Cardiorespiratory fitness is impaired and predicts mid-term postoperative survival in patients with abdominal aortic aneurysm disease

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New Findings

What is the central question of this study?

To what extent cardiorespiratory fitness (CRF) is impaired in patients with abdominal aortic aneurysmal (AAA) disease and corresponding implications for postoperative survival requires further investigation.

What is the main finding and its importance?

Cardiorespiratory fitness is impaired in patients with AAA disease. Patients with peak oxygen uptake < 13.1 mL $O_2.kg^{-1}.min^{-1}$ and ventilatory equivalent for carbon dioxide at anaerobic threshold ≥ 34 are associated with increased risk of post-operative mortality at 2 years. These findings demonstrate that CRF can predict mid-term postoperative survival in AAA patients which may help direct care provision.

Abstract

Preoperative cardiopulmonary exercise testing (PCPET) is a standard assessment used for the assessment of cardiorespiratory fitness (CRF) and risk stratification. However, to what extent CRF is impaired in patients undergoing surgical repair of abdominal aortic aneurysm (AAA) disease and corresponding implications for postoperative outcome requires further investigation. We measured CRF during an incremental exercise test to exhaustion using online respiratory gas analysis in patients with AAA disease (n = 124, aged 72 ± 7 years) and healthy sedentary controls (n = 104, aged 70 ± 7 years). Postoperative survival was examined for association with CRF and threshold values calculated for independent predictors of mortality. Patients who underwent PCPET prior to surgical repair had lower CRF [age-

adjusted mean difference of 12.5 mL O_2.kg^{-1}.min^{-1} for peak oxygen uptake ($\dot{V}O_2$ peak), $P <$ 0.001 *vs*. controls]. Following multivariable analysis, both $\dot{V}O_2$ peak and the ventilatory equivalent for carbon dioxide at anaerobic threshold ($\dot{V}_E/\dot{V}CO_2$-AT) were independent predictors of mid-term postoperative survival (2 years). Hazard ratios of 5.27 (95% confidence interval (CI) 1.62 to 17.14, $P = 0.006$) and 3.26 (95% CI 1.00 – 10.59, $P = 0.049$) were observed for $\dot{V}O_2$ peak < 13.1 mL O_2.kg^{-1}.min^{-1} and $\dot{V}_E/\dot{V}CO_2$-AT ≥ 34 respectively. Thus, CRF is lower in patients with AAA and those with a $\dot{V}O_2$ peak < 13.1 mL O_2.kg^{-1}.min^{-1} and $\dot{V}_E/\dot{V}CO_2$-AT ≥ 34 are associated with a markedly increased risk of post-operative mortality. Collectively, our findings demonstrate that CRF can predict mid-term postoperative survival in AAA patients which may help direct care provision.

Introduction

Abdominal Aortic Aneurysm (AAA) is a permanent focal dilatation of the infra-diaphragmatic aorta by 1.5 times the expected normal diameter or greater than 3 cm (Golledge *et al.*, 2006). It can be classified anatomically as supra-renal, juxta-renal or infra-renal in relation to the renal arteries, with infra-renal AAA being the most common. Rupture of a AAA is associated with a mortality rate of between 65% and 85% resulting in up to 8,000 deaths annually in the UK with approximately half of the deaths attributed to rupture occurring before the patient reaches hospital (Basnyat *et al.*, 1999; Ashton *et al.*, 2002).

Elective AAA surgery is thus indicated for healthy males with aneurysms of 5.5 cm or greater. The corresponding United Kingdom (UK) in-hospital postoperative mortality for elective open and endovascular (EVAR) AAA repair are considerably lower at 2.9% and 0.4% respectively (VSQI, 2017). However, the physiological insult of major surgery presents an increased oxygen demand during the perioperative period and patients need to achieve a sufficient oxygen (O_2) delivery in order to fulfil cellular demand and attain a successful

recovery. Shoemaker *et al*. (1992) demonstrated a strong relationship between the magnitude and duration of O_2 deficit in the intraoperative and early postoperative period, and the risk of organ failure and ultimately death. Robust preoperative risk assessment is therefore necessary to identify high-risk patients and optimise care during the perioperative period.

Preoperative cardiopulmonary exercise testing (PCPET) is a non-invasive procedure used to determine the level of cardiorespiratory fitness (CRF) of patients during a progressive exercise challenge to symptom limited maximum. In 2016, 47 % of patients in the UK had their fitness measured by CPET as part of a preoperative risk assessment prior to AAA surgery (VSQI, 2017). A cross-sectional association has been demonstrated between CRF and improved postoperative survival, and reduced morbidity including length of hospital stay (Carlisle & Swart, 2007; Hartley *et al.*, 2012; Prentis *et al.*, 2012; Goodyear *et al.*, 2013; Grant *et al.*, 2015) with values such as an anaerobic threshold (AT) < 10.2 mL $O_2.kg^{-1}.min^{-1}$, peak oxygen uptake ($\dot{V}O_2$ peak) < 15 mL $O_2.kg^{-1}.min^{-1}$, and a ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$-AT) > 42 used as cut-off scores. However, as with many other preoperative tests, the use of CPET needs to be optimised (Hollingsworth *et al.*, 2015). Thus, the primary aims of the present study were two-fold. First to confirm the extent to which cardiorespiratory fitness is impaired in AAA patients and define threshold PCPET variable scores that hold prognostic significance for postoperative survival.

Methods

Ethical approval

The Cardiff and Vale University Health Board (15/AIC/6352) approved the retrospective analysis of an anonymised database and thus patient consent was waived. For the healthy control participants, ethical approval was granted by American Medical International (Texas, USA) and the (former) University of Glamorgan (South Wales, Pontypridd, UK). All

procedures were carried out in accordance with the Declaration of Helsinki of the World Medical Association (Williams, 2008). The study was not registered in a database.

Experimental design

We conducted a retrospective cross-sectional analysis of AAA patients (anonymised longitudinal hospital-based database) with a matched apparently healthy cohort.

Participant/patient groups

Healthy participants

For the purposes of comparing baseline CRF, we used 108 consecutive historical controls with a mean age of 72, who had previously engaged in a health-screening program (Table 1).

AAA patients

One hundred and twenty four consecutive patients of similar age underwent PCPET to assess risk for aneurysm repair between 2008 and 2016 (Table 1). Patient data was gathered from medical notes and recorded by the clinician conducting PCPET and comprised of body mass index (BMI), smoking history, presence of ischaemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), hypertension, renal disease and anaemia. Postoperative mortality was determined by review of Office for National Statistics (ONS) records and included cause of death. Mid-term survival was calculated by comparison of surgery date and two-year follow up status.

Measurements

CPET

Healthy participants (Comparative analysis): Participants were retrospectively selected based on a normal 12-lead electrocardiographic response to a standardised incremental

exercise test to volitional exhaustion using the same protocol as outlined for patients. Endpoint determination was assessed by the supervising clinician if the participant developed fatigue, inappropriate dyspnoea, angina, ST segment depression or elevation of 1 mm, significant dysrhythmias, atrioventricular conduction disturbances or defective chronotropic responses. There were no adverse events during the exercise or recovery periods of the tests. All participants were asymptomatic and defined as sedentary since they did not engage in any formal recreational activity outside of everyday living (Bailey *et al.*, 2013a).

AAA patients (correlational analysis): Preoperative CPET were conducted using an electromagnetically braked cycle ergometer (Lode, Gronigen, The Netherlands) and a Medgraphics Ultima metabolic cart (MedGraphics^{TM}, Gloucester, UK). Calibration was undertaken in accordance with manufacturer's guidelines using a 3-litre volume syringe (Hans Rudolph, Kansas City, USA) and reference calibration gases. During data collection, the middle five of seven breaths were averaged. An exercise protocol was employed whereby patients cycled at 60 revolutions per minute for three minutes in an unloaded freewheeling state followed by a progressively ramped period of exercise (5 to 15 W.min^{-1} based on mass, stature, age, and gender) to volitional or symptom limited termination, followed by three minutes recovery (Wasserman, 2012). Medgraphics Breeze^{TM} software automatically determined $\dot{V}O_2$ peak (defined as the highest $\dot{V}O_2$ during the final 30 seconds of exercise reported), oxygen uptake efficiency slope (OUES) (Hollenberg & Tager, 2000), and peak oxygen pulse (O_2 pulse). The AT was manually interpreted by a clinician using the V-slope method (Beaver *et al.*, 1986), and supported by comparison of end tidal oxygen tension (ETO_2) and $\dot{V}_E/\dot{V}O_2$ plots. The $\dot{V}_E/\dot{V}CO_2$ was identified at the AT.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows (Version 23.0 Armonk, NY). Distribution normality was confirmed using repeated Shapiro-Wilk *W* tests. ***Analysis 1 (Comparative):*** Continuous data are presented as mean (standard deviation), and dichotomous variables as number (percentage). Differences in CRF between groups was established using independent samples Student *t*-tests with analysis of covariance performed to adjust for age. Patient counts were analysed using Chi-Square tests. Significance for all two-tailed tests was established at $P < 0.05$. ***Analysis 2 (Correlational):*** The secondary outcome measure, postoperative mortality was assessed using Cox proportional hazards (PHs) regression models. The PH assumption was tested with Schoenfeld residuals (Grambsch & Therneau, 1994). Continuous and dichotomous variables were first assessed using univariable Cox PH regression. Subsequent multivariable Cox PH models were developed with inclusion criteria of variables at the $P < 0.2$ level (from univariate analysis) and a backward stepwise approach employed. Receiver operator curves (ROC) were constructed for subsequent markers of CRF identified as independent predictors of postoperative mortality. For a marker of CRF to be considered a valid independent predictor of mortality, an area under ROC greater than 0.7 was required. Optimal threshold values for markers fulfilling this criterion were subsequently calculated by examination of the minimum distance between ROC plots and the upper left corner and presented with sensitivity and specificity. Dichotomised PCPET variables were employed to represent sub-threshold PCPET values and examined graphically using Kaplan-Meier plots which were compared using a log-rank test to demonstrate postoperative survival with significance established at $P < 0.05$. Confidence intervals (CI) were presented for all survival statistics.

Results

Patient outcomes: Two patients experienced AAA rupture prior to elective surgery and were discounted from the overall analysis. Ninety-nine patients were observed for a median time of 1,034 days following surgery, of which 76 were alive at the time of study analysis. Thirty-day and 90-day mortality was observed for one and seven patients respectively. Twenty-three patients were treated conservatively, of which 17 died with a median survival of 797 days at the time of study analysis.

Analysis 1 (Comparative): AAA patients were defined by lower CRF across a range of PCPET values when compared with similar aged apparently healthy sedentary controls. A mean difference of 13.6 (95% CI 12.0 to 15.2, $P < 0.001$) mL $O_2.kg^{-1}.min^{-1}$ was reported for $\dot{V}O_2$ peak (Figure 1). Covariate analysis for $\dot{V}O_2$ peak demonstrated an age-adjusted mean difference of 12.5 (95% CI 11.1 to 13.9, $P < 0.001$) mL $O_2.kg^{-1}.min^{-1}$ between groups.

Analysis 2 (Correlational): One patient died within 30 days of surgery and 20 deaths were reported two years post-surgery, of which half (10/20) were independent of AAA disease (ONS I71 code; abdominal aortic aneurysm with or without mention of rupture). Following multivariable analysis, both $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT were found to be independent predictors of mid-term (2 year) postoperative mortality (Table 2). A hazard ratio of 0.84 (95% CI 0.72 to 0.99) was observed for each unit (mL $O_2.kg^{-1}$ min^{-1}) increase in $\dot{V}O_2$ peak. Conversely, a hazard ratio of 1.11 (95% CI 1.03 to 1.20) was observed for each unit increase of $\dot{V}_E/\dot{V}CO_2$-AT. An area under ROC (Figure 2) of 0.708 (95% CI 0.585 to 0.830; $P = 0.005$) was observed for $\dot{V}O_2$ peak with an associated cut-off point of < 13.1 mL $O_2.kg^{-1}$ min^{-1} (sensitivity 65%, specificity 77%). The area under ROC for $\dot{V}_E/\dot{V}CO_2$-AT was 0.702 (95% CI

0.574 to 0.830; $P = 0.006$) with an associated cut point of ≥ 34 (sensitivity 70%, specificity 64%).

We applied our defined cut points for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT (herein defined as sub-threshold PCPET values) to stratify patients into high or low-risk subgroups. Subsequently, when entered into a further regression model, hazard ratios of 5.27 (95% CI 1.62 to 17.14, $P = 0.006$) for $\dot{V}O_2$ peak < 13.1 mL.kg^{-1}.min^{-1} and 3.26 (95% CI 1.00 – 10.59, $P = 0.049$) for $\dot{V}_E/\dot{V}CO_2$-AT ≥ 34 were apparent (Table 3). Thus, $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT were independent predictors of mid-term survival and patients with one or two sub-threshold PCPET values demonstrated reduced postoperative survival ($P = 0.01$) as illustrated in Figure 3. Previous work from our group (Rose *et al.*, 2018) has demonstrated that natural variation is present in magnitudes of up to ±13 and 10% respectively for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT, and therefore sub-threshold PCPET values should take account of this variation when optimising patient fitness stratification. Three zones were calculated whereby patients were either "fit" (≥ 13.1 mL.kg^{-1}.min^{-1} and < 34 for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT with natural variation accounted for), "intermediate fitness" (scores that could transcend the sub-threshold values when natural variation is considered), and "unfit" (< 13.1 mL.kg^{-1}.min^{-1} and ≥ 34 for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT with natural variation accounted for). Therefore our defined threshold values produced zones for fit, intermediate fitness, and unfit of >15, 15 to 11.6, and <11.6 mL.kg^{-1}.min^{-1} for $\dot{V}O_2$ peak and <31, 31 to 38, and >38 for $\dot{V}_E/\dot{V}CO_2$-AT.

Discussion

Consistent with our original hypotheses, our study has revealed two findings. First, CRF was shown to be impaired in AAA disease relative to an apparently healthy sedentary population of comparable age. Second, both $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT were able to independently identify patients at high-risk of mid-term postoperative mortality, but not during the intraoperative period. Collectively, our findings demonstrate that CRF can predict mid-term postoperative survival in AAA patients which may help direct care provision.

In the context of the present study, we speculate that impaired vascular function precipitated by inadequate antioxidant defence and corresponding elevation in oxidative-nitrosative stress, collectively associated with impaired CRF (Bailey *et al.*, 2013b) and AAA disease (Bailey *et al.*, 2006), may be responsible for inferior postoperative outcomes. Impaired vascular endothelial function has been observed in the early postoperative period following major colon cancer surgery (Ekeloef *et al.*, 2017) and warrants further investigation in this population. Furthermore, in addition to impaired $\dot{V}O_2$ peak, patients with high risk of postoperative mortality demonstrated elevated $\dot{V}_E/\dot{V}CO_2$-AT suggesting that inefficient ventilation of the lungs consequent to the mismatching of ventilation to perfusion is a significant risk factor.

As expected, CRF was impaired in AAA disease. Our study used an effectively controlled research design with a comparative sample of participants selected by convenience to account for the effect of age, gender and activity levels. Furthermore, our objectively determined 12-lead ECG assessments confirmed that the control participants were asymptomatic and free of any overt cardiovascular/ischaemic heart disease given a negative functional diagnostic exercise stress test. Of interest, increased prevalence of aneurysmal disease has been linked to populations exhibiting low levels of CRF and reduced blood flow, as demonstrated in

amputees and spinal injury, which has been hypothesised as a causative factor (Vollmar *et al.*, 1989; Yeung *et al.*, 2006).

The mean $\dot{V}O_2$ peak for patients with AAA disease reported in this study (14.4 mL.kg^{-1}.min^{-1}) was similar to that reported by Prentis *et al.* (2012). Our reported $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT were independent predictors of postoperative survival in agreement with previous studies (Carlisle & Swart, 2007; Hartley *et al.*, 2012). However, our defined sub-threshold values of < 13.1 mL.kg^{-1}.min^{-1} and ≥ 34 were lower than those previously reported emphasising the need for a more conservative approach. Of interest and contrary to other studies (Hartley *et al.*, 2012; Grant *et al.*, 2015), AT did not predict survival in our cohort of patients.

Studies with larger sample sizes have previously reported an association between PCPET values and postoperative survival however limitations are evident. The largest study which recruited 506 patients (Grant *et al.*, 2015) did not define sub-threshold PCPET values from their own dataset and instead adopted values from a study (Carlisle & Swart, 2007) with a similarly sized cohort to the present study. Furthermore, another large study (Hartley *et al.*, 2012) adopted sub-threshold PCPET values used to predict postoperative morbidity in heterogeneous populations (Snowden *et al.*, 2010). Thus, our findings demonstrating a lower than previously reported $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT, and no association for AT, hold novel value of clinical importance for patients undergoing surgery for AAA repair.

We support the value of reporting mid-term survival (defined as two years post-surgery in our data) for patients undergoing AAA repair as in-hospital mortality is now reported at relatively low levels of 2.9% and 0.4% for open and EVAR approaches respectively (VSQI, 2017). Furthermore, surgery is undertaken not to cure the disease, but to prevent future risk of rupture and thus decision making needs to account for a long-term risk assessment (Howell, 2017). Of the 20 deaths reported in our study at two years post-surgery, half (10/20) were independent of AAA disease (ONS I71 code; abdominal aortic aneurysm with or without

mention of rupture). Our findings did not support the ability of CRF to identify patients at high-risk of intraoperative mortality as only one patient died within 30 days of surgery. We acknowledge that the sample size (Altman, 1980) was based upon the primary outcome variable; to determine if CRF was impaired for patients with AAA disease when compared with age-matched apparently healthy sedentary controls, and retrospective analysis demonstrated 100% power at the $P < 0.05$ level for our given effect size (2.05).

Few studies have defined sub-threshold PCPET values indicative of increased postoperative risk in patients with AAA disease. Instead, many rely on previously defined values, which in some cases may have been determined from different patient populations. We therefore suggest that our defined threshold values hold potential to improve future identification of high-risk patients. Either $\dot{V}O_2$ peak or $\dot{V}_E/\dot{V}CO_2$-AT should be considered for risk appropriation, and if sub-threshold scores for both are presented, a cumulative effect is likely as demonstrated in Figure 3. Recent work from our group (Rose *et al.*, 2018) recommends that clinicians should not consider fitness as a single point estimate, but instead as a dynamic range of values defined by natural variation and calculated using critical difference (Fraser & Fogarty, 1989; Davison *et al.*, 2012). Thus, rather than advocating specific binary threshold values, zones along a spectrum of fitness should be adopted (Wilson, 2018). Using this methodology as calculated in our results, we recommend that clinicians adopt zones for fit, intermediate fitness, and unfit of >15, 15 to 11.6, and <11.6 $mL.kg^{-1}.min^{-1}$ and <31, 31 to 38, and >38 for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT respectively when identifying patients at risk of mid-term (2 year) postoperative mortality.

Given that we were unable to predict perioperative risk based upon the application of CRF (likely due to the relatively low levels of reported in-hospital mortality and underpowered sample size) interest arises as to why, in this vascular impaired population, there is an apparent need to wait for two years for the benefit of improved CRF to become apparent?

Furthermore, a well-established mechanistic grounding for the protective benefits of improved CRF is yet to be established.

Limitations

We have reported an association between PCPET and mid-term postoperative survival. However, in order to demonstrate an improved ability to identify high-risk patients, PCPET values should also be compared against, or in conjunction with, other risk prediction models such as the Revised Cardiac Risk Index (RCRI), Physiological and Operative Score for enumeration of Mortality and Morbidity (POSSUM), National Surgical Quality Improvement Program (NSQIP), and Surgical Outcome Risk Tool (SORT) (Reeves *et al.*, 2018).

Whilst CRF was shown to be impaired in AAA disease relative to a healthy sedentary population of comparable age, we were unable to determine if any of the control population exhibited AAA disease as they were not screened via Duplex ultrasonography.

Our (nested) sample of patients who underwent PCPET were not representative of the whole population who underwent surgery for aneurysmal repair at this centre and only included those who were referred for PCPET. Further investigation of the referral process is required to determine how many patients did not undergo PCPET and what the underlying reasons were. The decision to operate (or treat conservatively) was likely influenced by PCPET results as patients were routinely referred for PCPET to aid risk stratification. Patients treated conservatively demonstrated lower levels of CRF with $\dot{V}O_2$ peak reported at 12.1 $mL.kg^{-1}.min^{-1}$, a reduction of 2.3 (95% CI 0.29 to 4.28, P = 0.025) $mL.kg^{-1}.min^{-1}$. Despite these limitations, a clear impairment of CRF has been demonstrated in AAA disease, the extent of which may hold predictive value when assessing surgical risk.

Conclusions

This study defines the magnitude of impaired CRF demonstrated in AAA disease. PCPET values were unable to identify patients at high-risk of intraoperative mortality. However, our findings add to the body of evidence supporting the measurement of CRF used to identify patients at high-risk of mid-term postoperative mortality. In this specific subset of patients, $\dot{V}O_2$ peak of < 13.1 mL $O_2.kg^{-1}.min^{-1}$ and $\dot{V}_E/\dot{V}CO_2$-AT ≥ 34 allowed for the discrimination of patients at increased risk of mid-term postoperative mortality and we therefore recommend zones for fit, intermediate fitness, and unfit of >15, 15 to 11.6, and <11.6 $mL.kg^{-1}.min^{-1}$ and <31, 31 to 38, and >38 for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT respectively. Collectively, these findings demonstrate that CRF can predict mid-term postoperative survival in AAA patients which may help direct care provision.

Author's contributions

All authors were involved in the conception and design of study. R.G.D and I.R.A supervised the patient CPET tests. Postoperative outcome data was collated by R.G.D and I.M.W. G.A.R. performed the analysis with input from D.M.B, M.H.L and IMW. The manuscript was drafted by G.A.R and D.M.B. Funding was obtained by D.M.B. All authors provided revisions and approved the final version for submission.

Declaration of interest

The authors declare no conflict of interest.

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Table 1. Patient and participant demographics

	Healthy Participants (n = 108)	AAA Patients (n = 124)
Demographics:		
Age (years)	70 ± 7	72 ± 7*
Male/female (n)	80/28	102/22
BMI (kg/m^2)	27.1 ± 3.6	27.5 ± 4.7
Risk factors:		
Smoker/non-smoker (n)	33 (75)	113 (11)*
Hypertension	4 (4)	62 (50)*
Diabetes	7 (6)	7 (6)
IHD	0 (0)	23 (19)
COPD	0 (0)	20 (16)
Surgical approach:		
Open	N/A	88 (71)
EVAR	N/A	13 (10)
Conservative treatment	N/A	23 (19)

Values are mean ± SD or number (%). AAA, abdominal aortic aneurysm; BMI, body mass index; IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; EVAR, endovascular aneurysm repair. *different *vs* Healthy Participants ($P < 0.05$).

Table 2. Risk factor relationships with two-year postoperative mortality in AAA patients

	Hazard ratio (95% CI)	*P*-value
Univariable		
Demographics		
Age (years)	1.08 (0.99 – 1.17)	0.08
Female	0.49 (0.06 – 3.73)	0.49
BMI ($kg.m^{-2}$)	1.01 (0.87 – 1.16)	0.93
Clinical		
Aneurysm diameter (cm)	1.06 (0.53 – 2.13)	0.87
Infra-renal	0.44 (0.09 – 2.21)	0.32
Supra/juxta-renal	2.25 (0.45 – 11.18)	0.32
Statin	0.78 (0.24 – 2.52)	0.68
COPD	1.42 (0.32 – 6.42)	0.65
Cardiorespiratory		
$\dot{V}O_2$ peak ($mL.kg^{-1}.min^{-1}$)	0.81 (0.69 – 0.95)	0.01
$\dot{V}O_2$-AT ($mL.kg^{-1}.min^{-1}$)	0.74 (0.55 – 0.98)	0.03
$\dot{V}_E/\dot{V}CO_2$-AT	1.11 (1.03 – 1.20)	0.01
$\dot{V}_E/\dot{V}O_2$-AT	1.07 (0.98 – 1.18)	0.14
O_2 Pulse ($mL.beat^{-1}$)	0.85 (0.73 – 0.98)	0.03
OUES	1.00 (1.00 – 1.00)	0.12
Work load-AT (W)	0.98 (0.95 – 1.00)	0.06
Work load-peak (W)	0.98 (0.96 – 0.99)	0.01

Multivariable		
$\dot{V}O_2$ peak (mL.kg^{-1}.min^{-1})	0.84 (0.72 – 0.99)	0.04
$\dot{V}_E/\dot{V}CO_2$-AT	1.10 (1.01 – 1.19)	0.03

BMI, body mass index; IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for oxygen; AT, anaerobic threshold; O_2 Pulse, oxygen pulse at peak oxygen consumption; OUES, oxygen uptake efficiency slope.

Table 3. Regression analysis for selected CPET sub-threshold values predictive of two-year postoperative mortality in AAA patients

	Hazard ratio (95% CI)	***P*-value**	**2-year mortality n (%)**
$\dot{V}O_2$ peak < 13.1 mL.kg^{-1}.min^{-1}	5.27 (1.62 – 17.14)	0.006	13 (11)*
$\dot{V}O_2$ peak ≥ 13.1 mL.kg^{-1}.min^{-1}	Reference group		7 (6)
$\dot{V}_E/\dot{V}CO_2$-AT ≥ 34 units	3.26 (1.00 – 10.59)	0.049	15 (13)*
$\dot{V}_E/\dot{V}CO_2$-AT < 34 units	Reference group		5 (4)

*$P < 0.05$. $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$-AT, ventilatory equivalent for carbon dioxide at anaerobic threshold.

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Figure 1. Comparison of peak oxygen consumption between patients with abdominal aortic aneurysm disease and apparently healthy participants.
Bars represent mean and standard deviation. *Different *vs* Healthy Participants ($P < 0.05$).

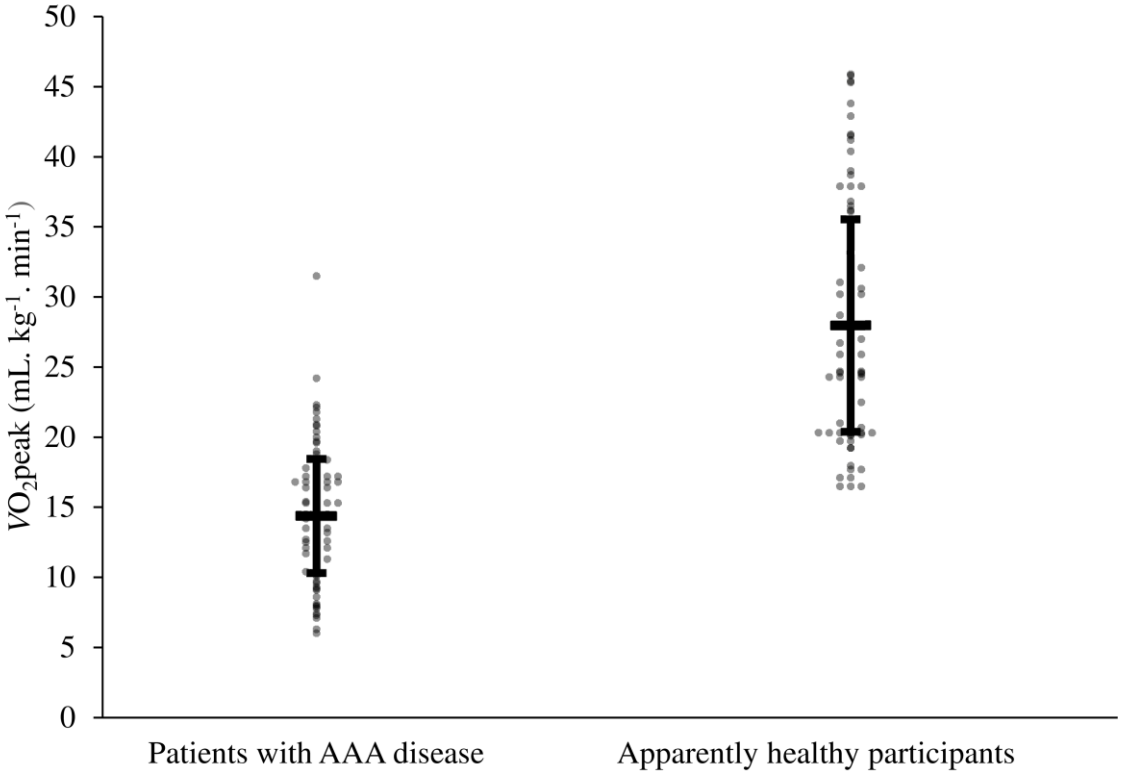
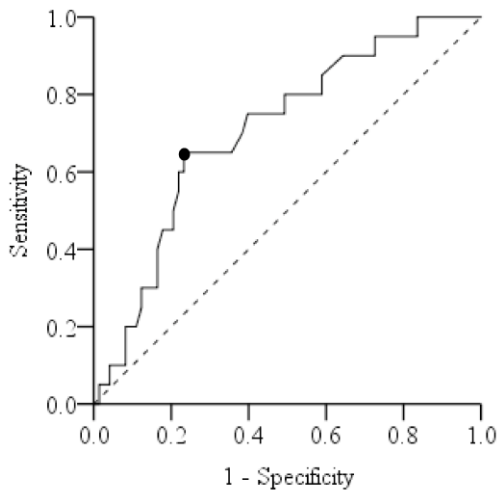
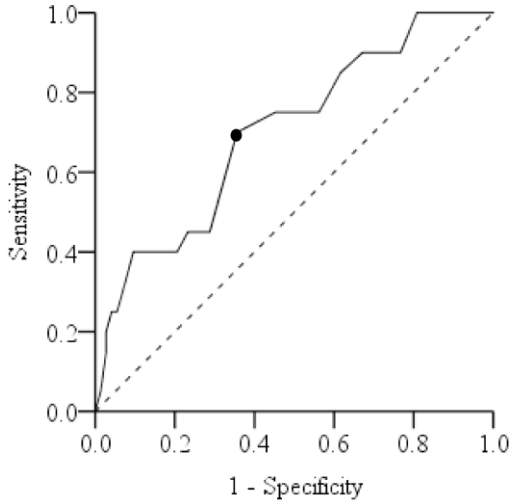


Figure 2. Area under Receiver Operator Curves
A: $\dot{V}O_2$ peak and **B:** $\dot{V}_E/\dot{V}CO_2$-AT. Symbols represent optimal cut points. Area under curve: **A** 0.708 (95% CI 0.585 to 0.830; $P = 0.005$; cut point 13.1 mL.kg^{-1}.min^{-1}); **B** 0.702 (95% CI 0.574 to 0.830; $P = 0.006$; cut point 34). $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$-AT, ventilatory equivalent for carbon dioxide at anaerobic threshold.



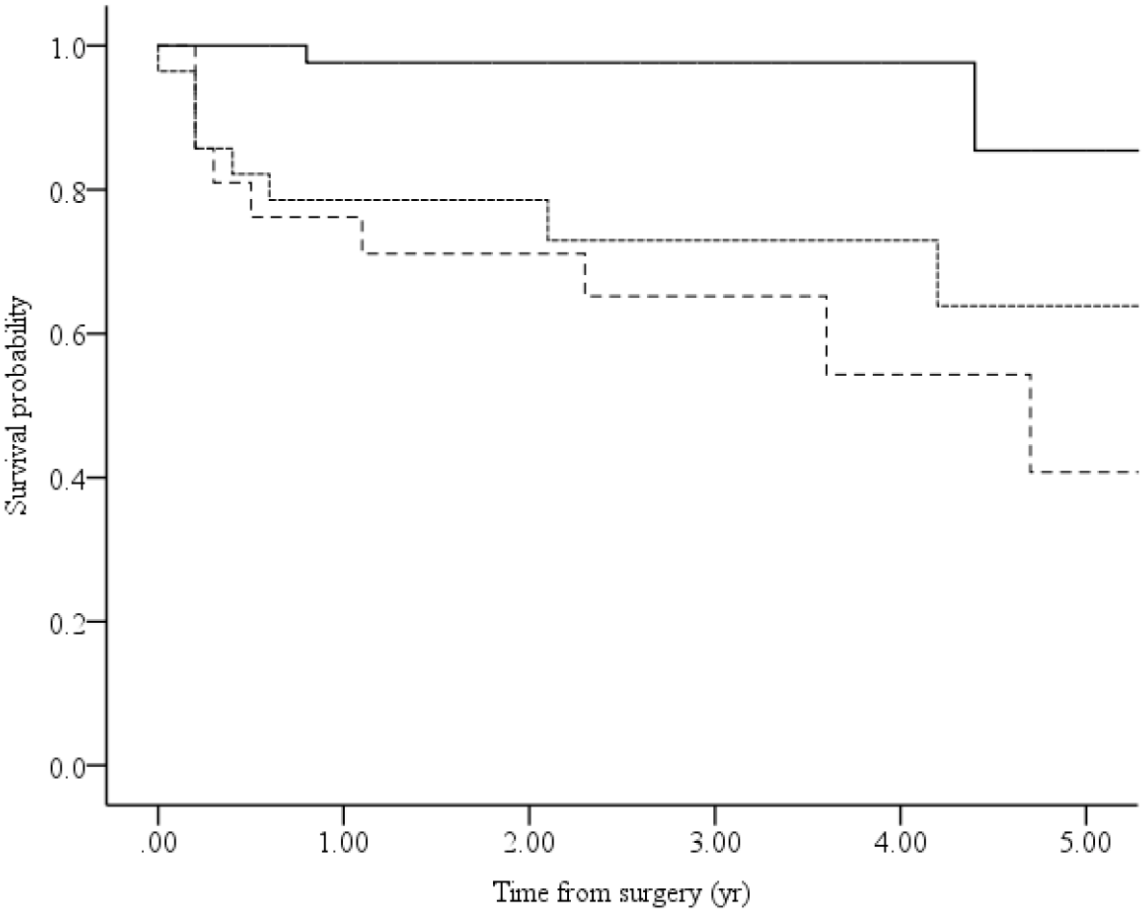
A. $\dot{V}O_2$ peak



B. $\dot{V}_E/\dot{V}CO_2$-AT

Figure 3. Kaplan-Meier plot for survival following AAA surgery stratified by the number of sub-threshold CPET values.

P = 0.01, log rank test. Sub-threshold CPET values: $\dot{V}O_2$ peak < 13.1 ml.kg^{-1}.min^{-1}, and $\dot{V}_E/\dot{V}CO_2$-AT ≥ 34.



Sub-threshold values		No, at risk				
0	—— 43	38	30	16	8	5
1	-------- 27	19	15	10	7	4
2	- - - - - 20	14	12	7	4	2