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Prognostic Markers of Outcome in Patients Undergoing Infra-inguinal Revascularisation: A Prospective Observational Pilot Study

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WHAT THIS PAPER ADDS

This study shows that NT-proBNP is predictive of outcomes beyond major cardiac events and can be used with cardiopulmonary exercise testing data to plan healthcare resource utilisation in patients having infra-inguinal revascularisation.

Objectives: The aim was to investigate whether cardiopulmonary exercise testing (CPET) variables derived from cycle and arm ergonometry correlate, and whether CPET variables and pre-operative N-terminal pro-brain natriuretic peptide (NT-proBNP) have prognostic significance and if the combination of the two has incremental value.

Methods: A prospective observational pilot study was conducted; 70 patients who underwent infra-inguinal bypass surgery were recruited. Pre-operatively subjects underwent CPET with both arm and leg ergonometry, to measure peak oxygen consumption, anaerobic threshold (AT), and ventilatory equivalents. In addition pre-operative serum samples of NT-proBNP were obtained. The primary endpoint was 1 year all-cause mortality; in addition, data were collected on complications, morbidity, length of stay, and major adverse cardiac events (MACE).

Results: The 1 year mortality rate was 6%, the overall complications rate was 23%, and the combined incidence of MACE and 1 year mortality was 10%. Cycle ergonometry peak VO_2 14 mL/kg/min (RR 5.5, 95% CI 1.4–22.4, $p = .007$) and AT $<$ 10mL/kg/min (RR 3.0, 95% CI 1.1–7.0, $p = .03$) were predictors of post-operative complications. Pre-operative NT-proBNP $>$ 320 ng/L (RR 18, 95% CI 2.5–140 $p = .0003$) was the sole predictor of 1 year mortality or MACE.

Conclusion: The measurement of pre-operative NT-proBNP in peripheral vascular disease patients undergoing infra-inguinal bypass can predict 1 year mortality and MACE. CPET variables from cycle ergonometry are predictors of post-operative complications in this patient group.

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INTRODUCTION

Peripheral vascular disease is a global issue; its prevalence increased by 23% between 2000 to 2010 alone. Approximately 20% of the UK population aged between 55 and 75 years[1] have some form of peripheral vascular disease (PVD). This group frequently has significant comorbidities, with over a third having ischaemic heart disease, and the in hospital mortality of 3.0% is similar to major elective colorectal and open aortic aneurysm surgery.[1,2] Post-operative complications are significant in patients undergoing lower limb revascularisation, with 15% of patients having a major complication, of whom 3.5% have myocardial infarctions.[2,3] It is desirable to have a method of objectively assessing risk in this patient group, as knowledge that an individual is at higher risk of complications pre-operatively may change management, for example by optimisation of comorbidities, change of planned procedure to one that confers less risk, and appropriate critical care admission. In addition, this may aid resource utilisation and service planning, as well as allowing for informed consent and shared decision making.

Cardiopulmonary exercise testing (CPET) is an objective assessment of the functional capacity of an individual, and has been shown to identify patients at increased risk of complications and mortality after major surgery.[4,5] The detection of anaerobic threshold (AT) by the *V*-slope method relies on an increase in the rate and amount of CO_2,

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which is assumed to be derived from the buffering of lactate produced by anaerobic metabolism because of a global limitation of oxygen delivery. In subjects with PVD, the localised blood flow limitation due to the disease process may induce localised ischaemia, and hence anaerobic metabolism and lactate production, despite global oxygen delivery being adequate. This "false" increase in lactate may make the detection of the AT by this method inaccurate.[6] In addition, subjects with PVD may not be able to complete this test on a cycle ergonometer because of claudication; however, exercise can be performed on an arm ergonometer, but the correlation between cycle ergonometry and its prognostic ability is unknown.

N-terminal pro-brain natriuretic peptide (NT-proBNP) is secreted by cardiac ventricular myocytes in response to ventricular wall stress induced by volume expansion, pressure overload, or ischaemia.[7,8] Elevated levels of pre-operative NT-proBNP have been shown to predict post-operative short and long-term morbidity and mortality in non-cardiac surgical patients and in mixed cohort vascular surgical patients.[9,10]

The aim of this study was to investigate whether CPET variables derived from cycle and arm ergonometry correlate, and whether CPET variables and NT-proBNP have prognostic significance and if the combination of the two has incremental value.

METHODS

A prospective observational pilot study was conducted to assess the ability of pre-operative CPET variables and a biomarker (NT-proBNP) to predict adverse post-operative outcome in 70 patients who underwent infra-inguinal revascularisation procedures. The patients were recruited between September 2012 and October 2014 and followed up for 1 year post-operatively. York Teaching Hospitals NHS Foundation Trust and Yorkshire and the Humber Research Ethics committee approved the study protocol. All patients gave written informed consent and the trial was registered with the identifier NCT01417910.

Study population

Patients who underwent elective and expedited infra-inguinal revascularisation procedures for symptoms of claudication or critical limb ischaemia were included in the study. Patients were excluded if they refused or were unable to give consent.

All patients had a standard pre-assessment process including routine medical history, clinical examination, and investigations. The revised cardiac risk index[11] was calculated from their history. Serum NT-proBNP levels were performed and measured by immunoassay (Elecsys pro BNP II; Roche Diagnostics, Mannheim, Germany, performed on a Cobas e411 instrument, measurement range 5—35,000 ng/L with a precision of 2.9—6.1%). Subjects were also asked to complete the 12 part Duke activity status index (DASI) questionnaire[12] to estimate peak oxygen and then underwent bike and arm CPET as follows.

Cardiopulmonary exercise test protocol

Patients were asked to complete a standard cardiopulmonary exercise test on a cycle ergonometer with the test protocol controlled by Cardioperfect software (Welch Allyn, Skaneateles Falls, NY, USA). A 12 lead exercise electrocardiogram (ECG) was linked to the BreezeSuite software package (Medical Graphics Corporation, Parkway, St Paul, MN, USA), which allowed recording of breath by breath measurements of oxygen uptake, CO_2 production and respiratory flow and volume parameters. Inspired and expired oxygen and carbon dioxide were measured breath by breath via a sealed mouthpiece and CPX Ultima metabolic monitor (Medical Graphics Corporation).

Baseline data were noted and subjects commenced unloaded cycling for 1 minute at a rate of 60—70 rpm, followed by a ramped protocol of increasing workload at 10 watts per minute. The test was continued to maximal exertion or symptom limitation, and the reason for termination noted. The AT was determined by the V-slope method, and ventilatory equivalent for carbon dioxide (VE/VCO_2) was measured at AT. Peak oxygen consumption was measured as the highest oxygen consumption achieved during the test.

Within 14 days of the initial cardiopulmonary exercise test, the subjects were retested with the same protocol on an arm ergonometer.

Intra-operative care

All patients received the standard anaesthetic care at the discretion of the anaesthetist involved. Treating clinicians were blinded to CPET and pre-operative biomarker results.

Post-operative follow-up

Patients were reviewed on post-operative days 1, 3, and 5, and had the Post-operative Morbidity Survey (POMS) completed.[13] Blood samples for troponin I assay were taken on Days 1 and 3. Patients' notes were reviewed at discharge or death for primary and secondary outcomes. The notes and hospital patient database were reviewed 12 months after surgery to measure 1 year mortality. In addition, the patient and their GP were also contacted directly by one of the researchers to confirm the accuracy of the data.

Outcome measures

The primary outcome measure was 1 year all-cause mortality. The secondary outcome measures were morbidity as measured by the POMS, hospital length of stay (LOS), critical care usage, in hospital major adverse cardiac events (MACE), 30 day all-cause mortality, 1 year MACE, and surgical and post-operative complications (defined as sepsis, wound dehiscence, MACE, cerebrovascular accident [CVA], renal failure, or graft failure)

CPET data obtained by cycle and arm ergonometry were compared.

MACE was defined as

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