Effect of peripheral arterial disease on the onset of lactate threshold during cardiopulmonary exercise test: study protocol

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ABSTRACT

Introduction: Cardiopulmonary exercise test (CPET) is widely used in preoperative assessment and cardiopulmonary rehabilitation. The effect of peripheral arterial disease (PAD) on oxygen delivery (VO2) measured by CPET is not known. The aim of this study was to investigate the effect of PAD on VO2 measurements during CPET.

Methods and analysis: We designed a prospective cohort study, which will recruit 30 patients with PAD, who will undergo CPET before and after treatment of iliofemoral occlusive arterial disease. The main outcome measure is the difference in VO2 at the lactate threshold (LT) between the 2 CPETs. The secondary outcome measure is the relationship between change in VO2 at the LT and peak exercise pretreatment and post-treatment and haemodynamic measures of PAD improvement (ankle–brachial index differential). For VO2 changes, only simple paired bivariate comparisons, not multivariate analyses, are planned, due to the small sample size. The correlation between ABI and VO2 rise will be tested by linear regression.

Ethics and dissemination: The study was approved by the North West-Lancaster Research and Ethics committee (reference 15/NW/0801). Results will be disseminated through scientific journal and scientific conference presentation. Completion of recruitment is expected by the end of 2016, and submission for publication by March 2017.

Trial registration number: NCT02657278.

INTRODUCTION

Cardiopulmonary exercise testing (CPET) is frequently used in the preoperative assessment of elderly patients,1 as well as in the evaluation and follow-up of patients with cardiopulmonary disease.2 Peripheral arterial disease (PAD) is highly prevalent in this population, due to its age and the presence of cardiovascular risk factors.3 CPET documents cardiorespiratory fitness by various means, including the measurement of systemic oxygen delivery (VO2) at the lactate threshold (LT)—the moment, during exercise, when muscles start working anaerobically—and at peak exercise. Low values suggest poor fitness and may indicate that surgery is of disproportionately high risk. Patients with PAD may develop ischaemia during leg exercise not because of poor cardiorespiratory reserve, but, independent of cardiorespiratory performance, because the blood supply to the muscles is impaired, eventually leading to early lactate release. On this basis, the LT may not reflect cardiorespiratory status, risk and prognosis in this group of patients. In addition, screening for PAD prior to CPET is not currently advocated or practiced.

To the best of our knowledge, there is no literature documenting or quantifying the effect of PAD on the results of CPET. Our hypothesis is that correction of PAD may cause improvement in VO2 proportional to the degree of improvement in the peripheral circulation. The aim of this study is to determine whether VO2 during CPET is influenced by the presence of haemodynamically significant PAD. More specifically, our research question was: in patients with PAD, does improvement in blood flow to the leg muscles result in a rise in VO2 at LT and peak exercise, as measured by CPET?
METHODS
Design
In order to answer our research question, we designed a prospective cohort study recruiting patients scheduled to undergo percutaneous or surgical correction of proximal (iliofemoral) occlusive PAD. We chose patients with iliofemoral (rather than infrapopliteal) disease because of the greater muscle mass experiencing ischaemia during CPET in this population (quadriceps, glutei). Inclusion and exclusion criteria are summarised in Table 1. We excluded patients with critical ischaemia because this condition (severe pain at rest with/without tissue loss) might affect their ability to perform a CPET.

Recruitment
Patients are recruited among those referred to the Liverpool Vascular and Endovascular Service for treatment of their PAD. Potential candidates are approached at the time of clinic attendance to determine interest in the study and offered a patient information leaflet as well as verbal information. Alternatively, they receive a study letter containing the patient information leaflet by post. In either case, patients are then approached by the study team by telephone >48 hours later to confirm participation. All participants are asked to provide written informed consent, which is obtained by either the study team by telephone >48 hours later to confirm participation. All participants are asked to provide written informed consent, which is obtained by either the first or the senior author.

Intervention
Patients undergo symptom limited CPET before and 4 weeks after surgical or endovascular correction of their PAD. The CPET protocol is described in detail in previous publications from our group.4,5 The test is performed according to the American Thoracic Society/American College of Chest Physicians recommendations.6,7 It includes ECG monitoring, measurement of ventilator parameters and recording of Borg breathlessness and leg fatigue score every minute. At the end of the test, the reason for cessation is documented. The test is incremental with a 10–25 W ramp aiming for the participant to exercise for 10–12 min based on predicted peak workload. The ramp chosen is one which would be expected to result in 8–10 min loaded exercise based on predicted maximum workload and ventilation. The same increment will be used for the pretreatment and post-treatment test. The test involves 3 min rest, 2 min free-pedal followed by continuous ramping until volition. Recording continues for 5 min recovery. The tests are blindly reported by two experienced clinicians (ND and PW). In event of disagreement, consensus is achieved between the two reporters by discussion. Other recorded variables include age, gender, height, weight, BMI, smoking status, haemoglobin concentration, ankle–brachial index (ABI—measured before and after treatment of PAD), medications and comorbidity. Resting flow-volume loops are used to derive forced expiratory volume in 1 s and forced vital capacity. Ventilation and gas exchange variables derived by CPET include VO₂, absolute and weight-adjusted, ventilatory equivalents for oxygen and carbon dioxide (VE/VO₂, VE/VCO₂); oxygen pulse (VO₂/heart rate), work rate and heart rate; all measured at estimated LT and at peak exercise.

Primary outcome measure
The difference in VO₂ at LT between the two CPETs.

Secondary outcome measures
The relationship between change in VO₂ at LT and peak exercise pretreatment and post-treatment and haemodynamic measures of PAD improvement (ABI differential).

Sample size
We could not find, in the literature, any data on patients with PAD undergoing CPET. We thus arbitrarily assumed that a difference in VO₂ at LT of 1 (SD 1.5) mL/kg/min would be deemed clinically significant, and calculated that 26 patients would be required to demonstrate this difference, at a 5% significance level and with 90% power. We thus decided to recruit 30 patients, in order to allow for a drop-out rate of 10–15%. This sample size will be achievable within 1 year, considering the patient throughput of the Liverpool Vascular and Endovascular Service.

Study outline
See figure 1. Recruitment is ongoing, with expected completion at the end of 2016. The study was registered at http://www.clinicaltrials.gov (NCT02657278) on 13 January 2016.

Table 1 Entry criteria

| Inclusion | Exclusion |
|-----------|-----------|
| Ability and willingness to give written informed consent | Critical ischaemia as presenting symptom (rest pain and/or tissue loss) |
| Iliofemoral PAD scheduled for surgical or percutaneous treatment | Age <18 years |
| Ability to perform a CPET on a cycle ergometer | Previous amputation |
| Intermittent claudication as presenting symptom | Inability to perform a CPET on a cycle ergometer |
| Age ≥18 years | Uncontrolled hypertension |
| | Unstable angina |
| | Acute coronary syndrome within 6 weeks of the test |
| | Terminal illness |
| | Advanced cancer |
| | Psychiatric illness or dementia precluding informed consent |

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Figure 1 Study outline.

**Data analysis**

Data are stored in a password-protected hospital server, accessible only by the researchers, according to internal information governance rules. Data will be analysed on completion of the study. We do not plan to perform any interim analyses. Continuous variables will be presented with mean and SD if normally distributed, or median and IQR if not. Parametric or non-parametric paired tests will be used according to the underlying distributions. For VO\(_2\), only simple paired bivariate comparisons, not multivariate analyses, are planned, due to the small sample size. The correlation between ABI and VO\(_2\) rise will be tested by linear regression (log transformation of data will be performed, if necessary, prior to this analysis).

**Ethics and governance**

The conduct of the study is monitored by the sponsor (University Hospital Aintree Research and Development, Lower Lane, Liverpool, UK), which also provides indemnity. Screening, recruitment and adverse event logs are updated in real time, as necessary, by the research team. Adverse events are immediately reported to the sponsor, as appropriate. Owing to the short duration of the study and the low likelihood of adverse events from the intervention, formal interim safety assessments are not planned.

**DISCUSSION**

This study was designed to ascertain whether PAD influences the results of CPET, by seeking an improvement in VO\(_2\) in patients treated for PAD, and by correlating this improvement (if any exists) with ABI differential measurements. The study was conceived because of lack of information, in the literature, on the effect of PAD on systemic VO\(_2\) measured by CPET by cycle ergometry, a commonly performed test, in different settings, to evaluate cardiorespiratory fitness. The study was not designed to provide conclusive results, rather as an exploratory investigation. Any evidence of a positive effect of (correction of) PAD on the outcome measures may stimulate further research and inform future sample size estimates. Furthermore, assuming a positive finding, the study may suggest caution in interpreting the results of CPET in patients with PAD, pending further evidence. It may also induce clinicians to screen for PAD prior to CPET. Although one of the secondary outcome measures is the correlation between changes in VO\(_2\) and ABI, the study is not specifically powered for this, nor could it be, due to the lack of evidence in the literature. Furthermore, ABI is only a crude measurement of the effect of treatment of PAD, and not solely dependent on the presence of PAD, and it is influenced by infraginginal disease, whose presence is not addressed by the treatment of the patients included in this study.

In conclusion, this study will provide further insight on the use and interpretation of CPET in the elderly, and evaluate PAD as a potential limiting factor of cardiorespiratory performance in this group of patients.

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