Laboratory Case Report

Using Cardiopulmonary Exercise Testing(CPET) to review cardiopulmonary and metabolic responses to incremental exercise, and discuss the clinical implications of the results within Peripheral Artery Disease patients

Contents

Abbreviation List

CPET : Cardiopulmonary Exercise Testing

PAD : Peripheral Artery Disease

IC : Intermittent Claudication

NHS : National Health Services

HF : Heart Failure

MI : Myocardial infarction

COPD : Chronic Obstructive Pulmonary Disease

VAT : Ventilatory Anaerobic Threshold

VT1 and VT2 : Ventilatory Threshold 1 and 2

VE : Ventilatory Exchange

VO_{2max} : Maximal consumed/utilised oxygen averaged over 30 seconds

RPE : Rate of Perceived Exertion

RER : Respiratory Exchange Ratio

BACPR : British Association for Cardiovascular Prevention and Rehabilitation

AACVPR : American Association of Cardiovascular and Pulmonary Rehabilitation

NICE : National Institute for Healthcare and Excellence

Introduction

Cardiopulmonary Exercise Testing(CPET) is a maximal exercise test that provides a global assessment of cardiopulmonary fitness as well as pulmonary and metabolic responses to incremental exercise(Taylor, Nichols, & Ingle, 2015). It combines exercise at maximal intensity with ventilatory gas analyses on a breath-by-breath basis to assess fitness and identify limitations to functional capacity. A CPET therefore has greater diagnostic and clinical utility than a submaximal or self-paced exercise test(Arena et al., 2007; Hodges, Sandercock, Das, & Brodie, 2006).

Peripheral Artery Disease(PAD) is characterized by the abnormal narrowing of the arteries of the limbs due to a build-up of fatty / calcified deposits resulting in decreased oxygen supply to the tissues(Ratchford & Evans, 2014). The disease is characterized by significant exercise intolerance, claudication pain and poor quality of life(Baloch, Abbas, Marone, & Ali, 2018). Physical activity is often symptom limited. PAD patients typically carry a greater risk of cardiovascular mortality and acute coronary events due to their typically advanced age and disease characteristics(Hirsch et al., 2006).

It is therefore important to comprehensively assess their fitness and responses to exercise to arrive at an intervention that can adequately address their impairment. The current evidence is directed towards using CPET data to stratify perioperative risk(Young et al., 2012), but there is a paucity of large datasets that use CPET in PAD cohorts to comment on :

- Disease severity
- Progression
- Baseline for exercise prescription
- Effectiveness of prescribed pharmaceutical or physical activity interventions

However, a recent study(PREDICT study) in the UK employed CPET in PAD patients to demonstrate how VE/VCO_2, VO_{2max} and VAT are variables that significantly affect long term patient

outcomes(Harwood et al., 2018). The study also shows the virtues of using CPET data to inform the creation and implementation of a supervised exercise program within physiological limits of claudication pain. The PREDICT study thus shows that it is possible to implement such protocols for PAD rehabilitation within the NHS and consequently improve the therapist's understanding of the wider risk profile and outcomes involved.

Aims

This report aims to :

- Comment on the functional capacity of the PAD patients in comparison to healthy individuals
- Provide a broad picture regarding the severity of the disease
- Demonstrate how the CPET results could inform risk assessment in PAD cohorts
- Arrive at comprehensive baseline data which can be used to prescribe safe and effective exercise for symptomatic and functional capacity improvements

Methodology

Setting

The testing was conducted at the Physiology Laboratory, University of Hull, UK. The laboratory is large, well lit and well ventilated with ambient temperatures which were comfortable for both the patient and assessor.

Equipment list

Type	Model
Cycle Ergometer	General Electric(GE) eBike Ergometer
Gas Analyser	Oxycon Pro
Face mask (for breath gas analysis)	-
3 Litre Calibration Syringe	Hans Rudolf 5530
Sphygmomanometer	Tango Automated Sphygmomanometer
Pulse Oximeter	Nonin Ox Finger Pulse Oximeter
Heart Rate Monitor	Polar FS1 HRM – Monitor and watch
ECG Machine	Marquette Hellige Cardiosmart ECG
ECG Electrodes	Pulse Medical (Gel electrodes)
Weighing Scale	Salter Electronic Weighing Scale
Stadiometer	Holtain Ltd
Inch tape	-
Stethoscope	Littman Stethoscope
Borg Scale of Perceived Exertion (RPE Scale)	Borg 6-20 RPE Scale

Table 1- Testing Equipment

Rationale for equipment selection and testing methodology

- CPET using cycle ergometry was the preferred testing method. This is because PAD patients find it difficult to tolerate treadmill testing and rarely complete maximal tests. However, in cycle ergometry, body weight is borne on the saddle rather than on the lower extremity which delays the onset of symptoms thereby improving performance in exercise testing(Oka, Roberta K., Altman, Giacomini, Szuba, & Cooke, 2005; Tuner et al., 2008).

- Cycle ergometry also induces more cardiovascular and metabolic response to exercise testing compared to treadmill testing(Tuner et al., 2008). This could be due to cycle ergometry being better tolerated by PAD patients resulting in longer exercise periods.
- Direct measurement of gas exchange is a reliable, reproduceable method of identifying abnormal haemodynamic responses using the *Oxycon Pro gas analyser*(Hannink et al., 2010) while baseline and exercise ECG help identify cardiac rhythm abnormalities.
- Ramp protocol of 10 watt per minute increments selected based on Wasserman et al.'s recommendations for populations who might be frail and have chronic disease burdens(Wasserman et al., 2011)

Informed Consent and Risk Assessment

Verbal and written informed consent were obtained from the participant. Anthropometric data, medical and treatment history were consequently obtained from an interview with the participant and hospital records. The patient also filled out the '*Pre-exercise medical screening questionnaire'* to aid in pre-exercise risk stratification.

Risk assessment was carried out based on :

- Medical history : Ensuring any diagnosis of heart failure, angina, COPD was appropriately managed and if the patient is clinically stable.
- The patient's resting ECG was also scrutinized for any evidence of previous abnormalities such as myocardial infarction, atrial fibrillation, left bundle branch block etc.
- BACPR and AACVPR guidelines for cardiovascular risk stratification were employed as screening tools(Hirsch et al., 2006)

- ACSM criteria for exercise testing : Absolute and relative contraindications were screened for and considered prior to the testing process.

Absolute Contraindications	Relative Contraindications
Recent significant change in resting ECG	Left main coronary artery stenosis
Unstable angina	Moderate stenotic valvular heart disease
Uncontrolled cardiac dysrhythmias	Electrolyte abnormalities/imbalance
Severe aortic stenosis	Severe hypertension; Systolic BP >200mmhg and Diastolic BP>110mmHg at rest
Uncontrolled symptomatic heart failure	Frequent/complex ectopy
Acute pulmonary embolus or pulmonary infarction	Hypertrophic cardiomyopathy
Acute myocarditis or pericarditis	Neuromotor, musculoskeletal or rheumatoid disorders
Suspected or known dissecting aneurysm	Fixed rate pacemaker
Acute systemic infection	Ventricular aneurysm
Thrombophlebitis or intracardiac thrombi	Uncontrolled metabolic disease (Diabetes, thyrotoxicosis etc)
Third degree atrioventricular block without pacemaker	Chronic Infectious disease (HIV)
Recent complicated MI	Mental or physical impairment resulting in inability to exercise adequately
	Advanced/complicated pregnancy

Table 2 – ACSM 2018 : Contraindications for exercise testing and participation

CPET Methodology

The following steps were employed as part of the exercise testing procedure :

- Short interview – to determine the participant's view on current health as well as to identify any patient described limiting factors to exercise performance
- Patient briefing – CPET procedure as well as safety measures explained to the patient
- Informed consent and Pre-exercise Medical Screening Questionnaire (University of Hull Ethics Committee)
- Height and weight were measured. The following baseline vitals were obtained in seated position :
    - Blood pressure
    - Resting heart rate
    - Breath rate
- Resting ECG obtained in supine position. Modified ECG electrode placement(Mason-Likar) utilised to for both baseline and exercise ECG testing.

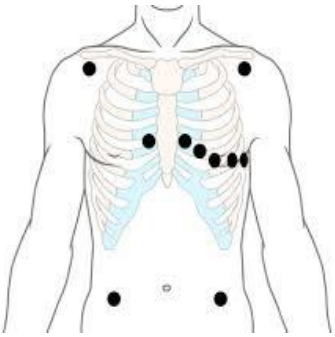

Figure 1 - Mason-Likar Placement

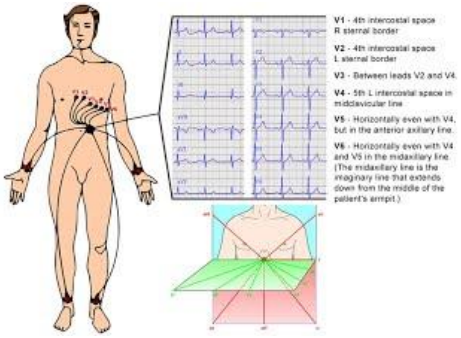

Figure 2 - Traditional 12-Lead ECG

- Oxycon Pro system calibrated with 3L Syringe. Patient positioned on eBike Ergometer and face mask fitted. Patient asked to remain at rest to check for any vitals or ECG disturbances due to change in body position
- Patient is instructed to cycle at a cadence of 60-70rpm to maintain consistency throughout the CPET
- 3 minutes of unloaded cycling – Considered as the warm up prior to testing
- Ramp protocol at 10W per minute – incremental exercise initiated after 3 minutes unloaded cycling. Expected working/exercise test time is 6-12 minutes(Wasserman et al., 2011)
- 3-minute cool down – patient is not required to cycle but vitals as well as gas analyser are monitored to identify any abnormal responses during the recovery phase
- Gas mask removed, patient vitals checked before permitting exit from testing area

Indications for termination of CPET

Indications for exercise termination

Chest pain suggestive of ischaemia
Ischaemic ECG changes
Complex ectopy
Second- or third-degree heart block
Fall in systolic pressure >20 mm Hg from the highest value during the test
Hypertension (>250 mm Hg systolic; >120 mm Hg diastolic)
Severe desaturation: Spo_2 ⩽80% when accompanied by symptoms and signs of severe hypoxaemia
Sudden pallor
Loss of coordination
Dizziness or faintness
Signs of respiratory failure
Mental confusion

Adapted from ATS/ACCP Statement on Cardiopulmonary Exercise Testing.

Figure 3 – Termination criteria(Hirsch et al., 2006)

Criteria for a maximal CPET

Achieving **one or more** of the given criteria(Wasserman et al., 2011) constitutes the completion of a maximal CPET :

- RER >1.15
- Achieved maximal HR during the test within 15% of their age predicted HR_{max}
- RPE >17
- VO2 plateau over 30 seconds

Anthropometric Data

Patient	Age	Measured Height (cm)	Measured Weight (kg)	BMI	Predicted HR_{max}	Resting Heart Rate
PAD 1	71	183	88.2	26.33	149 bpm	66 bpm

Table 3 – PAD Patient Anthropometric data

Patient is Caucasian male, classified as overweight due to BMI over normative values for his age, gender and ethnicity. Age predicted HR_{max} was calculated based on the Karvonen method (220-age)(Fox, Naughton, & Haskell, 1971).

Predicted data

Predicted data calculated using Wasserman-Hansen equations(Wasserman et al., 2011) under the assumption that the participant is sedentary owing to long standing PAD. The patient is male and CPET was performed on a cycle ergometer.

Age	**71**
Predicted Weight	83.87kg
Age predicted HR_{max} (220-age)	149
Predicted VO_{2max}	2064.86 ml/min (or 24.61 ml/kg/min)
Normative VAT threshold	49-63% of VO2
Predicted Oxygen Pulse	13.86 ml/beat

Table 4 – CPET Predicted Data for PAD Patient 1

Predicted peak oxygen consumption equations

	Sedentary male	Sedentary Female
Wasserman/ Hansen equations[a]	*Step 1*: Calculate Cycle factor = 50.72 − 0.372(age) Predicted weight = 0.79 (height) − 60.7 *Step 2*: Classify weight Measured weight= predicted weight *Step 3*: Select equation **Measured weight < Predicted weight** Peak V_{O_2} (mL • min^{-1}) = [(Predicted weight + Actual weight)/2] × cycle factor **Measured weight = Predicted weight** Peak V_{O_2} (mL • min^{-1}) = Measured weight × cycle factor **Measured weight > Predicted weight** Peak V_{O_2} (mL • min^{-1}) = (Predicted weight × cycle factor) + 6 × (Measured weight − predicted weight) *Step 4*: Mode of exercise consideration **If treadmill used for test** Multiply predicted V_{O_2} from step 3 × 1.11	*Step 1*: Calculate Cycle factor = 22.78 − 0.17 (age) Predicted weight = 0.65 (height) − 42.8 *Step 2*: Classify weight Measured weight = predicted weight *Step 3*: Select equation **Measured weight < Predicted weight** Peak V_{O_2} (mL • min^{-1}) = [(Predicted weight + Actual weight +86)/2] × cycle factor **Measured weight = Predicted weight** Peak V_{O_2} (mL • min^{-1}) = (Measured weight + 43) × cycle factor **Measured weight > Predicted weight** Peak V_{O_2} (mL • min^{-1}) = (Predicted weight + 43) × cycle factor + 6 × (Measured weight − predicted weight) *Step 4*: Mode of exercise consideration **If treadmill used for test** Multiply predicted V_{O_2} from step 3 × 1.11

Figure 4 - Wasserman-Hansen equations for peak VO2

The CPET data was collected and the relationship between the variables were represented graphically based on Wasserman's principles of exercise testing. The data analysed will be 15 second data as it provides better data to plot graphically than 5 second data. 5 second data leads to vast number of closely located points which creates a lot of noise/discordance within the graphs.

Wasserman describes a 9-panel plot.

Graph	Relationship (Y on X nomenclature)
Plot 1	VO2, VC_{O2}, Workload on Time
Plot 2	Heart rate and Oxygen Pulse on time
Plot 3	Heart rate, VC_{O2} on VO2
Plot 4	VE/VO2 and VE/ VC_{O2} on time
Plot 5	Not plotted due to insufficient data
Plot 6	V VC_{O2} on VE
Plot 7	Not plotted due to insufficient data
Plot 8	RER on time
Plot 9	Not plotted due to insufficient data

Table 5 – CPET 9-panel plots

Results

CPET Performance

The patient has completed a maximal CPET. This is evidenced by the fact that he has achieved nearly all the criteria for a maximal test where he has :

- Achieved RER >1.15 indicating maximal effort
- Plateau in oxygen consumption – clearly visible in plot 1
- Achieved 100% of his predicted HR_{max}

Peak workload achieved was 126 watts and incremental exercise time was 11 minutes and 15 seconds. RPE data was unavailable for this data set. Normal heart rate response in recovery is observed with >20 beats per minute decrease observed across the first minute and > 40 beats across the second minute of recovery.

Oxygen Consumption

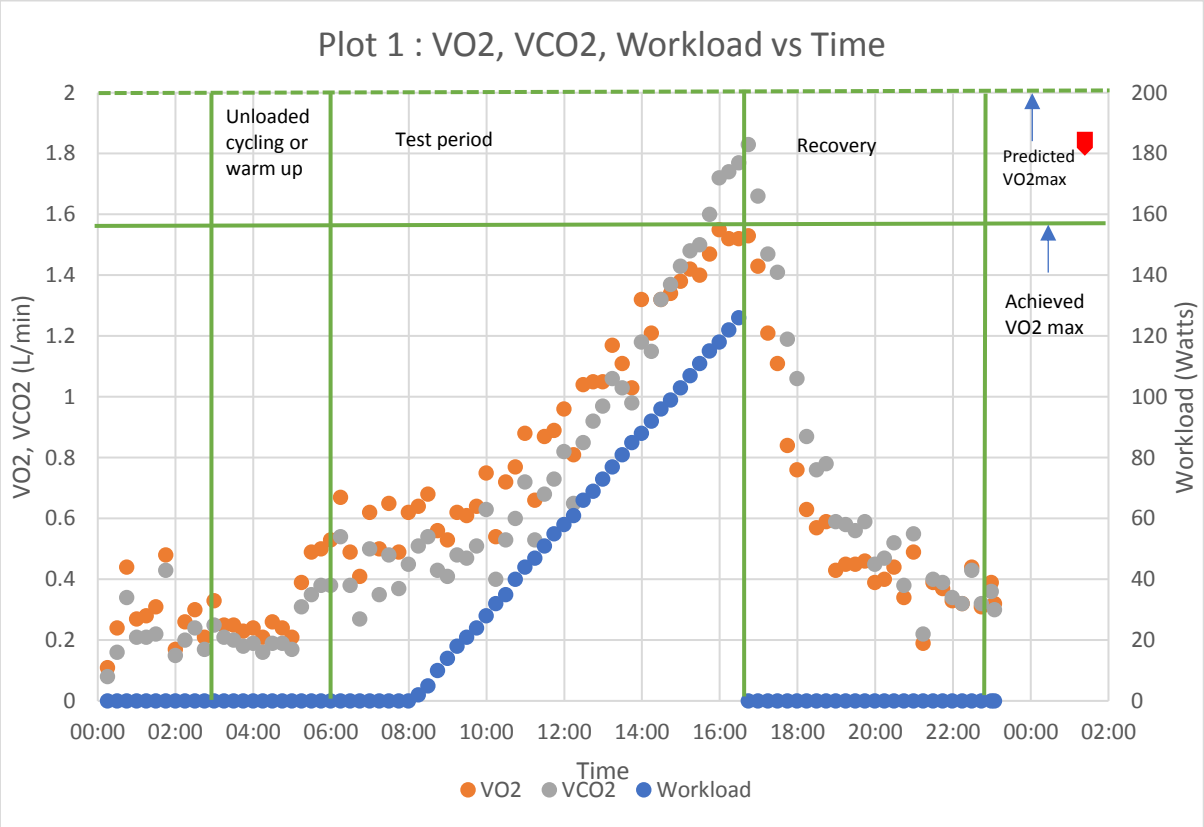

Figure 5 – Oxygen uptake and expired carbon dioxide throughout the test

Panel 1 shows the maximal oxygen intake achieved by the patient evidenced by a plateau in oxygen consumption in response to increasing workloads. In clinical populations, this plateau may not be evident in all patients who undergo a CPET(Coeckelberghs, Buys, Goetschalckx, Cornelissen, & Vanhees, 2016). So, the point highest value of oxygen consumption is recorded. This is termed as VO2 peak. Therefore, VO2 peak is a much more appropriate measure for oxygen consumption than VO_{2max} in clinical populations.

As per Wasserman-Hansen equations, the patient was predicted to achieve a maximal oxygen uptake of 2046.83ml/min (displayed on the graph by a dashed line). However, the patient only achieved 1550ml/min as his VO2 peak. This patient did achieve the desired plateau resulting in his VO_{2max} of 1535ml/min. He maintains this plateau for approximately 60 seconds.

Oxygen Pulse

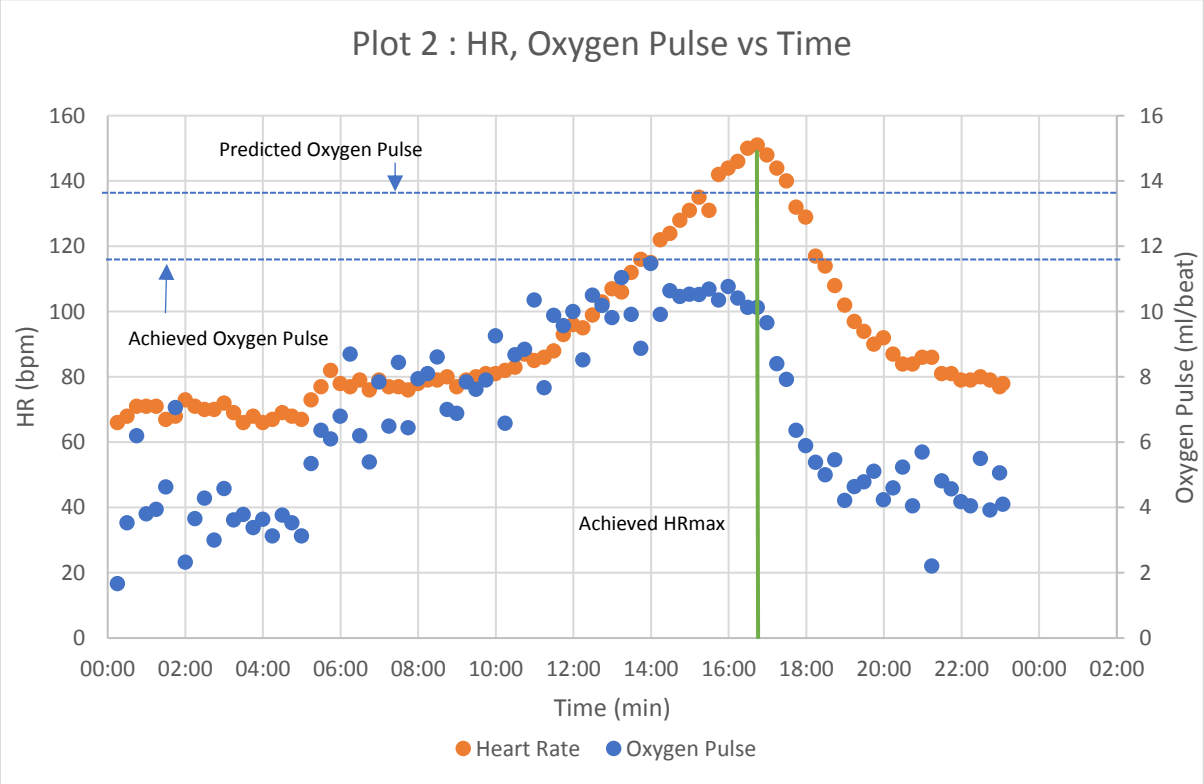

Figure 6 – Oxygen consumed per heart beat

This panel displays the volume of oxygen consumed per heart beat(Oxygen pulse) along with heart rate against time. The patient has achieved a peak oxygen pulse of 11.48ml/beat. However, the

patient was unable to sustain this for more than 15 seconds. The predicted oxygen pulse for this patient is 13.86ml per beat. This shows that the patient has fallen short of the predicted values.

Ventilatory Anaerobic Threshold

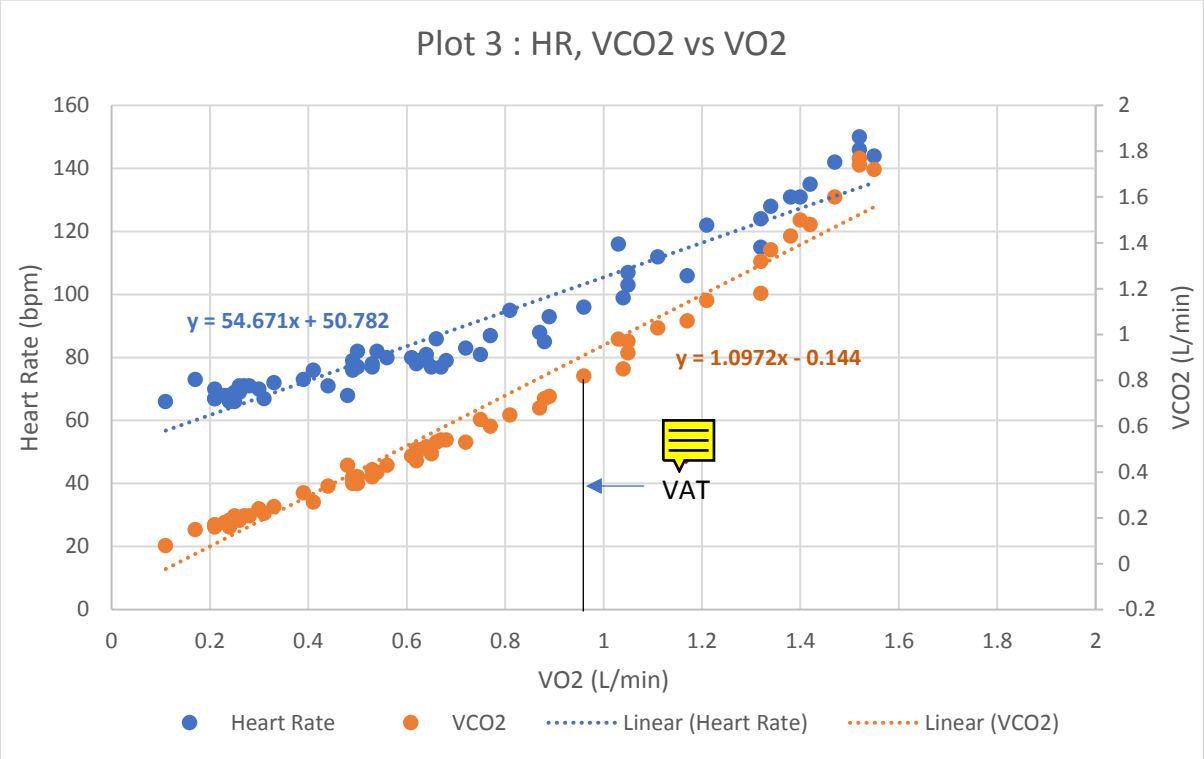

Figure 7 – Expired carbon dioxide and heart rate relationship against oxygen uptake

Plot 3 is used to identify the patient's VAT from the VC_{O2}/ VO_2 relationship. VAT is identified and expressed as a percentage of maximal oxygen uptake. The patient's VAT is identified to occur at 0.96 l/min VO_2 and 0.82 l/min VC_{O2}at a heart rate of 96bpm. Therefore, he has reached his VAT at 62% of VO_{2max}. This was achieved at a workload of 58 watts.

In healthy individuals, VAT is expected to lie between 48%-63% of VO_{2max} (Wasserman et al., 2011). Within this context, the patient meets normative criteria.

Ventilatory Response

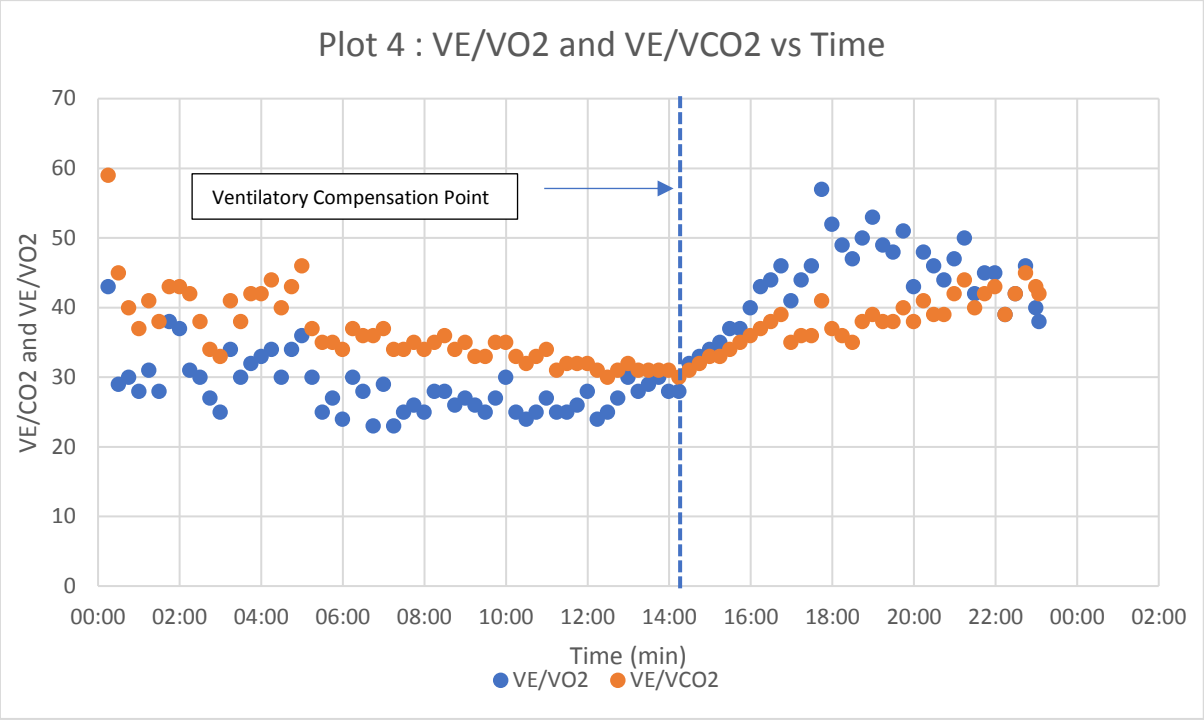

Figure 8 – Expired carbon dioxide and inspired oxygen per ventilatory exchange

Plot 4 displays the relationship between VE/CO_2 and VE/VO_2throughout the testing period. It helps identify the point where the inspired oxygen is insufficient to buffer the carbon dioxide and lactate build up. There is a clear shift or inflection in the graph noted at 14:15 mins where VE/VO_2 increases rapidly compared to VE/VCO_2. This point is termed at the ventilatory compensation point(Nichols, Taylor, & Ingle, 2015).

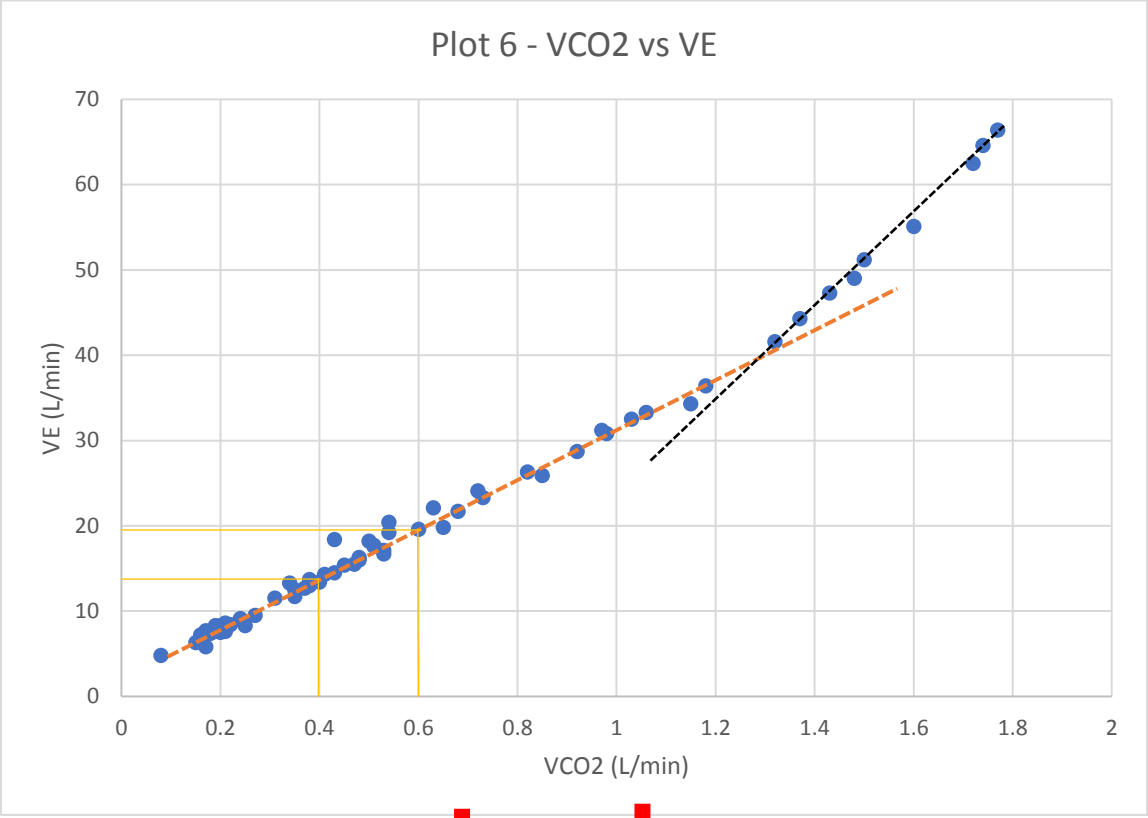

Figure 9 – Ventilatory Exchange and Carbon dioxide relationship

Plot 6 of the CPET gives further information about the ventilatory responses to incremental exercise. This plot is used to find out if the respiratory compensation point has been met. The RCP is the nadir value before the relationship becomes non-linear. Another important factor is the slope of this relationship, which helps identify disorders in the pulmonary system.

The slope is calculated before the RCP, i.e. where the relationship remains linear. For this patient, the slope was calculated to be 30.25 which shows a normal relationship(Poggio, Arazi, Giorgi, & Miriuka, 2010).

Other noteworthy relationships

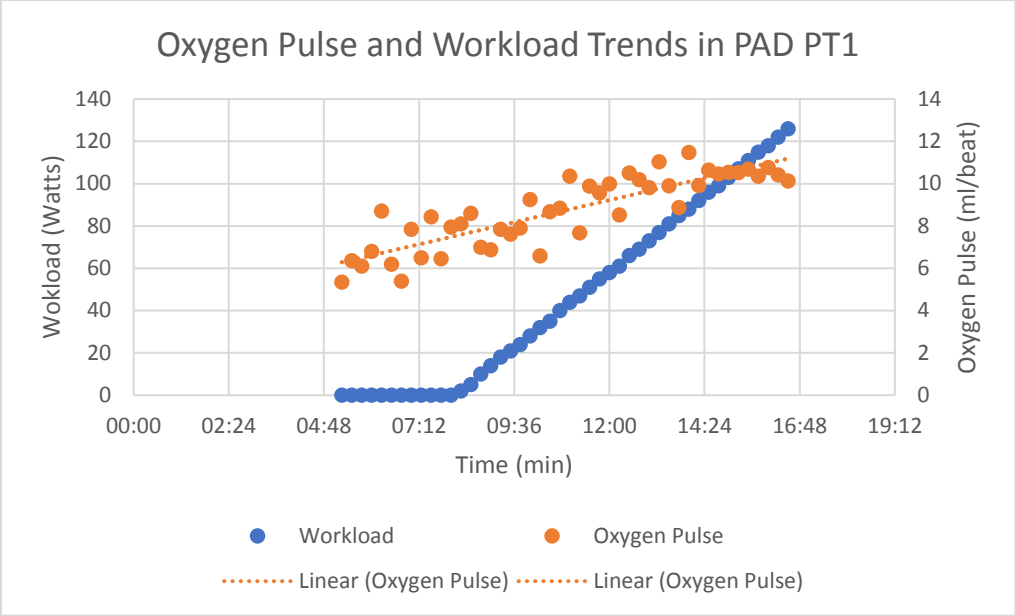

Figure 10 – Oxygen pulse and Workload relationship

A normal oxygen pulse-workload relationship is seen to be a steep linear increase, directly correlated to the increase in workload. However, in this patient we see a muted response. The slope is observed to be 8.1. For his age, the slope of this relationship should be closer to 10 ± 1.

Summary of Results – Comparisons to Normative Data

The following table summarizes the results of participant's CPET performance and compares his data to the normative values for a healthy male of his age.

Parameter	Measured Data	Normative Data
Peak VO_2	1550ml/min or 19ml/min/kg	23 ± 5.4 (Barron et al., 2015)
VAT	62% of VO_2 peak	48-63% of VO2 peak (Wasserman et al., 2011)
Oxygen Pulse	11.48ml/beat	19.3 ± 3.5 (Albouaini, Egred, Alahmar, & Wright, 2007)
Peak RER (Exercise)	1.16	1.11 ± 0.08(Wasserman et al., 2011)
VE/ VCO_2 Slope	30.25	19.12-30.66(Koch et al., 2009)
Peak Work Rate	126 Watts	188 ± 43 Watts (Albouaini et al., 2007; Meyer et al., 1994)

Table 6 – Summary of results

Discussion

Functional Capacity

As evidenced by the subnormal VO_{2max} and the dulled relationship between oxygen pulse and workload, the patient has impaired functional capacity. VO_{2max} is a good prognostic indicator within cardiovascular disease(Ingle et al., 2011). The patient's VO_{2max} falls within the lower bounds of normative data indicating some underlying pathology of the cardiovascular system.

The oxygen pulse-workload slope is a good indicator of skeletal muscle function(Harwood et al., 2018). The patient shows signs of deconditioning which is evidenced by the muted response observed in figure 10. The combination of the above factors show how PAD and IC has affected the exercise capacity of the patient and displays the virtues of using a CPET to identify this when simpler methods such as maximal walking distance via a treadmill test would be unable to identify these fine details(Bronas, 2007).

Disease Severity

VO_{2max}, Oxygen pulse-workload, VE/ VCO_2slope and VAT obtained from the CPET help comment on disease severity. The VO_{2max} and oxygen pulse measured are lower than the normative data. But VAT and VE/ VCO_2slope are more sensitive prognostic markers for cardiovascular disease than VO_{2max} (Ingle et al., 2011; Poggio et al., 2010). VAT is an important measure since all work below this threshold is equivalent to the aerobic capacity required to perform activities of daily living. The measured values for these parameters fall within the normative limits for age and sex. However, it is important to note that the modality of CPET (treadmill vs cycle ergometer) can impact the VO_{2max} and the VAT response(Balady et al., 2010). Typically. these parameters are identified at lower thresholds in treadmill testing.

Therefore, the above data leads to the conclusion that the disease burden remains but there is no major impact on functional capacity and general health as initially hypothesized. It also lends

weight to the argument that in the case of this patient, the functional capacity is affected by claudication pain than by the disease severity itself(Oka, R. K., Altman, Giacomini, Szuba, & Cooke, 2005).

Role of CPET Data in Risk Assessment

PAD patients carry a higher risk of cardiovascular mortality. However, up to 30% of all PAD patients have normal coronaries(Ratchford & Evans, 2014). Therefore, risk stratification using standardized tools may not be the most accurate. The addition of a CPET to standardized tests of cardiopulmonary function could improve overall patient outcomes by accurately estimating cardiovascular disease risk(Young et al., 2012).

As explained earlier, the results from the various relationships in the 9-panel Wasserman plot help establish a global picture of the disease with focus on the functional capacity as well as metabolic and pulmonary responses. With the emergence of VO_{2max}, VE/ VCO_2 slope and OUES as significant prognostic tools(Harwood et al., 2018; Ingle et al., 2011; Poggio et al., 2010), a statistically significant change in these parameters can indicate a change in the disease profile and consequently better risk stratify the patient.

Exercise Prescription and Programming

CPET data can be extremely helpful in planning an exercise intervention or assessing the efficacy of a prescribed intervention in patients who have a chronic disease burden. Exercise interventions can be prescribed on the basis of :

- VAT – Exercise training at VAT zone results in an increase in VO_2 at VAT by anywhere between 10 and 25% in sedentary or frail individuals(Balady et al., 2010). It is also noted that training between VT1 and VT2 results in a series of metabolic changes in the muscles. Consequently, regular exercise results in the elevation of the VAT and improved peripheral utilisation of oxygen and buffering of lactate resulting in improved functional capacity.

- VO_{2max} (Gold standard) – While VO_{2max} does not account for individual differences in metabolic stress, it is a much more effective form of exercise prescription at low to moderate intensity when compared to percentage heart rate reserve(Mann, Lamberts, & Lambert, 2013). Another study showed that exercise prescribed at 75% of VO_{2max} resulted in progressive increase in thresholds for blood lactate levels in heterogenous populations(Scharhag-Rosenberger, Meyer, Gässler, Faude, & Kindermann, 2010).

These methods of exercise prescription give superior results in terms of the participant's physiological responses to exercise. It subsequently helps accurately monitor the body's adaptations to exercise training by quantifying the VO_{2max} and VAT which are more sensitive to change than heart rate adaptations to exercise(Cortes et al., 1997; Mann et al., 2013).

With respect to PAD, the current guidelines in the UK recommend at least 30 minutes of walking daily(Hirsch et al., 2006). The patient must walk at a speed that induces claudication pain. However, this may not prove to be effective due to lack of supervision to ensure that patients follow the guideline.

A supervised exercise program is therefore more beneficial(Harwood et al., 2018) to the patients. While there is paucity of evidence exploring the utility of VO_{2max} and VAT to prescribe exercise within a PAD cohort, it is safe to assume that the available benefits from doing so will greatly improve the functional capacity of the patient and address symptoms of claudication.

Conclusion

CPET is being increasingly implemented within a clinical setting. The detailed assessment of the cardiopulmonary and metabolic physiology can inform clinical decision making within the context of pharmacological and exercise management. The modes of exercise prescription can be better modulated to suit the patient using CPET data and it would be foolish to discount the odds of superior results compared to the traditional methods of exercise prescription. Patients with chronic diseases can only benefit from an exercise rehabilitation point of view thereby displaying the value of CPET.

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