Title **Cardio-Pulmonary Exercise Test in Coronary Ischaemia Detection**

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Cardio-Pulmonary Exercise Test in Myocardial Ischaemia Detection

Abstract:

Exercise electrocardiography has low sensitivity for detection of myocardial ischaemia. However, when combined with cardio-pulmonary exercise testing (CPEX) the sensitivity and specificity of ischaemia detection improves significantly.

CPEX offers unique advantages over imaging techniques in tricky situations such as balanced ischemia. Early abnormal oxygen uptake would point towards profound coronary stenosis, that could be missed in perfusion imaging.

CPEX could be an invaluable tool in asymptomatic left bundle branch block (LBBB) pattern, without exposing patients to the risks of CT or invasive coronary angiography. Normal oxygen uptake curves would rule-out significant coronary stenosis as the cause of LBBB pattern. Else ways, abnormal oxygen uptake in patients with normal coronary arteries could indicate microvascular angina. Furthermore, exercise capacity is an excellent predictor of cardiovascular risk in those with and without heart disease.

Using two clinical cases we introduce the concept of gas-exchange and haemodynamic changes encountered in ischaemic heart disease.

Keywords:

CPEX, cardiopulmonary exercise test, ischaemic heart disease, coronary artery disease, exercise testing, treadmill test, exercise testing for coronary artery disease, angina, stable angina, breathlessness, dyspnoea on exertion

Introduction

Cardiac ischaemia can present with a variety of symptoms including chest pain, arm pain and breathlessness, or may be 'silent' [1]. Exertional symptoms raise the suspicion of coronary ischaemia due to the associated increase in the cardiac work and unmet energetic demands of the ischaemic myocardium [2]. The practice of exercise electrocardiogram (ECG) testing aims to reproduce the symptoms in a controlled environment and gives the physician excellent insight into cardio-respiratory function during stress [3]. However, recent guidelines removed exercise ECG testing from being the first line investigation for angina, due to relatively poor sensitivity and specificity [2, 4]. Cardio-pulmonary exercise testing (CPEX) measures gas-exchange in addition to the usual exercise parameters. It provides incremental information on cardiovascular and respiratory physiology. Recent studies have explored the utility of CPEX as an investigational tool for angina. With the help of two clinical cases we will describe the usefulness of CPEX in the investigation coronary artery disease. Supplementary table 1 shows the commonly used abbreviations in CPEX [5].

Case 1

A 64-year-old man presented with progressive breathlessness on exertion. He was treated for prostate cancer but had no other history. His cardiovascular clinical examination was unremarkable. Resting ECG, echocardiogram and full blood count were normal. On a routine treadmill exercise stress there were no significant ECG changes. A CPEX was then performed with a standard incremental step protocol on a treadmill using a COSMED CPEX (Italy) system. Spirometry prior to the test was normal. The total exercise duration was 9 minutes and 40 seconds. His gas-exchange results are shown below in Table 1. A typical treadmill exercise protocol as utilised in this patient is shown in supplementary table 2 [5].

Table 1 Gas-exchange and haemodynamic parameters (case 1)

There were no ECG changes suggestive of coronary ischaemia during peak exercise or recovery. Although the absolute values of gas-exchange were normal, abrupt flattening of the oxygen consumption and oxygen pulse (O_2pulse) were noticed close to peak exercise (Figure1). O_2 pulse, a common term in CPEX, is calculated by dividing oxygen consumption by simultaneously measured heart rate [6]. O_2 pulse progressively increases during exercise and promptly falls on stopping [6]. O_2 pulse has been shown to be a surrogate for stroke volume [7]. In patients with cardiac ischaemia, on reaching the ischemic threshold, a reduction in stroke volume due to myocardial dysfunction may result in impaired oxygen delivery (and hence consumption) which is reflected as an abrupt flattening of the O_2 pulse [8, 9]. Rapid improvement in left ventricular systolic function on cessation of exercise in those with significant coronary disease, also contributes to a delayed systolic blood pressure recovery after exercise [10].

Furthermore, there was an increase in oxygen consumption during early recovery. In a failing heart due to ischaemia, a paradoxical rise in O_2 pulse occurs on stopping the exercise, resulting from improved cardiac function due to relief of ischaemia [11]. A coronary angiography later showed significant stenosis in dominant right coronary artery, which was successfully stented, with resolution of breathlessness.

Figure 1 Oxygen and carbon-dioxide uptake curves (case 1)

Case 2

A 61 year old woman was referred to cardiac outpatients because of retrosternal chest pain, unrelated to exertion. An ECG showed left bundle branch block (LBBB) pattern. The echocardiogram was unremarkable apart from abnormal septal motion typical of LBBB pattern. To evaluate further, she underwent bi-cycle ergometer CPEX using an incremental

RAMP protocol. Spirometry prior to the test was normal. She exercised for 11 minutes and 58 seconds. Gas exchange results are shown in Table 2.

Table 2 Gas-exchange and haemodynamic parameters (case 2)

Her absolute values of gas-exchange were within normal limits. Figure 2 shows her oxygen uptake profile. Figure 2A shows steady increase in absolute oxygen consumption throughout exercise. Figure 2B shows steady increase in O_2 pulse, suggesting that there is no significant reduction in stroke volume during exercise. Figure 2C shows oxygen uptake as a function of work-rate ($O_2/\Delta WR$). In healthy subjects the normal oxygen uptake is 10 ml/min/Watt and this increase is a linear function throughout exercise [12]. In contrast in patients who develop severe cardiac ischaemia during exercise resulting in a sudden fall in cardiac output, oxygen delivery is impeded and anaerobic metabolism contributes significantly to the ATP generation [13]. This results in relative flattening of the $O_2/\Delta WR$, despite increasing workload and is another useful marker in suspecting coronary ischaemia [8]. It has been shown in those with coronary ischaemia, the flattening of $O_2/\Delta WR$ usually correlates with the flattening of the O_2 pulse, indicating the onset of ischemic myocardial dysfunction [8, 9]. The $O_2/\Delta WR$ is obtainable only on bicycle CPEX and not on treadmill CPEX. CT (computerised tomography) coronary angiography later confirmed normal coronary arteries.

Figure 2 Oxygen and carbon-dioxide uptake curves (case 2)

Discussion:

The latest European Society of Cardiology guidelines discounted exercise ECG testing as an investigation for suspected angina, due to lack of sensitivity and specificity [4]. We discuss how the addition of ventilatory parameters in CPEX can be an additional diagnostic toll in the investigation of angina.

Exercise ECG testing has traditionally been used in the investigation of suspected coronary artery disease. Until the last decade, it was the recommended first line tool for those with intermediate probability for coronary artery disease [14]. Apart from reproduction of patient symptoms in a controlled environment, exercise testing provides other valuable information including time to symptom onset, exercise induced arrhythmias, blood pressure and chronotropic response to exercise [14, 15]. Exercise capacity is an excellent predictor of cardio-vascular risk including mortality in both healthy subjects and in those with coronary artery disease [15]. Exercise ECG test is equivalent to that of myocardial perfusion imaging in predicting major adverse cardiovascular events, in those with suspected coronary artery disease [16]. However, during the myocardial ischemic cascade, metabolic abnormalities, diastolic dysfunction, systolic dysfunction and ECG changes occur in a sequential manner [17]. ECG changes occur late after systolic impairment, which explains the low sensitivity (60-70%) [18]. ST depression is only a functional sign of inadequate oxygen supply to meet the myocardial demands, and could occur in anaemia, lung disease or when the myocardial oxygen demand is high, as in left ventricular hypertrophy [19]. Hence the specificity of exercise testing is also poor (70-80%) [18]. The sensitivity and specificity are even lower in women [20].

Furthermore, there are interpretation difficulties in those with resting ECG abnormalities including resting ST segment depression, left ventricular hypertrophy, left bundle branch block, interventricular conduction abnormalities, Wolf-Parkinson White pattern and those on beta-blocker or Digoxin therapy [14, 20].

Bruce, who standardised treadmill exercise testing was one of the earliest to recognise that oxygen consumption at peak exercise (pVO_2) is reduced in patients with coronary artery disease[21]. Ehsani et al (1984) showed that in those with coronary artery disease, a reduction in exercise ejection fraction was associated with a lower pVO_2 [22]. Klainman (1996) proved

that pVO_2 and O_2 pulse were lower in coronary ischemia, compared to controls [23]. Klainman (1998) and later Inbar (2008) demonstrated that successful coronary angioplasty, improved pVO_2, anaerobic threshold and oxygen pulse [24]. CPEX could be also useful in diagnosing coronary artery disease in asymptomatic diabetic women. Smanio et al showed that CPEX is better than routine ECG stress testing in this cohort, but inferior to myocardial perfusion imaging [25]. Furthermore, CPEX has shown to be useful in assessing new medical therapies for coronary artery disease [26].

However, it was Belardinelli et al who delivered a convincing case for CPEX with two landmark papers. In his first study, he investigated two CPEX parameters - O_2 pulse and $O_2/\Delta WR$, in angina patients [8].

1) Abrupt flattening of $O_2/\Delta WR$ slope (Figure 3B). The normal relationship is linear with a value of 10 ml/min/W. Belardinelli chose a cut-off of slope < 3.9 ml/min/W to detect the onset of ischaemia [8]

2) Concomitant flattening of O_2 pulse (Figure 3A)

His group compared CPEX and ECG testing against exercise stress myocardial perfusion imaging (MPI) [8]. Patients with proven coronary artery disease demonstrated by invasive angiography, underwent CPEX and MPI for ischaemia testing. In 140 patients in whom MPI demonstrated ischaemia, CPEX correctly diagnosed ischaemia in 122 and among 62 patients who did not have perfusion defects, CPEX correctly ruled out ischaemia in 46. And had a superior sensitivity (89% vs 46%) and specificity (74% vs 66%) compared to ECG changes alone.

Figure 3: Oxygen uptake curves in healthy and ischemic subjects

In 2014, Belardinelli et al conducted another elegant study in out-patients referred to cardiology with chest pain. He performed MPI and invasive angiography on 73 patients with CPEX proven ischaemia and 71 patients in whom CPEX had ruled out ischaemia [9]. He showed CPEX parameters had a significantly higher sensitivity (88% vs 48%) and specificity (98% vs 55%) compared to ECG parameters alone. Myocardial dysfunction in the setting of coronary artery disease also results in inappropriately higher heart rate response to exercise, as a compensatory mechanism. Chaudhry et al (2017) showed that the heart rate-work load relationship is abnormal with increasing burden of coronary atheroma [27].

One of the major advantages of CPEX is its ability to identify non-obstructive coronary artery disease, where the patient has physiologically significant atheroma burden, but with non-obstructive arteries on angiography [28]. The PROMISE study showed the importance of diagnosing non-obstructive coronary artery atheroma, as it is associated with worse outcomes [29]. Microvascular coronary disease is one form of non-obstructive disease that predominantly affects women, with increased mortality and morbidity [30]. Chaudhry et al showed that CPEX could diagnose microvascular ischemia in the setting of exertional chest pain and normal coronary angiography[31]. Further medical therapy with anti-anginal Ranolazine improved the exercise capacity, as shown by rise in peak VO_2 and $O_2/\Delta WR$ slope. Hence CPEX could play a pivotal role in distinguishing microvascular angina from a false positive exercise ECG test, both being common amongst women.

CPEX is proving to be an excellent prognostic marker as well. The prevalence of myocardial ischaemia is shown to be lower in those who achieve ≥10 metabolic equivalents during exercise testing [32]. Kavanagh et al showed that every 1ml/kg/min advantage of peak VO_2, lowered mortality by 10% in those with known coronary artery disease[33]. In patients who underwent early coronary intervention for acute myocardial ischemia, a low peak oxygen consumption of

<16.3 ml/kg/min and a high VE/VCO_2 slope of >36.2 are shown to predict adverse events [34]. There is evidence to show that in suspected myocardial ischemia, those presenting with dyspnoea have higher mortality than those presenting with typical or atypical angina [35]. CPEX has shown to be a valuable tool in investigating dyspnoea and guiding the physician to specific investigations [5, 36].

In the ORBITA trial, revascularisation of significant single vessel coronary stenosis did not result in improvement in peak oxygen consumption [34]. Even in those with multi-vessel disease undergoing percutaneous coronary intervention after myocardial infarction, there seems to be no difference in peak oxygen consumption between those who underwent complete or incomplete revascularisation [37]. These studies suggest that epicardial stenosis may not be the only factor to determine exercise capacity, and the importance moving away from stenosis-centric attitude in the treatment of coronary artery disease [28].

The presence of a LBBB ECG pattern complicates the investigation of angina in stable outpatients. LBBB pattern is known to be associated with cardiomyopathy, conduction system abnormalities and coronary artery disease [38]. In those with LBBB pattern, exercise ECG testing is not useful in detecting ischaemia and myocardial perfusion imaging and dobutamine stress echocardiography are only of limited value, as the abnormal septal motion makes the image analysis difficult [39]. Case-2 showed appropriate heart rate and blood pressure response to exercise, the oxygen uptake and O_2 pulse progressively increased throughout exercise ruling out a failing heart and there was no flattening of O_2 pulse or $O_2/\Delta WR$ to suggest coronary ischaemia. We believe CPEX can play an important role in this situation, avoiding complex and invasive further investigations.

<u>Limitations:</u>

CPEX does not differentiate microvascular from macrovascular coronary disease [40]. The oxygen-work uptake 'relationship' of 10 ml/min/Watt cannot be translated to treadmill exercise [12, 41]. Attempts to use just O_2 pulse without $VO_2/\Delta WR$ relationship have shown to be less useful in investigating angina, especially in those with a lower ischaemic burden [42]. Therefore, a treadmill CPEX is less effective when ischaemia is suspected. CPEX is more sensitive in triple vessel disease than in double and single vessel disease [8, 9]. This could be rather advantageous, as MPI can miss 'balanced ischaemia' in left main stem or triple vessel coronary disease [2, 43]. Co-existing conditions that interfere with oxygen delivery, like anaemia, lung disease, pulmonary vascular disease and heart failure could affect the accuracy of ischaemia detection by CPEX [44].

Safety aspects in performing CPEX test:

Complications can occur during or immediately after exercise testing. The risk of death with CPEX testing is very low, 1 in 20,000 (0.005%) and the risk of death or major adverse event (death or hospitalisation) is 1 in 10,000 (0.01%) [45]. Absolute contraindications to perform CPEX test are only a handful- recent myocardial infarction (< 5 days), acute respiratory or cardiac failure, severe symptomatic valvular stenosis, aortic dissection, acute pulmonary embolism and uncontrolled arrhythmias causing haemodynamic compromise [46]. While physician supervision is advised in high risk patients (recent myocardial infarction but >5 days, cardiac arrhythmia or asymptomatic severe valvular stenosis), two physiologists or specialist nurses trained to recognise the complications and administer cardio-pulmonary resuscitation, can conduct most tests safely [5]. Continuous ECG monitoring, and blood pressure measurement every two minutes are mandatory during the exercise test and should continue six minutes into recovery [47].

Conclusion:

Ischaemia detection is one of the novel applications of CPEX. The sensitivity and specificity of CPEX seem to be inferior to stress imaging techniques, but superior to exercise ECG testing. More importantly, it can guide therapy in those presenting with dyspnoea and provide prognostic information. CPEX can be valuable tool in those with LBBB pattern, and suspected microvascular ischemia. While recent guideline has recognised CPEX as an ischemia testing tool [48], it is yet to be inducted into routine clinical practice. Future research could explore combined a scoring system based on CPEX parameters and non-invasive imaging in diagnosis and prognosis of coronary artery disease.

Summary points:

- CPEX increases sensitivity and specificity for detection of myocardial ischaemia compared to standard exercise ECG test
- CPEX is particularly useful when patients present with coronary artery disease present with breathlessness as their primary symptom
- CPEX can play a unique role in assessment of myocardial ischaemia in special circumstances including LBBB, without exposing patients to the risks of coronary angiography
- CPEX is an excellent prognostic marker in stable coronary artery disease and after acute myocardial infarction
- New studies continue to identify novel CPEX prognostic markers in coronary artery disease.
- A scoring system based on CPEX and another non-invasive imaging modality (like exercise echocardiography) can prove to be an excellent tool in the management of coronary artery disease.

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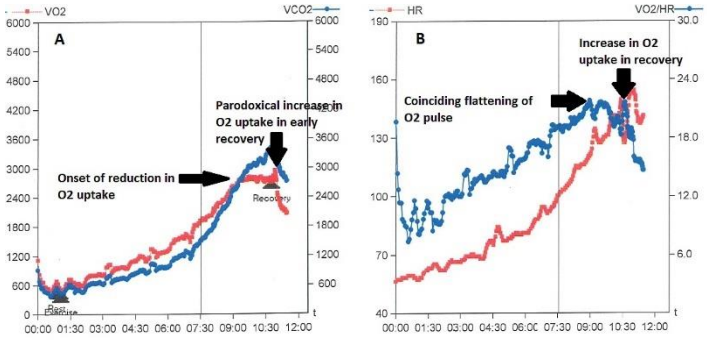
Figure legends:

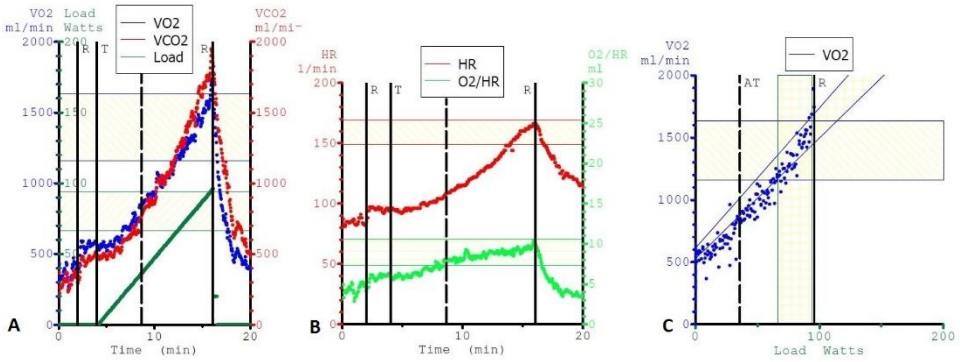
Figure 1



A: Abrupt flattening of oxygen uptake, and B: abrupt flattening of oxygen pulse at peak exercise (markers of ischaemia and reduction in stroke volume). Paradoxical rise in O_2 pulse in early recovery (resulting from improved cardiac function due to relief of ischaemia)

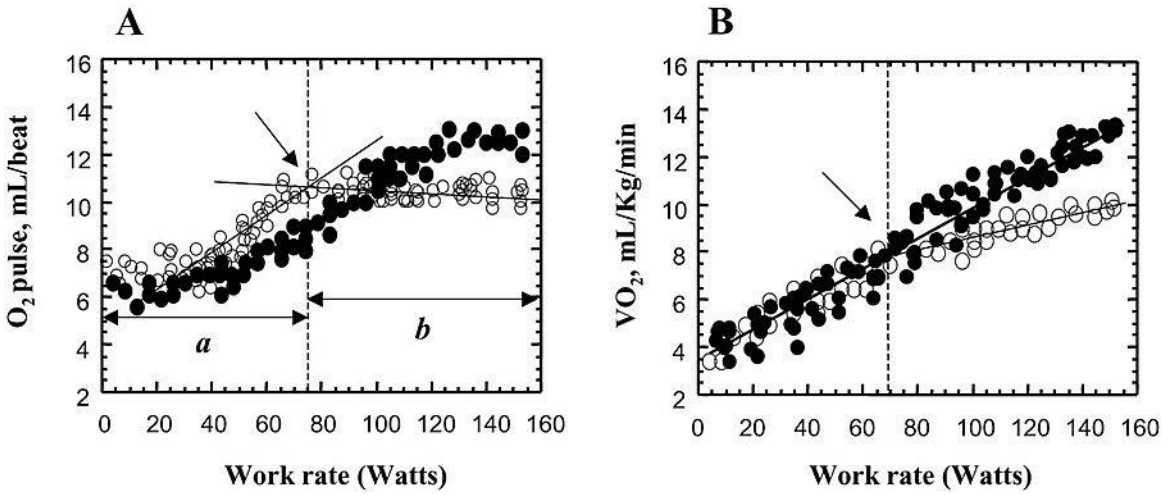
VO_2, body oxygen uptake; VCO_2, Carbon-dioxide exhaled from the body (ml/min); HR, heart rate; VO_2/HR, oxygen pulse

Figure 2



A: Steady increase in absolute oxygen consumption throughout exercise. B: Steady increase in O_2 pulse, suggesting that there is no significant reduction in stroke volume during exercise. C: Oxygen uptake as a function of work-rate ($O_2/\Delta WR$)

Figure 3**:** Oxygen uptake curves in healthy and ischemic subjects



(reproduced with Permission from Belardinelli et al (2003), Oxford University press[8])

A: In a healthy subject (closed circles) O_2 pulse steadily increases during incremental exercise and plateaus close to peak exercise. In an ischemic subject (open circles) the O_2 pulse plateaued early (arrow)

B: In the healthy subject (closed circles) the $O_2/\Delta WR$ relationship is linear. In an ischemic subject (open circles), the $O_2/\Delta WR$ is flattened at the inflection point (arrow).

Both changes in the ischemic subject occurred at the same time, reflecting myocardial dyskinesis

VO2-oxygen consumed, VO2/HR- oxygen consumption per heart rate (oxygen pulse)

Table 1: Gas-exchange and haemodynamic parameters (Case 1)

	Rest	*AT*	*Peak*	*Predicted*
RER	-	0.79	1.22	>1.15
VO_2 [ml/min]	579	1900	2738	127%
VO_2 [ml/min/kg]	5.6	18.3	26.3	
VE/VCO_2 slope	-	28.4	-	<32
Ventilation [L/min]	18.6	47.2	121.9	
MVV [L/min]	-	-	-	136.8
BR [litres]	-	-	14.9	>15
Heart rate [bpm]	57	100	134	86%
Blood pressure [mmHg]	140/90	-	170/90	-
Oxygen saturations [%]	99	-	98	-

RER-Respiratory Exchange Ratio; VO2- oxygen consumption; VE-ventilation; VCO2-carbon dioxide produced; MVV-Maximum Voluntary Ventilation; BR-Breathing Reserve

Table 2: Gas-exchange and haemodynamic parameters (Case 2)

	Rest	*AT*	*Peak*	*Predicted*
RER	-	0.91	1.12	>1.15
VO_2 [ml/min]	-	836	1735	124%
VO_2 [ml/min/kg]	-	11.6	24.1	
VE/VCO_2 slope	-	29	-	<32
Ventilation [L/min]	11.2	-	66.6	-
MVV [L/min]	-	-	-	93.2
BR [litres]	-	-	26.6	>15
Heart rate [bpm]	85	-	166	86%
Blood pressure [mmHg]	133/74	-	187/93	-
Resting oxygen saturations [%]	98	-	98	-

RER-Respiratory Exchange Ratio; VO2- oxygen consumption; VE-ventilation; VCO2-carbon dioxide produced; MVV-Maximum Voluntary Ventilation; BR-Breathing Reserve

Supplementary Table 1: Commonly used CPEX abbreviations

VO_2 (oxygen uptake)	Amount of oxygen consumed by the body per unit time
VCO_2	Amount of carbon dioxide exhaled from the body per unit time (ml/minute)
Peak VO_2	Highest VO_2 achieved during maximal effort (may be expressed as an absolute value (ml/min) or corrected for weight (ml/kg/min))
Oxygen pulse	Oxygen consumed by the body, per heartbeat. This depends on stroke volume and skeletal muscle oxygen extraction (ml/beats per minute)
RER (Respiratory Exchange Ratio)	Ratio of carbon dioxide output to oxygen uptake (VCO_2/VO_2) at a particular time during exercise
Anaerobic threshold (AT)	Exercise limit above which the subject's anaerobic high energy phosphate production supplements aerobic metabolism. This time-point during exercise is identified by raising levels of carbon dioxide production, reflecting the serum raise in lactic acid
VE	Minute ventilation. Volume of air inhaled or exhaled by the body in 1 minute (VE= tidal volume x respiratory frequency) L/min
MVV (Maximum Voluntary Ventilation)	The maximum potential ventilation achievable (estimated as FEV1 x 40)
BR (Breathing Reserve)	The difference between maximum voluntary ventilation and the achieved maximum exercise minute ventilation (BR=MVV-VE)

Supplementary Table 2: Typical treadmill CPEX protocol

	Warm-up 2 mins	**Stage 1 1 min**	**Stage 2 1 min**	**Stage 3 1 min**	**Stage 4 1 min**	**Stage 5 1 min**	**Stage 6 1 min**	**Stage 7 1 min**	**Stage 8 1 min**	**Stage 9 1 min**
Speed Kilometre/hour	2	1	2	3	4	5	6	7	8	3
Gradient	0%	1%	2%	3%	4%	5%	6%	7%	8%	0%