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Background. Patients with abdominal aortic aneurysms (AAA) represent a high-risk surgical group. Despite medical optimization and radiological stenting interventions, mortality remains high and it is difficult to improve fitness. The aim of this pilot study was to evaluate the effect of a 6 week, supervised exercise programme (30 min continuous moderate intensity cycle ergometry, twice weekly) on anaerobic threshold (AT) in subjects with AAA.

Methods. Thirty participants with an AAA under surveillance were randomized to either the supervised exercise intervention (n=20) or a usual care control group (n=10). AT was measured using cardiopulmonary exercise testing, at baseline (AT1), week 5 (AT2), and week 7 (AT3). The change in AT (AT3–AT1) between the groups was compared using a mixed model ANCOVA, providing the mean effect together with the standard deviation (SD) for individual patient responses to the intervention. The minimum clinically important difference (MCID) was defined as an improvement in AT of 2 ml O2 kg⁻¹ min⁻¹.

Results. Of the 30 participants recruited, 17 of 20 (exercise) and eight of 10 (control) completed the study. The AT in the intervention group increased by 10% (equivalent to 1.1 ml O2 kg⁻¹ min⁻¹) compared with the control (90% confidence interval 4–16%; P=0.007). The SD for the individual patient responses to the intervention was 8%. The estimated number needed to treat (NNT) for benefit was 5 patients.

Conclusions. The small mean benefit was lower than the MCID. However, the marked variability in the individual patient responses revealed that a proportion of patients did benefit clinically, with an estimated NNT of 5.

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Abdominal aortic aneurysm (AAA) disease is prevalent in the elderly male population (male:female ratio, 4:1) and accounts for 1–3% of all deaths among men aged 65–85 yr in developed countries. Patients presenting for surgical repair represent a high-risk group, due to the nature of the surgery and their associated co-morbidities, with perioperative mortality rates in the UK approaching 8%. Most initiatives to improve outcome have concentrated on medical optimization and endovascular surgery with significant benefits demonstrated in short-term survival.

Aerobic fitness levels in this patient population are often poor as a consequence of co-morbid disease processes, sedentary lifestyle, and age. In non-surgical patient populations, there is strong evidence demonstrating the beneficial effects of exercise on improving aerobic fitness in both the elderly and subjects with cardiorespiratory disease. Higher levels of preoperative aerobic fitness have been shown to correlate with a significant improvement in survival rates in individuals undergoing major non-cardiac surgery. In addition, one of the main conclusions of the EVAR 2 study was that vascular teams

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should be focusing on techniques to improve patient fitness before operation.\textsuperscript{13}

Cardiopulmonary exercise testing (CPET) provides a safe, reliable measure of patient fitness. The anaerobic threshold (AT) has been shown to be a good predictor of survival in patients undergoing AAA surgery,\textsuperscript{14} with a value of $<11\text{ ml O}_2\text{ kg}^{-1}\text{ min}^{-1}$ considered the threshold for classifying patients undergoing major intra-abdominal surgery as high risk.\textsuperscript{15} The AT can be measured non-invasively during sub-maximal exercise testing (utilizing CPET) and is an accurate, objective measure of cardiorespiratory fitness. We have recently demonstrated the reliability of repeat AT measurement (using cycle ergometry) in participants with vascular disease.\textsuperscript{16}

Despite the weight of evidence suggesting that enhanced fitness improves surgical outcome, there is a paucity of research examining the effects of exercise initiatives on patient fitness in the preoperative setting. The length of any preoperative fitness interventions in patients with aneurysmal disease would have to be short enough to minimize the risk of rupture\textsuperscript{17} but long enough to be effective. Significant improvements in fitness can be made in a relatively short time-frame in sedentary individuals,\textsuperscript{18} but little is known about the short-term trainability of patients with known AAA disease.

The aim of this pilot study was to evaluate whether a 6 week, supervised exercise programme in subjects with AAAs under surveillance could improve preoperative fitness as judged using AT measurement.

**Methods**

We obtained ethics approval from the South Tees Research and Ethics Committee to conduct this prospective, randomized, interventional, exploratory trial. Patients with AAAs under surveillance ($<5.5\text{ cm on abdominal ultrasound}$) were identified through vascular surgical clinics in three hospitals in the Tees Valley. After review of surgical notes, possible participants were invited for further screening as to suitability to participate in the study. This included a thorough history and physical examination followed by baseline ECG interpretation. Exclusion criteria included: inability to exercise from any cause, inability to complete the initial cardiopulmonary exercise test, current participation in an exercise or rehabilitation programme, or any contraindication to CPET as identified during the screening visit.\textsuperscript{19} After obtaining written informed consent and after study enrolment, participants were randomly allocated (via sealed envelopes) to a supervised exercise intervention or to the control group (usual care).

All participants underwent initial AT measurement (AT\textsubscript{1}) at week 0 to assess baseline fitness. This was followed by repeat assessment of fitness in weeks 5 (AT\textsubscript{2}) and 7 (AT\textsubscript{3}). AT measurement was achieved using CPET as outlined below. Participants in the exercise group undertook their programme between weeks 1 and 6 (Fig. 1).

The primary endpoint was the change in AT between weeks 0 and 7 to assess the impact of the exercise intervention. Although this is an exploratory randomized trial, and therefore not intended to be powered to detect small effects, we conducted an estimation of sample size to inform the study. Sample size estimation was conducted using Stata\textsuperscript{16} v.8 (College Station, TX, USA), and based on the results from our reliability study of 16 patients tested four times across a 6 week period.\textsuperscript{16} A ratio of approximately two intervention patients to one control was required for the present study. We define the minimum

\begin{figure}[h]
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\includegraphics[width=\textwidth]{study_flowchart.png}
\caption{Flow diagram of study outline.}
\end{figure}
clinically important difference (MCID) as a change in AT in the exercise training group of 2 ml O₂ kg⁻¹ min⁻¹. This is the change required to shift the distribution rightwards, such that there is a substantial improvement in the proportion of patients with an AT ≥11 ml O₂ kg⁻¹ min⁻¹ (from just over half the sample at baseline to ~75% at the study endpoint). With 80% power (2P=0.05) using the Stata® method ANCOVA, a sample size of 16 patients in the intervention group and eight in the control permits the detection of an improvement in AT of 2 ml O₂ kg⁻¹ min⁻¹ in the intervention group compared with the control. An allowance for attrition of 20% results in a required sample size (intervention/control) of 20/10.

The assessment of fitness was achieved by measuring AT. Participants underwent CPET using the MedGraphics Ultima system (Tewkesbury, UK). Testing was performed on a Lode Corival cycle ergometer (BV Medical Technology, Groningen, The Netherlands) following a standardized protocol. A resting 12-lead ECG was obtained before formal exercise testing. Twelve-lead ECG monitoring with ST segment analysis was performed continuously. A decision to terminate the test was made, if there was patient distress or development of >2 mm ST depression in any lead. The test protocol was not designed to determine the maximum aerobic capacity (V̇O₂ max). All usual patient medication was continued throughout the study period.

Participants initially cycled for a 3 min period with no resistance applied (un-ramped period). This period allowed the patient to warm up and for them to become accustomed to breathing through the mouthpiece. After this period, the resistance (ramp) on the cycle ergometer increased automatically by 20 W min⁻¹. A pedal rate of between 60 and 80 rpm was maintained. The test was terminated once the respiratory exchange ratio reached and was maintained at 1.10 or greater. The AT was determined using the v-slope method.

To eliminate possible confounding factors, testing was carried out at the same time of day, in the same environmental conditions by the same two investigators. The system was calibrated between each test. All tests were performed with trained medical/nursing staff in attendance and with resuscitation equipment immediately available. The investigator reading AT results (G.D.) was blinded to the group allocation.

The participants randomized to the exercise group attended a hospital-based exercise programme from weeks 1 to 6 of the study. They were required to attend twice weekly for the supervised sessions. The exercise sessions consisted of 30 min exercise on a static Life Fitness bicycle (C Series C9i/C7i Exercise Bike, Life Fitness, Cambridgeshire, UK) (plus a 5 min warm-up and cooling-down period). Participants exercised in groups of 3–4 (to provide companionship) with each individual having a tailored programme to suit individual fitness. An exercise consultant supervised all sessions with medical personnel in attendance, and with full resuscitation facilities available, at all times. For safety reasons, we used moderate continuous exercise rather than high-intensity interval training. To ensure reproducibility and maximal benefit, without exposing subjects to undue risk, the exercise intensity was self-graded using the 6–20 point Borg Rating of Perceived Exertion (RPE) Scale. Participants were required to exercise in zones 12–14 on the Borg scale. This corresponds to moderate exercise, in which individuals feel like they are exerting themselves 'somewhat hard', but are still able to converse comfortably with the exercise supervisor. This level of intensity was chosen due to its coincidence with the intensity at AT, as training at an intensity near the AT has been shown to be an adequate training stimulus for sedentary subjects.

Data were analysed for the sample as a whole, without including gender as a factor; this is appropriate, given the proportion of women in both the sample and the AAA population, and gives an unbiased estimate of the overall population effect. In addition, we elected not to stratify/minimize by sex in allocating patients to groups, due to the small number of females and the exploratory nature of the trial.

We used mixed effects modelling (SAS® Proc Mixed, SAS® Version 9.1, SAS Institute Inc., Cary, NC, USA) to analyse the effect of the training intervention on the AT. This method allows for and quantifies (as a standard deviation, SD) the individual patient differences in response to the intervention, which are frequently highly variable. An ANCOVA method was adopted to compare the two groups, with the change in AT (AT3–AT1) as the primary outcome and a baseline AT × group interaction term as the covariate to control for chance imbalance in AT between the control and the intervention groups at baseline. Preliminary screening revealed substantial heteroscedasticity (non-uniform error variance); hence, data were first log-transformed before analysis, providing ratio (per cent) differences between the intervention and the control groups together with a 90% confidence interval.

As a further preliminary exploration of the individual patient responses to treatment, we adopted the method proposed by Guyatt and colleagues to estimate the number needed to treat (NNT) for benefit for the continuous variable of the AT (MCID=2 ml O₂ kg⁻¹ min⁻¹). Confidence limits for this NNT are not presented, as a robust estimate requires a much larger sample size from a subsequent, definitive randomized trial.

Results

Thirty participants were recruited in total. Of these, 17 of 20 and eight of 10 completed the study period in the exercise and control groups, respectively, producing full data sets for analysis. Background characteristics of individuals completing the study period are shown in Table 1. Three recruits did not complete the exercise intervention; one withdrew with a varicella zoster infection, one underwent...
planned elective back surgery, and one suffered a cardiac arrest (ventricular fibrillation) during his seventh exercise session. This individual had undergone previous coronary artery bypass grafting (7 yr before) and had a good reported exercise capacity at study enrolment. He was successfully resuscitated by the research and hospital cardiac arrest team, subsequently undergoing uneventful re-do coronary bypass grafting with implantation of an implantable cardioverter defibrillator (ICD). Two participants randomized to the control group decided not to complete their three required CPET assessments.

The AT in the intervention group increased by 10% (a ratio of 1.10) compared with the control (90% confidence interval 4–16%; $P=0.007$) (Table 2). The SD for the individual patient responses to intervention was 8.0% (6.5–11.0%). This represents the variability in the mean effect of the intervention due to individual patient responses. The overall effect of the training intervention was therefore the variability in the mean effect due to individual patient responses.

The AT in the control group increased by 10% (1.10 compared with control on the change in AT was therefore an ‘unchanged’ AT (change within ± the MCID of 2 ml O$_2$ kg$^{-1}$ min$^{-1}$) with no patient in either group exhibiting a decrease of greater than or equal to the MCID (representative of ‘harm’ as opposed to benefit). However, the SD for individual responses of 8% suggests a clinically relevant benefit for some patients. Indeed, in the exercise intervention group, six of 17 patients improved their AT by $\geq 2$ ml O$_2$ kg$^{-1}$ min$^{-1}$ vs just one patient in the control group. The proportion benefiting from the intervention was estimated at 0.225, providing an NNT for benefit of 4.4, rounded up (as per convention) to five patients.

Six of 13 males in the exercise group (46%) significantly improved their AT compared with zero of four females.

### Discussion

The results of this pilot study confirm a fitness improvement in the exercise group compared with the control with a mean benefit of 10% (1.1 ml O$_2$ kg$^{-1}$ min$^{-1}$). Though statistically significant, this mean effect did not reach the level of improvement defined as clinically relevant (the MCID of 2 ml O$_2$ kg$^{-1}$ min$^{-1}$). The sample size estimation for the current study was based on detecting an effect of 2 ml O$_2$ kg$^{-1}$ min$^{-1}$, using data obtained from our reliability pilot study.16 That we subsequently observed a statistically significant mean effect substantially less than the MCID may appear paradoxical to some readers. The explanation is simply that the correlation between repeat measures observed in the pilot study (the reliability) and used in the sample size estimation equation was an imprecise estimate. The actual observed correlation between baseline and endpoint measures in the current study was higher than that seen in the pilot. Consequently, our estimate of the effect was more precise than anticipated resulting in a statistically significant, though clinically small, mean benefit.

Notwithstanding the relatively modest mean effect, the SD for individual responses of 8% (c. 0.8 ml O$_2$ kg$^{-1}$ min$^{-1}$) implies a clinically relevant benefit for some patients (responders). Indeed, six of 17 of the exercise group participants vs one of eight controls obtained a clinical benefit ($\geq$ the MCID). The estimated NNT for benefit was 5.

There are several possible reasons why the mean benefit of the intervention was not large enough to be clinically relevant. The volume of exercise prescribed to individuals (frequency × intensity × duration), the length of the intervention, or both may need to be increased to demonstrate a greater effect. To increase exercise volume, it would be possible to increase the intensity, the duration, or the frequency of the exercise training. However, each of these is not without potential problems or adverse effects. Increasing the frequency of an in-hospital exercise programme makes it impractical for many patients. Travel to a hospital is both costly and time-consuming, and could possibly limit the number of patients who would be able to participate owing to alternative commitments. A session of home-based prescribed exercise each week is a possible way to increase the frequency,25 but this would require a motivated patient population, to sustain the correct intensity to achieve consistency and would need to consider patient

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Participant characteristics, co-morbidities, and medications. CCS, Canadian Cardiovascular Society classification; MI, myocardial infarction; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Exercise group</td>
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<tr>
<td>Completed (M:F)</td>
<td>17 (13:4)</td>
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<tr>
<td>Mean age (yr)</td>
<td>69.5 (range 61–79)</td>
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<tr>
<td>Median AAA size (cm)</td>
<td>4.0 (range 3.0–5.1)</td>
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<th>Co-morbidities</th>
<th>Exercise group</th>
<th>Control group</th>
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<tr>
<td>Stable angina (CCS 1-11)</td>
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<td>1</td>
</tr>
<tr>
<td>Previous MI</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Previous CABG</td>
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<td>Beta-blocker</td>
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<tr>
<td>Statin</td>
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<tr>
<td>ACEI</td>
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<td>Calcium channel antagonist</td>
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<th>Table 2</th>
<th>Mean (sd) AT results (ml O$_2$ kg$^{-1}$ min$^{-1}$)</th>
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<tbody>
<tr>
<td>Group</td>
<td>AT1</td>
</tr>
<tr>
<td>Exercise (n=17)</td>
<td>10.6 (2.0)</td>
</tr>
<tr>
<td>Control (n=8)</td>
<td>10.4 (2.0)</td>
</tr>
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safety in this high-risk population. Similarly, increasing the duration of each exercise session would increase the exercise volume, but sustaining patient motivation for static cycle exercise beyond 30 min may be a challenge.

The intensity of our exercise sessions utilized a moderate continuous prescription, at a range of 12–14 on the Borg RPE scale. This intensity is broadly equivalent to the intensity at the AT, thought to be an adequate training stimulus for sedentary subjects. However, continuous exercise training at a higher intensity (relative to AT) leads to larger gains in AT. Moreover, there is some evidence that very high-intensity interval training may be more effective than continuous moderate intensity exercise training. In elderly heart failure patients, a superior cardiovascular training effect with aerobic interval training, with matched volume, at 95% of peak heart rate compared with moderate continuous training at 70% of peak heart rate has been reported. The intensity of our programme was chosen, in part, as the safety of high-intensity interval training in high-risk subjects is uncertain. Despite this, we had one serious adverse event, and on this basis, we would be reluctant to advocate a high intensity, interval-training programme, even in a hospital setting. The differing patient populations, contrasting exercise prescription, and greater length of intervention study make direct comparisons with our results difficult.

Increasing the length of the exercise intervention beyond 6 weeks may improve fitness further. Indeed evidence suggests that regular aerobic exercise for 12 weeks, at an intensity similar to our study, significantly improves fitness in elderly people. The individuals that we studied were surveillance patients; however, it may prove impractical to exercise individuals awaiting aneurysm repair for this length of time. The length of the exercise intervention, and subsequent fitness improvement, has to be balanced against risk of aneurysm rupture and current recommendations would not support such a time delay. The 2005 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report suggested that once a decision has been made to operate, the surgery should be carried out as expeditiously as possible, owing to the life-threatening nature of the disease process.

Maximum oxygen consumption (\( \dot{V}O_2 \) max) or peak oxygen consumption (\( \dot{V}O_2 \) peak) may prove to be more accurate markers of aerobic fitness improvement. These measurements, however, depend on pushing participants to volitional exhaustion and consequently raise safety concerns in high-risk individuals. \( \dot{V}O_2 \) peak measurement also depends on an individual’s motivation during exercise testing, raising some concerns in relation to repeatability in patient groups. In contrast, AT measurement can be safely achieved during sub-maximal exercise and is independent of subject motivation. The combination of the above and the fact that the evidence base for improved surgical outcome is founded on its measurement make AT the appropriate fitness measure in our opinion.

A recent publication by the European Society of Vascular Surgery has highlighted concerns relating to open AAA repair in the UK with a reported mortality of 7.9%. In comparison, the mean mortality for the remaining nine contributing countries (UK excluded) was 2.3%. If these data are accurate, the report highlights that major improvements are both possible and urgently required. It is therefore difficult to overemphasize the importance of risk reduction perioperatively in such high-risk individuals. Medical optimization of patients with beta-blockers, statins, antiplatelet agents, and angiotensin-converting enzyme inhibitors has gone some way to reducing this risk, as has endovascular surgery. Despite this, mortality rates remain unacceptably high, with fitness improvement before operation presenting an attractive alternative way of reducing this risk further. In the current study, we believe that the six exercise group participants who achieved improvement in AT of >2 ml O$_2$ kg$^{-1}$ min$^{-1}$ present a good example of this possibility. Potentially, this group of patients could change their preoperative risk stratification from high to intermediate or intermediate to low risk with such a shift in AT. It would therefore be reasonable to assume, on the evidence base of available literature, that such a shift in AT would equate to improved survival in such individuals.

With any prescribed exercise programme, it is always important to bear in mind the safety of participating individuals. Available literature reports a risk of serious adverse events of \(~1:10,000\) with exercise testing in high-risk individuals. Despite this, we had one individual who suffered a cardiac arrest during his seventh exercise session (at a comparable exercise intensity with that during exercise stress testing), and was fortunately resuscitated. He underwent successful revision coronary artery bypass grafting and ICD implantation, but may not have been so fortunate had his exercise been undertaken in a commercial gym or domestic environment. We cannot overestimate how important we feel that these high-risk patients should undergo training in a hospital environment, at an appropriate intensity, where appropriate staff and resuscitation equipment are immediately available, as exercise programmes are not without risk.

A limitation of our study is the small and unmatched groups, with more male than female patients. However, the latter reflects the population prevalence, with aneurysms being four times more common in males than females. Such a limitation can be explained by the exploratory nature of the study and finite number of AAA patients at our institution under surveillance. Clearly, it is vital to perform such exploratory phase research in a bid to inform a definitive, multi-centre trial, without the risk of major resource allocation wastage.

Notwithstanding the small mean benefit observed, there was marked variability in individual responses to treatment with an estimated NNT for benefit of five patients. If this impressive NNT could be translated into clinical practice, it could provide a springboard to improving outcome for
such high-risk surgery. We therefore believe that our results are encouraging and justify a larger, definitive randomized controlled trial.

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