome experienced an acute dissection. Three sudden cardiac deaths were reported. One was in a 56-year-old man with an EEA repair who refused to be followed up. His autopsy showed non-occlusive coronary artery disease. Second patient, a 61-year-old female with previous coarctation repair of unknown type and mechanical aortic valve died of unknown cause. In her case, an autopsy was not performed, so the cause of her death was undetermined. The third patient was 60-year-old male who underwent tissue valve replacement and had a long postoperative course. One patient died of myocardial infarction at the age of 85 years with other comorbidities such as chronic renal failure and dementia.

In NORPAP CoA subgroup 8% of patients dies during the follow up period of an average of 12 years. NORPAP data shows similar survival rates to other contemporary series (Choudhary, Canniffe et al. 2015/(Lee, Babu-Narayan et al. 2019) in this contemporary group of patients likely due to continuous advancement in technology and techniques(Mullen 2003) to identify and repair defects early, continuous surveillance and specialist being trained to provide a systematic approach to assess, recognize and manage complications(Kobayashi, Ando et al. 2009, Khairy, Ionescu-Ittu et al. 2010, Lee, Babu-Narayan et al. 2019).

Within the NORPAP CoA subgroup, 20% of the patients had concomitant heart defects, dominantly ventricular septal defects, The Sydney group excluded associated cardiac defects and only included patients with isolated coarctation.

Interestingly coarctation with ventricular septal defect within the NORPAP group had an equally good outcome compared with isolated coarctation. Historically coarctation with VSD has been regarded as a less favourable combination(Kobayashi, Ando et al. 2009). The associated congenital defects found with coarctation of the aorta were in keeping with the data published in literature(Becker, Becker et al. 1970). Bicuspid aortic valve is generally found in 20 to 85% of patients with coarctation of the aorta (Maron, Humphries et al. 1973, Simon and Zloto 1974, Cohen, Fuster et al. 1989, Stewart, Ahmed et al. 1993). Significant stenosis and regurgitation develops in two third of the cases, and AVR is required in 10% (Stewart, Ahmed et al. 1993) of the cases; these figures are concordant with that found in the NORPAP coarctation dataset. There has been no incidence of aortic dissection in the setting of coarctation and bicuspid aortic valve although 3% patient required aortic root replacement with aortic valve

replacement. We only found two cases of heart failure in the NORPAP coarctation cohort, one was related to coronary artery disease in an unrepaired coarctation of the aorta while the other case had valvular disease – predominantly aortic regurgitation.

The minimum age at repair was at day one of age while the oldest patient who had intervention on a native coarctation was 46 years old. Usually most coarctations are detected prenatally or in infancy, though there remains a small group of patients diagnosed late following presentation with upper limb hypertension. The most frequent repair in the NORPAP CoA cohort was end to end anastomosis (52%) followed by patch aortoplasty (12%), subclavian repair (11%) and interposition graft (7%). End to end anastomosis was the most common technique for repair of coarctation in other studies(Backer, Mavroudis et al. 1998, Jenkins and Ward 1999, Forbes, Kim et al. 2011, Choudhary, Canniffe et al. 2015, Nakamura and Stefanescu Schmidt 2016). What was interesting was that dacron patch aortoplasty was the second most favoured type of repair for the NORPAP group compared with subclavian flap repair in the publications. As most of the NORPAP CoA group had transitioned from a single paediatric surgical centre, it perhaps reflects the favoured surgical technique in that era – though, as has been seen in the NORPAP group, there is a moderate incidence of late patch aneurysm.

Historically many patients with repaired coarctation of the aorta were discharged from follow up in the belief that the surgery had been 'curative' .It is clear from NORPAP that intervention is frequently required notwithstanding the management of residual hypertension and other medical comorbidities and the 'lost tribe' of Norfolk patients were described in 2003 (de Bono and Freeman 2005). Practice has now changed such that regular life-long follow-up occurs, facilitated by the availability of and expertise with imaging modalities such as MRI, and this too contributed to the improved long-term outcomes. Most of the patients in NORPAP CoA cohort required a second intervention. This pertained to the coarctation site in 23% but followed closely by intervention on the bicuspid aortic valve with aortic valve replacement. In the benchmark paper I chose to compare with the NORPAP experience, 31% of patients had intervention for recoarctation. While the headline figure was a little higher, the finding that this was greater in those who had initial repair at a younger age was similar.

Some studies have reviewed the outcome of surgery in coarctation of aorta showing about 80% remain symptom-free for a median period of 20 years. In our cohort, 27% of the patients required redo surgery, the median time to the second intervention was 16 years, which was

instigated by routine surveillance. Between the second and third intervention the event-free period was a median of 8 years. Similarly the period from third intervention to fourth intervention the event-free period was median of 14 years. As there are no case studies available it is difficult to compare outcome with tertiary centres or data available internationally or nationally, although it has been published in other studies that event free survival has been 20 years (15-17).

Hypertension has been the predominant comorbidity in the NORPAP CoA cohort despite successful repair of coarctation. 24 hour BP monitoring and exercise testing has been a useful tool to screen hypertensive patients(Lee, Kowalski et al. 2012). The prevalence of hypertension has been reported between 19%(5) to 75% post-repair over long-term follow-up (19). Apart from the diagnostic criteria for hypertension and duration of follow-up, age at the time of repair remains a highly relevant factor. Clarkson et al reported a prevalence of only 7% in infants repaired before the age of 1 compared with 33% of patients repaired after the age of 14(19). Nevertheless, other studies have shown that only 30% of the patients remain normotensive at 32 years of follow-up (6). Koller et al reported patients operated between the age of 2 to 9 years of age had similar prevalence of hypertension as the control group and as such there was no difference seen. Similarly, exercise induced hypertension is common amongst the repaired coarctation group (20). Also BP was found to be higher on ambulatory monitoring as compared to the control with reduced diurnal variation (21). The main diagnosis was made on exercise test and repeatedly high reading in clinic setting in the NORPAP CoA subgroup. Although the recommendations are to perform ambulatory BP monitoring our young patients frequently refused and thus exercise BP response was undertaken. Most importantly all patients once they were diagnosed with hypertension were screened for recoarctation using magnetic resonance angiography surveillance for which was otherwise either every 7 years with end-to-end anastomosis and every 2-3 years for dacron patch and subclavian flap repairs.

About half of the CoA patients were hypertensive a higher incidence of hypertension compared with the Sydney dataset of 44% (Choudhary, Canniffe et al. 2015). This may be related to the way hypertension is assessed, but could also be due to the higher numbers of end-to-end anastomosis repairs (51% NORPAP vs. 44% Sydney). Another explanation is that hypertension prevalence estimates found by Clinical Commissioning Groups in the East of England are higher than expected compared with other parts of England. Hypertension was

more common in males (68%) than females (32%), which does not just mirror the two fold numbers of men with coarctation.

Most patients with hypertension were on single antihypertensive therapy about one third of the patient had single therapy, quarter with dual therapy, 10% had triple therapy and 4% quadruple therapy. Men appeared to have higher rates of drug use for hypertension compared to women but the reasons for this are uncertain. The literature has suggested beta-blocker, ACE inhibitor and angiotensin receptor blocker as appropriate antihypertensive(Warnes, Williams et al. 2008, Baumgartner, Bonhoeffer et al. 2010). In those patients with a concomitant bicuspid aortopathy and or aortic regurgitations, the Guidelines continue to advocate ACE inhibitors or beta blockers(Warnes, Williams et al. 2008, Baumgartner, Bonhoeffer et al. 2010). More recently the potential advantages of the TGF beta pathway modulation of aortic dilatation in other connective tissue aortopathies, suggest that angiotensin 2 receptor blockers may be beneficial(Brooke, Habashi et al. 2008, Baumgartner, Bonhoeffer et al. 2010).

Pulse wave velocity, which has been the main focus of my prospective study, is found to be high in hypertensive patients. The CAFÉ study monitored 2703 all comers with hypertension. Amlodipine was considered to be superior in the whole group having a more pronounced effect on reduction of central aortic pressure(Cameron, Meredith et al. 2006). In those patients with coarctation and no concomitant dilated aortopathy or aortic regurgitation, I consider that there would be a greater advantage for the first line use of Ca-channel blockers as opposed to atenolol and ACE inhibitors. Effective reduction of central aortic stiffness in patients with

coarctation may help to reduce the rate of progression of hypertension related complications and subsequent morbidity and mortality. This warrants further longitudinal studies to determine if calcium channel blockers should be considered as first line in coarctation patients with persistent hypertension, in the absence of significant restenosis.

Premature coronary artery disease was first described associated with coarctation of the aorta in 1912 (22) and in the subsequent years (1928-1947) was the cause of death in 3 of a 104 patients with coarctation of the aorta (23). Whilst Cohen's group reported 37% of coarctation patients had coronary artery disease, of whom 3 had coronary artery bypass grafting; the figures also included 13% sudden cardiac death and 9% heart failure (5). It has been postulated that vascular reactivity is responsible for the premature development of coronary artery disease (24) but of course, hypertension and hypercholesterolemia may accelerate this. A higher incidence

of coronary artery disease in coarctation patients has been documented but the coarctation itself did not appear to be the risk factor after correction for hypertension, hypercholesterolemia and diabetes mellitus (25). Rather than there being associated coronary vascular factors related to the presence of coarctation, it remains likely that it is presence of hypertension, particularly if treatment is delayed which remains the most significant aetiological factor. In the NORPAP CoA cohort the prevalence of coronary artery disease was just 6%. As previously discussed, this group of patients were started on antihypertensive (and screened for hypercholesterolemia, which was treated if raised even at younger age) and may be the reason for a relatively low IHD rates. Indeed, only 2 patients have had isolated percutaneous coronary intervention, though a further 8 have had concomitant coronary artery bypass grafting at the time of aortic valve replacement. The Sydney group did not reflect on the incidence of coronary artery disease, although one death was related to it(Choudhary, Canniffe et al. 2015).

Despite progress in interventional and surgical techniques, the importance of life long surveillance is to identify early recoarctation and progressive aneurysmal dilatation. Recoarctation is a common complication that may clinically suspected if that if there is a blood pressure difference of more than 20mmHg between the upper lower limbs. There are echo and MRI criteria for recoarctation and if there are borderline measurements then a catheter peak-to-peak gradient of 20mmHg or more (awake not under general anaesthetic) will suggest that intervention should occur(Baumgartner, Bonhoeffer et al. 2010). The age at initial repair is considered to be an important factor in the incidence of recoarctation. Koller et al, reviewed 362 cases 10 years post-surgery and found that recoarctation incidence was as high as 10% in patients who had repair done before the age of 2 years as compared with older children where the incidence was only 3.5%(17). However, others have reported higher incidence of recoarctation in older patients (6). One study suggested that the infant's weight plays an important factor in predicting the risk of recoarctation (34). The type of repair has shown be associated with recoarctation for example the subclavian flap approach has a higher rate than those with end to end anastomosis. (6, 19, 35). Presbitero et al reported in her series a risk of 8% in end-to-end anastomosis as compared to other repairs – where the incidence was as high as 25%. Similarly, in another study, there was reported incidence of 17.5% in those patients who were not suitable for end to end anastomosis (19). Initial balloon angioplasty has a higher incidence of recoarctation; a randomised trial has shown an incidence of rate 25% in the balloon angioplasty as compared with 6% in the surgical group (36). Assessment of the time frame for

development of recoarctation is not possible and hence imaging plays a pivotal role in long term follows up.

Aneurysm formation is a common complication, which occurs at the site of repair, or proximal aorta and may lead to aortic rupture. Aneurysm formation is again dependent upon the type of repair and the literature has shown the incidence to be as high as (20%) in patch aortoplasty (37). Knyshov et al published a series of 891 patients in which 48(5.4%) patients were found to have aneurysm formation and 18 patients out of the 48 died due to aortic rupture and endarteritis over a 20-year-old follow up (38). Aneurysm formation is also relatively frequent in patients following balloon angioplasty with an incidence of 5% at a median age of 14 months (39). There is some evidence to suggest that residual abnormal tissue predispose to aneurysm (40, 41). MRI is the most appropriate imaging modality to assess and determine the timing of surgery for aneurysm formation (42). Clearly all patients who have a documented aneurysm should be followed up on a yearly basis to assess the progression of an aneurysm and to decide on the need for intervention. More frequent interval MRI imaging of the coarctation site is appropriate in patch repairs (e.g. every 3 years compared with 7 years in end to end anastomoses) notwithstanding those patients in whom there is a concomitant bicuspid aortopathy. Patients with Turner syndrome and coarctation of the aorta (with or without a bicuspid aortic valve) also require more frequent imaging since aortic dissection occurs at a smaller diameter given the body surface – for which it must be corrected – and there are published Guideline measurements when surgery is recommended(Mortensen, Hjerrild et al. 2011, Erbel, Aboyans et al. 2015, Iung 2015).

There were no aortic dissections in the NORPAP cohort and the incidence of aneurysm formation was low. Only 8 patients (4%) were found to have an aneurysm, of which 5 were repaired (surgically or by covered stent) while 3 remain under surveillance. As compared with the centre against which I have chosen to benchmark the NORPAP dataset (Choudhury et al(Choudhary, Canniffe et al. 2015), a lower incidence of aneurysm formation was found (11% while NORPAP cohort 8%). The operative repairs in the NORPAP occurred in three patients with patch aortoplasty, one end-to-end anastomosis while one patient with interposition graft underwent aneurysm resection. No interposition graft aneurysms were reported in the Sydney cohort (14). Two patients with Dacron patch and end to end anastomosis are under observation in the NORPAP Cohort. Although NORPAP had more patch aortoplasty than subclavian flap repairs, the overall aneurysm rate formation was lower.

4.3 Factors associated with hypertension and mortality

Older age at latest follow-up and older age at corrective surgery were found to be significantly associated with hypertension in the multivariate analysis and with mortality in a univariate analysis, although there was no association between hypertension and mortality. Other factors including gender, aortic valve anatomy and number of procedures did not show any association. There are of course limitations in this analysis due to sample size. These finding are consistent with the data published in literature(Seirafi, Warner et al. 1998, Daniels 2001, Canniffe, Ou et al. 2013). Despite effective repair of coarctation patients are prone to hypertension and require life- long follow for optimal control of BP. It has been postulated that this may be due to altered aortic wall and abnormal vasculature that lead to develop of HTN. The Sydney group reported 44% of their patients(Choudhary, Canniffe et al. 2015) with HTN post repair while a recent paper with a cohort of 834 patients reported an incidence of 60% of HTN(Lee, Babu-Narayan et al. 2019).Like our data Lee et al showed age at latest review and age at intervention was strongly associated with hypertension. A number of other papers have also shown hypertension remains a major co morbidity despite repair and some require reintervention on their recoarctation. These results emphasise the need for all patients with coarctation of the aorta to have regular follow up, for detection and control of hypertension, surveillance for bicuspid aortic valve and associated complications with coarctation repair. In keeping with this, female patients with treated coarctation of the aorta showed be advised about risks associated with pregnancy. Hypertension can a problem during pregnancy, including elevated risk of eclampsia and they require careful monitoring(Regitz-Zagrosek, Roos-Hesselink et al. 2019) The association of advancing age and risk of death is established but less well documented. There is a higher risk of death in patients who have had corrected surgery at a later age. These patients will also have had diagnosis at a later stage when the potential adverse effects of coarctation (increased vascular stiffness, left ventricular strain, hypertension, increased peripheral vascular resistance) may be established leading to higher mortality rates in later life (Jenkins and Ward 1999, Brown, Burkhart et al. 2010, Alkashkari, Albugami et al. 2019)

In our cohort we had 18 deaths which was 7% of the total cohort with death rate 0.12% year over the period of >15 years. We are not clear about the cause of death apart from two patient which had concomitant associated ebstein and had a perioperative death and the other developed pulmonary hypertension, the patient was one of the longest surviving recipient of LV apex –descending aorta conduit. The age at the death 68.66±19.89 while the age at

diagnosis was 26.67±13.9years of age. There was a strong association of death with Age at registration and at first diagnosis. Also there was some correlation seen with pacing and conduction disease. I also used propensity scoring to assess the relation of death with HTN which was not significant (P=0.73) and Older age which was significant (P=0.04). Our overall outcome data suggest that advancement in technologies and therapies are likely to be associated with improvements in outcomes. There was higher incidence of death after the age of 40 with no relation to the anatomy of valve which is similar to that observed in another large cohort of 840 patients (Lee, Babu-Narayan et al. 2019). All patients with repaired or unrepaired coarctation all require regular follow-up to monitor blood pressure, co-morbidities and need for further treatment or intervention (Bhatt and Defaria Yeh 2015, Choudhary, Canniffe et al. 2015).

4.4 Age at Repair.

Surgical repair/intervention was undertaken in 69% of the patients with median age less than 1 while in 31% of the cases the surgical repair /intervention was at a median age greater than 1. Associated cardiac defects were common in Group 1 patients while they were rare in the older cohort although prevalence of bicuspid was equal in both groups (59% vs. 60%).

The type of interventional procedure (surgery or percutaneous) and the rate of repeat intervention rates were similar between the two groups with about 10% in both groups having up to 4 procedures including the index corrective procedures. Our data are consistent with that published the in literature, that patients having surgery at early age remain at great risk of further reintervention (9). The incidence of hypertension was higher in Group 2, despite successful repair. The dataset has also shown the incidence was lower in group 1 as compared to group two but still significantly higher than the normal population. Hypertension after repaired coarctation has been previously reported documented (44), and underlined that despite repair with no significant residual obstruction patients still continue to develop hypertension which may predispose to future complications (44). There was no significant difference in the frequency of either arrhythmias or conduction defects between group 1 and 2. (9% versus 16% and 3% versus 8% respectively). Nor was there any difference in endocarditis. Genetic syndromes were equally prevalent in both groups with no significant difference.

The prevalence of ischaemic heart disease was higher in group 2. This is concordant with the published literature, since late repairs affects aortic haemodynamics (with untreated

hypertension prior to intervention) being the likely factors leading to premature coronary artery disease (43). The incidence of aneurysm formation was much higher in group 2 (1% versus 12%) as dacron patch repair was more frequently used after the age of 1.

My hypothesis that early repair was associated with improved morbidity was not supported as although Group 1 had a generally good clinical outcome, they required a higher number of interventions and they still developed hypertension although the incidence was higher in the older group. While there have been no deaths in Group 1 (repair <1 year), the small numbers involved mean any effects on mortality based on age at intervention cannot be determined from NORPAP.

4.5 Gender

Further subgroup analysis was performed based on gender. 65% of the patients were male while 32% female (Please see table 3.12). Median age at the time of review in both cohorts was 36 years while median age at diagnosis was 9 years. The incidence of associated cardiac defects was slightly higher in men although this was not significant. Previous reports have found isolated subaortic obstruction is usually more common in males (31,32). Coarctation of the aorta is more common in males, which is consistent with NORPAP findings. Bicuspid aortic valve was similar by gender although previous reports have suggested this more common in the males (Tutar, Ekici et al. 2005).

Women are relatively protected through their early and middle years from IHD and the male incidence of IHD appears higher than the age related general population. Genetic syndromes were more common in females than males (8% versus 1%), as expected as patients with Turner syndrome classically present with coarctation of the aorta. Furthermore, cardiac comorbidities including hypertension, arrhythmias were similar in both groups. There was no gender difference in mortality in the NORPAP cohort but there was a significantly higher rate of recoarctation. There appears to be no reliable previous published data on the gender differences in the literature and this could be an interesting project in the future. Since those with early successful repair in the NORPAP cohort were seen to develop hypertension, in contrast with my original hypothesis, I designed a prospective study at Guys and St Thomas's ACHD centre, to investigate the effects of pulse wave velocity and aortic stiffness in patients with coarctation of the aorta. In addition I investigated whether altered aortic compliance was associated with

either systolic or diastolic myocardial dysfunction. The methods results and discussion are provided in Chapters 5-7.

The New Standards formulated by NHS England will commission adult congenital specialist care in non-surgical centres. NNUH has been at the vanguard of that specialist care and review of NORPAP has confirmed that the outcomes may be similar to internationally recognised centres like Sydney. NNUH is the only commissioned Level 2 centre in England that has not been a previous provider of structural intervention and or congenital cardiac surgery. As such, the Norfolk and Norwich experience and results underline that such care is appropriate. The continued expansion of the adult CHD population requires that other hospitals establish Level 2 centres. The new Standards underline that the care, management, expertise and investigations are to be at the same level as that provided by the congenital surgical centre. In this fashion, the surgical interventional centres will provide the complex iceberg of care required for intervention and surgery.

4.6 Limitations

This was a single-handed prospective consultant compiled dataset over a > 20 year period. Details on classification of diagnosis, surgery, interventions, and arrhythmias device therapy were reasonably complete although date of first clinic attendance and some physical examination data were was not collected (e.g. blood pressure and heart rate). From 2003 it was possible to retrospectively collect most of this data from the hospital's electronic data.

The NORPAP dataset was prospectively set up as a primarily clinical registry in a similar manner to that of other well established registries in Adult Congenital Heart Disease (ACHD) for example the Royal Brompton Dataset set up by Prof Jane Somerville a pioneer in ACHD (Somerville J. Grown-up congenital heart disease--medical demands look back, look forward 2000. Thorac Cardiovasc Surg. 2001 Feb;49(1):21-6). In the thesis several limitations had to be managed including missing data, lack of a registration date and identifying key outcomes including death. Given the importance of the growing problem of ACHD it was felt to be important to quality assure the dataset and perform analyses that could have a clinical influence.

Study follow up, treatment and investigations were on the basis of clinical decision making and patient need, not based on a research protocol. Follow up has now been established through

NHS Digital via the Cardiology Information Systems Officer who made the request for vital status for patients in the Coarctation dataset.

Since analysis of the NORPAP dataset is retrospective, the hypotheses proposed are based on what was felt to be relevant in terms of current knowledge about Coarctation of the Aorta and availability of relevant data.

The data collected in the NORPAP database is a register based on referrals to the Adult Congenital Heart Disease Clinics at Norwich and Papworth. In the UK patients with corrected or symptomatic congenital heart disease are increasingly being referred to specialist clinics for management and follow up. There is no clear data on the proportion of patients with Coarctation of the Aorta in the Eastern Region who are not being followed up in a specialist ACHD clinic although a small proportion are likely to be followed at centres in London which has traditionally had more resources to support these clinics. There will also be groups of patients with undetected Coarctation although it is assumed that they will be relatively asymptomatic. Overall however there is strong potential for referral bias and therefore it should be made clear that the results and inferences made in relation to the patients included can only be generalised with some caution to similar populations in other specialised units but not to wider populations with Coarctation

No patients were excluded from the database on clinical grounds but it was difficult to capture loss to follow up in our cohort, which is a major limiting factor. This problem has been highlighted in literature. In a study conducted in 2009 with focus on Tetralogy of Fallot, 38% of patients over the age of 30 years where not followed up by a specialist ACHD centre and 48% late reported deaths in the cohort was of patients which were followed up at a non specialist centres. One major reason at the time the Adult congenital services were not well developed, the patients were not well informed. Also they felt well and need for follow up was not a consideration. Similarly lack of knowledge and insight that treatment for congenital is a palliative procedure and patients require life long follow up by the patients, general physician and general cardiologist (Vis, van der Velde et al. 2011, Wray, Frigiola et al. 2013, Wren and O'Sullivan 2013).

A paper from USA and Canada, highlighted gaps in care for adult congenital heart disease. 12 centres participated in the study and 922 patients were recruited for the study. A gap greater than 3 years was identified in 42 % of the patients and more than a decade in 8% of the patients.

The major reason not attend of loss to follow up feeling well, unaware that require follow up or complete absence from medical care. The study highlighted that follow up disease complexity was predictive of the gap in care with 59% mild 42% moderate and 26% being complex. Being well was highly predictive of gap in care(Gurvitz, Valente et al. 2013). This is a common problem around the globe in this special cohort of patients and it is difficult to address these patients. To avoid this, specialist transitions nurses have been trained. Links between adult congenital specialist and paediatrics have been strengthened and transfer clinics have been developed. Patients are well informed by transition clinics and dissemination of information by their physician and availability of webpages and easy access to these services improves awareness and attendance. Education has also been promoted amongst the GP's and local general cardiologist. Also outreach clinics have been developed to work in conjunction with local cardiologist with interest in congenital heart disease to provide services locally. Despite all these measures, this remains a major limitation of the study.

Comparison of groups and outcome events is likely biased by confounding variables. Patients who are healthier may be more able to turn for appointments and monitoring more regularly, thus biasing any analysis of outcomes according to extent of scheduled follow-up. This is a particular problem in the comparison of outcomes for age <1 and age > 1 year, where only the infants who do well after surgery at a tertiary centre can attend NNUH for follow-up. Multivariable regression analysis can help to address confounders within the cohort but does not exclude bias or misleading associations. The number of deaths was small and a multivariate analysis was not possible although associations were established with age and age at corrective surgery. Direct comparison with a control cohort that is matched at patient level can also be a method to reduce confounding but this was not possible in this study.

4.7 Conclusions and recommendations

The NORPAP coarctation cohort had excellent long-term survival with low incidence of major cardiac events. Reintervention rate was relatively high but appropriate and reflected appropriate interval surveillance follow up. The NORPAP clinical team aimed to follow ESC guidelines. However, there has been a lack of structured protocols for magnetic resonance assessment – including cardiac function. This is now being addressed partly with the appointment of the second PTE ACHD consultant driving through the adoption of tertiary centre protocols as well as enthusiasm to develop the MRI services further. As ever, there

remains a time constraint between best practice and service delivery. Ambulatory BP monitoring could be more widely employed. My MD has reviewed the NORPAP cohort of ACHD patients and it remains of utmost importance to keep the database up to date to allow on-going observational outcomes to be reviewed. It is only in this way that long term outcomes will be established.

5 – Methods For Cardiac Magnetic Resonance Imaging

Cardiac Magnetic Resonance Imaging in Repaired coarctation of the aorta, assessment of Aortic Stiffness and Cardiac Function.

5.1 Brief rationale

Patients with repaired coarctation of the aorta have an excess early mortality attributable to coronary atherosclerosis and cardiac dysfunction (Cokkinos, Leachman et al. 1979, Steele, Fuster et al. 1987, Toro-Salazar, Steinberger et al. 2002). In support of this finding, studies have shown increased atherosclerotic burden in these patients, as measured by carotid intimal-medial thickness (Brili, Tousoulis et al. 2005, Sarkola, Redington et al. 2011). However, it has also been shown that even young patients with repaired coarctation have a reduced myocardial perfusion reserve despite not yet having developed any appreciable plaque burden(Cook, Ferketich et al. 2009). This suggests that the myocardium in these patients is already vulnerable to ischaemic insult. This is in keeping with growing evidence that the risk of sudden death from acute coronary events depends not only on the presence of rupture-prone atherosclerotic plaques but also on other pathophysiological processes that increase the vulnerability of the myocardium to injury(Naghavi, Libby et al. 2003).

One such mechanism is the interplay between the abnormal elastic properties of the central aorta, which is known to be present after coarctation repair, and the myocardial haemodynamics (Gardiner, Celermajer et al. 1994, Xu, Shiota et al. 1997, Brili, Dernellis et al. 1998, Brili, Tousoulis et al. 2005, Senzaki, Iwamoto et al. 2008). Looking critically at myocardial systolic function, it has been shown that these patients have left ventricular long-axis dysfunction, which is, in turn, related to the increased central aortic stiffness(Vogt, Kuhn et al. 2005). Indeed, increased aortic stiffness signifies adverse myocardial haemodynamic conditions including an increase in systolic blood pressure and

pulse pressure with increased systolic load and decreased myocardial perfusion pressure (Mottram, Haluska et al. 2005, Fernandes, Polak et al. 2008, Najjar, Scuteri et al. 2008). Furthermore, aortic stiffness has been shown to be highly predictive for cardiovascular events (Laurent, Boutouyrie et al. 2001, Boutouyrie, Tropeano et al. 2002, Cruickshank, Riste et al. 2002, Blacher, Safar et al. 2003).

Another complementary mechanism is impaired endothelial function and increased peripheral vascular resistance in these patients and arterial health in the upper body is demonstrably impaired.(Brili, Tousoulis et al. 2005) Flow mediated arterial dilatation is significantly impaired in the pre-coarctation vascular bed of healthy young adults despite successful repair of coarctation in childhood.(Gardiner, Celermajer et al. 1994) This includes myocardial resistance vessels and there can be further adverse myocardial conditions from this mechanism.(Cook, Ferketich et al. 2009) These mechanisms will likely first result in impaired myocardial relaxation and diastolic function.(Lip, Felmeden et al. 2000, Fernandes, Polak et al. 2008, Biernacka and Frangogiannis 2011, Roos, Djaberi et al. 2011) Cardiac Magnetic Resonance (CMR) can give a detailed phenotype of the vascular and cardiac physiology in these patients. The purpose of this study was to measure vascular resistance, arterial stiffness and diastolic myocardial performance after successful relief of aortic coarctation. Further, the purpose was to see how vascular resistance and arterial stiffness may affect myocardial performance.

5.2 Methods

5.2.1 Main aims of CMR analysis of coarctation of the aorta

To explore relationships between pulse wave velocity, arterial stiffness, myocardial structure and function in patients with repaired coarctation.

A. Descriptive statistics on pulse wave velocity, aortic stiffness, systemic vascular resistance and ventricular function

B. Explore the interactions of these variables and the influence of key clinical variables like age, gender, hypertension, age at intervention in univariate and if appropriate multivariate statistical models

5.2.2 Hypotheses to be tested

A. There are correlations between aortic stiffness, systemic vascular resistance, gender and age

B. Increased aortic stiffness and systemic vascular resistance can adversely influence ventricular stiffness and function

5.2.3.Study design

- Prospective observational study
- Carried out at Guys and St Thomas' hospital.

5.2.4 Main outcome variables

- Puse wave velocity across the coarctation site by Cardiac MRI.
- Aortic distensibility, which is measure of aortic stiffness.
- Measures of myocardial structure such as LA volume and Left ventricular hypertrophy
- Measures of cardiac systolic and diastolic function

This was a prospective, observational cross-sectional study to explore interactions of pulse wave velocity, aortic stiffness and cardiac function in patients after corrected coarctation of the aorta. The research protocol was carried out after clinical Cardiac MRI scan sequences had been completed and all patients provided written informed consent (or parental/ legal guardian consent if required) prior to any research scans. As this was primarily an exploratory study based on availability of consecutive eligible patients undergoing clinical assessments, a formal sample size estimation was not carried out.

5.3 Eligibility

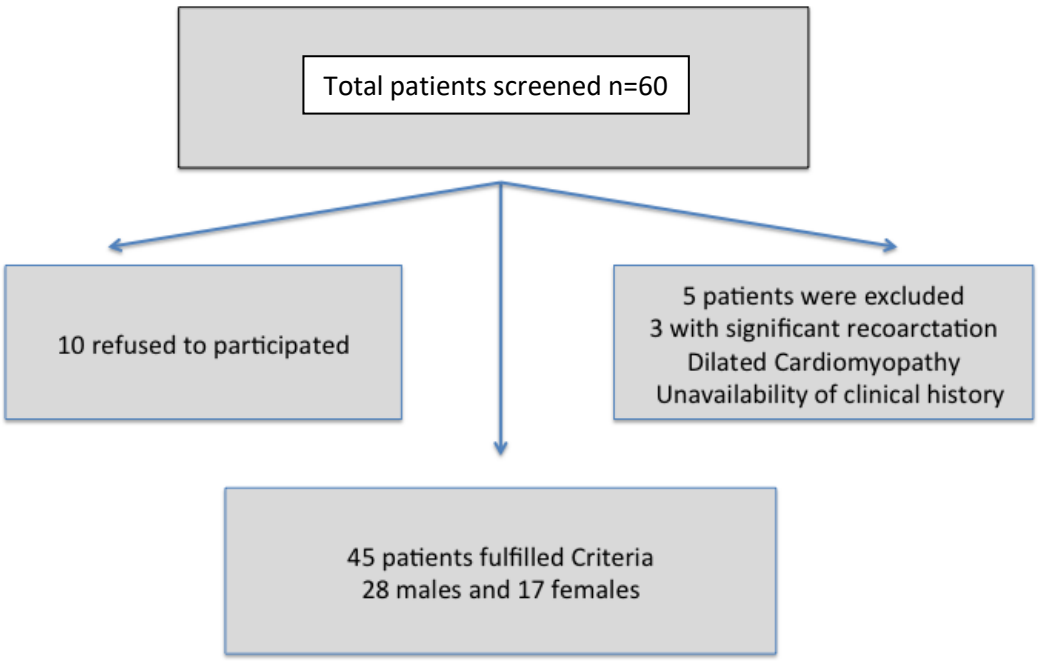
All patients with repaired coarctation of the aorta with normal cardiac function on echocardiography seen in the Adult Congenital Heart Disease Unit at Guys and St Thomas' were eligible to participate in the study. All patients were recruited between Jan 2013 to 31 Dec 2015. Patients were informed about the study in the outpatient clinic and consented prior to their CMR scan. The most important aspect of recruitment was ensuring that there were no patients included in the study with significant re-coarctation. Echocardiography used continuous wave Doppler to estimate the peak velocity across the repaired coarctation site with an assessment of diastolic tail as well. Any patient with a peak velocity of >3m/s was excluded from the study. Also, Cardiac MRI was also used at the time to assess the degree of re-coarctation and through plane flow pre and post coarctation as well as in plane flows were used for assessment as well as a visual assessment on 3D imaging and candy cane view of the aorta. There were strengths and limitations to this method, which are discussed in 5.5.3. Cardiac MRI, as well as Echocardiography, complemented each other to exclude significant re-coarctation. A flow diagram of patient recruitment has been added below.

Exclusion criteria:

i. Any significant residual coarctation - defined as maximum velocity >3 m/s across coarctation site as assessed by phase-contrast CMR and echocardiography or a Doppler ultrasound or CMR phase contrast profile showing a diastolic-tail trace.
ii. Any referral instigated for re-intervention to the aortic arch within a year after imaging.
iii. Any overt reduction in myocardial ejection fraction.
iv. Known coronary artery disease.
v. Other significant associated congenital or valvular heart defect except for competent and non-stenotic bicuspid aortic valve (e.g. mitral valve disease or repaired transposition of the great arteries).
vi. Standard exclusion for magnetic resonance imaging studies metal implants, claustrophobia, inability to fit into the magnet

Figure 5.1 Flow diagram of enrolment

There are approximately 600 adult congenital heart disease MRI scans each year at Guys and St Thomas' Hospitals or a total of 1800 scan over the recruitment period.



5.4 Study permissions and ethical approvals

Patients could only participate if they provided written informed consent for an additional 15 minutes of research protocol MRI imaging, in addition to their routine clinical MR examination based on departmental Research Ethics Committee approval (Study No: 09-H0802-78) included in Appendix B.

5.5 Clinical Assessment and Data Collection

Clinical data for each patient was retrieved from referral forms, and electronic patient database (EPR). Age at first repair, type of repair, associated surgery, total number of in interventions, different types of intervention such surgery or percutaneous balloon angioplasty and stents. Clinical outcomes were included in the dataset such as current clinical status, hypertension, ischaemic heart disease, cardiac arrhythmias, conduction disease, heart failure and development of recoarctation. The date of the last Cardiac MRI in correlation to the clinic appointment was the last date of assessment of the patient. Echocardiogram results were also taken by using TOMCAT (Database for all cardiac investigations storage).

5.6 Cardiac magnetic resonance (CMR)

Cardiac magnetic resonance (CMR) scans were performed on 1.5 Tesla Unit (Acheiva. Phillips Health Care Best Netherlands) at Guys and St Thomas's Hospital. Protocols used are described below.

5.6.1 Routine clinical LV mass and volumetric analysis (Bellenger, Davies et al. 2000, Schulz-Menger, Bluemke et al. 2013).

CMR measures of ventricular volumes and mass by using acquisition of 3 dimensional short axis cine continuous scan images with full coverage of the both ventricles. Left ventricle and right ventricle volume was assessed by planimetry and summed for the whole ventricle. Commercially available software (Phillips view forum) corrected for valve plane movement in the cardiac cycle and measurements the Left ventricular mass from the trabeculation and papillary muscles. The consistency of the ventricular volumes allows normalization according to the body surface area, age and gender (Maceira, Prasad et al. 2006, Maceira, Prasad et al. 2006). Diastolic dysfunction can also be assessed using CMR (Rathi, Doyle et al. 2008).

In this study we used fast breath hold technique to assess the ventricular volumes and LV mass, which is widely used and is reproducible. This method is commonly successfully in almost all

CMR labs due to quality of images and short acquisition time(Grothues, Smith et al. 2002, Schulz-Menger, Bluemke et al. 2013). Ventricular volumes were measured from three-dimensional stacks of short axis cine (As shown in figure below). The cardiac short axis was determined from three scout images. The initial transverse scout was used to align the vertical long axis connecting left ventricular apex to the centre of the Mitral valve, while the third horizontal long axis scout was aligned through the apex and the mitral valve on the vertical long axis image. A diastolic image at end expiration on the horizontal long axis image provided the reference image on which the short axis slices were positioned . At least 10 -12 slices were required to cover the whole ventricles TE3.8ms, TR was equal to RR interval, slice thickness 6-8mm, FOV 35x35cm, temporal 45-80ms resolution, flip angle of 35 degrees. Philips view forum was used to calculate the volumes by cine planimetry and summing the ventricular volumes. Left ventricular mass was calculated using the volumetric approach, with delineated endocardial and epicardial contours with inclusion of papillary muscles. LV mass was calculated by taking into account the slice thickness and interslice distance.

5.6.2 LA Volume and Area Calculation

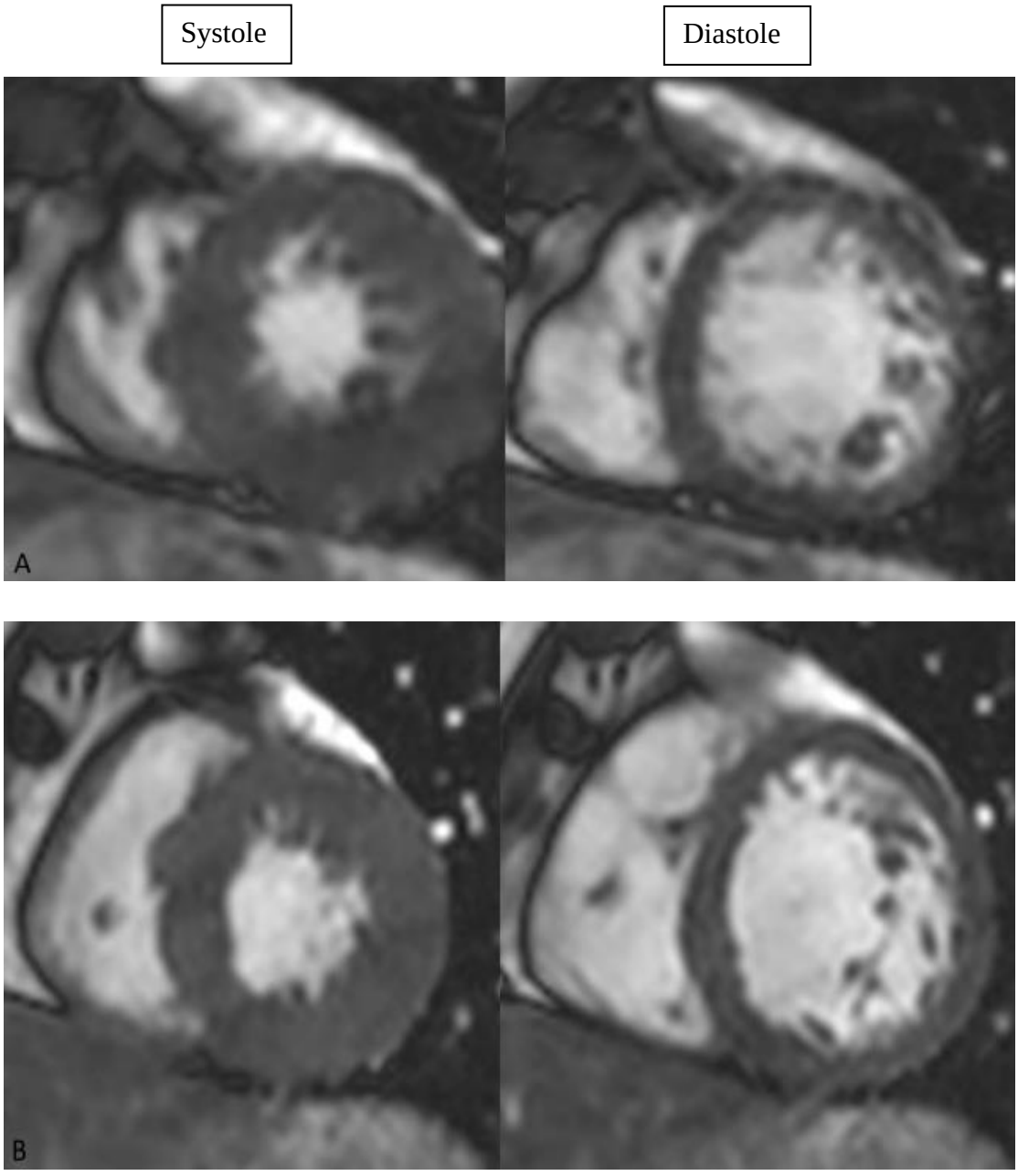
In our study we used the 2 chamber (CH) and 4CH cine images to assess the LA volumes as well as LA area. The image below shows 2CH and 4CH images with traced areas and calculated length in end-systole when the LA is the largest as shown in Figure 5.4: 2CH cine showing Area and length.

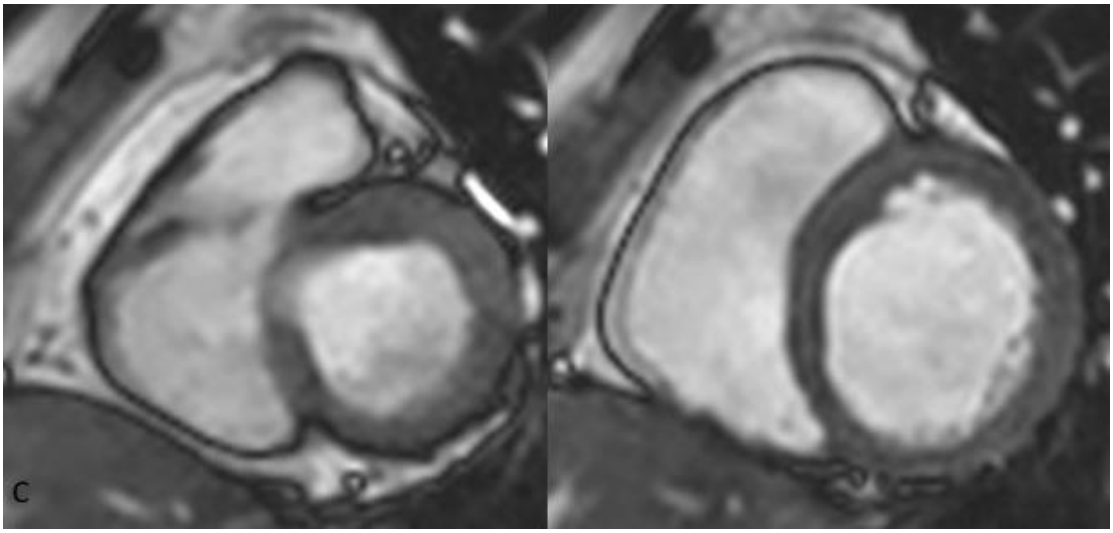
Another possible method would have been a transverse atrial stack for LA volumes but in keeping with time constraint we used 2CH and 4CH images were used for LA volumes calculation. We were consistent in our acquisition and measurement (Posina, Passick et al. 2011). Image quality was optimised, arrhythmia rejection was on to avoid image artefact and the volumes were planned carefully to avoid under or over-estimation.

Ventricular volumes were measured from three-dimensional stacks of short axis cine (As shown in figure below). Philips view forum was used to calculate the volumes by cine planimetry and summing the ventricular volumes. Left ventricular mass was calculated using the volumetric approach, with delineated endocardial and epicardial contours with inclusion of papillary muscles. LV mass was calculated by taking into account the slice thickness and interslice distance.

Figure 5.2 SHORT AXIS CINE IMAGES SHOWING 3 DIMENSION CONTINUOUS SEQUENCES.

Total 30 phases standardised for Ventricular volume and function assessment. Figure A shows the images at the apex of the heart in systole and diastole while B and C and mid level and base of the heart.





Other Global functional parameters were obtained from this sequence:

1. EDV - ESV = SV
2. SV/EDV = EF (%)
3. SV x HR = CO (ml/min)
4. $EDV_{Indexed}$ =EDV/BSA (ml/m^2)
5. $ESV_{Indexed}$ =ESV/BSA (ml/m^2
6. CO/BSA = CI (l/min/m^2)

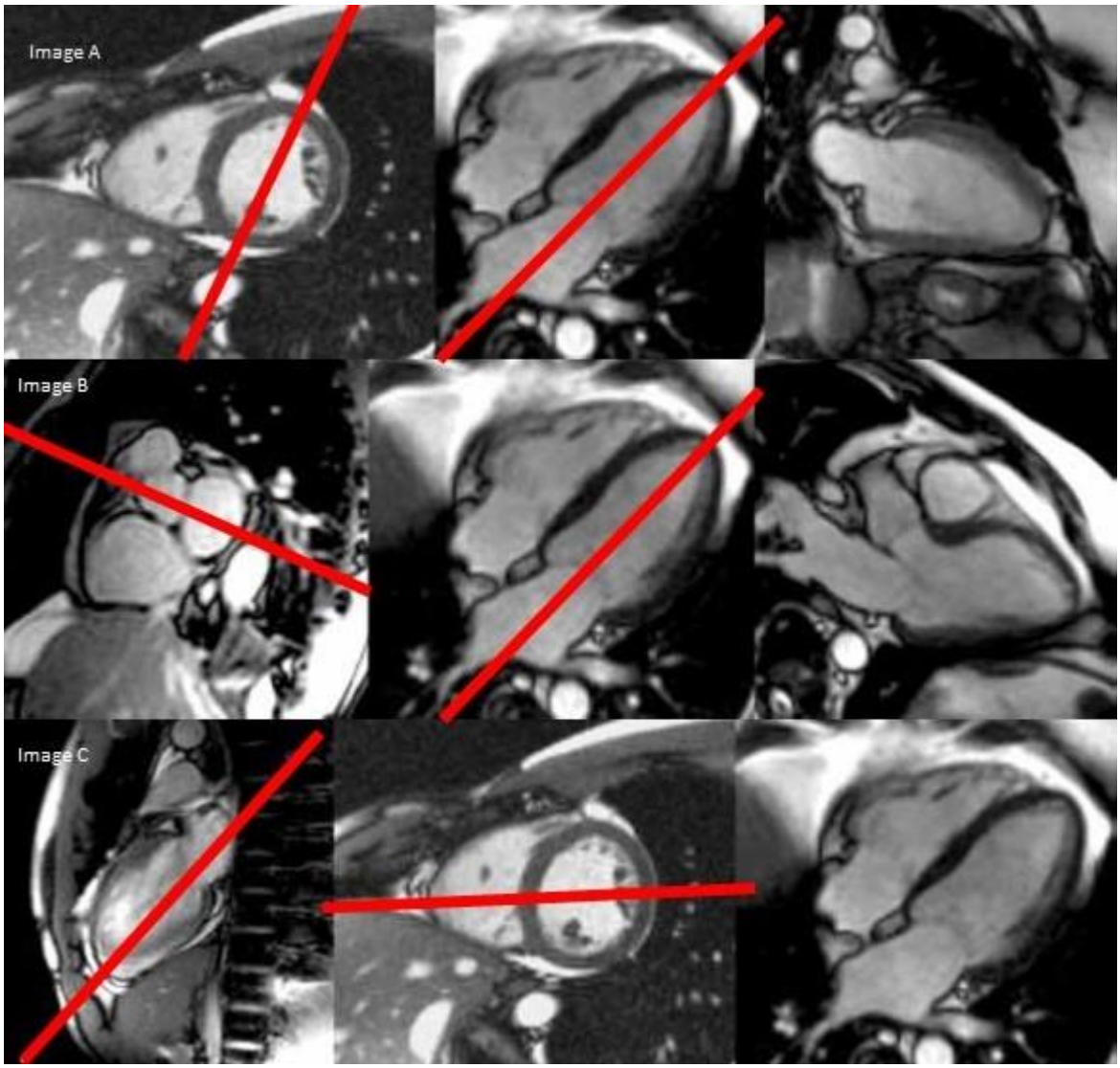
*EDV= end- diastolic volume, ESV = end-systolic volumes, SV = stroke volumes, EF = ejection fraction, HR = heart rate, CO = cardiac output, BSA = body surface area, CI = cardiac index. BSA calculated by 0.20247 x height (m)0.725 x mass (kg)0.425. where height is in meters and mass is in kg.

5.6.3 Cine images

Two chamber (CH), 4CH and 3CH, LVOT 1 and LVOT 2 cine images are taken as part of the clinical scan. There are obtained from the basal SA slice as shown in the figure 5.3.

Figure 5.3 IMAGES THAT CAN BE ALIGNED FROM THE BASAL SA SLICE

Image A. The left ventricular two chamber cine view- the plane bisects the LV through its anterior and inferior wall parallel to the interventricular septum in short axis view, plane through the mitral valve and apex on the four-chamber view.
Image B. The LV inflow (Mitral valve)/outflow (aortic valve) view is acquired by a plane passing across midpoint aorta and mitral valves on the most basal Short axis slice and bisect the LV through the mitral valve and apex on an 4chamber view
Image C. The left ventricular four chamber view is obtained by prescribing an image plane that is perpendicular to the interventricular septum on short axis view and a plane that's bisects through the mitral valve and the two-chamber view. (As per guidelines from SCMR and EUROCMR)



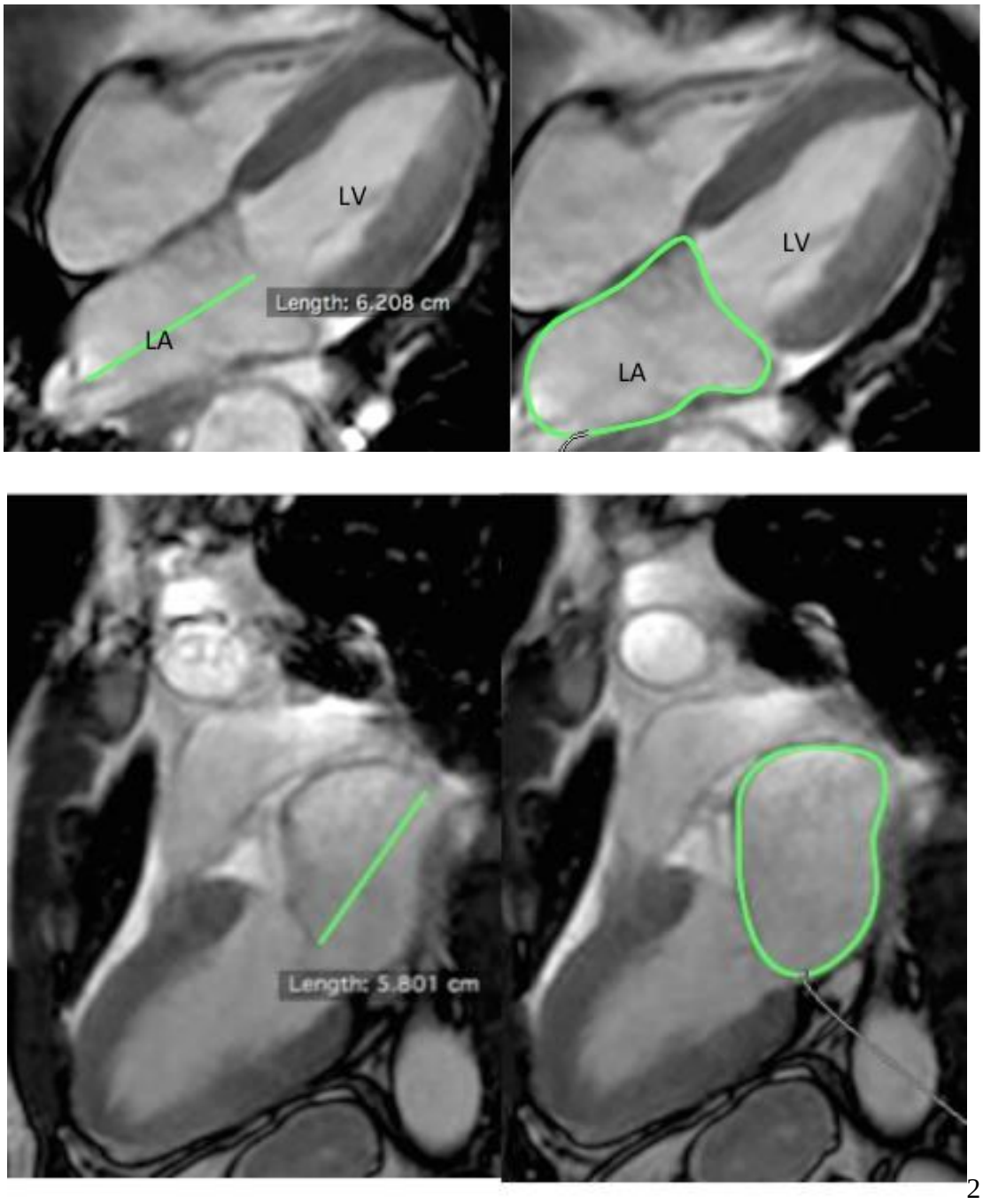
Two Chamber (CH), 4CH and 3CH images are used to assess cardiac function as well as valves. In our study we used the 2CH and 4CH cine images to assess the LA volumes as well as LA

area. The image below shows 2CH and 4CH images with traced areas and calculated length in end-systole when the LA is the largest. We used Biplane –area-length used in echocardiography to calculate LA volume. Images with contoured LA area and length are shown below.

Figure 5.4 Area and length assessment

Upper panel = 4 chamber end-systole showing area and length

Lower panel = 2 chamber end-systole showing area and length



2

*2CH = Two chamber, *4CH= Four chamber, *3CH= Three Chamber, *LVOT 1= Left ventricular outflow tract one, * LVOT 2= Left ventricular outflow tract two= LVOT 2, * LA = Left atrium. *AO = Aorta, *LV = Left ventricle, *RA= Right atrium, *RV= Right ventricle.

The following formula is used to calculate (A= area; L= length)

Left atrial Volume = $8/3\pi * A_1 * A_2 / L = (0.85)* A_1 * A_2 / L$

Left atrial volume index = Left atrial volume/body surface area

Table 5.1 NORMAL RANGE OF LEFT ATRIAL VOLUME (LAVI) INDEX IN FEMALE AND MALE IS DESCRIBED BELOW(Lang, Bierig et al. 2005, Maceira, Cosín-Sales et al. 2010)

	LAVI (ml/m2)
Reference range	16-28
Mildly abnormal	29-33
Moderately abnormal	34-39
Severely abnormal	> 40

Routine clinical through-plane velocity encoded cine and derivation of pulse-wave velocity and ascending aortic distensibility(Firmin, Nayler et al. 1987, Mohiaddin, Yang et al. 1994, Mohiaddin and Pennell 1998, Lotz, Meier et al. 2002, Gatehouse, Keegan et al. 2005, Hussain, Burch et al. 2012, Schulz-Menger, Bluemke et al. 2013).

Phase contrast CMR relies on the principle that particles moving in the direction of a magnetic field gradient acquire a shift in their rotation phase compared to stationary particles. Moving spins experience a phase shift proportional to their velocity, the gradient intensity and the square of the application time of the gradients within a range of -180 to +180 degree. The phase difference between the moving and the stationary particles can be used to determine the velocity of the moving spins. The expected maximal flow velocity must be defined before starting the measurements. The highest peak velocity is then coded to correspond as a phase shift of +180 and the lowest velocity is coded to correspond to a phase shift of 180 degree. The overall inaccuracy of 2D flow has been estimated at 3-5% for both retrospective and prospective gating. The 2D phase contrast imaging involves the following (Figure 5-5): The vessel of interest is assessed perpendicular to the velocity vector as shown in figure A. Two images are generated simultaneously magnitude image (anatomy figure B) and the phase image (Velocity mapping figure C). The temporal resolution depends upon the number of phases in

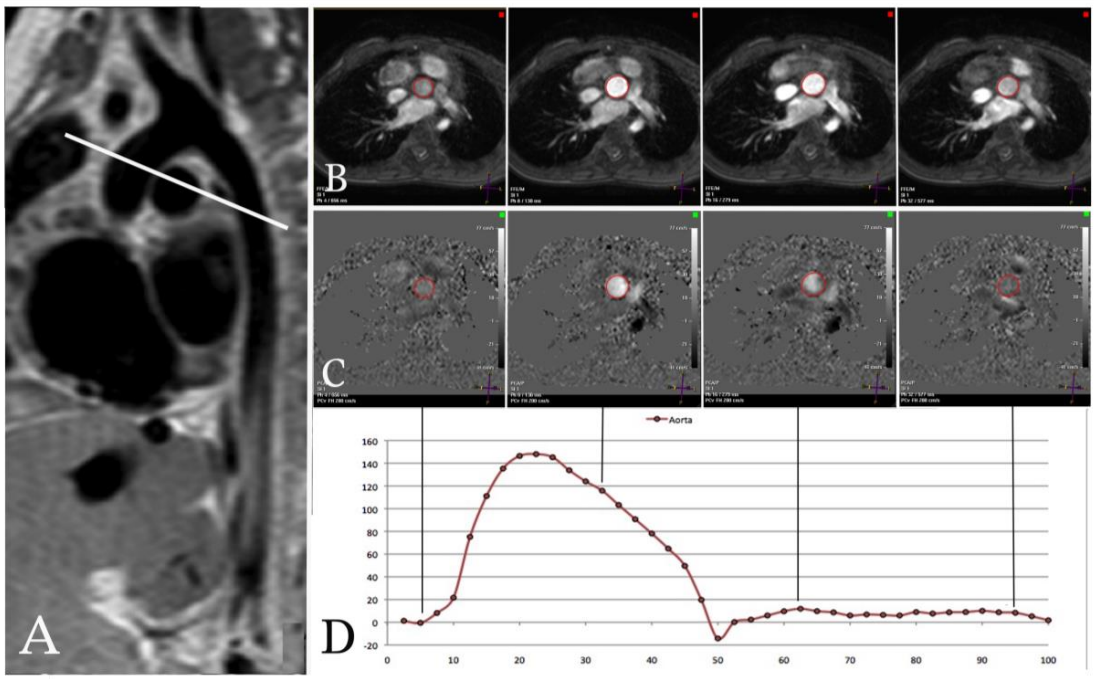
the cardiac cycle. We used 30 phases for our study. The mean flow is calculated as the area of the vessel multiplied by the mean velocity. Plotting flow versus time as shown in figure D generates a flow curve. The flow under the flow curve is integrated to calculate the mean flow volume throughout the one average cardiac cycle. 2D flow is considered the current gold standard for vessel quantification and allows non-invasive quantification of flow velocity, regurgitant flow fraction and cardiovascular shunts. Through Plane Velocity encoded Cine - Flow Maps: the parameter for flows maps and cine images has been shown in table 5.2 below.

TABLE 5.2 PARAMETERS USED TO ACQUIRE FLOW MAPS AND CINE IMAGES

	PC MR	2D Cine	3D SSFP	CE MRA
TE (ms)	2.7±0.2	1.8±0.3	1.5±0.2	1.1±0.1
TR (ms)	4.5±0.4	3.7±0.6	3.6±0.2	3.8±0.1
Acquisition	Oblique sagittal	Oblique sagittal	Coronal 3D volumetric acquisition	Coronal 3D volumetric acquisition
Acquired Resolution (mm)	2.2±0.1	1.4±0.4	0.8±0.2	1.2±0.01
Slice thickness	6-8	6 -8	1.6±0.7	1.8
Temporal Resolution	8.4±5.5	24.5±4.7		
FA	15-20	45-60	70	30
Sense Factor	1	1	1.2±0.3	1.5
TE- echo time TR - Repetition time FA - flip angle				

FIGURE 5.5 2D FLOW ACQUISITION FOR THE ASCENDING AORTA FLOW.

A Plane selection perpendicular to the velocity direction in the ascending aorta B. Magnitude images along a cardiac cycle C. Phase images D flow curve average over one cardiac cycle. For our study velocity was assessed in the ascending aorta, pre-coarctation (distal arch prior to stent or surgical anastomosis) and in the descending aorta at the level of diaphragm. These areas for flows were required to assess the aortic stiffness across the aorta.



Source Israel Valverde Images

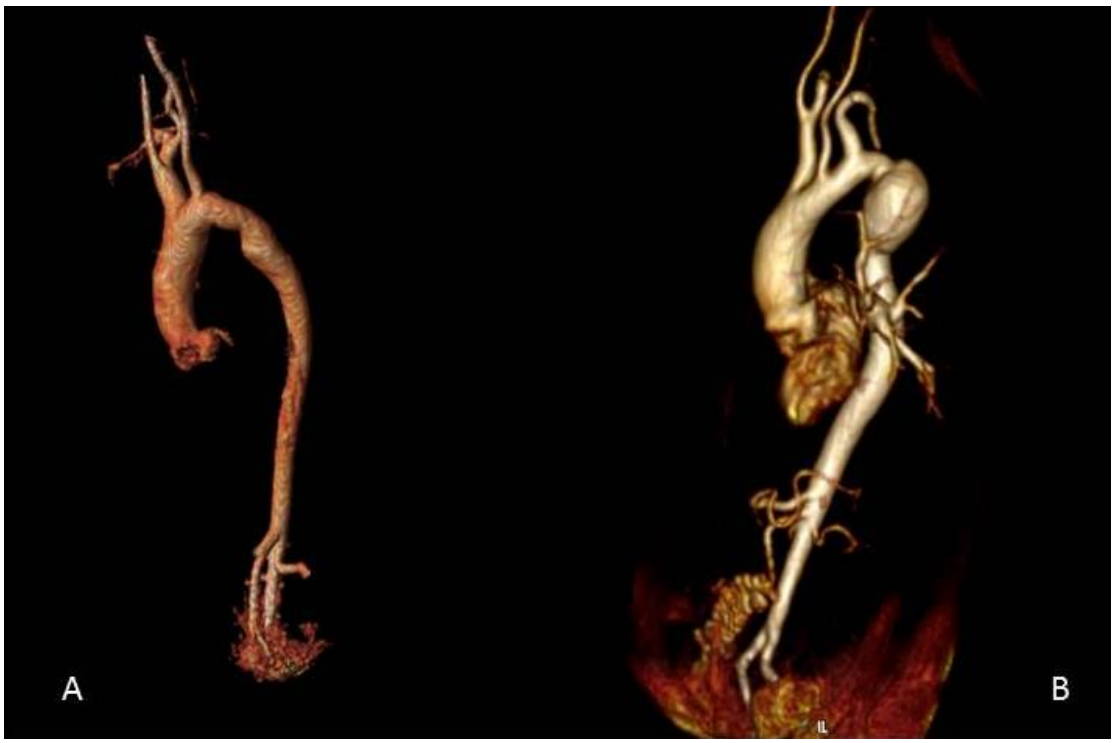
Through plane flow at the level of ascending aorta, descending aorta and diaphragm were measured. Also an inplane flow was used at the site of coarctation to rule out significant coarctation.

5.6.4 *Routine clinical aortic geometry using contrast-enhanced angiogram.*

Cine images with optimization of location and pathology can show the pathology directly such as stenosis or they may be a drop out showing lack of communication. Three-dimensional angiography with late gadolinium enhancement shows the pathology in high-resolution images, which also shows flow in collaterals. Velocity mapping can be planned on these images. CMR angiography shows the size, shape and extent of the aorta. A combination of cine images and spin echo are excellent at showing intraluminal and extra luminal thrombus.

Spin echo can also be used to assess stents in the aorta. We performed CMR angiography as a part of all clinical scans of the aorta to delineate the anatomy as well as the stent placement. The image below shows aneurysm formation in subclavian flap repair in figure A and a large aneurysm in a patch aortoplasty.

Figure 5.6 ANEURYSM FORMATION.
Small aneurysm distal to repair in Image A and. Image B shows a large aneurysm following Dacron repair.



5.6.5 Three-dimensional balanced steady state free precession whole heart imaging.

Three-dimensional acquisition techniques have opened up improved visualization of cardiac anatomy without the requirement for expert planning and it has proven to be a useful tool in complex congenital heart disease cases.

This technique enables both slice-by-slice examination and reconstruction and visualization of the cardiac volumes. The technique has refined over the period of time and large amount of data is acquired over a short period of time(Miquel, Hill et al. 2003, Razavi, Hill et al. 2003). This has been particular helpful in assessment of complex congenital cases as this allows reconstruction of complex anatomy offline. We utilized this technique to assess the dimensions of aorta and also to reconstruct the whole aorta for distance calculation between ascending

aorta to distal arch (repair or stent site), from distal arch to diaphragmatic descending aorta as planned per flow across these sites.

Figure 5.7 THREE - DIMENSIONAL STEADY STATE FREE PRECISIONS IMAGING SEQUENCE.

Cutting through different planes the whole aorta is reconstructed. This image shows previous surgical repair.

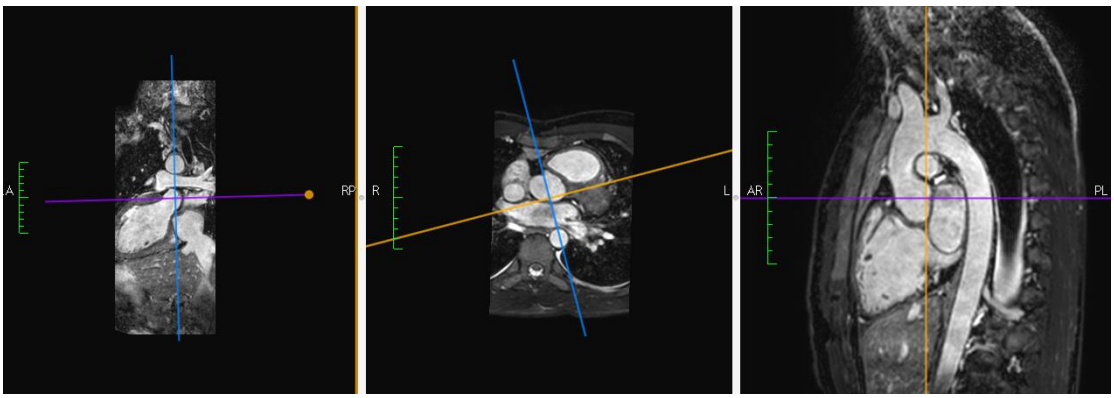
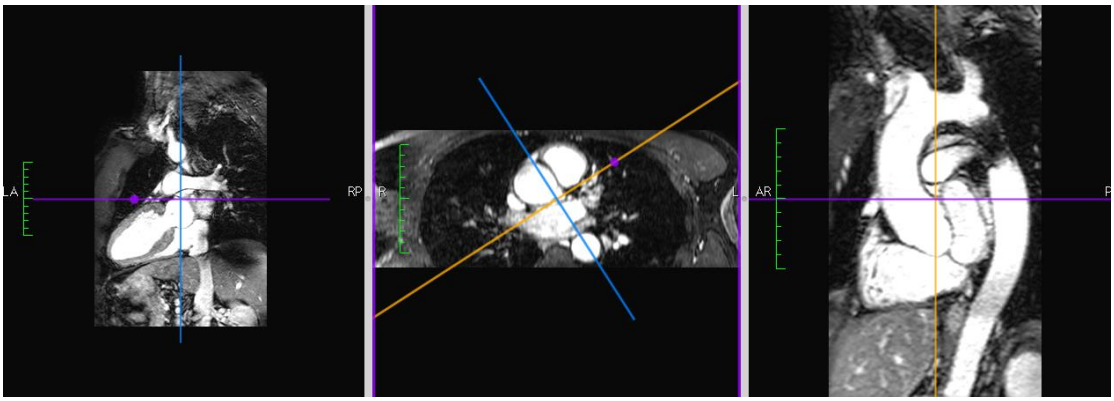


Figure 5.8 THREE - DIMENSIONAL STEADY STATE FREE PRECISIONS IMAGING SEQUENCE.

Cutting through different planes the whole aorta is reconstructed. There is a drop out in the area of stent placement.



Source Both images Israel Valverde and Isma Rafiq

5.7 Calculation of pulse wave velocity

Pulse wave velocity and assessment

Pulse wave velocity initially was measured by tonometry and there was higher risk of underestimation or over estimation depending upon the region studied at the time. We were able to obtain global PWV across the aorta and its measured at three points ascending, descending and diaphragm. The main benefit of MRI based PWV measurement is acquisition of regional PWV data as well as global. They are two main methods used

- Time to upstroke (TTU) – this method time to upstroke of the wave form is considered to be a good method but because of susceptibility but may be subject to noise

- Time to foo (TTF) – this method is very reliable if different regional points are used. The more regional points and wave formed generated will give an accurate measurement of pulse velocity. To measure accurate aortic stiffness and PWV is calculated at different regions in the aorta. Blood pressure was taken at the time of acquiring the flow maps.

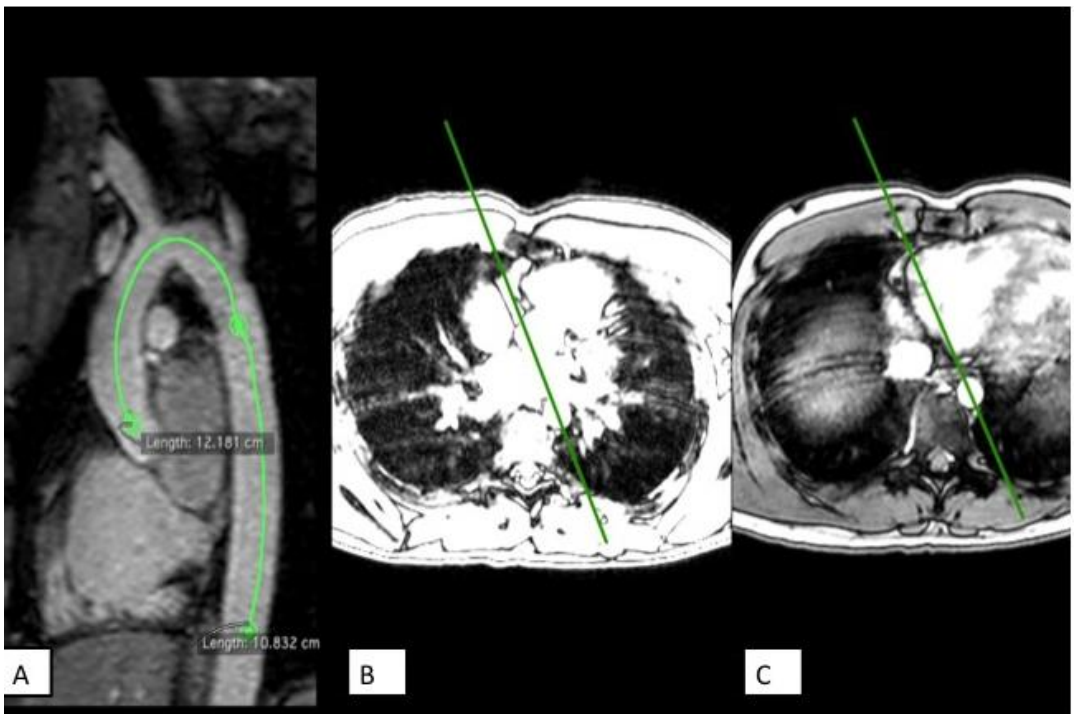
A number of studies have been conducted to correlated the accuracy of MRI based PWV. Roger et all validated multi slice 2D PC MRI based PWV velocity by correlating with applanation tonometer and no significant different was seen (Rogers, Hu et al. 2001, Suever, Oshinski et al. 2012). Similarly it was validated against intravascular pressure measures and a very good agreement was found between two methods (Grotenhuis, Westenberg et al. 2009). We used the Time to foot method by which Pulse wave velocity (PWV) was calculated according to a previously validated method (44). PWV was calculated as □x/□d where □x is the aortic path between two imaging levels while □r was the time delay between the arrival of lower end of the velocity (foot) at these levels (Grotenhuis, Westenberg et al. 2009, Hussain, Burch et al. 2012). Arrival of the foot pulse wave was calculated by using the method intersecting tangents with MATLAB 7.9 (release 7.9b) software (Math works Natick MA)."

PWV was calculated as Δx/Δd where Δx is the aortic path between two imaging levels while Δr was the time delay between the arrival of lower end of the velocity (foot) at these levels. Arrival of the foot pulse wave was calculated by using the method intersecting tangents with MATLAB 7.9 (release 7.9b) software (Math works Natick MA). Figures below show the method of calculation of PWV –velocity. Cine MRI images of the proximal descending aorta were used to give tradition based aortic stiffness in the aorta. The aortic stiffness b index was given as b1/4 1n (SDP/DBP)/(As-Ad)/Ad). 1n is the natural algorithm. SBP is the systolic BP and measured in mmHG and DBP is the diastolic BP and measured in mmHg. As the maximum

is the maximum systolic area measure in mm2 while Ad is the maximum diastolic area(Ou, Celermajer et al. 2008).

Figure 5.9 IMAGE A PLANNING OF ACQUISITION FOR PWV.

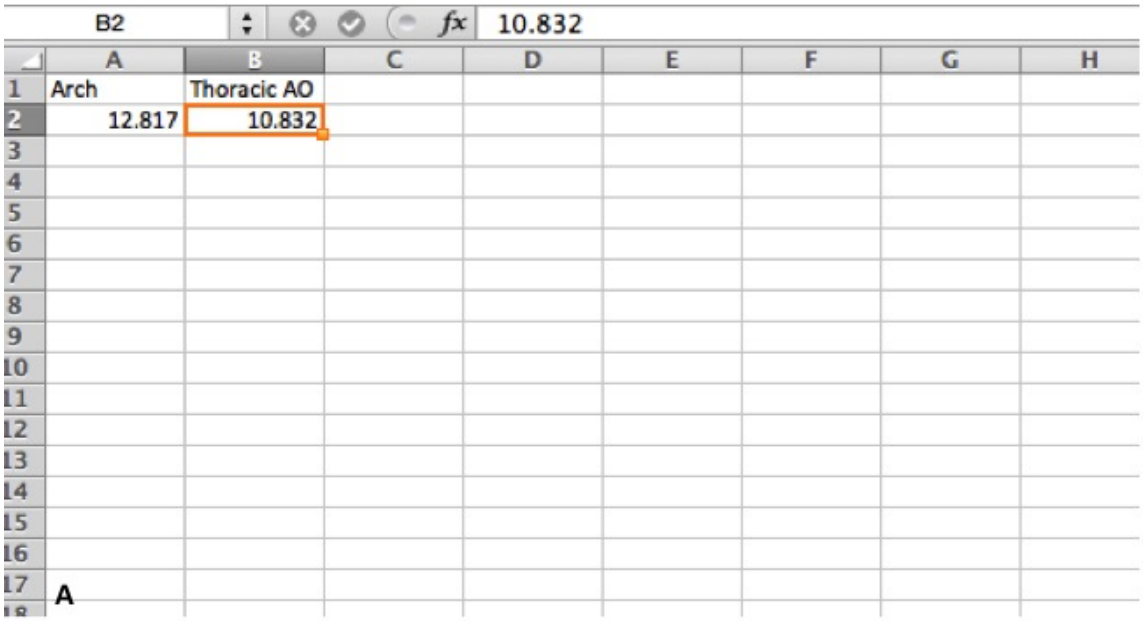
Sagittal view of the aorta showing 3 distance points one from ascending aorta to descending aorta and then diaphragmatic aorta. Image B shows phase contrast flow taken at ascending aorta while C shows the flow in the descending aorta at the diaphragm level.

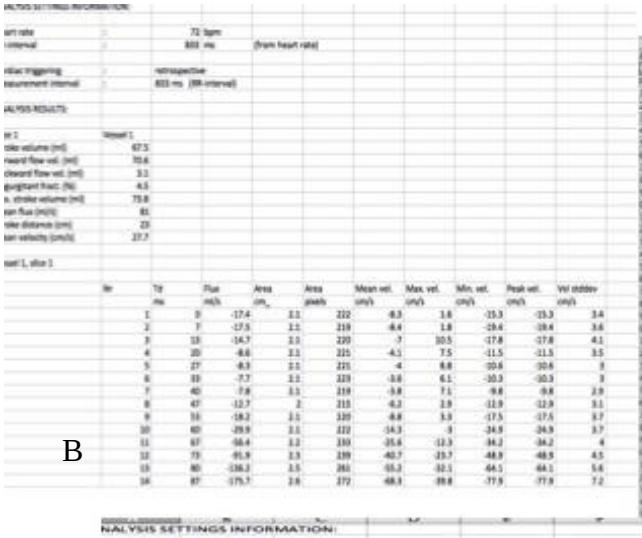


These measurements are key points to generate the pulse wave velocity. 2D phase contrast flow velocity dataset was assessed by using Phillips view forum, and data analysis was stored in the form of excel sheet. Velocity was assessed at three levels, ascending aorta, pre-coarctation and diaphragmatic aorta. To complete the analysis distance was calculated between these point sets and stored in excel sheet. All this data was entered into software (MATLAB 7.9 (release 7.9b) software (Math works Natick MA)). The dataset sheets with generated graphs are shown below.

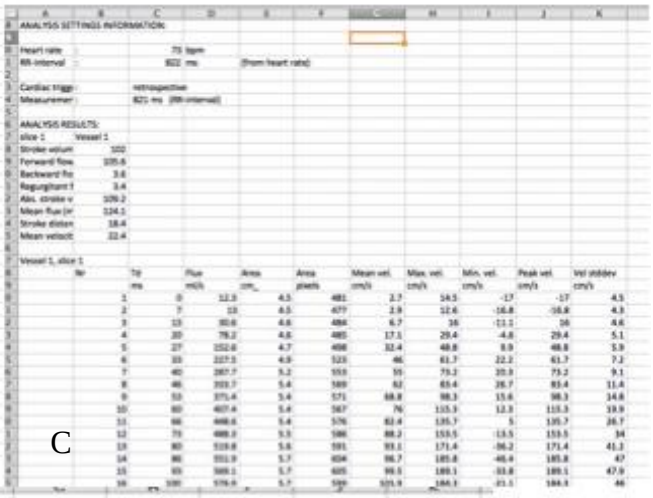
Figure 5.10 DATASET OF FLOW MAPS AND THE GRAPHS CREATED BY USING MATLAB 7.9.

Schematic presentation of 2D phase flow velocity, distance calculated at intersecting points at the level of flow
A is aortic length,
B flow analysis at diaphragm,
C flow analysis, descending aorta precoarctation,
D flow analysis at ascending aorta.
E Curve A shows the curve of the PWV and transit time between ascending aorta and precoarctation site at descending aorta while curve B shows the transit time and PWV velocity between the precoarctation site and the diaphragmatic aorta. The final graph C shows the transit time and PWV velocity across the whole aorta. We used the PWV velocity across the whole aorta for our study.

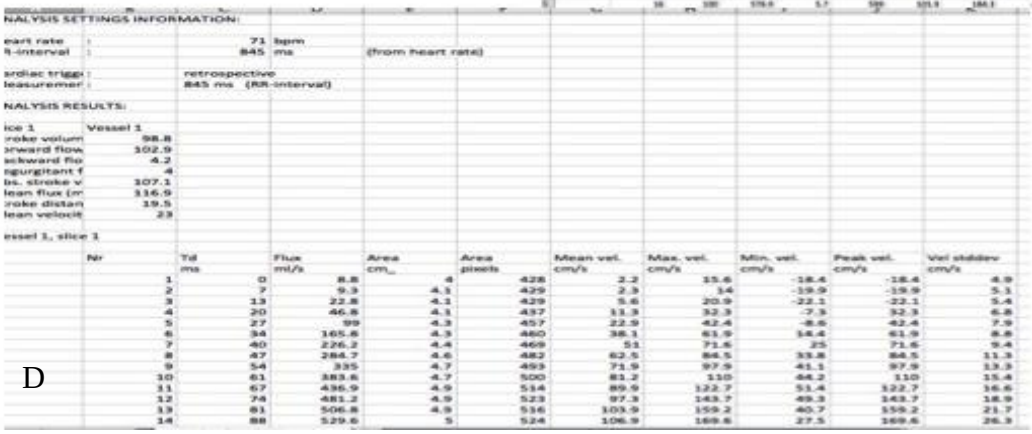




B

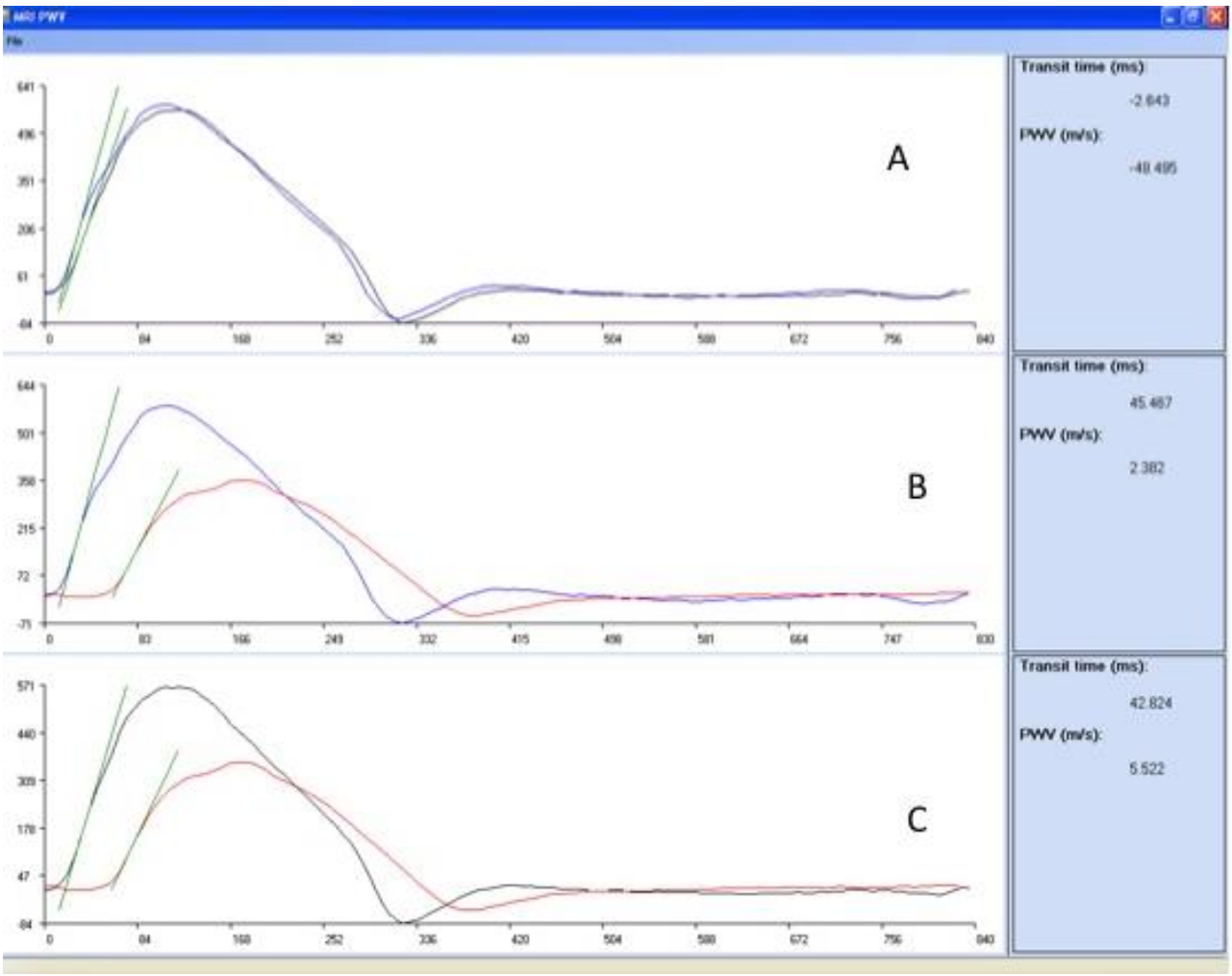


C



D

E


A
Transit time (ms):
-2.643
PWV (m/s):
-49.495
B
Transit time (ms):
45.467
PWV (m/s):
2.382
C
Transit time (ms):
42.824
PWV (m/s):
5.522

5.8 Myocardial motion and derived strain(*Nagel, Stuber et al. 1998*).

Assessment of LV function is the most important part of cardiac imaging. With Cardiac MRI and Echocardiography we are able to assess the systolic and diastolic function of the Left ventricle, which is guide for clinical and long-term outcome. At the same time we are aware that LV ejection fraction is not sensitive in picking subtle changes in the Left ventricle (Sutherland, Stewart et al. 1994, Nagueh, Bachinski et al. 2001). Cardiac strain is defined as measurement for deformation in the left ventricle and is defined as a change in fiber length by the end of systole. On echocardiogram it has been difficult to perform standardized studies as it is image based and a quality of image is variable and may not be good for myocardial analysis (Miyatake, Yamagishi et al. 1995, Amundsen, Helle-Valle et al. 2006). CMR has been developed number of methods to assess myocardial strain, which is described below

5.8.1 Myocardial Tagging

Myocardial tagging is a technique, which has been mainly limited to research. Images are acquired and assessed by two methods.

HARP – Harmonic phase analysis.

SPAMN-Spatial modulation of magnetization.

Tissue tagging is not used clinically as it is too time consuming to carry out. On the contrary **FT_CMR** is a novel method in which quantity's strains and motion by using a standard in state steady free state sequence (SSFP), which forms a part of a normal LV study.

5.8.2 FT_CMR tracking.

FT_CMR can analyse myocardial strain and motion to risk stratify patients and predict long-term prognosis. We assessed cardiac function for subtle changed by using CMR_FT in context with LV systolic and diastolic function. Images were acquired as part of clinical scan.

5.8.3 Method used for Aortic Coarctation subgroup

a. Cine images of Short axis were used, a basal slice below the mitral valvular apparatus was chosen, second slice at the mid papillary level was taken as a mid-slice and the third slice was the apical

b. Tom Tick Software was used to perform feature tracking. Tracking line was drawn on the endocardium and appropriately tracked and adjusted to the cardiac endocardial contours.
c. Data was saved for circumferential strain and strain rate.

Figure 5.11 IMAGE A AND IMAGE B - FT.

Image A shows the FT- tracking from the apical region, Image B shows FT from the mid LV and C from the basal region. Radial strain and circumferential was analysed.

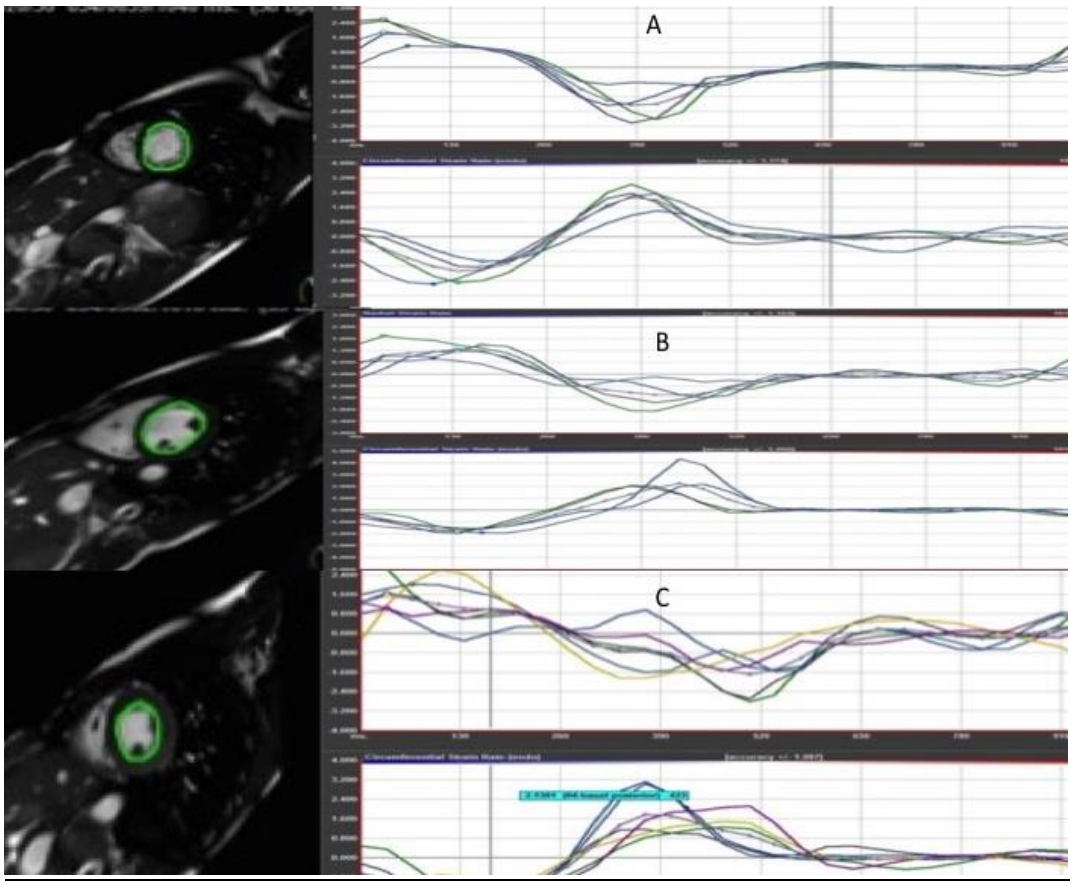


Table 5.3 A AND B BELOW SHOWS THE NORMAL VALUES ARE BASED ON Taylor et al. (2012).

Table A: peak systolic strain and systolic strain rate (SR) in different cardiac segments

	Peak systolic stain (%)	Peak systolic SR (s-1)	Early diastolic SR (s-1)
Longitudinal	-21.3±48	-1.22±036	1.25±0.39
Epicardial	-11.9 to -30.7	-0.51 to -1.93	0.49 to 2.01
Epicardial	-17.3±4.1	-0.99±0.30	0.97±0.33
	-9.3 to -30.7	-0.40 to -1.58	0.32 to 1.62
Mean	-19.1±4.1	-1.11± 0.30	1.11±0.33
	- 11.1 to27.1	-0.52 to -1.70	0.46 to 1.76
Circumferential	-26.2+3.8	-1.56+0.29	1.43±0.35
Epicardial	-18.7 to -33.5	-0.99 to 2.13	0.74 to2.12
Epicardial	-10.8+2.5	-0.61±0.13	0.53±0.18
	- 5.9 to -15.7	-0.36 to -0.86	0.18 to 0.88
Mean	-18.4±2.9	-1.09± 0.19	0.99± 0.24
	-12.7 to -24.1	- 0.72 to -1.46	0.52 to 1.46
Radial	39.8±8.3	1.63±0.36	-1.54±0.48
Endocardial	23.5 to 56.1	0.92 to 2.34	-0.60 to 2.48

Table B: peak systolic circumferential strain in different segments and views

	Peak systolic circumferential strain (%)			
	Apical	**Mid**	**Basal**	**P (all levels)**
Global	-29.3±6.2	-26.1±3.8	-28.4±4.2	p<0.001
Anterior	-25.6±7.9	- 28.6±6.8	-27.6±8.0	p<0.002
Anteroseptal	-30.6 ± 8.2	- 24.7 ±6.1	-28.8 ±8.6	p<0.001
Septal		- 24.6 ±6.0	-32.3 ±8.1	p<0.001
Inferior	-32.1±7.9	- 29.0±6.3	- 31.7± 8.5	p=0.001
Inferolateral		- 26.0±6.6	-28.5± 9.3	p=0.006
Lateral	-28.8±7.0	25.8±7.1	-26.2±9.1	p=0.003
P(All segments)	P>0.001	P<0.001	P<0.001	

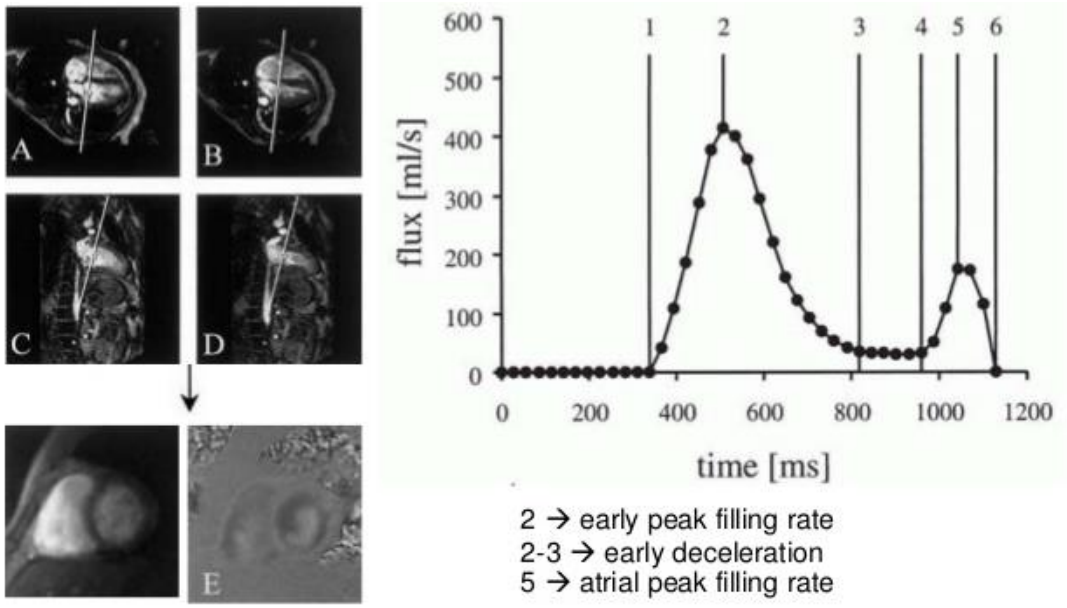
5.9 Clinical Data and Other Parameters used to assess diastolic dysfunction

5.9.1 Mitral Valve flow and diastolic Dysfunction

Transmitral flow (Mitral valve inflow) was assessed by through plane phase contrast imaging. The acquisition plane is defined by two and four chamber views in diastole. The plane is placed on the top of the opened mitral valve perpendicular to LV inflow. Magnitude and phase contrast image were obtained with a phase contrast flow. Flow was acquired in at least 30 cardiac phases for appropriate assessment transmittal flow. Quality was further assured by ensuring patients were in sinus rhythm, achieved the required number of cardiac phases, direction of velocity coding was checked (VENC of 150cm/sec was used for all cases and images were reviewed and analysed by Phillips post processing software at the time of assessment to reassure accurate direction of coding and the quality of inflow.

Velocity encoded phase contrast cine was performed through plane at the mitral valve with temporal resolution of 6-8mm as shown in figure 5k. Left ventricular filling rate was quantified using previously validated metrics: first third filling fraction and peak filling rate standardized to the end diastolic volumes. The peak flow rate was measured from end-systole to the point at which the peak flow occurred and the first third fraction was calculated by finding the difference in counts from end-systole to the time at which the end -diastole ended and then divided by the stroke counts, measuring the fraction(Inouye, Massie et al. 1984)

Figure 5.12 SHOWING MITRAL VALVE INFLOW AND CALCULATION OF LEFT VENTRICULAR FILLING RATE(Westenberg 2011) : Source online slide presentation Thaiwat Tatsanawiwat- Principles of Cardiac MRI



All images were analysed using preformed images off-line by a single blinded observer with over 3 years of CMR experience with discussion and oversight by the CMR supervisor (see Acknowledgments).

Diastolic dysfunction was defined as:

- reduced filling rate (first third filling fraction<0.45 and peak filling rate <2 EDV's/s) OR
- reduced early diastolic strain rate (circumferential strain rate <1.4/s and radial strain rate >-1.2/s) OR
- increased indexed left atrial volume (>45mls/m^2).

Clinical data was recorded from the clinical database. Blood pressure was taken supine at the same time as the CMR examination (Datex Ohmeda oscillometric blood pressure device, GE Healthcare, WI, USA). Readings were taken in the right arm, and as temporally close to the velocity-encoded phase-contrast sequences as possible. The right atrial pressure was estimated at 5mmHg for the purpose of systemic vascular resistance (SVR) calculation. SVR was therefore calculated, using net flux in the ascending aorta (from velocity-encoded phase-

contrast cine) as the cardiac output, as: SVR = ((MBP-5)/CO) x 80, where SVR was measured in dyn.sec.cm^{-5}; MBP was the mean blood pressure (mm Hg), and CO was cardiac output (litres/ min).

5.10 Statistical analysis plan

The mean +/- standard deviations are presented for normally distributed variables. Pulse wave velocity was compared against matched age and sex normal values (Voges, Jerosch-Herold et al. 2012) using a unpaired t-test. Systemic vascular resistance was measured against an accepted normal adult mean using a one-sample t-test.(Baim and Grossman 2006) A significance level of 0.05 was used for all tests. All statistical analyses were conducted using IBM SPSS version 21 (Armonk, NY: IBM Corp.)

Univariate analyses for PWV and SVR were performed using bivariate correlation in the case of continuous dependent variables; using independent t-tests in the case of binary variables and using one-way ANOVA in the case of categorical variables. Variables analysed against vascular indices were also entered into a forward stepwise multivariable regression model. The choice of variables for the multivariable regression was informed by likely variables from the univariate analysis. This was an exploratory study which relied on the availability of eligible patients undergoing clinical MRI scans during the period of study and therefore formal sample size estimations were not carried out.

Age (years) mean (SD) [range]

Age at intervention years mean (SD) [range]

Gender male N (%)

Systolic BP at MRI mean mmHg (SD) [range]

Diastolic BP at MRI mean mmHg (SD) [range]

Heart rate beats/min mean (SD)

Hypertension (n=22)

Bicuspid valve (n=26)

CMR derived indices

LV ejection fraction % mean (SD)

EDVi

ESVi

LV mass

Early diastolic strain

PFR/EDV

First third filling fraction

Systematic vascular resistance mean (SD) dyn.s.cm-5

Pulse wave velocity mean (SD) m/s

6. CARDIAC MAGNETIC RESONANCE OF COARCTATION OF THE AORTA: RESULTS

6.1 Patient Demographics

Fifty consecutive patients referred for assessment of coarctation/ coarctation repair were recruited. Overall 5 patients were excluded from the analysis: 3 had significant residual obstruction, one had severely impaired ventricular function secondary to undiagnosed dilated cardiomyopathy and one due to unavailability of previous history. Therefore 45 patients (28 males, 17 female) were included in the analysis.

Ten patients had undergone aortic coarctation stenting and 35 had undergone surgical repair (6 subclavian flap repairs, 7 Dacron patch repair and 17 end-to-end coarctation repair, 2 missing surgical report, 3 balloon angioplasty). 22 were hypertensive (diagnosed in clinic), of which 19 were on active treatment. Of these 20% were on beta-blockers, 29% on ACE inhibitors/angiotensin receptor blockers and 7% on calcium channel blockers. Three patients smoked, 1 patient had diabetes alone and 1 patient had diabetes and hypercholesterolemia. Twenty-six had a bicuspid aortic valve and 19 had tricuspid aortic valve.

6.2 Representative images from Coarctation patients included in the study showing different aortic pathologies, aortic valve disease

Figure 6.1 Image A and B Image A showing a bicuspid aortic valve (blue arrow points at the valve) while Image B SHOWS a trileaflet valve.

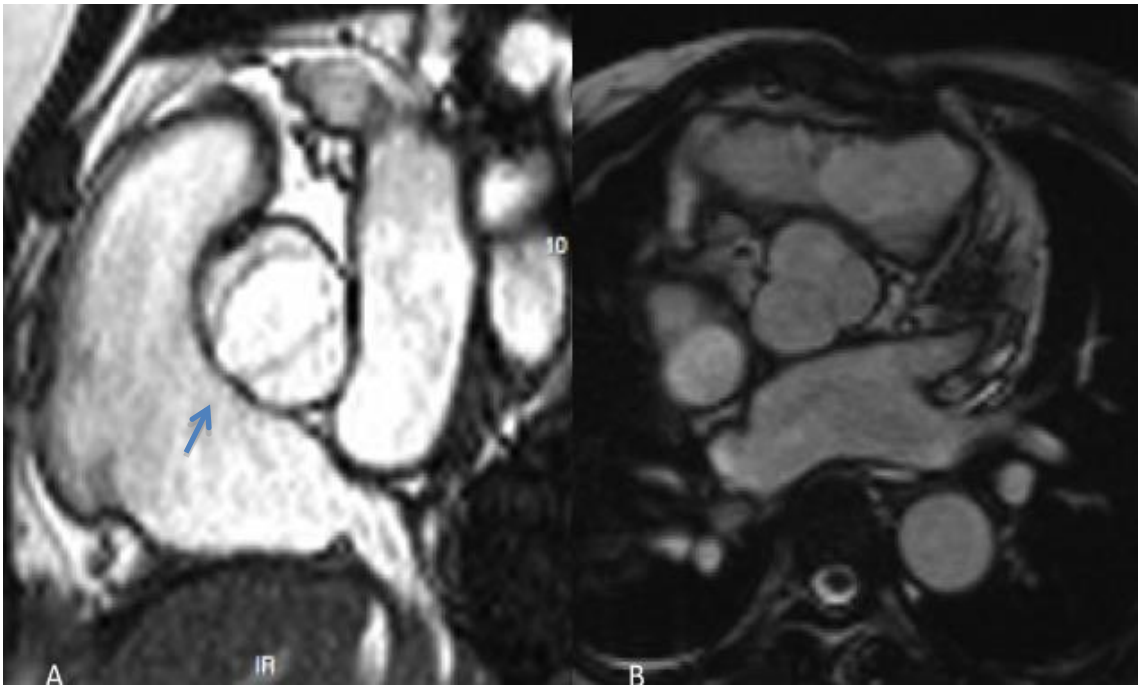


Figure 6.2 IMAGE C AND D SAX- VIEW, IMAGE C SHOWING MILD LEFT VENTRICULAR HYPERTROPHY (DIASTOLE) AND IMAGE D SYSTOLE.

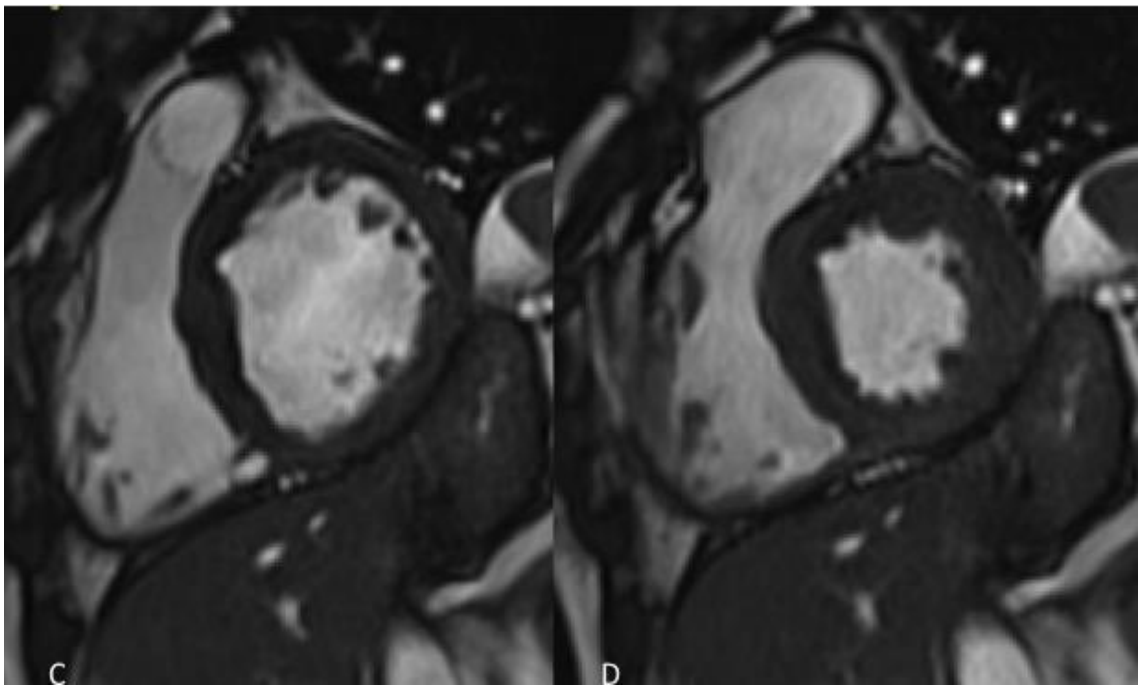


Figure 6.3 Image E showing recoarctation after end to end anastomosis repair while Figure F no evidence of recoarctation after end to end anastomosis repair

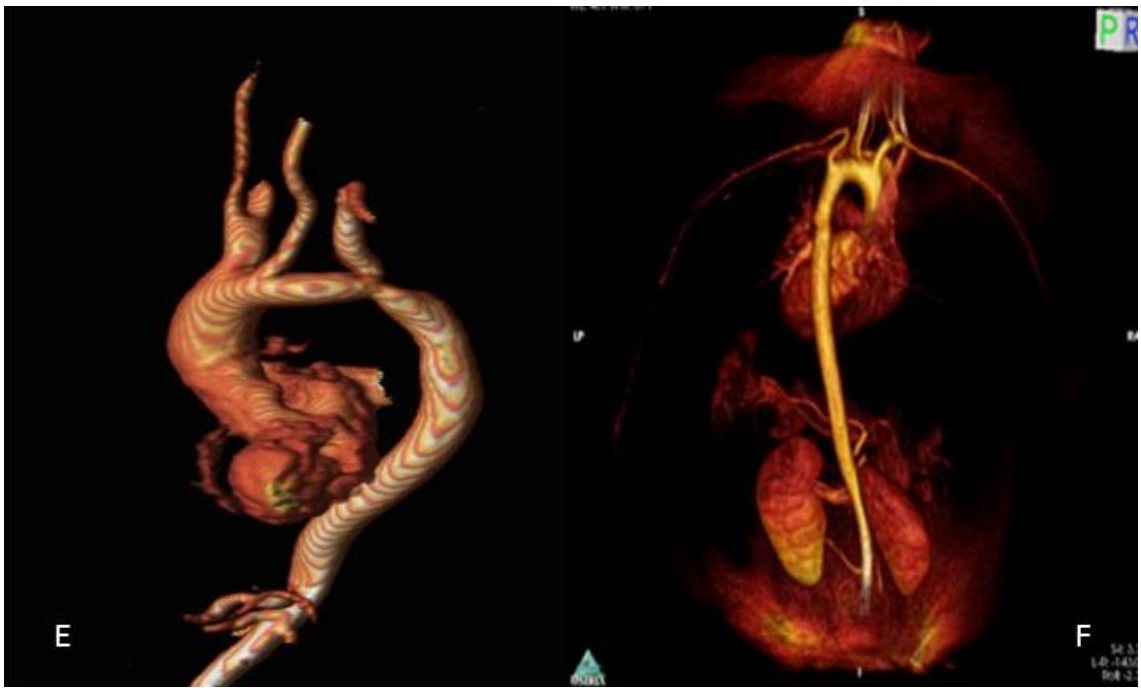


Figure 6.4 IMAGE G AND H FROM SHOWING SATISFACTORY COARCTATION REPAIR BUT DILATED ASCENDING AORTA.

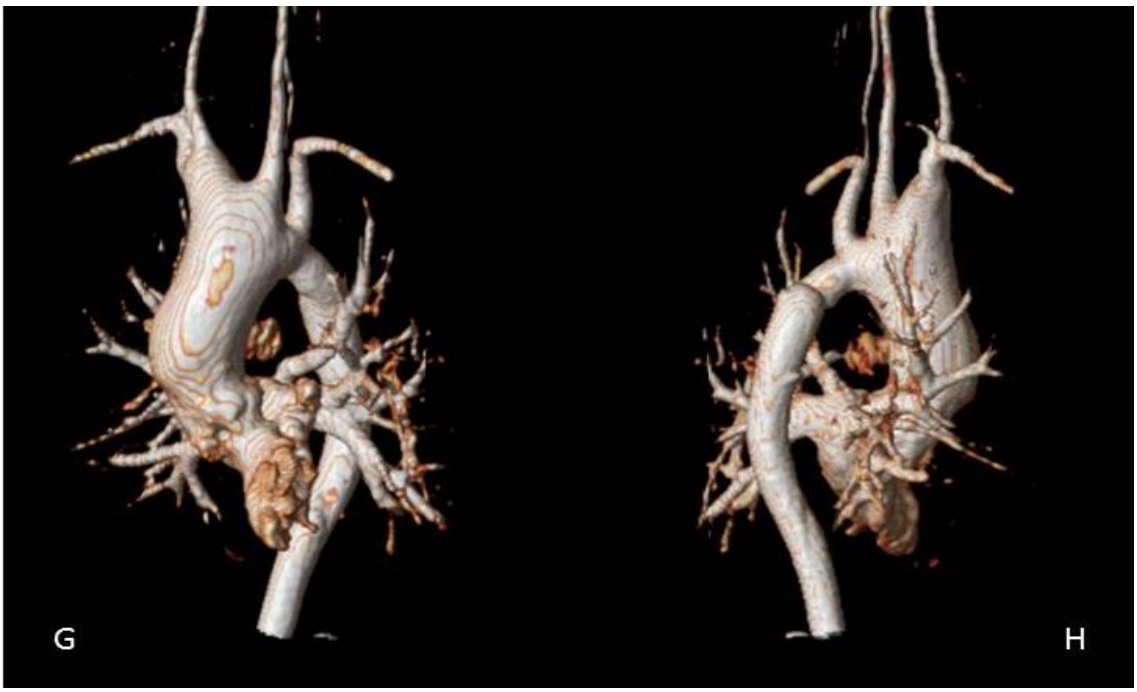
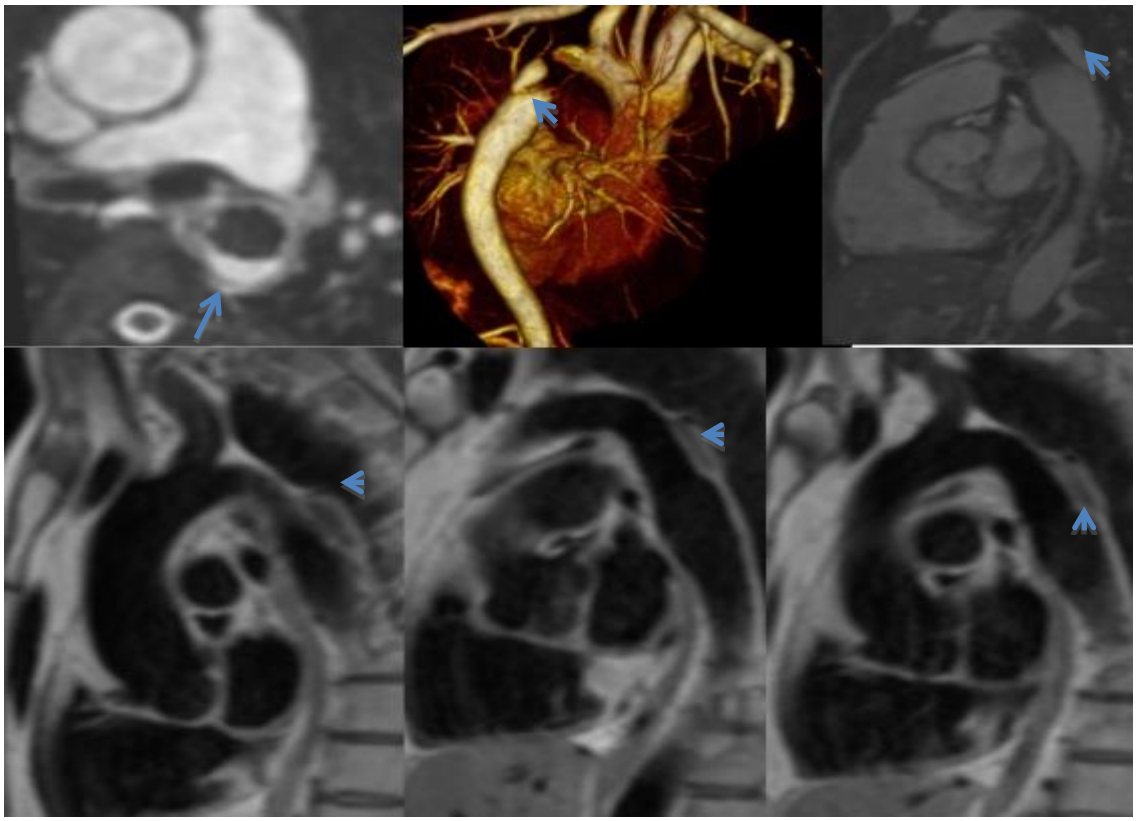


Figure 6.5 Shows a dissection flap

(Blue arrows points at the dissection flap in different sequences – Cine image (Transverse), MRA, Sagittal cine, Black blood sagittal stack of aorta (All 3 pictures in the bottom row)



6.3 Analysis of pulse wave velocity (PWV) and systolic vascular resistance (SVR)

Pulse wave velocity was significantly increased compared to expected normal values for age and sex (5.84 +/-0.48 m/s compared to age and sex corrected normal mean 4.54 m/s; p<0.001). Resting systemic vascular resistance was 1345 +/- 360, which was significantly higher than the normal population mean of 1170 dyn.s.cm-5; p=0.002. Figures below shows univariate correlations between age at CMR, age at first intervention, PWV and SVR. As expected age at CMR and first intervention are correlated, and these show a significant relationship with both PWV and SVR. PWV and SVR also show a marginally significant association (p=0.04). **In addition to the tables provided below figures and charts summarising the relationship between baseline variables. PWV, SVR and cardiac function are provided in Appendix A.**

TABLE 6.1 BASELINE DEMOGRAPHICS

Parameters	Value
Age (years) mean (SD) [range]	32.6 (11.9) [18-60]
Age at intervention years mean (SD) [range]	8.5 (13.1) [0.02-56.0]
Gender male N (%)	28 (62%)
Systolic BP at MRI mean mmHg (SD) [range]	137 (22.9) [90-190]
Diastolic BP at MRI mean mmHg (SD) [range]	77 (11.7) [46-100]
Heart rate beats/min mean (SD)	66.8 (10.3)
Hypertension (n=22)	49%
Bicuspid valve (n=26)	58%
CMR derived indices	
LV ejection fraction % mean (SD)	64% (6.41)
EDVi	82.7 (17.0)
ESVi	30.3 (9.5)
LV mass	67.0 (25.8)
Early diastolic strain	0.42 (0.26)
PFR/EDV	2.86 (0.90)
First third filling fraction	0.62 (0.19)
Systematic vascular resistance mean (SD) dyn.s.cm^{-5}	1345 (360)
Pulse wave velocity mean (SD) m/s	5.84 (0.48)

6.4 Vascular Indices (univariate analyses)

Pulse wave velocity was significantly increased compared to expected normal values for age and sex (5.84 +/-0.48 m/s compared to age and sex corrected normal mean 4.54 m/s; p<0.001). Resting systemic vascular resistance was 1345 +/- 360, which was significantly higher than the normal population mean of 1170 dyn.s.cm^{-5}; p=0.002. Table 6.2 shows univariate correlations between age at CMR, age at first intervention, PWV and SVR. As expected, age at CMR and first intervention are correlated, and these show a significant relationship with both PWV and SVR. PWV and SVR also show a marginally significant association (p=0.04).

Table 6.2 CORRELATIONS

PWV & SVR was significantly correlated with age (at MRI and at initial repair). SVR showed a modest relation to PWV

		Age at intervention	Age	PWV	SVR
Age at intervention	Pearson Correlation	1	.615**	.330*	.338*
	Sig. (2-tailed)		.000	.029	.023
	N	45	45	44	45
Age	Pearson Correlation	.615**	1	.470**	.363*
	Sig. (2-tailed)	.000		.001	.014
	N	45	45	44	45
PWV	Pearson Correlation	.330*	.470**	1	.309*
	Sig. (2-tailed)	.029	.001		.041
	N	44	44	44	44
SVR	Pearson Correlation	.338*	.363*	.309*	1
	Sig. (2-tailed)	.023	.014	.041	
	N	45	45	44	45

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Tables 3 to 8 explore univariate association between PWV and SVR with gender (Table 6.3), hypertension (Table 6.4), aortic valve type, whether bicuspid or tricuspid (Table 6.5), type of repair (Table 6.6), presence or absence of risk factors (Table 6.7) or type or material used for repair (Table 6.8). PWV was significantly higher in females (p=02), patients with hypertension (p=0.04), and those with a foreign material repair (p=0.01). SVR was significantly higher in females (p=0.04) otherwise there were no other significant associations.

Table 6.3-PULSE WAVE VELOCITY, SYSTEMIC VASCULAR RESISTANCE AND GENDER

Association of pulse wave velocity and systemic vascular resistance and gender (PWV and SVR higher in female compared to male)

Sex		Mean	Std. Deviation	Std. Error Mean
PWV	female	7.2†	4.7	1.1
	male	5.0	1.1	0.2
SVR	female	1482.7‡	274.7	66.6
	male	1262.0	383.3	72.4

† Female versus male p = 0.02

‡ Female versus male p= 0.04

Table 6.4 PULSE WAVE VELOCITY, SYSTEMIC VASCULAR RESISTANCE AND HYPERTENSION

Association of pulse wave velocity and systemic vascular resistance with hypertension

PWV (p=0.037) but not SVR (p=.068) is associated with hypertension.

	Hypertension	Mean	Std. Deviation	Std. Error Mean
PWV	Yes	6.8†	4.2	0.9
	No	4.9	1.1	0.2
SVR	Yes	1458.1	262.3	55.9
	No	1293.9	315.9	67.4

† Hypertension versus not p = 0.04

Table 6.5 PULSE WAVE VELOCITY, SYSTEMIC VASCULAR RESISTANCE AND ANATOMY

Association of pulse wave velocity and systemic vascular resistance with aortic valve type (no significant association)

Aortic valve		Mean	Std. Deviation	Std. Error Mean
PWV	Bicuspid	6.2	3.8	0.7
	Tricuspid	5.3	2.1	0.5
SVR	Bicuspid	1365.6	270.6	53.1
	Tricuspid	1317.8	461.5	105.9

Table 6.6 ASSOCIATION OF SVR AND PWV WITH TYPE OF REPAIR

SVR and PWV not related to intervention type (p= 0.789 & 0.13 respectively by ANOVA, no significant association)

Type of procedures		Mean	Std. Deviation
SVR	end to end	1333.8	308.0
	subclavian flap	1377.2	261.0
	Dacron	1501.7	244.3
	Stent	1364.7	542.3
	Total	1377.4	358.3
PWV	end to end	4.7	0.9
	subclavian flap	5.6	1.8
	Dacron	7.4	4.9
	Stent	7.4	4.9
	Total	5.9	3.4

TABLE 6.7 ASSOCIATION OF SVR AND PWV WITH RISK FACTORS

(SVR & PWV not related to other conventional risk factors (of smoking, diabetes and hyperlipidemia) (p=0.13 and 0.47 respectively)

	Any risk factor	N	Mean	Std. Deviation
SVR	conventional risk factor	5	1576.8	330.1
	no risk factor	40	1316.5	356.3
PWV	conventional risk factor	5	6.8	3.4
	no risk factor	39	5.7	3.2

Table 6-8 Association of SVR and PWV with material used for repair

However, presence of foreign material shows relatively higher PWV (p=0.011) but no difference in SVR (p=0.276)

	Foreign Material	N	Mean	Std. Deviation
PWV	foreign material	16	7.4	4.7
	native tissue	28	4.9	1.1
SVR	foreign material	17	1421.1	438.8
	native tissue	28	1299.4	301.2

6.5Multivariate analysis of Vascular Indices

6.5.1 Systematic vascular resistance

The following variables were entered into forward stepwise regression: age (entered as a constant variable and is therefore not shown), age at intervention, sex, bicuspid aortic valve; hypertension; foreign material (stent/Dacron patch) (Table 6.9). Only current age showed a significant positive association with SVR (R=0.61; p<0.001).

TABLE 6.9 MULTIVARIABLE ANALYSIS FOR SVR

Multivariable analysis for SVR[a]

Model		Beta Intercept	P value	Correlation coefficient
1	Hypertension	.078[b]	.553	.093
	Foreign Material	.091[b]	.511	.103
	Female	.159[b]	.209	.195
	Bicuspid aortic valve	-.041[b]	.738	-.052
	Age at intervention	.051[b]	.748	.050

a. Dependent Variable: SVR

b. Predictors in the Model: (Constant), Age

6.5.2. Pulse wave velocity

The same variables were entered into forward stepwise regression as for the SVR analysis in Table 6.10: age, age at intervention, sex, bicuspid valve; hypertension; foreign material (stent/Dacron patch). Again, only current age showed a significant positive association with PWV (R=0.47; p=0.001)

TABLE 6.10 MULTIVARIABLE ANALYSIS FOR PWV

Multivariable analysis for PWV[a]

Model		Beta Intercept	P value	Correlation coefficient
1	Hypertension	.175[b]	.231	.186
	Foreign Material	.216[b]	.156	.220
	Female	.259[b]	.063	.286
	Bicuspid aortic valve	.143[b]	.299	.162
	Age at intervention	.055[b]	.756	.049

a. Dependent Variable: PWV

b. Predictors in the Model: (Constant), Age

6.5.3 Functional Analysis (Table 6.11)

Eleven patients were shown to have diastolic dysfunction defined as:

- reduced filling rate (first third filling fraction<0.45 and peak filling rate <2 EDV's/s) OR
- reduced early diastolic strain rate (circumferential strain rate <1.4/s and radial strain rate >-1.2/s) OR
- increased indexed left atrial volume (>45mls/m^2).

TABLE 6.11 ASSOCIATION OF SVR AND PWV WITH DIASTOLIC DYSFUNCTION

Association of SVR and PWV with diastolic dysfunction

SVR (p=0.017) was significantly higher in patients with diastolic dysfunction but PWV (p=0.934) was not. There was no difference in left ventricular mass between the two groups. (p=0.88)

	Diastolic Dysfunction	N	Mean	Std. Deviation
PWV	Normal	33	5.8	3.4
	Dysfunction	11	5.9	2.3
SVR	Normal	34	1273.9	356.3
	Dysfunction*	11	1566.1	281.0
LV Mass	Normal	32	66.7	27.3
	Dysfunction	11	68.0	17.7

* p= 0.017

5

7 Discussion of Cardiac Magnetic Resonance analysis of patients with Coarctation of the Aorta

7.1Main Discussion

The mean age of patients studied was 33 years, 80% had prior surgical coarctation repair, 60% had bicuspid aortic valves and about half were hypertensive. Aortic stiffness measured by pulse wave velocity (PWV) and arteriolar resistance by systemic vascular resistance (SVR) are elevated even after adequate coarctation relief. Although significant univariate associations between PWV and SVR were found with age, gender, hypertension and type of material used for repair, the only significant independent predictor of aortic stiffness and arteriolar resistance in a multivariate analysis was age at MRI. Using left atrial volumes, ventricular filling rates and early diastolic strain rate, it is possible to detect a group of patients with diastolic dysfunction and this group was shown to have a significantly higher systemic vascular resistance.

Images were added to the results section (*See Chapter -6)* to show the nature of disease we had in the coarctation group. Figure -1 with image A and B shows a morphological bicuspid and trileaflet valve. Figure - 2 Image C and D shows SAX stack, which was used to assess cardiac volumes and function. Figure 3- Image E shows significant narrowing, this patient was excluded from the study, while Image F shows remarkable repair with no significant recoarctation. These finding were also confirmed on inplane phase contrast flow and by measuring dimension on 3D whole heart. Figure 4- Image G and H shows dilated ascending aorta in the setting of repaired coarctation of the aorta and bicuspid aortic valve. Figure 5, shows a series of cine. MRA and black blood images showing a dissection flap post stent implantation. This case highlights, that cardiac imaging has given congenital heart disease a new direction to provide regular surveillance at a low risk and no radiation at all (Lauenstein, Goehde et al. 2004, Lee, Haims et al. 2004, Klenk, Gawande et al. 2014).

In my study, I used LA volumes, first third filling fraction <0.45, early filling rate, 2EDVs/s OR Reduced early diastolic strain rate (circumferential strain rate,1.4m/ and radial strain rate >-1.2/s to define diastolic dysfunction but in last years and currently T 1 map which emerged a s an important marker to assess diffuse fibrosis and cardiac function. This may help to transform cardiac care in our cohort of patients. In contrast to late gadolinium enhancement, which highlights regional scarring, T1 maps targets tissues diffuse fibrotic process. A tissue,

which may appear normal on cine images and late gadolinium enhancement, may still be abnormal.

T1 is the time after which a tissue's longitudinal magnetization has returned to 63% of its original value after an inversion and saturation phase. In essence T1 map is a single parameter – in which T1 times of the tissue voxels are reflected by signal intensities of corresponding pixels on absolute scale.(Messroghli, Niendorf et al. 2003, Moon, Messroghli et al. 2013).

The findings are congruent with previous studies showing increased arteriolar resistance(Sehested, Baandrup et al. 1982, Gidding, Rocchini et al. 1985, Gardiner, Celermajer et al. 1994, Barton, Ni et al. 2001) and increased aortic stiffness(Xu, Shiota et al. 1997, Brili, Tousoulis et al. 2005, Vogt, Kuhn et al. 2005, Sarkola, Redington et al. 2011, Mizia-Stec, Trojnarska et al. 2012) in patients with successful coarctation repair. There are also previous echocardiographic and CMR data suggesting that myocardial function is reduced in patients after successful coarctation repair.(Lam, Mullen et al. 2010, Kutty, Rangamani et al. 2013, Lombardi, Northrup et al. 2013, Faganello, Fisicaro et al. 2016, Shang, Sarikouch et al. 2016) Although our patients had evidence of overall normal average ejection fraction, with about a quarter with had evidence of diastolic dysfunction. The study findings build on the previous literature by demonstrating association between the known changes in SVR and reduced diastolic function. A previous small study in children had suggested an association of arterial stiffness with diastolic function however this association was not found in my study.(Lombardi, Northrup et al. 2013) This may be due to the age of my study group, increased specificity of the aortic stiffness assessment used in my study, or the relatively small sample size.

In my study, the influence of age was the only independent predictor of aortic stiffness and arteriolar resistance. It is known that raised SVR is often found in young adult hypertensive patients causing an upstream increase in transmural pressure resulting in stretching of large central arteries and typically presents with elevated diastolic BP (Franklin 2005). Isolated systolic hypertension, however, is usually found in older patients and is the typical pattern of blood pressure increase seen with increased arterial stiffness (O'Rourke, Staessen et al. 2002, Franklin 2005). However, both systolic and diastolic blood pressure is known to increase after successful coarctation repair(Cohen, Fuster et al. 1989), as well as an increase in the pulse pressure(Pedersen, Pedersen et al. 2015). The long-term increase in blood pressure is likely due to arterial stiffening and increase in SVR. The early effect of increased diastolic blood

pressure and activation of the renin-angiotensin system was demonstrated by Rocchini et al as early as 1976.(Rocchini, Rosenthal et al. 1976) In this relatively young adult population, an increase in SVR may be a more important indicator of diastolic myocardial function then the aortic stiffness. It is possible that an association between increased aortic stiffening and diastolic function may have been observed if my study had included an older cohort of patients. The observation that there was no numerical difference in PWV in those with and without diastolic dysfunction supports the lack of association in spite of the relatively small number of patients with diastolic dysfunction.

Given that an increased SVR, occurs early after coarctation repair (Rocchini, Rosenthal et al. 1976, Sehested, Baandrup et al. 1982, Gidding, Rocchini et al. 1985, Gardiner, Celermajer et al. 1994), it could be hypothesised that increased arteriolar resistance is the cause rather than the effect of the diastolic dysfunction that was seen in the minority of my study patients. A trial of earlier measurement and treatment of increased arteriolar resistance is therefore warranted in this patient group. There have been a number of studies where a trial of drug therapy has shown effect to reduce arteriolar resistance in the normal controls. In coarctation patients there would be potential benefit in a prospective study to assess the effects of different antihypertensive drugs, measuring any changes in arteriolar resistance and/or aortic stiffness. The particular drug of choice for such a study would be a calcium channel blocker (CCB), since there is evidence in non-coarctation related hypertension that central aortic stiffness is reduced as well as an associated decrease in arteriolar resistance as a result of the vasodilatory effect of CCB's. A head to head comparison with ACEi or beta-blockers would be appropriate as a pilot.

Although my study demonstrated that patients with prosthetic material had higher arterial stiffness, this effect disappeared in the multivariate model when age was taken into account. This is an important negative finding and supports the hypothesis that stent angioplasty is an effective means of achieving coarctation relief. Babu-Naryan et al had found a significant decrease in left ventricular mass, increased aortic distensibility as well as improved left ventricular function 10 months after stenting. No other haemodynamic assessments were made but supports studies showing equivalent blood pressure control when comparing stent angioplasty and surgery in older patients(Rodes-Cabau, Miro et al. 2007).

It has been postulated that, despite early surgical repair, patients may have abnormal vascular reactivity leading to increased resistance and late systolic hypertension. Similar findings have

been reported in the stent group leading to exercise induced hypertension due to a rigid segment of the aorta. Hagar et al reported in his largest series of surgical cohort (COALA n=404 with a follow -up of 27 years) that 57% of patients had persistent hypertension, with only 13% having a significant residual gradient. Risk factors included repair with prosthetic material, male gender, residual gradient and older age(Hager, Kanz et al. 2007). My study has shown that prosthetic material has no effect on arterial stiffness in a multivariate model when age is taken in account, which is reassuring for stent cohort. Current clinical practice in adults leans towards stent angioplasty for isolated aortic coarctation due to the ease of the procedure and lower incidence of procedural complications and my findings lend support to this approach (Rodes-Cabau, Miro et al. 2007).

Several studies have focused on systolic hypertension (Hamid, Motwani et al. 2015, Quennelle, Powell et al. 2015, Di Salvo, Castaldi et al. 2016, Rinnstrom, Dellborg et al. 2016) and increased aortic stiffness (Lam, Mullen et al. 2009, Shang, Sarikouch et al. 2016) as key outcome determinants in coarctation of the aorta. My findings suggest that future studies should pay close attention to systemic vascular resistance with CMR assessment and clinicians should be more assiduous in lowering diastolic blood pressure. There should be new studies set up to assess patients early after intervention with serial targeted scans to detect systolic and diastolic myocardial dysfunction in patients after coarctation repair(Lam, Mullen et al. 2009, Kutty, Rangamani et al. 2013, Faganello, Fisicaro et al. 2016). This is associated with an enlarged left atrium, reduced early diastolic strain rates and reduced ventricular filling rates.

There are at least 4 commonly applied T1 mapping sequences which have demonstrated excellent reproducibility and accuracy, which are MOLLI, ShMOLLI, SASHA and SAPPHIRE(Riesenkampff, Messroghli et al. 2015). Several T1 parameters have been proposed to be biomarkers of myocardial disease such native T1 map, post contrast T1 map and Extracellular volume which is the most trending at present (Miller, Naish et al. 2013, Miller, Naish et al. 2013) Riesenkamoff et al showed in his study that patients with abnormal ECV correlated with diastolic dysfunction. Also they found abnormal ECV values in TOF, Systemic RV and TGA's with atrial repair(Riesenkampff, Messroghli et al. 2015). Further studies involving patients with coarctation of aorta are warranted. It may point us in a direction of the most effective type of repair, long-term outcome and help with better control of hypertension.

○ *7.2 Limitations*

- The sample size was small – a frequent problem in congenital heart research. Furthermore, a number of suitable patients who I approached would not consent to partake. This could have biased my results.
- I am not the first to experience difficulties recruiting to MRI research projects where numbers reported have historically been small. The advantage of MRI is that measurements are reproducible with small inter period variability when undertaken by the same person. Then, as Babu-Naryan demonstrated(Babu-Narayan, Mohiaddin et al. 2011), variations can be detected following an intervention – i.e. pre and post stent implantation – even in relatively small numbers (18 patients in her report).
- Multiple statistical comparisons increase the chance of false positive results due to the play of chance – a Type 1 error. I tried to choose variables which appeared relevant to the questions being addressed.
- No formal sample size estimations were carried out as this was an exploratory study. Future studies would benefit from sample size estimations based on the results presented here and in other studies.
- Avoiding arrhythmias reduced image artefact and volume analysis was carefully checked to avoid over-estimation. The main limitation for calculation of PWV by this method is there is no availability of commercial software and the whole process requires manual checking which is time consuming to ensure consistency with other methods including invasive estimation (Wentland, Grist et al. 2014)
- In-plane flow data alone may be error-prone and relatively insensitive compared to a combination of different images, including through-plane flow. This is because optimal slice position within the peak velocity jet is sometimes difficult to achieve.
- Underestimation of velocity by MRI could have been a possibility and wherever possible this was cross checked with information from echocardiography. MRI settings were adjusted according to patients' heart rate to achieve the required number of cardiac phases for velocity assessment. Image artefact was addressed by flow plane repositioning.
- A formal assessment of inter- and intra-observer variability in the context of this analysis would help to provide additional quality assurance. A second observer

reviewed all the main measurements to provide additional quality control but variability between measurements was not documented.

- To improve the quality of the results a comparison of patient values including pulse wave velocity and arterial stiffness could have been done for each individual patient compared against a proper matched control. Unfortunately, this was not possible due to time and resource constraints but could be done as part of a future research project. The lack of a control group will limit the potential validity and generalisability of the results.

7.3 Conclusion

Adult patients with a previous successful coarctation repair show increased aortic stiffness and increased arteriolar resistance relative to standard control populations and this has a close association with age. Increased systemic vascular resistance is associated with impaired left ventricular relaxation in the patients studied.

7.4 Recommendations

These findings support further research in this area, a clinical trials and high quality observational studies would be warranted looking at the efficacy of monitoring and reducing central aortic pressure using targeted therapies such as addition of a calcium channel blockers, renin angiotensin aldosterone system modulators or isosorbide mononitrate(Kaufman, Nunes et al. 2010).

8 Thesis summary and overview including observations for future studies.

The NORPAP dataset has comprehensively collated information about adults with congenital heart conditions from 1993. It was only in 2008 that a small clinic at Papworth was commenced and in 2014 that a second ACHD consultant joined the Norwich service. The outcomes and interventions that I summarise below support the confidence shown by NHS England in proposing to commission Level 2 (Specialist Cardiology Services) for ACHD at NNUH.

8.1 Overview of the ACHD Dataset

- The expansion in absolute numbers has risen steadily since 1993. Predominantly outpatient based, follow up surveillance needs specialist trained consultant-led clinical expertise, appropriate imaging and support infrastructure (e.g. GUCH cardiac specialist nurses, maternal medicine etc). Within the proposed NHS England congenital network, Specialist Cardiology Centres (Level 2) will provide expert care closer to home and my review of the NORPAP experience has demonstrated that this can be safely and appropriately provided at a centre without adult congenital cardiac surgery or structural intervention. It is to be expected that more Level 2 centres are likely be developed to service the numbers of patients. The review also highlights the most frequent causes of local admissions (arrhythmias and heart failure) with implications for an appropriate in-patient bed base.
- The distribution of the congenital heart conditions (10% complex, 37% intermediate, 53% simple) are compatible with my literature review. The natural and unnatural (palliated) history of the first two groups and even the simpler conditions, require life-long surveillance. Over all 62% of the patients required either de novo or re-intervention (some individuals had 4 or more interventions).
- Analysis of the overall dataset led me to focus on Coarctation of Aorta.

8.2 Overview of the Subgroup CoA & CMR CoA study

- I noted potentially higher incidence of CoA in the NORPAP dataset as compared with that documented in literature which may be due to sampling error or greater representation of older surviving patients in our cohort compared to other series.

- 91% of the patients required intervention in the CoA cohort. Many patients required further interventions frequently at least 5% of the patients had a 4th intervention of the 203 patients with initial repair.
- Mortality was low as compared - as compared with that documented in the literature.
- Initial surgical repair predominantly included end to end anastomosis followed by patch aortoplasty and subclavian flap repair and interposition or extra-anatomical grafts. The frequency of patch aortoplasty was higher than a benchmark paper against which I compared outcomes.
- Incidence of premature coronary artery disease was low in the NORPAP cohort
- Prevalence of hypertension was high in the NORPAP cohort (50%) and was found to be higher in males.
- 13% of the patients required cardiac surgery for concomitant pathology remote from the coarctation site including aortic valve replacement and ascending aorta grafting for aortic dilatation.
- Serious complication rates were low
- Subgroup analysis by age of repair showed that those who received a repair in the neonatal period or as a child required frequent re-intervention and had an appreciable risk of persistent hypertension in the absence of re-coarctation. Patients who had CoA repaired later in life had higher rates of persistent hypertension than those repaired at a younger age.
- The coarctation subset has shown excellent long-term survival – so much better than that reported historically. I discuss the reasons for this, which include appropriate and timely treatment of hypertension, coarctation reintervention guided by imaging (MRI and echo) and careful regular follow up in dedicated adult congenital clinics.
- The persistent hypertension, despite no significant residual coarctation is likely to be related to an intrinsic abnormality of the elastic properties of the aorta in patients with coarctation. Increased central aortic stiffness, with the concomitant systolic hypertension, has been suggested to be a cause of the reduced myocardial perfusion pressure demonstrated with nuclear myocardial perfusion imaging (reduced myocardial perfusion reserve in the absence of obstructive coronary disease).
    - In view of the NORPAP data and my study of the literature, I designed a Cardiac MRI (CMR) study of patients with coarctation of the aorta. I found that adult

patients with a previous successful coarctation repair show increased aortic stiffness and arteriolar resistance compared to published data from similar normal subjects (not age/gender matched). This has close association with age. Increased systemic vascular resistance is associated with impaired left ventricular relaxation in those patients that I studied.

- Central aortic stiffness is a predictor for cardiovascular events. Of the 50% of patients with coarctation of the aorta who were hypertensive, many were treated with beta-blockers or ACE inhibitors as suggested by the Guidelines – particularly in the presence of concomitant dilated aortopathy. Calcium channel blockers have been found to reduce central aortic stiffness in non-coarctation patients. In those with isolated coarctation and hypertension, calcium channel blockers may be the preferred first line therapy. A multi-centre longitudinal study to assess these effects would help to clarify the role of calcium channel blockers and other anti-hypertensive agents in this setting.

- I have reviewed the limitations of the dataset and made recommendations to improve particularly the CMR imaging protocols. I have undertaken an extensive literature review of coarctation of the aorta.
- As a consequence of my interest in cardiovascular haemodynamics in patients with congenital heart conditions, I wrote the outline proposal for my research successor's MD [who has studied the haemodynamics of right sided regurgitant valves and their hepatic effects (with MRI elastography) – which has now been completed.

8.3 Recommendations:

- A dedicated person is required for maintaining and completing the dataset as
    1. Longitudinal outcome data, a resource for future publications and to benchmark the care against other centres,
    2. To develop and implement research opportunities
- Congenital imaging -MRI is required in the region to develop clinical and research opportunities
- In CoA subset further studies are required involving drug trials to assess the effect of antihypertensive treatment on the pulse wave velocity in the Coarctation of Aorta.

- Similar techniques can be used to assess aortic dilatation those with associated congenital aortopathy with conotruncal conditions (e.g. Fallot's tetralogy, pulmonary atresia with VSD) or bicuspid aortic valve.

Appendix A: Ethical approvals

Our Vision
To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Dr Isma Rafiq
University of East Anglia
Department of Medicine
Norwich Medical School
Norwich
Norfolk
NR4 7TJ

19th July 2021

Dr Alisdair Ryding
Cardiology Department
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

direct dial: 01603 287690

e-mail: alisdair.ryding@nnuh.nhs.uk
website: www.nnuh.nhs.uk

Dear Isma

MD Thesis: Coarctation of the aorta: management in a non-surgical centre & evaluation of aortic stiffness & cardiac function

I am writing to confirm that the Cardiology Directorate approves the use of data in the Adult Congenital Heart Disease Registry set up by Dr Freeman to be used for quality improvement purposes including your MD thesis. Any information in the thesis or associated documents must not include any patient identifiable details. Please note that this approval applies specifically for your thesis and if the data are used for publication, then separate approvals may be required.

Yours sincerely

Dr Alisdair Ryding
Consultant Cardiologist and Cardiology Service Director

CC Dr Leisa Freeman

Guy's and St Thomas' NHS
NHS Foundation Trust

KING'S College LONDON
University of London

Consent Form Version 2 16.07.2009

PATIENT INFORMATION SHEET

Study title: MRI sequence development in a clinical setting.

REC Study No: 09-H0802-78.

Chief Investigator: Prof Eike Nagel.

You are being invited to take part in some research during your Magnetic Resonance Imaging (MRI) scan. Before you decide whether to take part it is important that you understand why the research is being done and what it will involve. Please take your time to read the following information carefully.

Your doctor has requested that you undergo an MRI scan as part of your clinical care. Unlike most medical imaging methods, MRI **does not use ionising radiation** but instead uses magnetic fields and radio−frequency (RF) waves to produce images of the internal structure of the human body. A clinical examination will consist of a number of sequences of magnetic and RF pulses with each sequence producing an image or set of images. Whilst MRI is an established and safe technique we are continually looking for ways of improving the information that we get from the scan. Improved information from the scan means better quality images and better care for patients. With MRI small adjustments in the way we take the images (sequences) can lead to very different results. In order to work out whether an adjustment we make is useful we need to try it out in patients.

In addition to the imaging you need for clinical reasons we would also like to test new imaging sequences during your scan. From your point of view this simply involves spending a few extra minutes in the MRI scanner. Your normal MRI scan will last approximately 60 minutes. The extra time required for this research would add a

maximum further 15 minutes. We will not administer any extra dye or medication to you over and above what is required for clinical purposes. The extra scanning is not painful or dangerous. There are no known extra risks to you should you agree to this extra scanning.

It is entirely voluntary whether you allow us to perform this extra scanning for research purposes. If you refuse your clinical care will not be affected and you do not have to give a reason for your refusal. You are free to change your mind at any point during the scan. Should you do so we will not take any further research images.

Information collected during this research will be kept strictly confidential. The procedures for handling, processing, storage and destruction of your data are compliant with the Data Protection Act 1998. Any information about you, which leaves the NHS, will be entirely anonymous, as your name and address will be removed.

If you have any questions please ask a member of the MRI department staff. If you are happy to take part we will ask you to sign a consent form.

Guy's and St Thomas' NHS
NHS Foundation Trust

KING'S College LONDON
University of London

Consent Form Version 2 16.07.2009

CONSENT FORM

Study title: MRI Sequence Development in a Clinical Setting
REC Study No: 09-H0802-78
Chief Investigator: Prof Eike Nagel

May we take some extra images for research?

This will require no extra injections and will take a maximum of an extra 15 minutes in the scanner. Participation is entirely voluntary and choosing not to participate will not affect your medical care.

Please initial box

1. I confirm that I have read and understand the information sheet dated 16/07/2009 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand I may choose at any point not to have any further research scans without giving any reason, without my medical care or legal rights being affected. ☐

3. I give my consent to have some additional scans for research. ☐

_____	_____	_____
Name of Patient	Signature	Date
_____	_____	_____
Name of Person taking consent (if different from researcher)	Signature	Date
_____	_____	_____
Researcher	Signature	Date

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix B: Additional Figures and Tables summarising Cardiac MRI analysis of corrected Coarctation of the Aorta dataset (refer also to Chapter 6)

These figures compliment the results presented in Chapter 6.

Figure A1 Relation of PWV and SVR with Age (stratified by medina values)

There is a significant relationship with age and PWV and SVR.

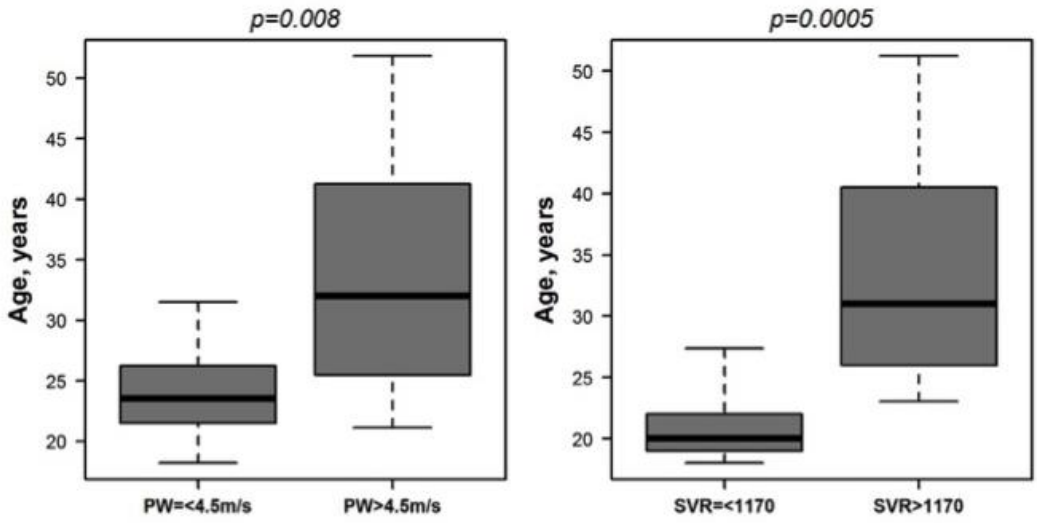


Figure A2 Relationship of PW &SVR with Age at Intervention

Age at intervention was weakly related to SVR.

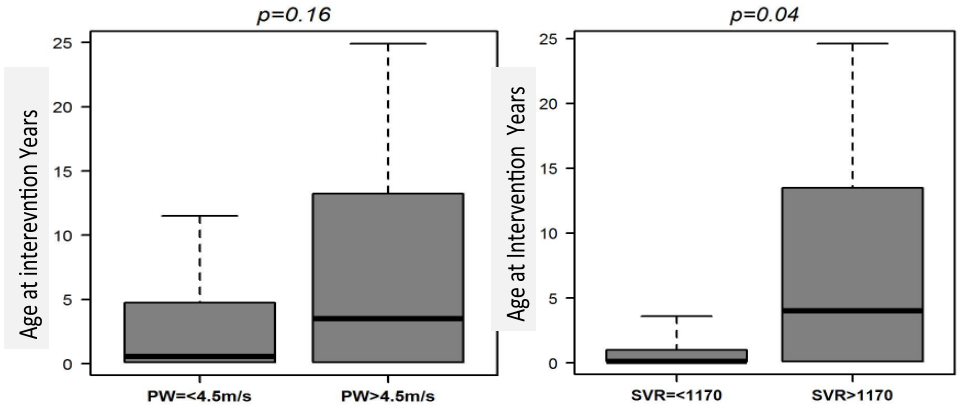


Figure A3 Relation of PWV & SVR with Heart Rate showing a weak relationship between SVR and HR

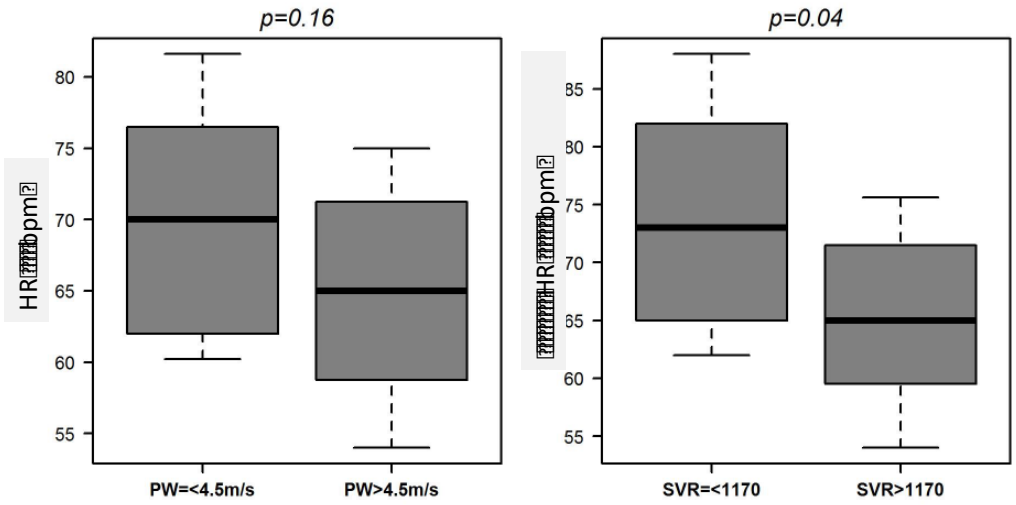


Figure A4 PWV and SVR relation with Height and Weight. There was no clear relation of PWV and SVR with height and weight.

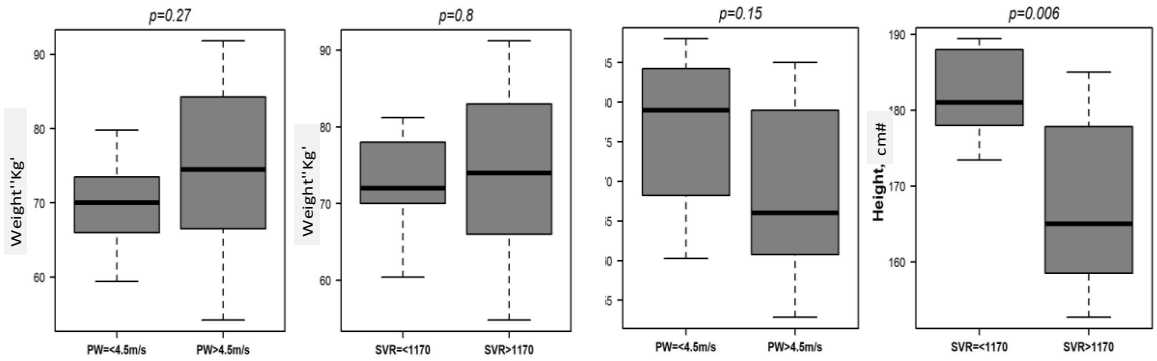


Figure A5 PWV and SVR relation to systolic BP and diastolic BP. There was no significant relationship between PWV and SVR with Systolic and diastolic BP

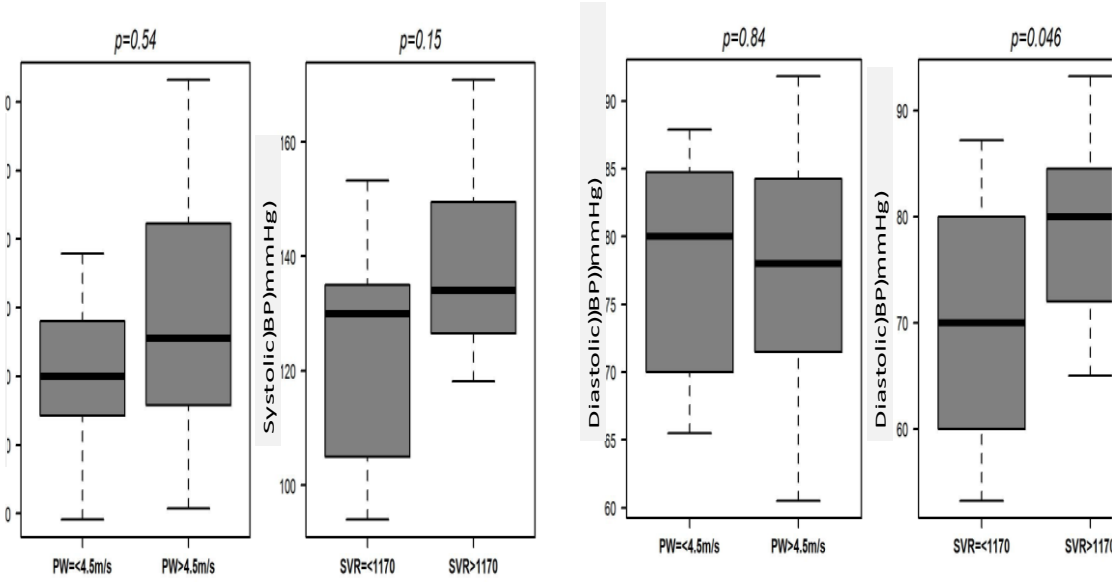


Figure A6: Left ventricular ejection fraction showing a weak association with SVR

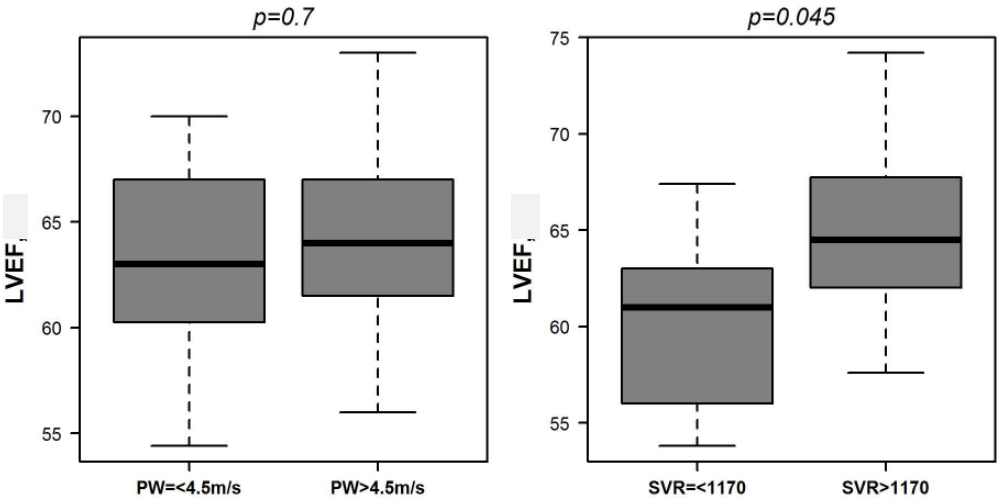


Figure A7 No clear association with Left ventricular end diastolic volume index

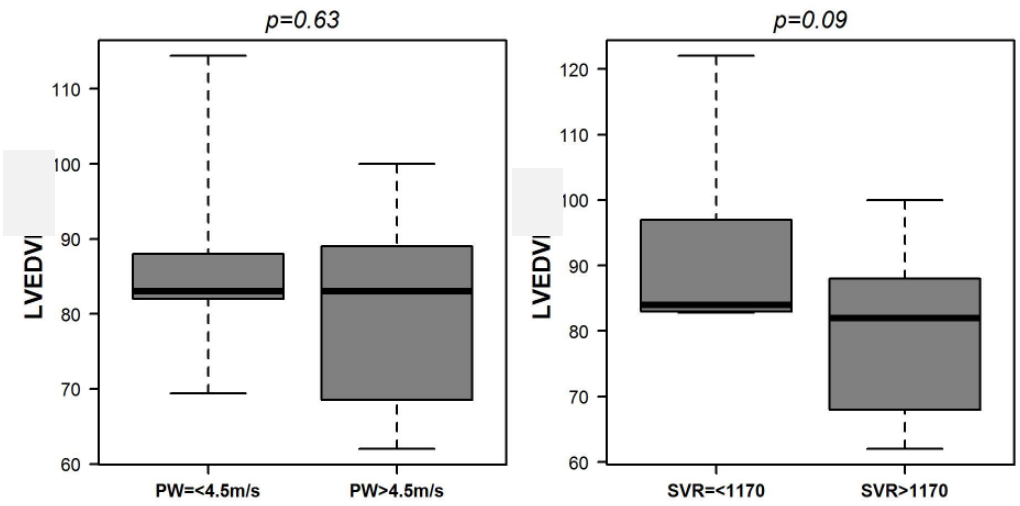


Figure A8 PWV and SVR relation to LESVI. There was no clear associations between LV end systolic volumes

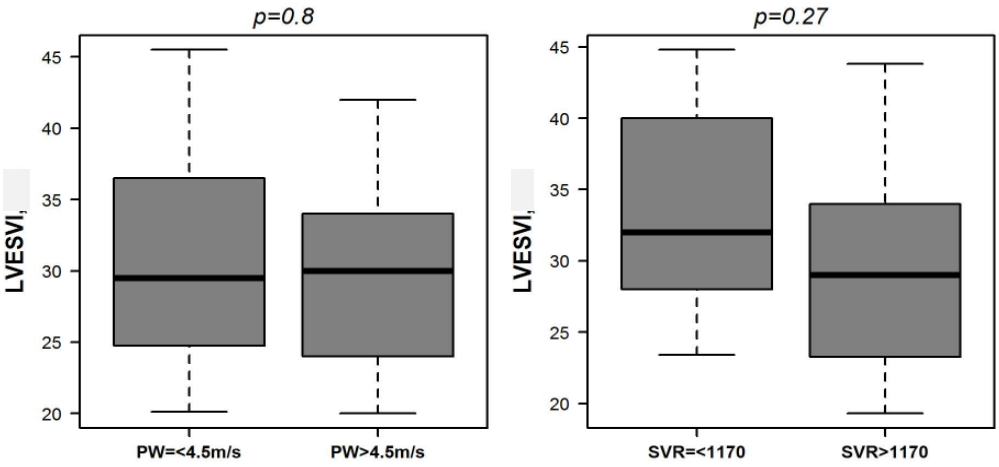


Figure A9 No clear association with LV mass

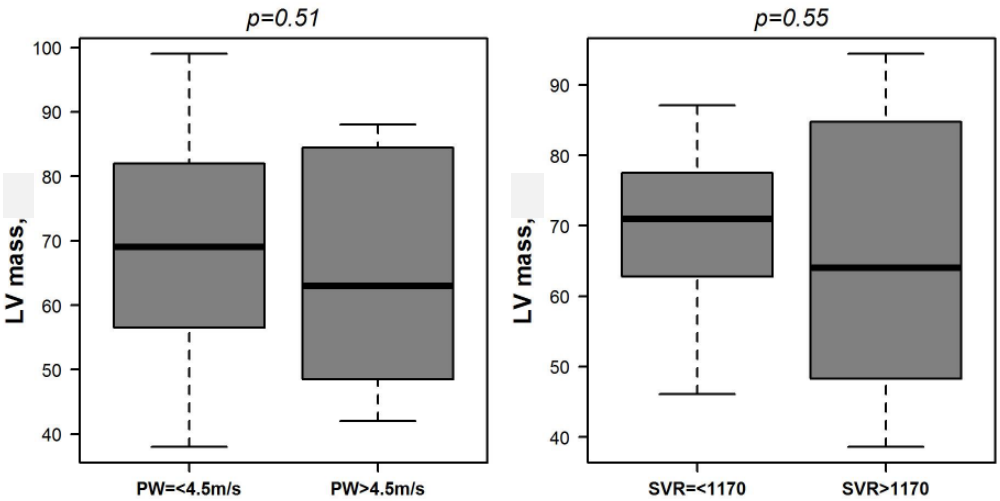


Figure A10 No association with first third filling fraction.

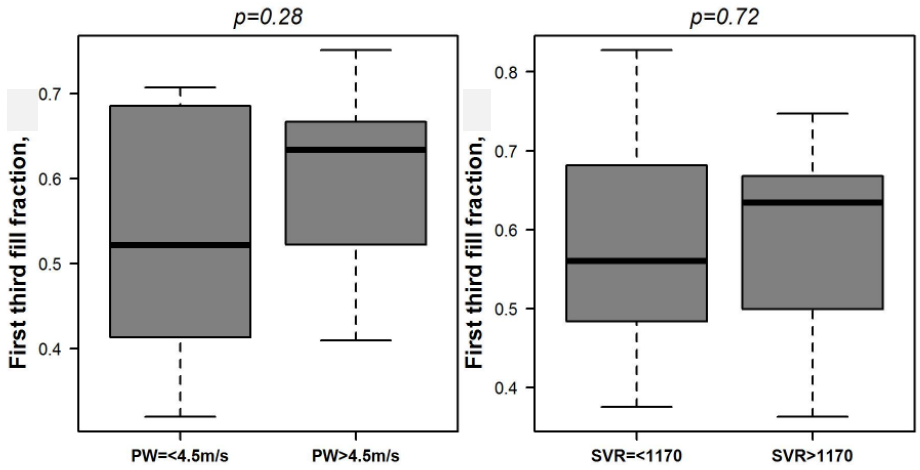


Figure A11

- Correlations between age (column 1), age at corrective intervention (column 2), PWV (column 3) and SVR (column 4).
- For example row 1 shows the age distribution in the group and respectively across row 1, association with age at intervention, PWV and SVR. PWV and SVR was significantly correlated with age. PWV was significantly associated

with SVR as shown in the figure below. Associations are repeated when the same covariates are plotted.

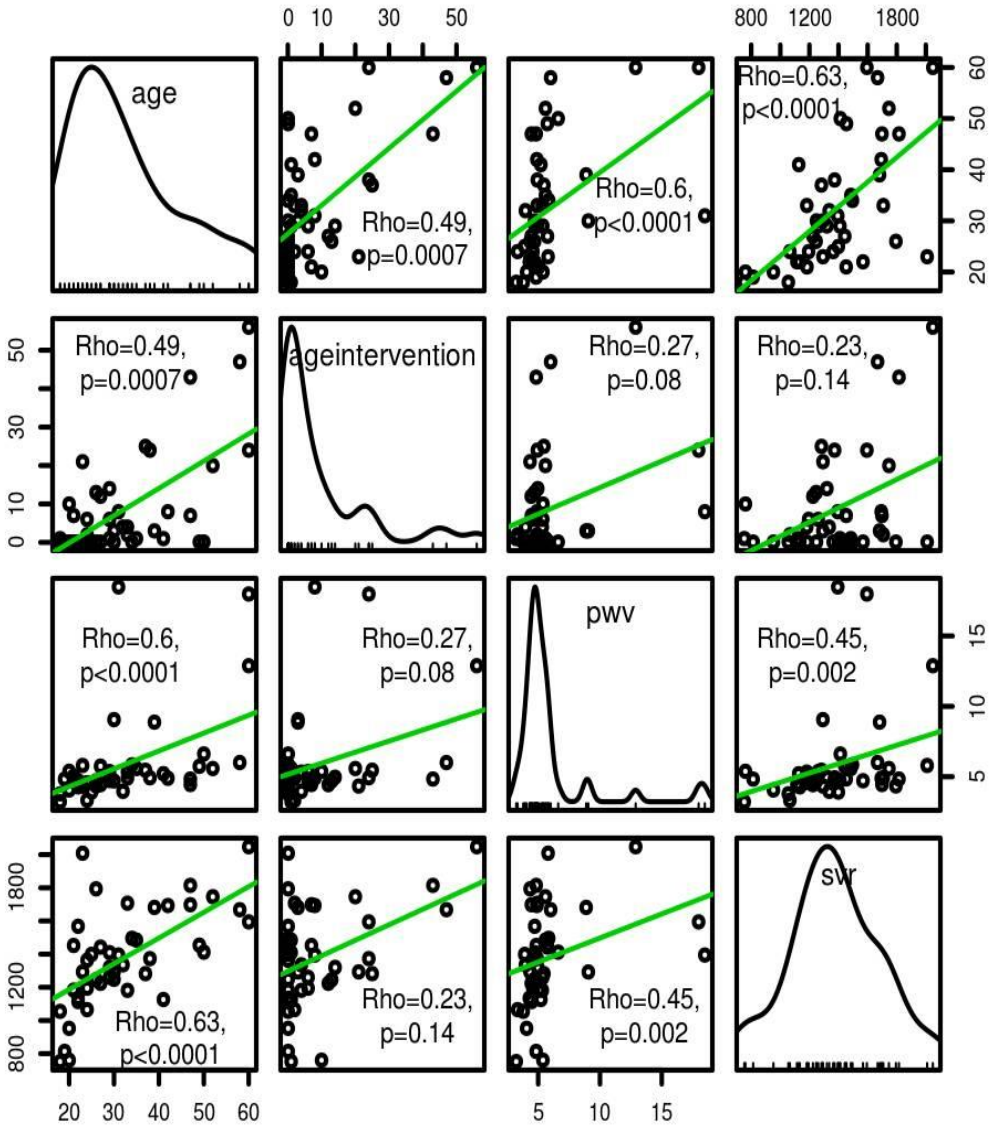


Figure A12

Association of pulse wave velocity and systemic vascular resistance and gender (There was no association of PWV with gender although SVR was found to be slightly higher in the females.)

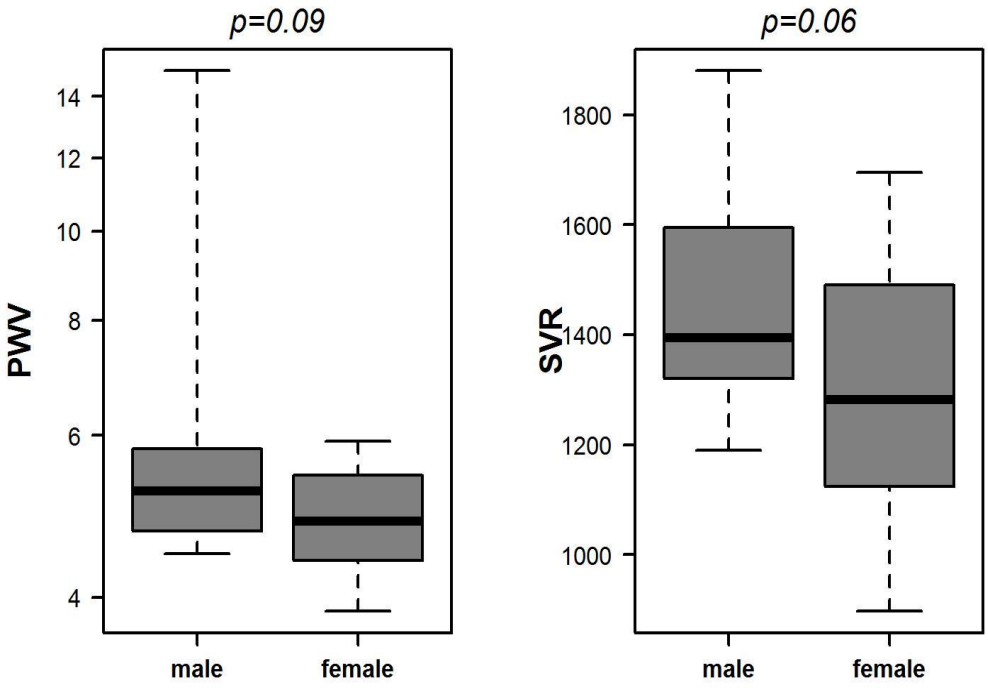


Figure A13

Association of pulse wave velocity and systemic vascular resistance with hypertension showing a weak association of PWV and hypertension

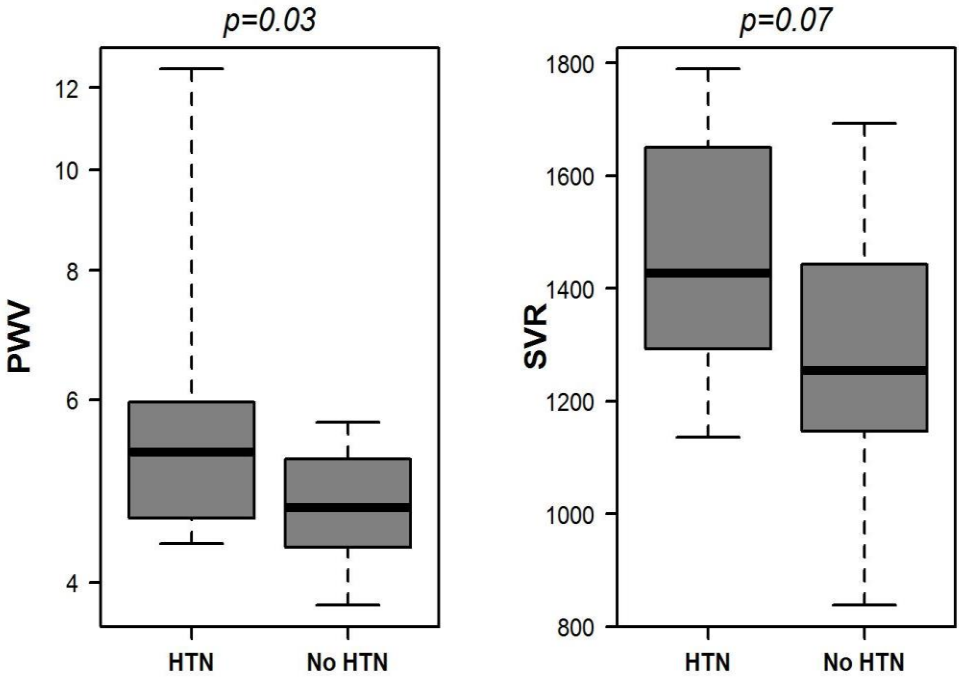


Figure A14

Association of pulse wave velocity and systemic vascular resistance with aortic valve type (no significant association)

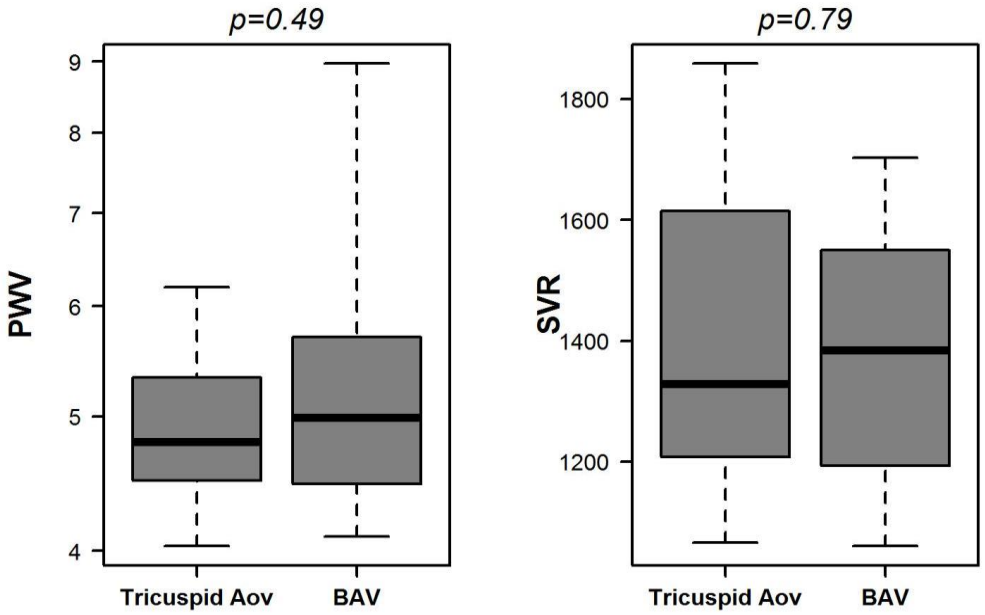


Figure A15 Association of SVR and PWV with type of repair

Figure A15 has shown that there is no relation of PWV and SVR to Surgical and percutaneous intervention. Further analysis depending upon the type of repair again has no significant association with type of repair Figure A16

SVR and PWV not related to intervention type (p= 0.789 & 0.13 respectively by, no significant association)

Figure A15

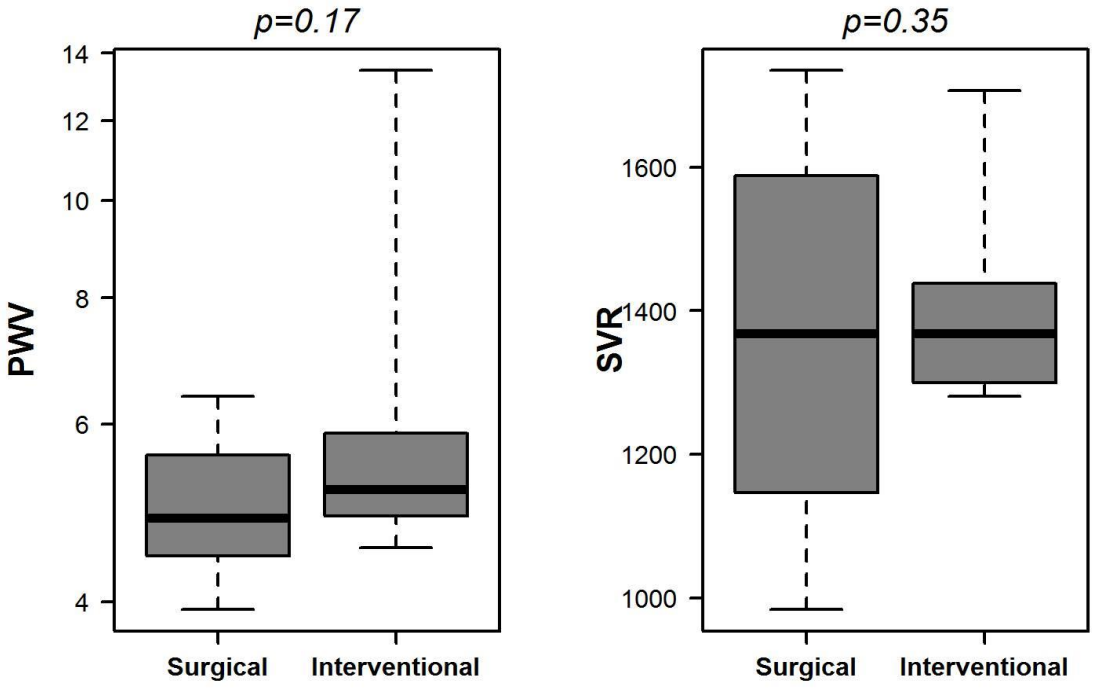


Figure A16

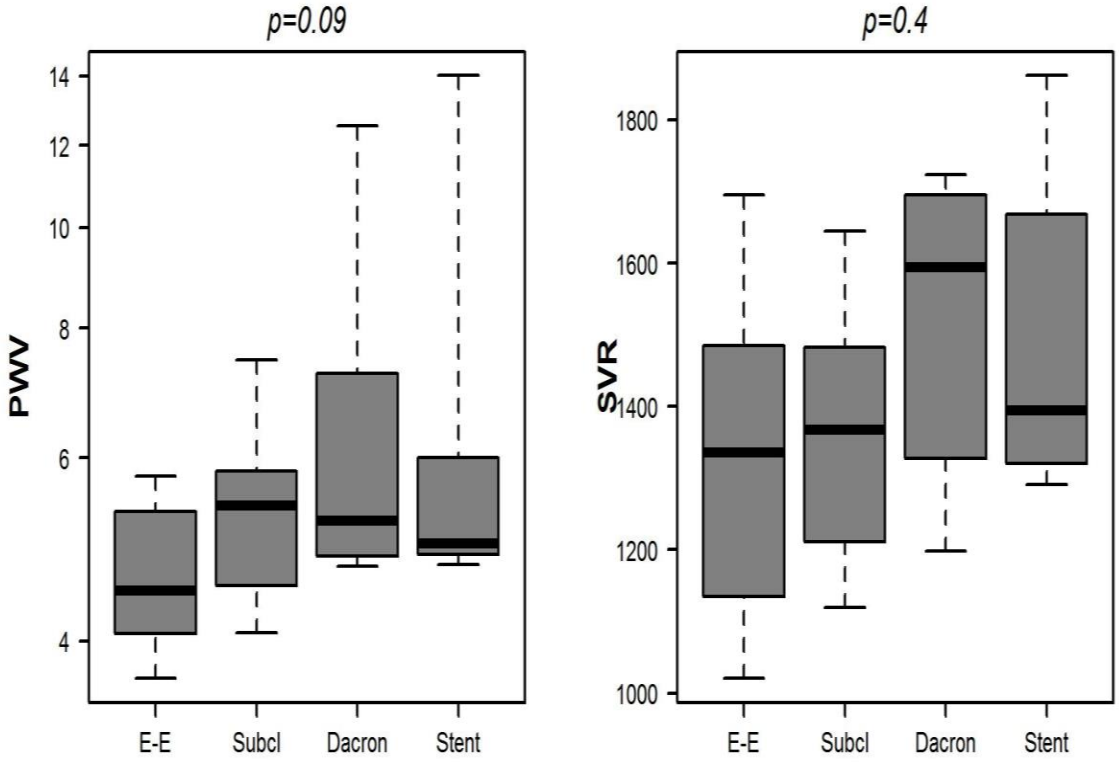
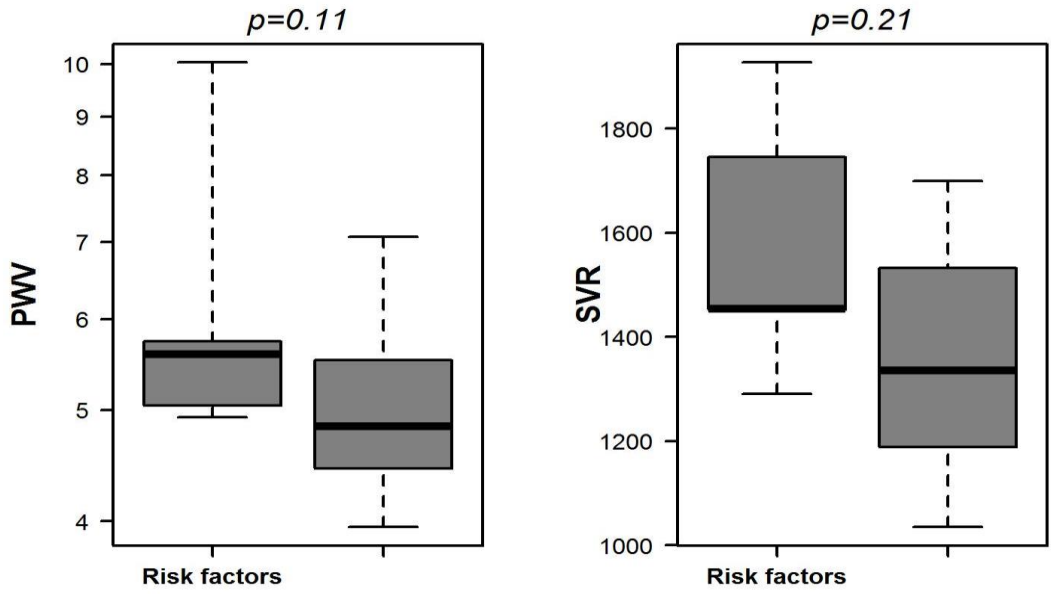


Figure A17

SVR and PWV are not related to other conventional risk factors (of smoking, diabetes and hyperlipidemia)



Multivariate analysis of Vascular Indices
Systematic vascular resistance

The following variables were entered into forward stepwise regression: age (entered as a constant variable and is therefore not shown), age at intervention, sex, bicuspid aortic valve; hypertension; foreign material (stent/Dacron patch) (Table 9). Only current age showed a significant positive association with SVR (R=0.61; p<0.001).

Table A1

Multivariable analysis for SVR[a]

Model		*Beta Intercept*	*P value*	*Correlation coefficient*
	Hypertension	*.078[b]*	*.553*	*.093*
	Foreign Material	*.091[b]*	*.511*	*.103*
1	*Female*	*.159[b]*	*.209*	*.195*
	Bicuspid aortic valve	*-.041[b]*	*.738*	*-.052*
	Age at intervention	*.051[b]*	*.748*	*.050*

a. Dependent Variable: PWV

b. Predictors in the Model: (Constant), Age

The same variables were entered into forward stepwise regression as for the SVR analysis in Table 10: age, age at intervention, sex, bicuspid valve; hypertension; foreign material (stent/Dacron patch). Again only current age showed a significant positive association with PWV (R=0.47; p=0.001)

Table A0-1

Multivariable analysis for PWV[a]

Model		Beta Intercept	P value	Correlation coefficient
1	Hypertension	.175[b]	.231	.186
	Foreign Material	.216[b]	.156	.220
	Female	.259[b]	.063	.286
	Bicuspid aortic valve	.143[b]	.299	.162
	Age at intervention	.055[b]	.756	.049

a. Dependent Variable: PWV

b. Predictors in the Model: (Constant), Age

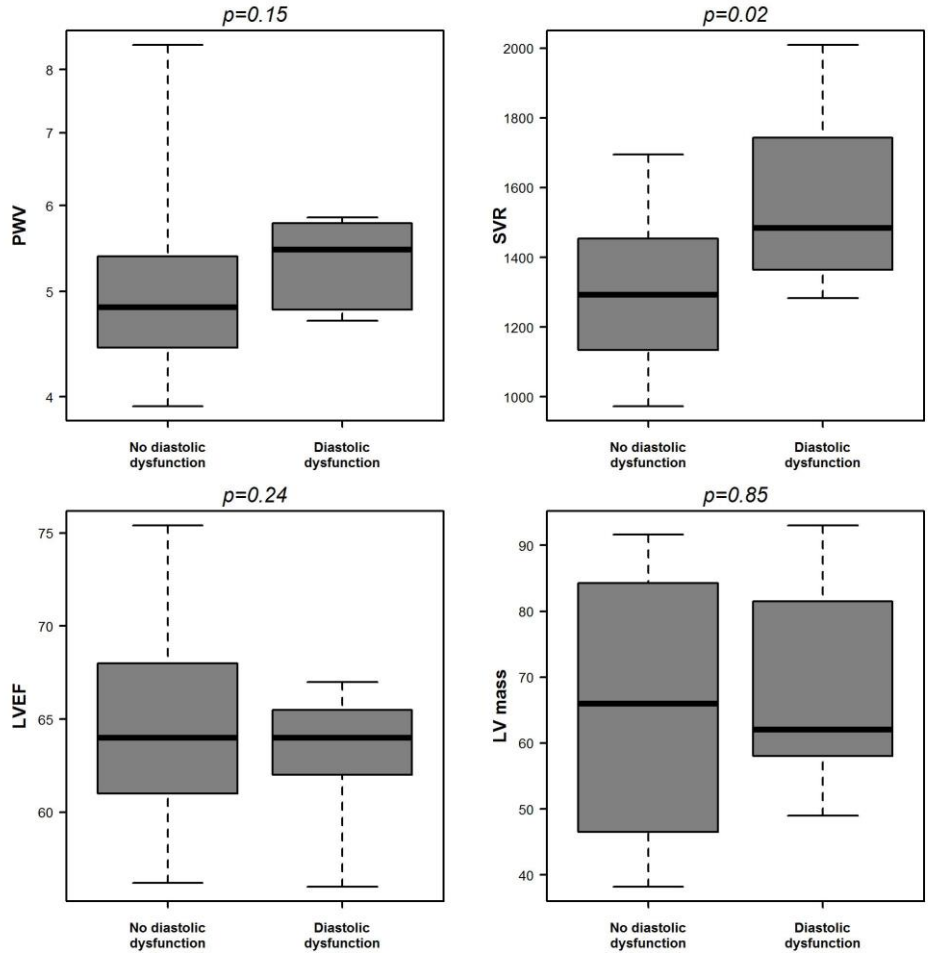
6 Functional Analysis

Eleven patients were shown to have diastolic dysfunction defined as:

- *reduced filling rate (first third filling fraction<0.45 and peak filling rate <2 EDV's/s) OR*
- *reduced early diastolic strain rate (circumferential strain rate <1.4/s and radial strain rate >-1.2/s) OR*
- *increased indexed left atrial volume (>45mls/m^2).*

Figure A18 Association of SVR and PWV with diastolic dysfunction

SVR (p=0.02) was significantly higher in patients with diastolic dysfunction but PWV (p=0.9) was not. There was no difference in left ventricular mass between the two groups. (p=0.88)



References

.

"<Br-J-Cardiol-2002-9-92-98.pdf>."

"<CCT-OCT05-INT.pdf>."

(1980). "Report of the New England Regional Infant Cardiac Program." Pediatrics **65**(2 Pt 2): 375-461.

2014, N. E. P. c. h. d. s. a. s. s. from https://www.engage.england.nhs.uk/consultation/congenital-heart-disease-standards/user_uploads/chd-consultation-doc-fin.pdf.

Aebert, H., J. Laas, P. Bednarski, U. Koch, M. Prokop and H. G. Borst (1993). "High incidence of aneurysm formation following patch plasty repair of coarctation." Eur J Cardiothorac Surg **7**(4): 200-204; discussion 205.

Ahmadi, N., V. Nabavi, F. Hajsadeghi, F. Flores, S. Azmoon, H. Ismaeel, D. Shavelle, S. S. Mao, R. Ebrahimi and M. J. Budoff (2011). "Impaired aortic distensibility measured by computed tomography is associated with the severity of coronary artery disease." Int J Cardiovasc Imaging **27**(3): 459-469.

Al-Mallah, M. H., K. Nasir, R. Katz, J. A. Lima, D. A. Bluemke, R. S. Blumenthal, S. Mao, W. G. Hundley and M. J. Budoff (2014). "Relation of thoracic aortic distensibility to left ventricular area (from the Multi-Ethnic Study of Atherosclerosis [MESA])." Am J Cardiol **113**(1): 178-182.

Alkashkari, W., S. Albugami and Z. M. Hijazi (2019). "Management of coarctation of the aorta in adult patients: state of the art." Korean circulation journal **49**(4): 298-313.

Almeida de Oliveira, S., L. A. Lisboa, L. A. Dallan, F. C. Abreu, C. E. Rochitte and J. M. de Souza (2003). "Extraanatomic aortic bypass for repair of aortic arch coarctation via sternotomy: midterm clinical and magnetic resonance imaging results." Ann Thorac Surg **76**(6): 1962-1966.

Amundsen, B. H., T. Helle-Valle, T. Edvardsen, H. Torp, J. Crosby, E. Lyseggen, A. Stoylen, H. Ihlen, J. A. Lima, O. A. Smiseth and S. A. Slordahl (2006). "Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging." J Am Coll Cardiol **47**(4): 789-793.

Asmar, R., A. Benetos, J. Topouchian, P. Laurent, B. Pannier, A. M. Brisac, R. Target and B. I. Levy (1995). "Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies." Hypertension **26**(3): 485-490.

Asmar, R. G., J. A. Topouchian, A. Benetos, F. A. Sayegh, J. J. Mourad and M. E. Safar (1997). "Non-invasive evaluation of arterial abnormalities in hypertensive patients." J Hypertens Suppl **15**(2): S99-107.

Attenhofer Jost, C. H., H. V. Schaff, H. M. Connolly, G. K. Danielson, J. A. Dearani, F. J. Puga and C. A. Warnes (2002). "Spectrum of reoperations after repair of aortic coarctation: importance of an individualized approach because of coexistent cardiovascular disease." Mayo Clin Proc **77**(7): 646-653.

Babu-Narayan, S. V., R. H. Mohiaddin, T. M. Cannell, I. V. Muhll, K. Dimopoulos and M. J. Mullen (2011). "Cardiovascular changes after transcatheter endovascular stenting of adult aortic coarctation." Int J Cardiol **149**(2): 157-163.

Backer, C. L., C. Mavroudis, E. A. Zias, Z. Amin and T. J. Weigel (1998). "Repair of coarctation with resection and extended end-to-end anastomosis." Ann Thorac Surg **66**(4): 1365-1370; discussion 1370-1361.

Baguet, J. P., B. A. Kingwell, A. L. Dart, J. Shaw, K. E. Ferrier and G. L. Jennings (2003). "Analysis of the regional pulse wave velocity by Doppler: methodology and reproducibility." J Hum Hypertens **17**(6): 407-412.

Baim, D. S. and W. Grossman (2006). Grossman's cardiac catheterization, angiography, and intervention. Philadelphia, Lippincott Williams & Wilkins.

Barton, C. H., Z. Ni and N. D. Vaziri (2001). "Enhanced nitric oxide inactivation in aortic coarctation-induced hypertension." Kidney Int **60**(3): 1083-1087.

Baumgartner, H., P. Bonhoeffer, N. M. De Groot, F. de Haan, J. E. Deanfield, N. Galie, M. A. Gatzoulis, C. Gohlke-Baerwolf, H. Kaemmerer, P. Kilner, F. Meijboom, B. J. Mulder, E. Oechslin, J. M. Oliver, A. Serraf, A. Szatmari, E. Thaulow, P. R. Vouhe, E. Walma, C. Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of, C. Association for European Paediatric and E. S. C. C. f. P. Guidelines (2010). "ESC Guidelines for the management of grown-up congenital heart disease (new version 2010)." Eur Heart J **31**(23): 2915-2957.

Baumgartner, H., J. De Backer, S. V. Babu-Narayan, W. Budts, M. Chessa, G.-P. Diller, B. Lung, J. Kluin, I. M. Lang and F. Meijboom (2021). "2020 ESC Guidelines for the management of adult congenital heart disease: The Task Force for the management of adult congenital heart disease of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Adult Congenital Heart Disease (ISACHD)." European heart journal **42**(6): 563-645.

Beauchesne, L. M., H. M. Connolly, N. M. Ammash and C. A. Warnes (2001). "Coarctation of the aorta: outcome of pregnancy." J Am Coll Cardiol **38**(6): 1728-1733.

Becker, A. E., M. J. Becker and J. E. Edwards (1970). "Anomalies associated with coarctation of aorta: particular reference to infancy." Circulation **41**(6): 1067-1075.

Bellenger, N. G., L. C. Davies, J. M. Francis, A. J. Coats and D. J. Pennell (2000). "Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance." J Cardiovasc Magn Reson **2**(4): 271-278.

Benetos, A., D. Vasmant, P. Thiery and M. Safar (1991). "Effects of ramipril on arterial hemodynamics." J Cardiovasc Pharmacol **18 Suppl 2**: S153-156.

Bergdahl, L. and A. Ljungqvist (1980). "Long-term results after repair of coarctation of the aorta by patch grafting." J Thorac Cardiovasc Surg **80**(2): 177-181.

Bhatt, A. B. and D. Defaria Yeh (2015). "Long-term outcomes in coarctation of the aorta: an evolving story of success and new challenges." Heart **101**(15): 1173-1175.

Biernacka, A. and N. G. Frangogiannis (2011). "Aging and Cardiac Fibrosis." Aging Dis **2**(2): 158-173.

Blacher, J., M. E. Safar, A. P. Guerin, B. Pannier, S. J. Marchais and G. M. London (2003). "Aortic pulse wave velocity index and mortality in end-stage renal disease." Kidney Int **63**(5): 1852-1860.

Bobby, J. J., J. M. Emami, R. D. Farmer and C. G. Newman (1991). "Operative survival and 40 year follow up of surgical repair of aortic coarctation." Br Heart J **65**(5): 271-276.

Boonyasirinant, T., P. Rajiah, R. M. Setser, M. L. Lieber, H. M. Lever, M. Y. Desai and S. D. Flamm (2009). "Aortic stiffness is increased in hypertrophic cardiomyopathy with myocardial fibrosis: novel insights in vascular function from magnetic resonance imaging." J Am Coll Cardiol **54**(3): 255-262.

Boutouyrie, P., A. I. Tropeano, R. Asmar, I. Gautier, A. Benetos, P. Lacolley and S. Laurent (2002). "Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study." Hypertension **39**(1): 10-15.

Brickner, M. E., L. D. Hillis and R. A. Lange (2000). "Congenital heart disease in adults. Second of two parts." N Engl J Med **342**(5): 334-342.

Brili, S., J. Dernellis, C. Aggeli, C. Pitsavos, C. Hatzos, C. Stefanadis and P. Toutouzas (1998). "Aortic elastic properties in patients with repaired coarctation of aorta." Am J Cardiol **82**(9): 1140-1143, A1110.

Brili, S., D. Tousoulis, C. Antoniades, C. Aggeli, A. Roubelakis, S. Papathanasiu and C. Stefanadis (2005). "Evidence of vascular dysfunction in young patients with successfully repaired coarctation of aorta." Atherosclerosis **182**(1): 97-103.

Brooke, B. S., J. P. Habashi, D. P. Judge, N. Patel, B. Loeys and H. C. Dietz, 3rd (2008). "Angiotensin II blockade and aortic-root dilation in Marfan's syndrome." N Engl J Med **358**(26): 2787-2795.

Brouwer, M. H., C. E. Kuntze, T. Ebels, M. D. Talsma and A. Eijgelaar (1991). "Repair of aortic coarctation in infants." J Thorac Cardiovasc Surg **101**(6): 1093-1098.

Brown, M. L., H. M. Burkhart, H. M. Connolly, J. A. Dearani, F. Cetta, Z. Li, W. C. Oliver, C. A. Warnes and H. V. Schaff (2013). "Coarctation of the aorta: lifelong surveillance is mandatory following surgical repair." J Am Coll Cardiol **62**(11): 1020-1025.

Brown, M. L., H. M. Burkhart, H. M. Connolly, J. A. Dearani, D. J. Hagler and H. V. Schaff (2010). "Late outcomes of reintervention on the descending aorta after repair of aortic coarctation." Circulation **122**(11_suppl_1): S81-S84.

Bunton, T. E., N. J. Biery, L. Myers, B. Gayraud, F. Ramirez and H. C. Dietz (2001). "Phenotypic alteration of vascular smooth muscle cells precedes elastolysis in a mouse model of Marfan syndrome." Circ Res **88**(1): 37-43.

Cameron, J. D., I. T. Meredith and S. A. Hope (2006). "Letter by Cameron et al regarding article, "Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study"." Circulation **114**(15): e538; author reply e540-531.

Campbell, M. (1970). "Natural history of coarctation of the aorta." Br Heart J **32**(5): 633-640.

Canniffe, C., P. Ou, K. Walsh, D. Bonnet and D. Celermajer (2013). "Hypertension after repair of aortic coarctation—a systematic review." International journal of cardiology **167**(6): 2456-2461.

Cavalcante, J. L., J. A. Lima, A. Redheuil and M. H. Al-Mallah (2011). "Aortic stiffness: current understanding and future directions." J Am Coll Cardiol **57**(14): 1511-1522.

Celermajer, D. S. and J. E. Deanfield (1991). "Adults with congenital heart disease." BMJ **303**(6815): 1413-1414.

Chadha, S. L., N. Singh and D. K. Shukla (2001). "Epidemiological study of congenital heart disease." Indian J Pediatr **68**(6): 507-510.

Chong, W. Y., W. H. Wong, C. S. Chiu and Y. F. Cheung (2006). "Aortic root dilation and aortic elastic properties in children after repair of tetralogy of Fallot." Am J Cardiol **97**(6): 905-909.

Choudhary, P., C. Canniffe, D. J. Jackson, D. Tanous, K. Walsh and D. S. Celermajer (2015). "Late outcomes in adults with coarctation of the aorta." Heart **101**(15): 1190-1195.

Clarkson, P. M., M. R. Nicholson, B. G. Barratt-Boyes, J. M. Neutze and R. M. Whitlock (1983). "Results after repair of coarctation of the aorta beyond infancy: a 10 to 28 year follow-up with particular reference to late systemic hypertension." Am J Cardiol **51**(9): 1481-1488.

Cohen, M., V. Fuster, P. M. Steele, D. Driscoll and D. C. McGoon (1989). "Coarctation of the aorta. Long-term follow-up and prediction of outcome after surgical correction." Circulation **80**(4): 840-845.

Cokkinos, D. V., R. D. Leachman and D. A. Cooley (1979). "Increased mortality rate from coronary artery disease following operation for coarctation of the aorta at a late age." J Thorac Cardiovasc Surg **77**(2): 315-318.

Connelly, M. S., G. D. Webb, J. Somerville, C. A. Warnes, J. K. Perloff, R. R. Liberthson, F. J. Puga, R. L. Collins-Nakai, W. G. Williams, L. A. Mercier, V. F. Huckell, J. P. Finley and R. McKay (1998). "Canadian Consensus Conference on Adult Congenital Heart Disease 1996." Can J Cardiol **14**(3): 395-452.

Connelly, M. S., G. D. Webb, J. Somerville, C. A. Warnes, J. K. Perloff, R. R. Liberthson, F. J. Puga, R. L. Collins-Nakai, W. G. Williams, L. A. Mercier, V. F. Huckell, J. P. Finley and R. McKay (1998). "[Canadian Consensus Conference on Congenital Heart Defects in the Adult 1996]." Can J Cardiol **14**(4): 533-597.

Cook, S. C., A. K. Ferketich and S. V. Raman (2009). "Myocardial ischemia in asymptomatic adults with repaired aortic coarctation." Int J Cardiol **133**(1): 95-101.

Cruickshank, K., L. Riste, S. G. Anderson, J. S. Wright, G. Dunn and R. G. Gosling (2002). "Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function?" Circulation **106**(16): 2085-2090.

Daniels, S. R. (2001). "Repair of coarctation of the aorta and hypertension: does age matter." The Lancet **358**(9276): 89.

de Bono, J. and L. J. Freeman (2005). "Aortic coarctation repair--lost and found: the role of local long term specialised care." Int J Cardiol **104**(2): 176-183.

Deal, K. and C. F. Wooley (1973). "Coarctation of the aorta and pregnancy." Ann Intern Med **78**(5): 706-710.

Di Salvo, G., B. Castaldi, S. Gala, L. Baldini, F. Del Gaizo, F. A. D'Aiello, A. Mormile, A. Rea, G. Scognamiglio, G. Pacileo, S. Keating, B. M. Fadel, L. Berrino, A. Perna, M. G. Russo and R. Calabro (2016). "Atenolol vs enalapril in young hypertensive patients after successful repair of aortic coarctation." J Hum Hypertens **30**(6): 363-367.

Dietl, C. A., A. R. Torres, R. G. Favaloro, C. L. Fessler and G. L. Grunkemeier (1992). "Risk of recoarctation in neonates and infants after repair with patch aortoplasty, subclavian flap, and the combined resection-flap procedure." J Thorac Cardiovasc Surg **103**(4): 724-731; discussion 731-722.

Diller, G. P., R. Alonso-Gonzalez, K. Dimopoulos, M. Alvarez-Barredo, C. Koo, A. Kempny, C. Harries, L. Parfitt, A. S. Uebing, L. Swan, P. S. Marino, S. J. Wort and M. A. Gatzoulis (2013). "Disease targeting therapies in patients with Eisenmenger syndrome: response to treatment and long-term efficiency." Int J Cardiol **167**(3): 840-847.

Diller, G. P. and M. A. Gatzoulis (2007). "Pulmonary vascular disease in adults with congenital heart disease." Circulation **115**(8): 1039-1050.

Diller, G. P., A. Kempny, R. Alonso-Gonzalez, L. Swan, A. Uebing, W. Li, S. Babu-Narayan, S. J. Wort, K. Dimopoulos and M. A. Gatzoulis (2015). "Survival Prospects and Circumstances of Death in Contemporary Adult Congenital Heart Disease Patients Under Follow-Up at a Large Tertiary Centre." Circulation **132**(22): 2118-2125.

Doyle, A., P. B. Mark, N. Johnston, J. Foster, J. M. Connell, H. Dargie, A. Jardine and N. Padmanabhan (2008). "Aortic stiffness and diastolic flow abnormalities in end-stage renal disease assessed by magnetic resonance imaging." Nephron Clin Pract **109**(1): c1-8.

Drenthen, W., P. G. Pieper, J. W. Roos-Hesselink, W. A. van Lottum, A. A. Voors, B. J. Mulder, A. P. van Dijk, H. W. Vliegen, S. C. Yap, P. Moons, T. Ebels, D. J. van Veldhuisen and Z. Investigators (2007). "Outcome of pregnancy in women with congenital heart disease: a literature review." J Am Coll Cardiol **49**(24): 2303-2311.

Engelfriet, P., E. Boersma, E. Oechslin, J. Tijssen, M. A. Gatzoulis, U. Thilen, H. Kaemmerer, P. Moons, F. Meijboom, J. Popelova, V. Laforest, R. Hirsch, L. Daliento, E. Thaulow and B. Mulder (2005). "The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. The Euro Heart Survey on adult congenital heart disease." Eur Heart J **26**(21): 2325-2333.

Engelings, C. C., P. C. Helm, H. Abdul-Khaliq, B. Asfour, U. M. Bauer, H. Baumgartner, D. Kececioglu, M. A. Korten, G. P. Diller and O. Tutarel (2016). "Cause of death in adults with congenital heart disease - An analysis of the German National Register for Congenital Heart Defects." Int J Cardiol **211**: 31-36.

Erbel, R., V. Aboyans, C. Boileau, E. Bossone, R. Di Bartolomeo, H. Eggebrecht, A. Evangelista, V. Falk, H. Frank, O. Gaemperli, M. Grabenwoger, A. Haverich, B. Iung, A. John Manolis, F. Meijboom, C. A. Nienaber, M. Roffi, H. Rousseau, U. Sechtem, P. A. Sirnes, R. S. von Allmen, C. J. Vrints and m. Authors/Task Force (2015). "Corrigendum to: 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases." Eur Heart J **36**(41): 2779.

Erben, Y., G. S. Oderich, H. J. M. Verhagen, M. Witsenburg, A. T. van den Hoven, E. S. Debus, T. Kolbel, F. R. Arko, 3rd, G. B. Torsello, G. F. Torsello, P. F. Lawrence, M. P. Harlander-Locke, J. M. Bacharach, W. D. Jordan, Jr., M. K. Eskandari and D. J. Hagler (2019). "Multicenter experience with endovascular treatment of aortic coarctation in adults." J Vasc Surg **69**(3): 671-679 e671.

Faganello, G., M. Fisicaro, G. Russo, A. Iorio, C. Mazzone, E. Grande, F. Humar, A. Cherubini, C. Pandullo, G. Barbati, L. Tarantini, A. Benettoni, M. Pozzi, A. Di Lenarda and G. Cioffi (2016). "Insights

from Cardiac Mechanics after Three Decades from Successfully Repaired Aortic Coarctation." Congenit Heart Dis **11**(3): 254-261.

Fedak, P. W., M. P. de Sa, S. Verma, N. Nili, P. Kazemian, J. Butany, B. H. Strauss, R. D. Weisel and T. E. David (2003). "Vascular matrix remodeling in patients with bicuspid aortic valve malformations: implications for aortic dilatation." J Thorac Cardiovasc Surg **126**(3): 797-806.

Feltes, T. F., E. Bacha, R. H. Beekman, 3rd, J. P. Cheatham, J. A. Feinstein, A. S. Gomes, Z. M. Hijazi, F. F. Ing, M. de Moor, W. R. Morrow, C. E. Mullins, K. A. Taubert, E. M. Zahn, Y. American Heart Association Congenital Cardiac Defects Committee of the Council on Cardiovascular Disease in the, C. Council on Clinical, R. Council on Cardiovascular, Intervention and A. American Heart (2011). "Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association." Circulation **123**(22): 2607-2652.

Ferguson, M. and A. H. Kovacs (2016). "An Integrated Adult Congenital Heart Disease Psychology Service." Congenit Heart Dis **11**(5): 444-451.

Fernandes, V. R., J. F. Polak, S. Cheng, B. D. Rosen, B. Carvalho, K. Nasir, R. McClelland, G. Hundley, G. Pearson, D. H. O'Leary, D. A. Bluemke and J. A. Lima (2008). "Arterial stiffness is associated with regional ventricular systolic and diastolic dysfunction: the Multi-Ethnic Study of Atherosclerosis." Arterioscler Thromb Vasc Biol **28**(1): 194-201.

Firmin, D. N., G. L. Nayler, R. H. Klipstein, S. R. Underwood, R. S. Rees and D. B. Longmore (1987). "In vivo validation of MR velocity imaging." J Comput Assist Tomogr **11**(5): 751-756.

Fletcher, S. E., J. P. Cheatham and S. Froeming (1998). "Aortic aneurysm following primary balloon angioplasty and secondary endovascular stent placement in the treatment of native coarctation of the aorta." Cathet Cardiovasc Diagn **44**(1): 40-44.

Forbes, T. J., S. Garekar, Z. Amin, E. M. Zahn, D. Nykanen, P. Moore, S. A. Qureshi, J. P. Cheatham, M. R. Ebeid, Z. M. Hijazi, S. Sandhu, D. J. Hagler, H. Sievert, T. E. Fagan, J. Ringewald, W. Du, L. Tang, D. F. Wax, J. Rhodes, T. A. Johnston, T. K. Jones, D. R. Turner, C. A. Pedra, W. E. Hellenbrand and C. Congenital Cardiovascular Interventional Study (2007). "Procedural results and acute complications in stenting native and recurrent coarctation of the aorta in patients over 4 years of age: a multi-institutional study." Catheter Cardiovasc Interv **70**(2): 276-285.

Forbes, T. J., D. W. Kim, W. Du, D. R. Turner, R. Holzer, Z. Amin, Z. Hijazi, A. Ghasemi, J. J. Rome, D. Nykanen, E. Zahn, C. Cowley, M. Hoyer, D. Waight, D. Gruenstein, A. Javois, S. Foerster, J. Kreutzer, N. Sullivan, A. Khan, C. Owada, D. Hagler, S. Lim, J. Canter, T. Zellers and C. Investigators (2011). "Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (Congenital Cardiovascular Interventional Study Consortium)." J Am Coll Cardiol **58**(25): 2664-2674.

Franklin, S. S. (2005). "Arterial stiffness and hypertension: a two-way street?" Hypertension **45**(3): 349-351.

Freeman, L. J. (2008). "Grown up congenital heart (GUCH) disease: a half century of change." Clin Med **8**(2): 169-171.

Freeman, L. J., S. Wood, T. Hardiman and A. J. Page (2002). "Grown-up congenital heart disease: experience in a district general hospital." British journal of cardiology **9**(2): 92-98.

Gardiner, H. M., D. S. Celermajer, K. E. Sorensen, D. Georgakopoulos, J. Robinson, O. Thomas and J. E. Deanfield (1994). "Arterial reactivity is significantly impaired in normotensive young adults after successful repair of aortic coarctation in childhood." Circulation **89**(4): 1745-1750.

Gatehouse, P. D., J. Keegan, L. A. Crowe, S. Masood, R. H. Mohiaddin, K. F. Kreitner and D. N. Firmin (2005). "Applications of phase-contrast flow and velocity imaging in cardiovascular MRI." Eur Radiol **15**(10): 2172-2184.

Gidding, S. S., A. P. Rocchini, C. Moorehead, M. A. Schork and A. Rosenthal (1985). "Increased forearm vascular reactivity in patients with hypertension after repair of coarctation." Circulation **71**(3): 495-499.

Golden, A. B. and W. E. Hellenbrand (2007). "Coarctation of the aorta: stenting in children and adults." Catheter Cardiovasc Interv **69**(2): 289-299.

Greutmann, M., D. Tobler, A. H. Kovacs, M. Greutmann-Yantiri, S. R. Haile, L. Held, J. Ivanov, W. G. Williams, E. N. Oechslin, C. K. Silversides and J. M. Colman (2015). "Increasing mortality burden among adults with complex congenital heart disease." Congenit Heart Dis **10**(2): 117-127.

Grover, S., J. S. Brandt, U. M. Reddy and C. V. Ananth (2021). "Chronic hypertension, perinatal mortality and the impact of preterm delivery: a population-based study." BJOG.

Gupta, I., M. L. Gupta, A. Parihar and C. D. Gupta (1992). "Epidemiology of rheumatic and congenital heart diseases in school children." J Indian Med Assoc **90**(3): 57-59.

Hager, A., S. Kanz, H. Kaemmerer, C. Schreiber and J. Hess (2007). "Coarctation Long-term Assessment (COALA): significance of arterial hypertension in a cohort of 404 patients up to 27 years after surgical repair of isolated coarctation of the aorta, even in the absence of restenosis and prosthetic material." J Thorac Cardiovasc Surg **134**(3): 738-745.

Hamid, T., M. Motwani, H. Schneider, J. S. Dua, A. Hoschtitzky, B. Clarke and V. S. Mahadevan (2015). "Benefit of endovascular stenting for aortic coarctation on systemic hypertension in adults." Arch Cardiovasc Dis **108**(12): 626-633.

Harrison, D. A., P. R. McLaughlin, C. Lazzam, M. Connelly and L. N. Benson (2001). "Endovascular stents in the management of coarctation of the aorta in the adolescent and adult: one year follow up." Heart **85**(5): 561-566.

Heesen, W. F., F. W. Beltman, A. J. Smit, J. F. May, P. A. de Graeff, J. H. Muntinga, T. K. Havinga, F. H. Schuurman, E. van der Veur, B. Meyboom-de Jong and K. I. Lie (2001). "Reversal of pathophysiologic changes with long-term lisinopril treatment in isolated systolic hypertension." J Cardiovasc Pharmacol **37**(5): 512-521.

Heinemann, M. K., G. Ziemer, T. Wahlers, A. Kohler and H. G. Borst (1997). "Extraanatomic thoracic aortic bypass grafts: indications, techniques, and results." Eur J Cardiothorac Surg **11**(1): 169-175.

Herment, A., M. Lefort, N. Kachenoura, A. De Cesare, V. Taviani, M. J. Graves, C. Pellot-Barakat, F. Frouin and E. Mousseaux (2011). "Automated estimation of aortic strain from steady-state free-precession and phase contrast MR images." Magn Reson Med **65**(4): 986-993.

Hessling, G. (2016). "[Arrhythmia in adults with congenital heart disease : Acute and long-term management]." Herzschrittmacherther Elektrophysiol.

Ho, S. Y. and R. H. Anderson (1979). "Coarctation, tubular hypoplasia, and the ductus arteriosus. Histological study of 35 specimens." Br Heart J **41**(3): 268-274.

Hoffman, J. I. (1990). "Congenital heart disease: incidence and inheritance." Pediatr Clin North Am **37**(1): 25-43.

Hoffman, J. I. and S. Kaplan (2002). "The incidence of congenital heart disease." J Am Coll Cardiol **39**(12): 1890-1900.

Holzer, R. J., J. L. Chisolm, S. L. Hill and J. P. Cheatham (2008). "Stenting complex aortic arch obstructions." Catheter Cardiovasc Interv **71**(3): 375-382.

Hussain, T., M. Burch, G. F. Greil, M. Cecelja and M. Fenton (2012). "Central aortic stiffness, hypertension, and coronary allograft vasculopathy in children." J Heart Lung Transplant **31**(12): 1318-1320.

Inouye, I., B. Massie, D. Loge, N. Topic, D. Silverstein, P. Simpson and J. Tubau (1984). "Abnormal left ventricular filling: an early finding in mild to moderate systemic hypertension." Am J Cardiol **53**(1): 120-126.

Ishikawa, T., S. Iwashima, A. Ohishi, Y. Nakagawa and T. Ohzeki (2011). "Prevalence of congenital heart disease assessed by echocardiography in 2067 consecutive newborns." Acta Paediatr **100**(8): e55-60.

Isner, J. M., R. F. Donaldson, D. Fulton, I. Bhan, D. D. Payne and R. J. Cleveland (1987). "Cystic medial necrosis in coarctation of the aorta: a potential factor contributing to adverse consequences observed after percutaneous balloon angioplasty of coarctation sites." Circulation **75**(4): 689-695.

Iung, B. (2015). "New ESC guidelines: aortic disease." Heart **101**(6): 421-423.

Izzo, J. L., Jr. (2004). "Arterial stiffness and the systolic hypertension syndrome." Curr Opin Cardiol **19**(4): 341-352.

Jenkins, N. and C. Ward (1999). "Coarctation of the aorta: natural history and outcome after surgical treatment." Qjm **92**(7): 365-371.

Jenkins, N. P. and C. Ward (1999). "Coarctation of the aorta: natural history and outcome after surgical treatment." QJM **92**(7): 365-371.

Jensen, H. A., K. L. Brown, C. Pagel, D. J. Barron and R. C. Franklin (2014). "Mortality as a measure of quality of care in infants with congenital cardiovascular malformations following surgery." Br Med Bull **111**(1): 5-15.

Jurcut, R., A. M. Daraban, A. Lorber, D. Deleanu, M. S. Amzulescu, C. Zara, B. A. Popescu and C. Ginghina (2011). "Coarctation of the aorta in adults: what is the best treatment? Case report and literature review." J Med Life **4**(2): 189-195.

Kaemmerer, H., M. Gorenflo, M. Hoeper, D. Huscher, P. Ewert and D. Pittrow (2013). "[Pulmonary arterial hypertension in patients with congenital heart disease: current issues and health care situation]." Dtsch Med Wochenschr **138**(23): 1247-1252.

Kaufman, R., I. Nunes, J. A. Bolognese, D. L. Miller, D. Salotti, J. M. McCarthy, W. B. Smith, G. A. Herman and P. U. Feig (2010). "Single-dose effects of isosorbide mononitrate alone or in combination with losartan on central blood pressure." J Am Soc Hypertens **4**(6): 311-318.

Khairy, P., R. Ionescu-Ittu, A. S. Mackie, M. Abrahamowicz, L. Pilote and A. J. Marelli (2010). "Changing mortality in congenital heart disease." J Am Coll Cardiol **56**(14): 1149-1157.

Khalil, A., R. Aggarwal, S. Thirupuram and R. Arora (1994). "Incidence of congenital heart disease among hospital live births in India." Indian Pediatr **31**(5): 519-527.

Khoshdel, A. R., A. Thakkinstian, S. L. Carney and J. Attia (2006). "Estimation of an age-specific reference interval for pulse wave velocity: a meta-analysis." J Hypertens **24**(7): 1231-1237.

Khoshnood, B., N. Lelong, L. Houyel, A. C. Thieulin, J. M. Jouannic, S. Magnier, A. L. Delezoide, J. F. Magny, C. Rambaud, D. Bonnet, F. Goffinet and E. S. Group (2012). "Prevalence, timing of diagnosis and mortality of newborns with congenital heart defects: a population-based study." Heart **98**(22): 1667-1673.

Klenk, C., R. Gawande, L. Uslu, A. Khurana, D. Qiu, A. Quon, J. Donig, J. Rosenberg, S. Luna-Fineman, M. Moseley and H. E. Daldrup-Link (2014). "Ionising radiation-free whole-body MRI versus (18)F-fluorodeoxyglucose PET/CT scans for children and young adults with cancer: a prospective, non-randomised, single-centre study." Lancet Oncol **15**(3): 275-285.

Knyshov, G. V., L. L. Sitar, M. D. Glagola and M. Y. Atamanyuk (1996). "Aortic aneurysms at the site of the repair of coarctation of the aorta: a review of 48 patients." Ann Thorac Surg **61**(3): 935-939.

Kobayashi, M., M. Ando, N. Wada and Y. Takahashi (2009). "Outcomes following surgical repair of aortic arch obstructions with associated cardiac anomalies." Eur J Cardiothorac Surg **35**(4): 565-568.

Koller, M., M. Rothlin and A. Senning (1987). "Coarctation of the aorta: review of 362 operated patients. Long-term follow-up and assessment of prognostic variables." Eur Heart J **8**(7): 670-679.

Kopel, L., F. Tarasoutchi, C. Medeiros, R. T. Carvalho, M. Grinberg and S. G. Lage (2001). "Arterial distensibility as a possible compensatory mechanism in chronic aortic insufficiency." Arq Bras Cardiol **77**(3): 258-265.

Kovacs, A. H., C. Silversides, A. Saidi and S. F. Sears (2006). "The role of the psychologist in adult congenital heart disease." Cardiol Clin **24**(4): 607-618, vi.

Kovacs, A. H. and E. M. Utens (2015). "More Than Just the Heart: Transition and Psychosocial Issues in Adult Congenital Heart Disease." Cardiol Clin **33**(4): 625-634, ix.

Krieger, E. V. and K. Stout (2010). "The adult with repaired coarctation of the aorta." Heart **96**(20): 1676-1681.

Kumar, S., U. B. Tedrow and J. K. Triedman (2015). "Arrhythmias in Adult Congenital Heart Disease: Diagnosis and Management." Cardiol Clin **33**(4): 571-588, viii.

Kutty, S., S. Rangamani, J. Venkataraman, L. Li, A. Schuster, S. E. Fletcher, D. A. Danford and P. Beerbaum (2013). "Reduced global longitudinal and radial strain with normal left ventricular ejection fraction late after effective repair of aortic coarctation: a CMR feature tracking study." Int J Cardiovasc Imaging **29**(1): 141-150.

Lacour-Gayet, F., J. Bruniaux, A. Serraf, P. Chambran, G. Blaysat, J. Losay, J. Petit, J. Kachaner and C. Planche (1990). "Hypoplastic transverse arch and coarctation in neonates. Surgical reconstruction of the aortic arch: a study of sixty-six patients." J Thorac Cardiovasc Surg **100**(6): 808-816.

Lam, Y. Y., M. J. Mullen, M. G. Kaya, M. A. Gatzoulis, W. Li and M. Y. Henein (2009). "Left ventricular long axis dysfunction in adults with "corrected" aortic coarctation is related to an older age at intervention and increased aortic stiffness." Heart **95**(9): 733-739.

Lam, Y. Y., M. J. Mullen, M. G. Kaya, M. A. Gatzoulis, W. Li and M. Y. Henein (2010). "Left ventricular and ascending aortic function after stenting of native coarctation of aorta." Am J Cardiol **105**(9): 1343-1347.

Lang, R. M., M. Bierig, R. B. Devereux, F. A. Flachskampf, E. Foster, P. A. Pellikka, M. H. Picard, M. J. Roman, J. Seward, J. S. Shanewise, S. D. Solomon, K. T. Spencer, M. S. Sutton, W. J. Stewart, G. Chamber Quantification Writing, G. American Society of Echocardiography's, C. Standards and E. European Association of (2005). "Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology." J Am Soc Echocardiogr **18**(12): 1440-1463.

Lauenstein, T. C., S. C. Goehde, C. U. Herborn, M. Goyen, C. Oberhoff, J. F. Debatin, S. G. Ruehm and J. Barkhausen (2004). "Whole-body MR imaging: evaluation of patients for metastases." Radiology **233**(1): 139-148.

Laurent, S., P. Boutouyrie, R. Asmar, I. Gautier, B. Laloux, L. Guize, P. Ducimetiere and A. Benetos (2001). "Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients." Hypertension **37**(5): 1236-1241.

Lawrie, G. M., M. E. DeBakey, G. C. Morris, Jr., E. S. Crawford, W. F. Wagner and D. H. Glaeser (1981). "Late repair of coarctation of the descending thoracic aorta in 190 patients. Results up to 30 years after operation." Arch Surg **116**(12): 1557-1560.

Lee, C. I., A. H. Haims, E. P. Monico, J. A. Brink and H. P. Forman (2004). "Diagnostic CT scans: assessment of patient, physician, and radiologist awareness of radiation dose and possible risks." Radiology **231**(2): 393-398.

Lee, M. G., S. V. Babu-Narayan, A. Kempny, A. Uebing, C. Montanaro, D. F. Shore, Y. d'Udekem and M. A. Gatzoulis (2019). "Long-term mortality and cardiovascular burden for adult survivors of coarctation of the aorta." Heart **105**(15): 1190-1196.

Lee, M. G., R. Kowalski, J. C. Galati, M. M. Cheung, B. Jones, J. Koleff and Y. d'Udekem (2012). "Twenty-four-hour ambulatory blood pressure monitoring detects a high prevalence of hypertension late after coarctation repair in patients with hypoplastic arches." J Thorac Cardiovasc Surg **144**(5): 1110-1116.

Lee, R. T. and R. D. Kamm (1994). "Vascular mechanics for the cardiologist." J Am Coll Cardiol **23**(6): 1289-1295.

Lehmann, E. D., J. R. Parker, K. D. Hopkins, M. G. Taylor and R. G. Gosling (1993). "Validation and reproducibility of pressure-corrected aortic distensibility measurements using pulse-wave-velocity Doppler ultrasound." J Biomed Eng **15**(3): 221-228.

Leirgul, E., T. Fomina, K. Brodwall, G. Greve, H. Holmstrøm, S. E. Vollset, G. S. Tell and N. Øyen (2014). "Birth prevalence of congenital heart defects in Norway 1994-2009—A nationwide study." American Heart Journal.

Lip, G. Y., D. C. Felmeden, F. L. Li-Saw-Hee and D. G. Beevers (2000). "Hypertensive heart disease. A complex syndrome or a hypertensive 'cardiomyopathy'?" Eur Heart J **21**(20): 1653-1665.

Lombardi, K. C., V. Northrup, R. L. McNamara, L. Sugeng and C. G. Weismann (2013). "Aortic stiffness and left ventricular diastolic function in children following early repair of aortic coarctation." Am J Cardiol **112**(11): 1828-1833.

Loomba, R. S., M. W. Buelow, S. Aggarwal, R. R. Arora, J. Kovach and S. Ginde (2016). "Arrhythmias in Adults with Congenital Heart Disease: What Are Risk Factors for Specific Arrhythmias?" Pacing Clin Electrophysiol.

Lotz, J., C. Meier, A. Leppert and M. Galanski (2002). "Cardiovascular flow measurement with phase-contrast MR imaging: basic facts and implementation." Radiographics **22**(3): 651-671.

Maceira, A. M., J. Cosín-Sales, M. Roughton, S. K. Prasad and D. J. Pennell (2010). "Reference left atrial dimensions and volumes by steady state free precession cardiovascular magnetic resonance." Journal of cardiovascular magnetic resonance **12**(1): 1-10.

Maceira, A. M., S. K. Prasad, M. Khan and D. J. Pennell (2006). "Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance." J Cardiovasc Magn Reson **8**(3): 417-426.

Maceira, A. M., S. K. Prasad, M. Khan and D. J. Pennell (2006). "Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance." Eur Heart J **27**(23): 2879-2888.

Macmahon, B., T. McKeown and R. G. Record (1953). "The incidence and life expectation of children with congenital heart disease." Br Heart J **15**(2): 121-129.

Mahadevan, V. S., I. F. Vondermuhll and M. J. Mullen (2006). "Endovascular aortic coarctation stenting in adolescents and adults: angiographic and hemodynamic outcomes." Catheter Cardiovasc Interv **67**(2): 268-275.

Marelli, A. J., R. Ionescu-Ittu, A. S. Mackie, L. Guo, N. Dendukuri and M. Kaouache (2014). "Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010." Circulation **130**(9): 749-756.

Marelli, A. J., A. S. Mackie, R. Ionescu-Ittu, E. Rahme and L. Pilote (2007). "Congenital heart disease in the general population: changing prevalence and age distribution." Circulation **115**(2): 163-172.

Marelli, A. J., J. Therrien, A. S. Mackie, R. Ionescu-Ittu and L. Pilote (2009). "Planning the specialized care of adult congenital heart disease patients: from numbers to guidelines; an epidemiologic approach." Am Heart J **157**(1): 1-8.

Maron, B. J., J. O. Humphries, R. D. Rowe and E. D. Mellits (1973). "Prognosis of surgically corrected coarctation of the aorta. A 20-year postoperative appraisal." Circulation **47**(1): 119-126.

McLeod, C. J. and C. Warnes (2016). "Recognition and management of arrhythmias in adult congenital heart disease." Curr Opin Cardiol **31**(1): 117-123.

Mendelsohn, A. M., D. C. Crowley, A. Lindauer and R. H. Beekman, 3rd (1992). "Rapid progression of aortic aneurysms after patch aortoplasty repair of coarctation of the aorta." J Am Coll Cardiol **20**(2): 381-385.

Miquel, M. E., D. L. Hill, E. J. Baker, S. A. Qureshi, R. D. Simon, S. F. Keevil and R. S. Razavi (2003). "Three- and four-dimensional reconstruction of intra-cardiac anatomy from two-dimensional magnetic resonance images." Int J Cardiovasc Imaging **19**(3): 239-254; discussion 255-236.

Miyatake, K., M. Yamagishi, N. Tanaka, M. Uematsu, N. Yamazaki, Y. Mine, A. Sano and M. Hirama (1995). "New method for evaluating left ventricular wall motion by color-coded tissue Doppler imaging: in vitro and in vivo studies." J Am Coll Cardiol **25**(3): 717-724.

Mizia-Stec, K., O. Trojnarska, L. Szczepaniak-Chichel, M. Gabriel, A. Bartczak, A. Cieplucha, J. Chudek, S. Grajek, A. Tykarski and Z. Gasior (2012). "Asymmetric dimethylarginine and vascular indices of atherosclerosis in patients after coarctation of aorta repair." Int J Cardiol **158**(3): 364-369.

Mohiaddin, R. H. and D. J. Pennell (1998). "MR blood flow measurement. Clinical application in the heart and circulation." Cardiol Clin **16**(2): 161-187.

Mohiaddin, R. H., G. Z. Yang and P. J. Kilner (1994). "Visualization of flow by vector analysis of multidirectional cine MR velocity mapping." J Comput Assist Tomogr **18**(3): 383-392.

Moodie, D. S. (1990). "Aortic dissection and coarctation." Curr Opin Cardiol **5**(5): 649-654.

Mortensen, K. H., B. E. Hjerrild, K. Stochholm, N. H. Andersen, K. E. Sorensen, E. Lundorf, A. Horlyck, E. M. Pedersen, J. S. Christiansen and C. H. Gravholt (2011). "Dilation of the ascending aorta in Turner syndrome - a prospective cardiovascular magnetic resonance study." J Cardiovasc Magn Reson **13**: 24.

Mottram, P. M., B. A. Haluska, R. Leano, S. Carlier, C. Case and T. H. Marwick (2005). "Relation of arterial stiffness to diastolic dysfunction in hypertensive heart disease." Heart **91**(12): 1551-1556.

Mullen, M. J. (2003). "Coarctation of the aorta in adults: do we need surgeons?" Heart **89**(1): 3-5.

Nagel, E., M. Stuber, E. Fleck, P. Boesiger and O. M. Hess (1998). "Myocardial tagging for the analysis left ventricular function." MAGMA **6**(2-3): 91-93.

Naghavi, M., P. Libby, E. Falk, S. W. Casscells, S. Litovsky, J. Rumberger, J. J. Badimon, C. Stefanadis, P. Moreno, G. Pasterkamp, Z. Fayad, P. H. Stone, S. Waxman, P. Raggi, M. Madjid, A. Zarrabi, A. Burke, C. Yuan, P. J. Fitzgerald, D. S. Siscovick, C. L. de Korte, M. Aikawa, K. E. Airaksinen, G. Assmann, C. R. Becker, J. H. Chesebro, A. Farb, Z. S. Galis, C. Jackson, I. K. Jang, W. Koenig, R. A. Lodder, K. March, J. Demirovic, M. Navab, S. G. Priori, M. D. Rekhter, R. Bahr, S. M. Grundy, R. Mehran, A. Colombo, E. Boerwinkle, C. Ballantyne, W. Insull, Jr., R. S. Schwartz, R. Vogel, P. W. Serruys, G. K. Hansson, D. P. Faxon, S. Kaul, H. Drexler, P. Greenland, J. E. Muller, R. Virmani, P. M. Ridker, D. P. Zipes, P. K. Shah and J. T. Willerson (2003). "From vulnerable plaque to vulnerable

patient: a call for new definitions and risk assessment strategies: Part II." Circulation **108**(15): 1772-1778.

Nagueh, S. F., L. L. Bachinski, D. Meyer, R. Hill, W. A. Zoghbi, J. W. Tam, M. A. Quinones, R. Roberts and A. J. Marian (2001). "Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy." Circulation **104**(2): 128-130.

Najjar, S. S., A. Scuteri, V. Shetty, J. G. Wright, D. C. Muller, J. L. Fleg, H. P. Spurgeon, L. Ferrucci and E. G. Lakatta (2008). "Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging." J Am Coll Cardiol **51**(14): 1377-1383.

Nakamura, K. and A. Stefanescu Schmidt (2016). "Treatment of Hypertension in Coarctation of the Aorta." Curr Treat Options Cardiovasc Med **18**(6): 40.

Nistri, S., J. Grande-Allen, M. Noale, C. Basso, P. Siviero, S. Maggi, G. Crepaldi and G. Thiene (2008). "Aortic elasticity and size in bicuspid aortic valve syndrome." Eur Heart J **29**(4): 472-479.

Niwa, K., J. K. Perloff, S. M. Bhuta, H. Laks, D. C. Drinkwater, J. S. Child and P. D. Miner (2001). "Structural abnormalities of great arterial walls in congenital heart disease: light and electron microscopic analyses." Circulation **103**(3): 393-400.

Nortan, J. J. (1984-1995). "Coarctation of the Aorta. In: Moller JH, ed.Surgery of Congenital Heart Disease:." Pediatric Cardiac CareConsortium. Armonk, NY: Futura Publishing Co: 143-157.

O'Rourke, M. F., J. A. Staessen, C. Vlachopoulos, D. Duprez and G. E. Plante (2002). "Clinical applications of arterial stiffness; definitions and reference values." American journal of hypertension **15**(5): 426-444.

O'Rourke, M. F., J. A. Staessen, C. Vlachopoulos, D. Duprez and G. E. Plante (2002). "Clinical applications of arterial stiffness; definitions and reference values." Am J Hypertens **15**(5): 426-444.

Ou, P., D. S. Celermajer, O. Jolivet, F. Buyens, A. Herment, D. Sidi, D. Bonnet and E. Mousseaux (2008). "Increased central aortic stiffness and left ventricular mass in normotensive young subjects after successful coarctation repair." Am Heart J **155**(1): 187-193.

Oyen, N., G. Poulsen, H. A. Boyd, J. Wohlfahrt, P. K. Jensen and M. Melbye (2009). "Recurrence of congenital heart defects in families." Circulation **120**(4): 295-301.

Parikh, S. R., R. A. Hurwitz, J. E. Hubbard, J. W. Brown, H. King and D. A. Girod (1991). "Preoperative and postoperative "aneurysm" associated with coarctation of the aorta." J Am Coll Cardiol **17**(6): 1367-1372.

Parks, W. J., T. D. Ngo, W. H. Plauth, Jr., E. R. Bank, S. K. Sheppard, R. I. Pettigrew and W. H. Williams (1995). "Incidence of aneurysm formation after Dacron patch aortoplasty repair for coarctation of the aorta: long-term results and assessment utilizing magnetic resonance angiography with three-dimensional surface rendering." J Am Coll Cardiol **26**(1): 266-271.

Pedersen, T. A., E. B. Pedersen, K. Munk, V. E. Hjortdal, K. Emmertsen and N. H. Andersen (2015). "High pulse pressure is not associated with abnormal activation of the renin-angiotensin-aldosterone system in repaired aortic coarctation." J Hum Hypertens **29**(4): 268-273.

Perloff, J. K. (1991). "Congenital heart disease in adults. A new cardiovascular subspecialty." Circulation **84**(5): 1881-1890.

Pirro, M., G. Schillaci, M. R. Mannarino, G. Savarese, G. Vaudo, D. Siepi, R. Paltriccia and E. Mannarino (2007). "Effects of rosuvastatin on 3-nitrotyrosine and aortic stiffness in hypercholesterolemia." Nutr Metab Cardiovasc Dis **17**(6): 436-441.

Presbitero, P., D. Demarie, M. Villani, E. A. Perinetto, G. Riva, F. Orzan, M. Bobbio, M. Morea and A. Brusca (1987). "Long term results (15-30 years) of surgical repair of aortic coarctation." Br Heart J **57**(5): 462-467.

Protogerou, A., J. Blacher, G. S. Stergiou, A. Achimastos and M. E. Safar (2009). "Blood pressure response under chronic antihypertensive drug therapy: the role of aortic stiffness in the REASON (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind) study." J Am Coll Cardiol **53**(5): 445-451.

Quennelle, S., A. J. Powell, T. Geva and A. Prakash (2015). "Persistent Aortic Arch Hypoplasia After Coarctation Treatment Is Associated With Late Systemic Hypertension." J Am Heart Assoc **4**(7).

Rafiq, I. and L. Freeman (2015). "Clinical genomics and the adult with congenital heart disease: new opportunities." Heart **101**(3): 242.

Raissadati, A., J. Haukka, T. Patila, H. Nieminen and E. Jokinen (2020). "Chronic Disease Burden After Congenital Heart Surgery: A 47-Year Population-Based Study With 99% Follow-Up." J Am Heart Assoc **9**(9): e015354.

Ramlakhan, K. P., D. Tobler, M. Greutmann, M. Schwerzmann, L. Baris, A. T. Yetman, P. Nihoyannopoulos, P. Manga, E. Boersma, A. P. Maggioni, M. R. Johnson, R. Hall, J. W. Roos-Hesselink and R. i. group (2020). "Pregnancy outcomes in women with aortic coarctation." Heart.

Rao, P. S., O. Galal, P. A. Smith and A. D. Wilson (1996). "Five- to nine-year follow-up results of balloon angioplasty of native aortic coarctation in infants and children." J Am Coll Cardiol **27**(2): 462-470.

Rathi, V. K., M. Doyle, J. Yamrozik, R. B. Williams, K. Caruppannan, C. Truman, D. Vido and R. W. Biederman (2008). "Routine evaluation of left ventricular diastolic function by cardiovascular magnetic resonance: a practical approach." J Cardiovasc Magn Reson **10**: 36.

Razavi, R. S., D. L. Hill, V. Muthurangu, M. E. Miquel, A. M. Taylor, S. Kozerke and E. J. Baker (2003). "Three-dimensional magnetic resonance imaging of congenital cardiac anomalies." Cardiol Young **13**(5): 461-465.

Rees, S., J. Somerville, C. Ward, J. Martinez, R. H. Mohiaddin, R. Underwood and D. B. Longmore (1989). "Coarctation of the aorta: MR imaging in late postoperative assessment." Radiology **173**(2): 499-502.

Regitz-Zagrosek, V., J. W. Roos-Hesselink, J. Bauersachs, C. Blomstrom-Lundqvist, R. Cifkova, M. De Bonis, B. Iung, M. R. Johnson, U. Kintscher and P. Kranke (2019). "2018 ESC guidelines for the management of cardiovascular diseases during pregnancy." Kardiologia Polska (Polish Heart Journal) **77**(3): 245-326.

Reller, M. D., M. J. Strickland, T. Riehle-Colarusso, W. T. Mahle and A. Correa (2008). "Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005." J Pediatr **153**(6): 807-813.

Report of the British Cardiac Society Working, P. (2002). "Grown-up congenital heart (GUCH) disease: current needs and provision of service for adolescents and adults with congenital heart disease in the UK." Heart **88 Suppl 1**: i1-14.

Rheuban, K. S., M. A. Carpenter, R. Jedeikin, J. F. Dammann, B. A. Alford, I. L. Kron, H. P. Gutgesell and S. P. Nolan (1985). "Aortic aneurysm after patch aortoplasty for coarctation in childhood." Am J Cardiol **55**(5): 612.

Rinnstrom, D., M. Dellborg, U. Thilen, P. Sorensson, N. E. Nielsen, C. Christersson and B. Johansson (2016). "Left ventricular hypertrophy in adults with previous repair of coarctation of the aorta; association with systolic blood pressure in the high normal range." Int J Cardiol **218**: 59-64.

Rocchini, A. P., A. Rosenthal, A. C. Barger, A. R. Castaneda and A. S. Nadas (1976). "Pathogenesis of paradoxical hypertension after coarctation resection." Circulation **54**(3): 382-387.

Rodes-Cabau, J., J. Miro, A. Dancea, R. Ibrahim, E. Piette, C. Lapierre, L. Jutras, J. Perron, C. I. Tchervenkow, N. Poirier, N. S. Dahdah and C. Houde (2007). "Comparison of surgical and transcatheter treatment for native coarctation of the aorta in patients > or = 1 year old. The Quebec Native Coarctation of the Aorta study." Am Heart J **154**(1): 186-192.

Roifman, I., J. Therrien, R. Ionescu-Ittu, L. Pilote, L. Guo, M. A. Kotowycz, G. Martucci and A. J. Marelli (2012). "Coarctation of the aorta and coronary artery disease: fact or fiction?" Circulation **126**(1): 16-21.

Roos, C. J., R. Djaberi, J. D. Schuijf, E. J. de Koning, T. J. Rabelink, J. W. Smit, A. M. Pereira, I. Al Younis, B. van der Hiel, A. J. Scholte, J. J. Bax and J. W. Jukema (2011). "Relationship between vascular stiffness and stress myocardial perfusion imaging in asymptomatic patients with diabetes." Eur J Nucl Med Mol Imaging **38**(11): 2050-2057.

Rosenthal, E. (2005). "Coarctation of the aorta from fetus to adult: curable condition or life long disease process?" Heart **91**(11): 1495-1502.

Ross, R. D., S. K. Clapp, S. Gunther, S. M. Paridon, R. A. Humes, Z. Q. Farooki and W. W. Pinsky (1992). "Augmented norepinephrine and renin output in response to maximal exercise in hypertensive coarctectomy patients." Am Heart J **123**(5): 1293-1299.

Roth, T. S. and J. A. Aboulhosn (2016). "Pulmonary Hypertension and Congenital Heart Disease." Cardiol Clin **34**(3): 391-400.

Rudolph, A. M., M. A. Heymann and U. Spitznas (1972). "Hemodynamic considerations in the development of narrowing of the aorta." Am J Cardiol **30**(5): 514-525.

Russell, G. A., P. J. Berry, K. Watterson, J. P. Dhasmana and J. D. Wisheart (1991). "Patterns of ductal tissue in coarctation of the aorta in the first three months of life." J Thorac Cardiovasc Surg **102**(4): 596-601.

Sarkola, T., A. N. Redington, C. Slorach, W. Hui, T. Bradley and E. Jaeggi (2011). "Assessment of vascular phenotype using a novel very-high-resolution ultrasound technique in adolescents after aortic coarctation repair and/or stent implantation: relationship to central haemodynamics and left ventricular mass." Heart **97**(21): 1788-1793.

Schulz-Menger, J., D. A. Bluemke, J. Bremerich, S. D. Flamm, M. A. Fogel, M. G. Friedrich, R. J. Kim, F. von Knobelsdorff-Brenkenhoff, C. M. Kramer, D. J. Pennell, S. Plein and E. Nagel (2013). "Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees task force on standardized post processing." J Cardiovasc Magn Reson **15**: 35.

Sehested, J., U. Baandrup and E. Mikkelsen (1982). "Different reactivity and structure of the prestenotic and poststenotic aorta in human coarctation. Implications for baroreceptor function." Circulation **65**(6): 1060-1065.

Seirafi, P. A., K. G. Warner, R. L. Geggel, D. D. Payne and R. J. Cleveland (1998). "Repair of coarctation of the aorta during infancy minimizes the risk of late hypertension." The Annals of thoracic surgery **66**(4): 1378-1382.

Senzaki, H., Y. Iwamoto, H. Ishido, S. Masutani, M. Taketazu, T. Kobayashi, T. Katogi and S. Kyo (2008). "Ventricular-vascular stiffening in patients with repaired coarctation of aorta: integrated pathophysiology of hypertension." Circulation **118**(14 Suppl): S191-198.

Shaddy, R. E., M. M. Boucek, J. E. Sturtevant, H. D. Ruttenberg, R. B. Jaffe, L. Y. Tani, V. E. Judd, L. G. Veasy, E. C. McGough and G. S. Orsmond (1993). "Comparison of angioplasty and surgery for unoperated coarctation of the aorta." Circulation **87**(3): 793-799.

Shang, Q., S. Sarikouch, S. Patel, A. Schuster, M. Steinmetz, P. Ou, D. A. Danford, P. Beerbaum and S. Kutty (2016). "Assessment of ventriculo-vascular properties in repaired coarctation using cardiac magnetic resonance-derived aortic, left atrial and left ventricular strain." Eur Radiol.

Shige, H., A. Dart and P. Nestel (2001). "Simvastatin improves arterial compliance in the lower limb but not in the aorta." Atherosclerosis **155**(1): 245-250.

Silversides, C. K., M. Kiess, L. Beauchesne, T. Bradley, M. Connelly, K. Niwa, B. Mulder, G. Webb, J. Colman and J. Therrien (2010). "Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: outflow tract obstruction, coarctation of the aorta, tetralogy of Fallot, Ebstein anomaly and Marfan's syndrome." Can J Cardiol **26**(3): e80-97.

Simon, A. B. and A. E. Zloto (1974). "Coarctation of the aorta. Longitudinal assessment of operated patients." Circulation **50**(3): 456-464.

Simsolo, R., B. Grunfeld, M. Gimenez, M. Lopez, G. Berri, L. Becu and M. Barontini (1988). "Long-term systemic hypertension in children after successful repair of coarctation of the aorta." Am Heart J **115**(6): 1268-1273.

Somerville, J. (1997). "Management of adults with congenital heart disease: an increasing problem." Annu Rev Med **48**: 283-293.

Stacey, R. B., A. G. Bertoni, J. Eng, D. A. Bluemke, W. G. Hundley and D. Herrington (2010). "Modification of the effect of glycemic status on aortic distensibility by age in the multi-ethnic study of atherosclerosis." Hypertension **55**(1): 26-32.

Steele, P. M., V. Fuster, M. Cohen, D. G. Ritter and D. C. McGoon (1987). "Isolated atrial septal defect with pulmonary vascular obstructive disease--long-term follow-up and prediction of outcome after surgical correction." Circulation **76**(5): 1037-1042.

Stefanadis, C., C. Stratos, H. Boudoulas, C. Kourouklis and P. Toutouzas (1990). "Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease." Eur Heart J **11**(11): 990-996.

Stewart, A. B., R. Ahmed, C. M. Travill and C. G. Newman (1993). "Coarctation of the aorta life and health 20-44 years after surgical repair." Br Heart J **69**(1): 65-70.

Stoica, S. C., K. D. McNeil, K. Perreas, L. D. Sharples, D. K. Satchithananda, S. S. Tsui, S. R. Large and J. Wallwork (2001). "Heart-lung transplantation for Eisenmenger syndrome: early and long-term results." Ann Thorac Surg **72**(6): 1887-1891.

Stuart, A. G. (2012). "Changing lesion demographics of the adult with congenital heart disease: an emerging population with complex needs." Future Cardiol **8**(2): 305-313.

Suarez de Lezo, J., M. Pan, M. Romero, A. Medina, J. Segura, D. Pavlovic, C. Martinez, I. Tejero, J. Perez Navero, F. Torres and et al. (1995). "Balloon-expandable stent repair of severe coarctation of aorta." Am Heart J **129**(5): 1002-1008.

Sutherland, G. R., M. J. Stewart, K. W. Groundstroem, C. M. Moran, A. Fleming, F. J. Guell-Peris, R. A. Riemersma, L. N. Fenn, K. A. Fox and W. N. McDicken (1994). "Color Doppler myocardial imaging: a new technique for the assessment of myocardial function." J Am Soc Echocardiogr **7**(5): 441-458.

Tan, J. L. and M. Mullen (2005). "Emergency stent graft deployment for acute aortic rupture following primary stenting for aortic coarctation." Catheter Cardiovasc Interv **65**(2): 306-309.

Tennant, P. W., M. S. Pearce, M. Bythell and J. Rankin (2010). "20-year survival of children born with congenital anomalies: a population-based study." Lancet **375**(9715): 649-656.

Teuwen, C. P., T. T. Ramdjan, M. Gotte, B. J. Brundel, R. Evertz, J. W. Vriend, S. G. Molhoek, H. G. Dorman, J. M. van Opstal, T. C. Konings, P. van der Voort, E. Delacretaz, C. Houck, A. Yaksh, L. J. Jansz, M. Witsenburg, J. W. Roos-Hesselink, J. K. Triedman, A. J. Bogers and N. M. de Groot (2015). "Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects." Circ Arrhythm Electrophysiol **8**(5): 1065-1072.

Thakur, J. S., P. C. Negi, S. K. Ahluwalia, R. Sharma and R. Bhardwaj (1995). "Congenital heart disease among school children in Shimla hills." Indian Heart J **47**(3): 232-235.

Toro-Salazar, O. H., J. Steinberger, W. Thomas, A. P. Rocchini, B. Carpenter and J. H. Moller (2002). "Long-term follow-up of patients after coarctation of the aorta repair." Am J Cardiol **89**(5): 541-547.

Triedman, J. K. (2002). "Arrhythmias in adults with congenital heart disease." Heart **87**(4): 383-389.

Tutar, E., F. Ekici, S. Atalay and N. Nacar (2005). "The prevalence of bicuspid aortic valve in newborns by echocardiographic screening." Am Heart J **150**(3): 513-515.

Tyagi, S., R. Arora, U. A. Kaul, K. K. Sethi, D. S. Gambhir and M. Khalilullah (1992). "Balloon angioplasty of native coarctation of the aorta in adolescents and young adults." Am Heart J **123**(3): 674-680.

van der Bom, T., B. J. Bouma, F. J. Meijboom, A. H. Zwinderman and B. J. Mulder (2012). "The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation." Am Heart J **164**(4): 568-575.

Van der Horst, R. L. and M. S. Gotsman (1972). "Racial incidence of coarctation of aorta." Br Heart J **34**(3): 289-294.

van der Linde, D., E. E. Konings, M. A. Slager, M. Witsenburg, W. A. Helbing, J. J. Takkenberg and J. W. Roos-Hesselink (2011). "Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis." J Am Coll Cardiol **58**(21): 2241-2247.

van Varik, B. J., R. J. Rennenberg, C. P. Reutelingsperger, A. A. Kroon, P. W. de Leeuw and L. J. Schurgers (2012). "Mechanisms of arterial remodeling: lessons from genetic diseases." Front Genet **3**: 290.

Varma, C., L. N. Benson, J. Butany and P. R. McLaughlin (2003). "Aortic dissection after stent dilatation for coarctation of the aorta: a case report and literature review." Catheter Cardiovasc Interv **59**(4): 528-535.

Verheugt, C. L., C. S. Uiterwaal, E. T. van der Velde, F. J. Meijboom, P. G. Pieper, A. P. van Dijk, H. W. Vliegen, D. E. Grobbee and B. J. Mulder (2010). "Mortality in adult congenital heart disease." Eur Heart J **31**(10): 1220-1229.

Vitarelli, A., Y. Conde, E. Cimino, I. D'Angeli, S. D'Orazio, S. Stellato, V. Padella and F. Caranci (2006). "Aortic wall mechanics in the Marfan syndrome assessed by transesophageal tissue Doppler echocardiography." Am J Cardiol **97**(4): 571-577.

Vitarelli, A., M. Giordano, G. Germano, M. Pergolini, P. Cicconetti, F. Tomei, A. Sancini, D. Battaglia, O. Dettori, L. Capotosto, V. De Cicco, M. De Maio, M. Vitarelli and P. Bruno (2010). "Assessment of ascending aorta wall stiffness in hypertensive patients by tissue Doppler imaging and strain Doppler echocardiography." Heart **96**(18): 1469-1474.

Voges, I., M. Jerosch-Herold, J. Hedderich, E. Pardun, C. Hart, D. D. Gabbert, J. H. Hansen, C. Petko, H. H. Kramer and C. Rickers (2012). "Normal values of aortic dimensions, distensibility, and pulse wave velocity in children and young adults: a cross-sectional study." J Cardiovasc Magn Reson **14**: 77.

Vogt, M., A. Kuhn, D. Baumgartner, C. Baumgartner, R. Busch, M. Kostolny and J. Hess (2005). "Impaired elastic properties of the ascending aorta in newborns before and early after successful coarctation repair: proof of a systemic vascular disease of the prestenotic arteries?" Circulation **111**(24): 3269-3273.

Vriend, J. W., W. Drenthen, P. G. Pieper, J. W. Roos-Hesselink, A. H. Zwinderman, D. J. van Veldhuisen and B. J. Mulder (2005). "Outcome of pregnancy in patients after repair of aortic coarctation." Eur Heart J **26**(20): 2173-2178.

Vriend, J. W. and B. J. Mulder (2005). "Late complications in patients after repair of aortic coarctation: implications for management." Int J Cardiol **101**(3): 399-406.

Waddell, T. K., L. Bennett, R. Kennedy, T. R. Todd and S. H. Keshavjee (2002). "Heart-lung or lung transplantation for Eisenmenger syndrome." J Heart Lung Transplant **21**(7): 731-737.

Warnes, C. A. (2003). "Bicuspid aortic valve and coarctation: two villains part of a diffuse problem." Heart **89**(9): 965-966.

Warnes, C. A., R. G. Williams, T. M. Bashore, J. S. Child, H. M. Connolly, J. A. Dearani, P. del Nido, J. W. Fasules, T. P. Graham, Jr., Z. M. Hijazi, S. A. Hunt, M. E. King, M. J. Landzberg, P. D. Miner, M. J. Radford, E. P. Walsh and G. D. Webb (2008). "ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart

Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease)." Circulation **118**(23): e714-833.

Webb, G. D. and R. G. Williams (2001). "Care of the adult with congenital heart disease: introduction." J Am Coll Cardiol **37**(5): 1166.

Westenberg, J. J. (2011). "CMR for Assessment of Diastolic Function." Curr Cardiovasc Imaging Rep **4**(2): 149-158.

Williams, B., P. S. Lacy, J. K. Cruickshank, D. Collier, A. D. Hughes, A. Stanton, S. Thom, H. Thurston, Cafe and A. Investigators (2009). "Impact of statin therapy on central aortic pressures and hemodynamics: principal results of the Conduit Artery Function Evaluation-Lipid-Lowering Arm (CAFE-LLA) Study." Circulation **119**(1): 53-61.

Wilson, R. A., R. W. McDonald, J. D. Bristow, M. Cheitlin, D. Nauman, B. Massie and B. Greenberg (1992). "Correlates of aortic distensibility in chronic aortic regurgitation and relation to progression to surgery." J Am Coll Cardiol **19**(4): 733-738.

Wray, J., A. Frigiola, C. Bull and N. Adult Congenital Heart disease Research (2013). "Loss to specialist follow-up in congenital heart disease; out of sight, out of mind." Heart **99**(7): 485-490.

Wren, C., C. A. Irving, J. A. Griffiths, J. J. O'Sullivan, M. P. Chaudhari, S. R. Haynes, J. H. Smith, J. R. Hamilton and A. Hasan (2012). "Mortality in infants with cardiovascular malformations." Eur J Pediatr **171**(2): 281-287.

Wren, C. and J. J. O'Sullivan (2013). "Loss to follow-up of adults with repaired congenital heart disease." Heart **99**(7): 440-441.

Wren, C., Z. Reinhardt and K. Khawaja (2008). "Twenty-year trends in diagnosis of life-threatening neonatal cardiovascular malformations." Arch Dis Child Fetal Neonatal Ed **93**(1): F33-35.

Wu, M. H., H. C. Chen, C. W. Lu, J. K. Wang, S. C. Huang and S. K. Huang (2010). "Prevalence of congenital heart disease at live birth in Taiwan." J Pediatr **156**(5): 782-785.

Xu, J., T. Shiota, R. Omoto, X. Zhou, S. Kyo, M. Ishii, M. J. Rice and D. J. Sahn (1997). "Intravascular ultrasound assessment of regional aortic wall stiffness, distensibility, and compliance in patients with coarctation of the aorta." Am Heart J **134**(1): 93-98.

Yasmin, C. M. McEniery, K. M. O'Shaughnessy, P. Harnett, A. Arshad, S. Wallace, K. Maki-Petaja, B. McDonnell, M. J. Ashby, J. Brown, J. R. Cockcroft and I. B. Wilkinson (2006). "Variation in the human matrix metalloproteinase-9 gene is associated with arterial stiffness in healthy individuals." Arterioscler Thromb Vasc Biol **26**(8): 1799-1805.

Yetman, A. T., D. Nykanen, B. W. McCrindle, J. Sunnegardh, I. Adatia, R. M. Freedom and L. Benson (1997). "Balloon angioplasty of recurrent coarctation: a 12-year review." J Am Coll Cardiol **30**(3): 811-816.

Zabal, C., F. Attie, M. Rosas, A. Buendia-Hernandez and J. A. Garcia-Montes (2003). "The adult patient with native coarctation of the aorta: balloon angioplasty or primary stenting?" Heart **89**(1): 77-83.

Zomer, A. C., C. S. Uiterwaal, E. T. van der Velde, J. G. Tijssen, E. C. Mariman, C. L. Verheugt, I. Vaartjes, P. G. Pieper, F. J. Meijboom, D. E. Grobbee and B. J. Mulder (2011). "Mortality in adult

congenital heart disease: are national registries reliable for cause of death?" Int J Cardiol **152**(2): 212-217.