Cardiopulmonary exercise testing and survival following elective abdominal aortic aneurysm repair

Grant SW[1,2], Hickey GL[2,3], Wisely NA[4], Carlson ED[1], Hartley RA[4], Pichel AC[5], Atkinson D[5], McCollum CN[1]

1. University of Manchester, Manchester Academic Health Science Centre, University Hospital of South Manchester, Academic Surgery Unit, Education and Research Centre, Manchester, UK

2. University College London, National Institute for Cardiovascular Outcomes Research, Institute of Cardiovascular Science, London, UK

3. Centre for Health Informatics, Manchester Academic Health Science Centre, University of Manchester, Oxford Road, Manchester, UK

4. University of Manchester, Manchester Academic Health Science Centre, University Hospital of South Manchester, Department of Anaesthesia, Manchester, UK

5. Central Manchester University Hospitals, Manchester Academic Health Science Centre, Manchester Royal Infirmary, Department of Anaesthesia, Manchester, UK

Address for correspondence:
Professor Charles McCollum,
Academic Surgery Unit, Education & Research Centre,
University Hospital of South Manchester,
Southmoor Road, Manchester, UK, M23 9LT
Telephone - +44 (0)161 291 5853
Fax - +44 (0)161 291 5854,
E-mail: cnmcc@manchester.ac.uk

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ABSTRACT

Background:

Cardiopulmonary exercise testing (CPET) is increasingly used in the pre-operative assessment of patients undergoing major surgery. The objective of this study was to investigate whether CPET can identify patients at risk of reduced survival following abdominal aortic aneurysm (AAA) repair.

Methods:

Prospectively collected data from consecutive patients who underwent CPET prior to elective open or endovascular (EVAR) AAA repair at two tertiary vascular centres between January-2007 and October-2012 were analysed. A symptom limited maximal CPET was performed on each patient. Multivariable Cox Proportional Hazards regression modelling was used to identify risk factors associated with reduced survival.

Results:

The study included 506 patients with a mean age of 73.4 (range 44-90). The majority (82.6%) were men and most (64.6%) underwent EVAR. The in-hospital mortality was 2.6%. Median follow-up was 26-months. The three-year survival for patients with zero or one sub-threshold CPET value ($\dot{V}O_2$ at AT<10.2 ml kg^{-1} min^{-1}, Peak $\dot{V}O_2$ <15 ml kg^{-1} min^{-1} or $\dot{V}E/\dot{V}CO_2$ at AT>42) was 86.4% compared to 59.9% for patients with three sub-threshold CPET values. Risk factors independently associated with survival were female gender (HR=0.44, 95%CI 0.22-0.85,*P*=0.015), diabetes (HR=1.95, 95%CI 1.04-3.69,*P*=0.039), pre-operative statins (HR=0.58, 95%CI 0.38-0.90, *P*=0.016) haemoglobin g dl^{-1} (HR=0.84, 95%CI 0.74-0.95,*P*=0.006), peak $\dot{V}O_2$<15 ml kg^{-1} min^{-1} (HR=1.63, 95%CI 1.01-2.63,*P*=0.046) and $\dot{V}E/\dot{V}CO_2$ at AT>42 (HR=1.68, 95%CI 1.00-2.80,*P*=0.049).

Conclusions:

CPET variables are independent predictors of reduced survival following elective AAA repair and can identify a cohort of patients with reduced survival at three years post procedure. CPET is a potentially useful adjunct for clinical decision making in patients with AAA.

INTRODUCTION

Accurately assessing perioperative risk and predicting longer term clinical outcomes are essential in elective abdominal aortic aneurysm (AAA) repair as for most patients it is a purely prophylactic procedure. A number of different methods of assessing perioperative risk have been proposed in patients undergoing AAA repair including risk prediction models,[1] biomarkers,[2] assessment of functional capacity[3] and genetic testing.[4] Recent guidelines have emphasised that when indicated a pre-operative assessment of a patients functional capacity should be performed for patients undergoing major vascular surgery.[5-8]

Cardiopulmonary exercise testing (CPET) provides a gold standard assessment of functional capacity. It has been used in elite sport performance and research for some time and is now increasingly utilised in the pre-operative assessment of patients prior to major non cardiac surgery. The ability of CPET to identify patients who are at an increased risk of adverse peri-operative outcomes has been assessed in a variety of settings.[9 10]

The evidence for its role in risk stratifying patients undergoing abdominal aortic aneurysm (AAA) repair has so far been limited to a number of small single-centre studies.[3 11-13] As a result of this there is uncertainty about its usefulness in the pre-operative assessment of patients with AAA. A recent systematic review called for more research into its role in the pre-operative assessment of patients undergoing vascular surgery.[14]

A previous study by our group has demonstrated that variables derived from CPET were independent predictors of 30 and 90-day mortality following elective AAA repair.[15] Whilst short-term outcomes are clearly important for both patients and clinicians, better understanding of the risks of mid-term adverse outcomes is important for clinical decision making. The objective of this study was therefore to investigate whether pre-operative CPET derived variables are predictors of survival following elective open and endovascular AAA repair (EVAR).

METHODS

Data were collected prospectively as part of the standard multi-disciplinary assessment on all patients who underwent a symptom limited maximal exercise CPET prior to elective AAA repair at Central Manchester Foundation Trust and University Hospital of South Manchester between 24th January 2007 and 01st October 2012. The cohort significantly overlaps with a previous study by our group on CPET and peri-operative mortality following elective AAA repair.[15] Both contributing hospitals are part of Vascular Governance North West which has approval from both the NRES

Committee North West (09/H1010/2+5) and Section 251 approval. As stated in the terms of the VGNW ethical approval, because this project involved the analysis of pseudonymous, non-identifiable patient data specific ethical approval was not required.

CPET was performed using a cycle ergometer and a ramped test (Wasserman) protocol,[16] with the Ultima^{TM} CardiO$_2$$^{®}$ MedGraphics equipment (Medical Graphics, St Paul, Minnesota, USA) linked into the BreezeSuite^{TM} software package (Medical Graphics, St Paul, Minnesota, USA). CPET equipment was maintained under manufacturer maintenance contracts and calibrated prior to testing in keeping with manufacturer recommendations. All CPET tests were performed and interpreted by appropriately trained consultant anaesthetists to a set of standardised clinical criteria across the two participating centres'

Baseline data were recorded and the patient then cycled for three minutes with no resistance at a rate of approximately 60 revolutions per minute. After these three minutes increasing resistance was applied at between 5 and 20 Watts per minute. Each CPET was performed to achieve maximal patient effort. Criteria used to determine whether maximal effort was achieved were I) heart rate > 80% of predicted peak heart rate, II) respiratory Exchange Ratio > 1.15, III) criteria for ventilatory limitation to exercise reached (breathing reserve < 15%). The CPET was terminated if ST depression of > 2mm on the exercise ECG was observed, a cadence of > 40 rpm could not be maintained, the patient experienced distressing cardio-respiratory or musculoskeletal symptoms or at the request of the patient. Following the test patients were monitored until cardio-respiratory parameters returned to baseline levels. Data for the following CPET variables were collected: $\dot{V}O_2$ at anaerobic threshold (AT) in ml kg^{-1} min^{-1}, Peak $\dot{V}O_2$ in ml kg^{-1} min^{-1} and $\dot{V}E/\dot{V}CO_2$. The following discriminatory thresholds for these CPET variables were selected a priori based on published studies shown to identify those at increased risk of morbidity and death among patients undergoing major non-cardiac surgery; $\dot{V}O_2$ at AT < 10.2 ml kg^{-1} min^{-1},[17] Peak $\dot{V}O_2$ < 15 ml kg^{-1} min^{-1},[18] $\dot{V}E/\dot{V}CO_2$ at AT >42.[3] Absolute patient weight in kg was used to calculate all variables. AT was determined using a combination of V-slope and ventilatory equivalent methods and recorded in ml kg^{-1} min^{-1}.[19] $\dot{V}$E/ $\dot{V}$ CO_2 was recorded at AT, or when AT was unclear, taken to be the lowest recorded value during the incremental part of the exercise test.[20]

Inducible cardiac ischaemia (ICI) was recorded when ≥ 1mm of ST segment depression in two or more adjacent ECG leads on the CPET exercise ECG and/or gas analysis changes consistent with ischaemia were present.[21] Reversible ischaemia present on either stress myoview or dobutamine stress echocardiogram within five years of surgery was also classified as ICI. Patients continued their

usual medication up until CPET testing and heart rate limiting medications were not stopped. Patient co-morbidity data were collected either by the clinician responsible for the patient or a clinical audit team. Preoperative laboratory investigations included haemoglobin (anaemia defined as < 13.0 g dl^{-1} for men and <11.0 g dl^{-1} for women), urea (abnormal defined as >7.5 mmol l^{-1}), creatinine (abnormal defined as >120µmol l^{-1}) and diagnosis of a juxta/supra renal AAA as defined by the operating surgeon. The primary outcome measure was survival following elective AAA repair. Follow–up data were collected using the NHS Demographic Batch Service on 1st August 2013.

Statistical analysis

All variables missing for more than 15 per cent of subjects were excluded from analysis. For remaining variables, missing data were imputed with the median value for continuous or categorical variables and the baseline value for dichotomous variables. If AT could not be determined from the CPET it was assumed to be <10.2 ml kg^{-1} min^{-1}. Continuous variables are reported as mean ± standard deviation (SD), and categorical and dichotomous variables reported as number (percentage). Patient characteristics were compared between open AAA repair and EVAR groups using the student t test for age and the $\chi 2$ test for dichotomous variables.Categorical and dichotomous variables were examined graphically using Kaplan-Meier graphs, and compared using the log rank test. Continuous variables were assessed by fitting univariate Cox proportional hazards (PH) regression models. The functional form of continuous variables other than CPET measurements was assessed by fitting smoothing curves to Martingale residual plots.

Multivariate Cox PH models were developed by including variables that were significant at the *P* <0.20 level at univariate analysis. The PH assumption was formally and graphically assessed using the Grambsch-Therneau test based on scaled Schoenfeld residuals.[22] Variables found to significantly violate the PH assumption were used to stratify the baseline hazards function. All statistical analyses were performed using R (version 3.0.1) statistical computing software.[23] A P-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics and in-hospital mortality

During the study period 506 patients performed a preoperative CPET and went on to have elective AAA repair. The median time between CPET and surgery was 56 days (first quartile – third quartile 26-90). The mean age at operation was 73.4 (range 44-90) and the majority (82.6%) of patients were men. The majority (327, 64.6%) of patients underwent endovascular AAA repair. The differences in

patient characteristics between these groups are shown in Table 1. Those undergoing EVAR were more likely to be older, have a history of IHD and demonstrate limited functional capacity (as determined by CPET). Patients who underwent EVAR were less likely to have treated hypertension or a juxta/supra renal AAA repair. AT could not be determined in 53 (10.5%) patients. The in-hospital mortality rate was 1.86% in the EVAR group, 4.00% in the open repair group and 2.61% overall.

Survival analysis

The median follow up time was 26 months with a maximum follow up time of 67 months. There were 90 deaths overall in the study cohort. Inspection of the Kaplan-Meier graph stratified by open surgery and EVAR (Figure 1) demonstrated that operation type failed to satisfy the PH assumption (Grambsch-Therneau test $P = 0.007$) due to a crossing in the curves at approximately six months. Therefore the model was stratified on this variable. Following univariate analysis, the following variables were significant at the $P < 0.20$ level: age ($P = 0.013$), gender ($P = 0.157$), diabetes ($P = 0.035$), inducible cardiac ischemia (P = 0.147), statins ($P = 0.019$), creatinine ($P < 0.001$), elevated urea ($P = 0.001$), haemoglobin ($P < 0.001$) and the CPET variables, $\dot{V}E/\dot{V}CO_2$ at AT < 42 ($P = 0.005$), Peak $\dot{V}O_2$ < 15 ml kg^{-1} min^{-1} ($P < 0.001$) and AT < 10.2 ml kg^{-1} min^{-1} ($P = 0.003$). The number of sub-threshold CPET variables was an important risk factor for reduced survival as shown in Figure 2 ($P <$ 0.001). As shown in Table 2, patients with zero or one sub-threshold CPET variables had a three-year survival of 86.4% compared to 59.9% in patients with three sub-threshold CPET variables.

A strong linear relationship between peak $\dot{V}O_2$ (ml kg^{-1} min^{-1}) and AT (ml kg^{-1} min^{-1}) for all pairwise-complete records was demonstrated (Pearson's sample correlation coefficient r = 0.81; regression slope = 0.508, $P < 0.001$) as shown in Figure 3. As there is significantly more missing data for AT, but the relationship between AT and Peak $\dot{V}O_2$ is strong, which would introduce co-linearity into the regression modelling, AT was not included in the multivariate analyses. The final model is shown in Table 3. Patient characteristics associated with reduced survival included male gender, diabetes not taking pre-operative statins, low haemoglobin, $\dot{V}E/\dot{V}CO_2$> 42 at AT and peak $\dot{V}O_2$ < 15 ml kg^{-1} min^{-1}. The final model satisfied the assumption of proportional hazards (Grambsch-Therneau test $P =$ 0.285).

DISCUSSION

This study demonstrates that variables derived from pre-operative CPET testing are independent risk factors for reduced survival following elective AAA repair. Patients with multiple sub-threshold CPET values had significantly reduced survival compared to those with zero or one abnormal value. Peak $\dot{V}$

$\dot{V}O_2$ (< 15 ml kg^{-1} min^{-1}) and $\dot{V}$E/ $\dot{V}CO_2$ (>42) were independent predictors of reduced survival. These results are applicable to patients undergoing both open AAA repair and EVAR.

This is the largest study to date of exploring the association between preoperative CPET variables and survival following elective AAA repair. It is also the first study to report that CPET variables are associated with survival in a cohort of patients that includes patients undergoing EVAR. Coupled with the previous analysis on short-term outcomes following elective AAA repair conducted by our group, each CPET variable studied has be shown to be potentially useful for predicting outcomes following elective AAA repair. For 30-day mortality $\dot{V}O_2$ at AT < 10.2 ml kg^{-1} min^{-1} is an independent predictor of outcome with a peak $\dot{V}O_2$ < 15 ml kg^{-1} min^{-1} being an independent predictor of 90-day mortality .[15] For survival a peak $\dot{V}O_2$ < 15 ml kg^{-1} min^{-1} and a $\dot{V}E/\dot{V}CO_2$ at AT of > 42 were independent predictors. An AT < 10.2 ml kg^{-1} min^{-1} may have been an independent predictor of reduced survival but it was not examined in the multivariate analysis due to co-linearity.

AT and peak $\dot{V}O_2$ are both measures of aerobic or functional capacity and it is therefore not surprising that a strong linear relationship between the two was demonstrated. The association between AT and early mortality has been demonstrated in series of patients undergoing major non-cardiac surgery which have included some open AAA repairs.[7 10 17] AT is not reliant on patient motivation and has been shown to be a reproducible measure of aerobic capacity in preoperative patients.[26] Although its estimation can be subjective it has been shown to be reliably interpreted between different clinicians.[27] However the AT may not be apparent in all patients. The approach adopted for imputing missing AT data in this study was selected by the research team as it was felt that for patients in whom AT could not be determined it was more likely to be sub-threshold. This approach is a potential limitation and as a result peak $\dot{V}O_2$ rather than AT was included in the multivariate analysis.

Peak $\dot{V}O_2$ is simply the highest $\dot{V}O_2$ achieved by an individual during an exercise test. The Peak $\dot{V}O_2$ achieved during a test is therefore effort dependent. $\dot{V}O_2$ max represents the limit of functional capacity for an individual and is reached when there is a plateauing of the $\dot{V}O_2$ response to exercise despite an increasing work rate. $\dot{V}O_2$ max is rarely achieved in clinical practice but when a maximal effort CPET is performed by an individual, the peak $\dot{V}O_2$ achieved should provide a reasonable reflection of their $\dot{V}O_2$ max. In this study, all CPET was performed with the intention of achieving a maximal patient effort. This is not the case in other centres in the UK where sub-maximal testing may be performed.[10] Given these results, where safe and feasible, CPET should be performed to a

maximal effort to facilitate risk stratification. Peak $\dot{V}O_2$ is also associated with increased perioperative in patients undergoing lung resection surgery.[18]

An elevated $\dot{V}$ E/ $\dot{V}$ CO_2 (>42) has previously been shown to be an important predictor of mid-term mortality in AAA repair.[3] An elevated $\dot{V}$ E/ $\dot{V}$ CO_2 is likely to be multi-factorial in nature and represent systemic disease severity.[28] In patients with heart failure abnormal $\dot{V}$ E/ $\dot{V}$ CO_2 has been significantly correlated with increased ventilation perfusion mismatch, decreased cardiac output, elevated pulmonary pressures, decreased alveolar-capillary membrane conductance, and diminished heart rate variability.[29] $\dot{V}$ E/ $\dot{V}$ CO_2 as a predictor has the advantage of high test reliability and does not depend on the mode of exercise or testing protocol used.[28]

Other risk factors that were associated with an increased risk of reduced survival in this study included low pre-operative haemoglobin, not taking pre-operative statins, diabetes and male gender. Anaemia has been found to correlate with unfavourable outcomes in both surgical and non-surgical population,[30] and has been found to be associated with reduced long-term survival following EVAR.[31] This study adds further evidence to the existing literature,[32 33] that statin usage is associated with improved outcomes following AAA repair. Diabetes has previously been found to be associated with reduced survival in patients undergoing AAA repair.[34] The improved survival in women in this study is unusual and may be a reflection of patient selection practices at the two centres.

This study represents contemporary practice at two tertiary vascular centres with good in-hospital mortality rates. CPET was performed as part of routine multi-disciplinary preoperative assessment and was utilised in clinical decision making. As a result of the non-randomised, observational nature of the study, there were significant differences in the patient characteristics between the open AAA repair and EVAR groups. Patients with limited functional capacity were more likely to undergo EVAR and those undergoing open repair were more likely to have unfavourable anatomy for EVAR. However as the objective of the study was not to compare treatment groups this is not a limitation of the study. Although this is the largest study to date of CPET in AAA repair, the sample size remains relatively small for a modelling study and this is reflected in the wide confidence intervals produced on multivariable analysis.

All CPET data were collected prospectively in a standardised way across the two centres, however, a potential limitation of the study is that tests were not independently reviewed prior to analysis to ensure standardisation. This was not felt to be necessary by the research team due to the standardisation of methods across the two centres. A limitation of the study is that the recording of

ICI differed between the two centres with one deriving ICI exclusively from the CPET test and the other recording ICI as present also based on the use of non-invasive stress testing. As a result ICI was not exclusively defined by CPET testing it has not been included as a CPET variable for this study.

A potential limitation of the analysis approach is that although CPET variables are recorded as continuous variables they were dichotomised for this analysis. This was a pragmatic choice based on clinical judgement and previously published studies,[3,17,18] to balance model fit and model complexity given the relatively small number of outcomes. Although the median follow-up time is relatively short, three-year survival is clearly an important outcome following elective AAA repair as data from randomised controlled trials suggests that from approximately two years onwards survival is the same for patients who undergo open AAA repair or EVAR.[24,25]

This study demonstrates that preoperative CPET to maximal effort can identify patients with reduced survival following elective AAA repair independent of the type of repair. These risks can be weighed against the risk of AAA rupture which is frequently expressed in terms of rupture risk per year to facilitate clinical decision making. The costs of CPET are relatively low at approximately £200 per patient at our centres. CPET is also safe with only a minimal risk of adverse events.[28] However, the exact value of its contribution to pre-operative assessment along with its cost-effectiveness is still uncertain. Further studies assessing the utility of CPET alongside clinical prediction models are required.

DETAILS OF AUTHORS CONTRIBUTIONS

All authors were involved in the conception and design of the study. NW, ACP, DA performed the CPET tests. EDC and RAH collected and collated the data. EDC and SWG cleaned the data. GH performed the analysis with input from SWG. SWG drafted the manuscript which was revised by GH, NW, DA and CNM. All authors approved the final version for submission. CNM will act as guarantor for the study.

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DECLARATION OF INTERESTS

The authors declare no conflicts of interest.

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TABLES

Table 1: Differences in patient characteristics for patients undergoing open AAA repair and EVAR

Patient Characteristic	Overall cohort n=506 (%)	Open repair n=178 (%)	EVAR n= 328 (%)	p value	Missing data n=506 (%)
Age	73.4 (44 – 90)	70.5 (48 – 86)	75.0 (44 – 90)	<0.001	0 (0.0)
Female	87 (17.2)	39 (21.9)	48 (14.7)	0.053	1 (0.2)
Diabetes	50 (9.9)	15 (9.0)	35 (11.9)	0.441	47 (9.3)
Ischaemic heart disease	214 (42.3)	51 (31.5)	163 (55.8)	<0.001	52 (10.3)
Treated hypertension	178 (35.2)	80 (46.5)	98 (31.0)	<0.001	18 (3.6)
Antiplatelet medication	330 (65.2)	124 (70.1)	206 (63.8)	0.187	6 (1.2)
Statin	324 (64.0)	123 (69.5)	201 (62.2)	0.126	6 (1.2)
Haemoglobin g l^{-1}	13.3 ± 1.8	13.6 ± 1.9	13.2 ± 1.8	0.022	14 (2.8)
Urea >7.5mmol l^{-1}	7.4 ± 3.3	7.1 ± 2.5	7.6 ± 3.6	0.407	13 (2.6)
Creatinine > 120µmol l^{-1}	103.7 ± 51.6	99.3 ± 31.8	106.0 ± 59.6	0.099	9 (1.8)
Supra/juxta renal	59 (11.7)	46 (26.0)	13 (4.2)	<0.001	20 (4.0)
AAA diameter (mm)	63.1 ± 10.1	64.0 ± 11.0	62.5 ± 9.5	0.125	32 (6.3)
AT < 10.2 ml kg^{-1} min^{-1}	189 (37.4)	46 (27.2)	143 (50.3)	<0.001	53 (10.5)
$\dot{V}_E/\dot{V}_{CO_2}$ at AT >42	80 (15.8)	17 (10.0)	63 (19.3)	0.006	2 (0.4)
Peak $\dot{V}_{O_2}$ < 15 ml kg^{-1} min^{-1}	256 (50.6)	66 (37.1)	190 (57.9)	<0.001	0 (0.0)
ICI	46 (9.1)	12 (6.7)	34 (10.5)	0.222	3 (0.6)
≥2 sub-threshold CPET values	213 (42.1)	49 (27.3)	164 (50.2)	<0.001	0 (0.0)
3 sub-threshold CPET values	54 (10.7)	10 (5.6)	44 (13.5)	0.010	0 (0.0)

Continuous data (with the exception of age which is shown as mean and range) are shown as mean ± standard deviation and dichotomous data are shown as number (percentage). p value calculated using χ^2 test with the exception of age which was calculated using a student t test: AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; M, male; F, female; AT, anaerobic threshold; $\dot{V}_E/\dot{V}_{CO_2}$, ventilatory equivalents for carbon dioxide; peak $\dot{V}_{O_2}$, peak oxygen consumption; ICI, inducible cardiac ischaemia.

Table 2: Survival following elective AAA repair stratified by number of sub-threshold CPET variables

Number of sub-threshold CPET variables	1 year survival	3 year survival
0-1	94.4%	86.4%
2	86.9%	78.0%
3	76.7%	59.9%

Table 3: Results of Cox proportional hazards multivariable analysis for survival after abdominal aortic aneurysm repair. The baseline hazard function is stratified on operation type (open surgery or EVAR).

	Hazard ratio (95%CI)	*P*
Age (years)	1.008 (0.977-1.041)	0.603
Female	0.436 (0.224-0.849)	0.015
Diabetes	1.954 (1.035-3.687)	0.039
Inducible cardiac ischemia	1.640 (0.901-2.986)	0.106
Statin	0.583 (0.376-0.905)	0.016
Creatinine (μmol l^{-1})	1.002 (0.998-1.006)	0.278
Urea (mmol l^{-1})	1.066 (0.988-1.151)	0.101
Haemoglobin (g dl^{-1})	0.842 (0.744-0.953)	0.006
$\dot{V}E/\dot{V}CO_2$> 42 at AT	1.628 (1.009-2.627)	0.046
Peak VO_2 < 15 (ml kg^{-1} min^{-1})	1.676 (1.002-2.803)	0.049

HR, hazard ratio; CI, confidence interval; AT, anaerobic threshold; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalents for carbon dioxide; peak $\dot{V}O_2$, peak oxygen consumption

LEGENDS TO ILLUSTRATIONS

Figure 1: Kaplan-Meier graph for survival following elective AAA repair by procedure type. Survival is initially worse in the open AAA repair group with the survival curves crossing at approximately 6 months and survival subsequently worse in the EVAR group ($P < 0.001$, log rank test).

Figure 2: Kaplan-Meier graph for survival following elective AAA repair by the number of sub-threshold CPET values ($P < 0.001$, log rank test).

Figure 3: Plot of Peak VO_2 against AT for pairwise-complete records. Green triangles indicate the patient was alive at the end of follow-up; blue circles indicate that death occurred during follow-up. The vertical dashed lines on the bottom axis indicate the measured Peak VO_2 for patients who did not have a recorded AT measurement (coloured as appropriated). The black dotted line indicates the linear model regression line (Pearson's sample correlation coefficient $r = 0.81$; regression slope = 0.508 ($P < 0.001$)). The red lines delineate the thresholds used to dichotomise sub-threshold CPET values.