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ARTICLE

The Effect of beta-blockade on objectively measured physical fitness in patients with abdominal aortic aneurysms – A blinded interventional study

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Abstract

Background: Perioperative beta-blockade is widely used, especially before vascular surgery; however, its impact on exercise performance assessed using cardiopulmonary exercise testing (CPET) in this group is unknown. We hypothesized that beta-blocker therapy would significantly improve CPET-derived physical fitness in this group.

Methods: We recruited patients with abdominal aortic aneurysms (AAA) of <5.5 cm under surveillance. All patients underwent CPET on and off beta-blockers. Patients routinely prescribed beta-blockers underwent a first CPET on medication. Beta-blockers were stopped for one week before a second CPET. Patients not routinely taking beta-blockers underwent the first CPET off treatment, then performed a second CPET after commencement of bisoprolol for at least 48 h. Oxygen uptake ($\dot{V}_{O_2}$) at estimated lactate threshold ($\hat{\theta}_L$) and $\dot{V}_{O_2}$ at peak were primary outcome variables. A linear mixed-effects model was fitted to investigate any difference in adjusted CPET variables on and off beta-blockers.

Results: Forty-eight patients completed the study. No difference was observed in $\dot{V}_{O_2}$ at $\hat{\theta}_L$ and $\dot{V}_{O_2}$ at peak; however, a significant decrease in $\dot{V}_E/\dot{V}_{CO_2}$ at $\hat{\theta}_L$ and peak, an increase in workload at $\hat{\theta}_L$, O_2 pulse and heart rate both at $\hat{\theta}_L$ and peak was found with beta-blockers. Patients taking beta-blockers routinely (chronic group) had worse exercise performance (lower $\dot{V}_{O_2}$).

Conclusions: Beta blockade has a significant impact on CPET-derived exercise performance, albeit without changing $\dot{V}_{O_2}$ at $\hat{\theta}_L$ and $\dot{V}_{O_2}$ at peak. This supports performance of preoperative CPET on or off beta-blockers depending on local perioperative practice.

Clinical trial registration: NCT 02106286.

Key words: abdominal aortic aneurysm; anaerobic threshold; beta-blockers; cardiopulmonary exercise test; fitness; surgery

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Editor's key points

- This study investigated the effect of acute and chronic beta blockade on performance during CPET in vascular surgical patients.
- Oxygen uptake was lower in patients receiving beta blockers long-term.
- Initiation or withdrawal of beta blockade had no significant effect on oxygen uptake.
- There were modest but statistically significant improvements in some other CPET measurements.
- Clinicians should consider the effects of beta blockers on CPET performance in elderly vascular patients.

Beta-blockers are widely used by patients undergoing vascular surgery because of the high prevalence of cardiac disease and hypertension, and are still advocated by current guidelines to prevent perioperative cardiac complications,[1 2] despite the fact that some of the evidence in their support[3] has now been discredited.[4 5]

Physical fitness, assessed by cardiopulmonary exercise testing (CPET) provides an integrated quantitative assessment of the cardiorespiratory system at rest and under the stress of maximal exercise, testing the physiological reserve required to withstand the stress of major surgery. CPET derived variables are now reliably linked to postoperative outcome after major surgery[6 7] including major vascular surgery.[8–10] The effect of perioperative beta-blockade on objectively measured physical fitness is currently unknown. This is of particular importance in vascular patients treated with chronic beta blockade, or in whom de novo perioperative beta blockade is considered.

This prospective, blinded, observational study was designed to assess the effects of beta-blocker therapy on CPET derived variables in patients with abdominal aortic aneurysms (AAA). We hypothesized that beta-blocker therapy would significantly improve CPET derived physical fitness variables, which are used in the perioperative risk stratification of AAA patients. Using the results we hoped to recommend whether in this patient group preoperative CPET should be performed 'on' or 'off' beta-blockers.

Methods

Patients and study design

This study was approved by the North West – Liverpool East Research and Ethics Committee (11/NW/0810) and registered with clinicaltrials.gov (NCT02106286). Written informed consent was obtained from all patients. Between April 2012 and August 2013 we recruited consecutive, unselected patients who attended our vascular laboratory for routine AAA surveillance. We approached all patients aged >18 yrs undergoing active AAA surveillance (AAA <5.5 cms) who were able to perform a CPET, and had a WHO performance status of ≤2. We excluded patients who had a known contraindication to beta-blockers, severe ischaemic heart disease, stage IV or V chronic kidney disease, uncontrolled hypertension, those unable to consent, and absolute contraindications to CPET based on the ATS/ACCP guidelines.[11]

Patients were classified into 2 cohorts: (i) chronically beta-blocked group (patients on long-term beta-blocker therapy at baseline) or (ii) acutely beta-blocked group (patients not on long-term beta-blockers at baseline). All patients underwent two CPETs; one on and one off beta-blockers at least one week apart. Patients in the 'chronic' group underwent their first CPET whilst on their present medication; the beta-blocker was then stopped for at least one week before a second CPET. The 'acute' group underwent the first CPET without any alteration in medical therapy, then, at least one week later, a second CPET was performed after the commencement of bisoprolol once daily, 48 h before the test (minimum two doses, adjusted for body weight: 1.25 mg if the patient weighed 50–75 kg, 2.5 mg if 75–100 kg and 3.75 mg if >100 kg). All patients were informed of potential risks of the alteration in their medical therapy at the time of consent. The recruitment of both types of patients replicated real clinical practice where acute commencement or withdrawal of beta blockade before a perioperative CPET is routinely encountered.

Measurements

CPET (Geratherm Respiratory GmbH; Love Medical Ltd, Manchester, United Kingdom) followed a standard protocol described elsewhere.[12] CPET was reported by two experienced clinicians (MW and PW) with an experienced clinician scientist (SJ) resolving any differences. All 3 clinicians were blind to patient group allocation and beta-blocker treatment. Patient characteristics recorded included age, gender, height, weight, BMI, smoking status, haemoglobin concentration, aneurysm ultrasound details, medication details (type and dose of beta-blocker therapy) and co-morbidity, including prior patient self-reported diagnoses of diabetes, ischaemic heart disease, myocardial infarction, cerebrovascular disease, chronic obstructive pulmonary disease or heart failure. Resting flow-volume loops were used to derive Forced Expiratory Volume over 1 s (FEV1) and Forced Vital Capacity (FVC). Ventilation and gas exchange variables included oxygen uptake ($\dot{V}_{O_2}$) both absolute and weight adjusted, ventilatory equivalents for oxygen and carbon dioxide ($\dot{V}_E/\dot{V}_{O_2}$; $\dot{V}_E/\dot{V}_{CO_2}$), oxygen pulse ($\dot{V}_{O_2}$/heart rate), work rate and heart rate; all measured both at estimated lactate threshold ($\hat{\theta}_L$) and at peak exercise. Our primary objective was to assess the change in these variables caused by beta blockade after adjustment for confounders. $\dot{V}_{O_2}$ at $\hat{\theta}_L$ and $\dot{V}_{O_2}$ at peak were primary outcome variables with $\dot{V}_E/\dot{V}_{CO_2}$, workload, O_2 pulse, absolute $\dot{V}_{O_2}$ and heart rate both at $\hat{\theta}_L$ and peak treated as exploratory outcomes.

Statistical methods

We estimated that 32 patients undergoing AAA surveillance were required in order to detect a 10% difference in $\dot{V}_{O_2}$ at $\hat{\theta}_L$. This estimate was based on a standard deviation of 1.5, using a two-tailed paired *t*-test with 90% power and allowing for a 25% drop out.

Continuous variables are summarized in terms of mean (SD) or median (IQR) if non-normal and categorical variables are presented as frequency (%). Univariate statistical comparisons of patient characteristics between beta-blockade groups were conducted; for continuous variables, using a two-sample *t*-test or a Mann-Whitney U-test when non-normal and for categorical variables, using a χ^2 test or a Fisher's Exact test when cell frequencies were insufficient.

For the primary analysis, a linear mixed-effects model was fitted in order to investigate any difference in CPET variables when on and off a beta-blocker. A linear regression model with robust standard errors was used where the fit was inadequate and a log-transformation of O_2 pulse was performed before analysis. Models were adjusted for beta-blockade group (chronic or acute) and a two-way interaction was investigated. Sensitivity analysis was conducted adjusting for age, gender, BMI, smoking status and