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Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery

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Background. Studies of preoperative cardiopulmonary exercise testing (CPET) have shown that a reduced oxygen uptake at anaerobic threshold (AT) and elevated ventilatory equivalent for carbon dioxide (VE/VCO_2) were associated with reduced short- and medium-term survival after major surgery. The aim of this study was to determine the relative values of these, and also clinical risk factors, in identifying patients at risk of death after major intra-abdominal, non-vascular surgery.

Methods. Patients aged >55 yr, undergoing elective colorectal resection, radical nephrectomy, or cystectomy between June 2004 and May 2009 had CPET during their routine pre-assessment clinic visit. We performed a retrospective analysis of known clinical risk factors and data from CPET to assess their relationship to all-cause mortality after surgery.

Results. Eight hundred and forty-seven patients underwent surgery, of whom 18 (2.1%) died. A clinical history of ischaemic heart disease (RR 3.1, 95% CI 1.3–7.7), a VE/VCO_2 >34 (RR 4.6, 95% CI 1.4–14.8), and an AT ≤ 10.9 ml kg^{-1} min^{-1} (RR 6.8, 95% CI 1.6–29.5) were all significant predictors of all-cause hospital and 90 day mortality. The effect of reduced AT was most pronounced in patients with no history of cardiac risk factors (RR 10.0, 95% CI 1.7–61.0).

Conclusions. The routine measurement of AT and VE/VCO_2 using CPET for patients undergoing high-risk surgery can accurately identify the majority of high-risk patients, while the use of clinical risk factors alone will only identify a relatively small proportion of at-risk patients.

Keywords: cardiovascular function; colorectal surgery; cystectomy, nephrectomy; exercise test; mortality; oxygen consumption, anaerobic threshold; postoperative complications

Accepted for publication: 26 March 2010

Key points

- Patients who die after major surgery are likely to have reduced functional capacity.
- Ischaemic heart disease is the only clinical indicator associated with mortality after major surgery.
- Patients with no cardiac risk factors are equally at risk from impaired functional capacity.

Patients developing serious complications after major surgery often exhibit features of inadequate global or local tissue oxygenation during the perioperative period, usually as a result of inadequate cardiorespiratory function.[1][2] Accurate identification of at-risk patients would help the clinician make appropriate decisions about offering surgery, and would allow more effective use of expensive resources such as postoperative critical care.

Simple risk indices based on clinical data have been devised, but have limitations. For example, the POSSUM score requires intraoperative and preoperative data, and the Lee's cardiac risk index (LCRI) was specifically devised to predict the risk of postoperative cardiac events, rather than all-cause mortality.[3][4]

Two studies of preoperative cardiopulmonary exercise testing (CPET) in patients undergoing major abdominal surgery demonstrated that an oxygen consumption value at anaerobic threshold (AT) of <11 ml kg^{-1} min^{-1} was associated with increased mortality after surgery.[5][6]

In the first of these papers, the significance of the AT value of 10.9 ml kg^{-1} min^{-1} or less was determined by mapping the values of measured AT in surgical patients with the stages of the Weber and Janicki classification of heart failure, which classifies heart failure into five groups of severity according to variables obtained from CPET.[5] The third stage in this classification has an upper limit of 10.9 ml kg^{-1} min^{-1}, and Older and colleagues[6] observed that 10 out of the 11 postoperative cardiorespiratory deaths in his series occurred in patients with an AT of 10.9 ml kg^{-1} min^{-1} or less.

A further study found that both a raised ventilatory equivalent for carbon dioxide (VE/VCO_2), as measured using CPET, and the presence of one or more Lee's cardiac risk factors were significant predictors of medium-term mortality after aortic surgery.[7]

The aim of this study was to evaluate whether variables measured by CPET (AT and VE/VCO_2) and clinical data from LCRI are still useful predictors of all-cause hospital and

90 day mortality in patients undergoing non-vascular intra-abdominal surgery.

Methods

York Hospital Ethics Committee approval was obtained for the analysis of data from the secure database storing general medical and surgical outcome data and results of investigations, of all patients who undergo CPET at our general surgery and urology pre-assessment clinic. As this was a retrospective analysis of anonymized data, the requirement for written consent was waived.

Patients

All patients aged >55 yr being considered for colorectal surgery, bladder, or kidney cancer excision who performed or attempted a CPET as part of their routine preoperative evaluation at the Pre-Assessment Clinic (PAC) between June 2004 and June 2009 were included. Patients aged <55 yr were also tested if undergoing one of the above procedures and were known to have cardiorespiratory co-morbidity diabetes or renal insufficiency. Patients who did not proceed to undergo the proposed surgery were excluded from the analysis.

Cardiopulmonary exercise testing

CPET was performed as part of the patient's routine 2 h preoperative visit to the General Surgical and Urological PAC. During this visit, standard medical history, physical examination, and laboratory investigations were performed. A 12-lead resting ECG was recorded before the exercise test.

CPET was performed on a standard cycle ergometer, with test protocol controlled by Cardioperfect[TM] software (Welch Allyn Inc., Skaneateles Falls, NY, USA), which in addition recorded a 12-lead exercise ECG during the test, and was linked into the BreezeSuite[TM] software package (Medical Graphics Corporation, Parkway, St Paul, MN, USA). This allows recording of breath-by-breath measurements of oxygen uptake, carbon dioxide production, and respiratory flow and volume parameters. These measurements were obtained by the patient applying a sealed mouthpiece and nose-clip before the test, which was then connected to a MedGraphics preVent[TM] pneumotach device (Medical Graphics Corporation) to measure both respiratory flow and inspired and expired oxygen and carbon dioxide levels. A CPX Ultima metabolic monitor (Medical Graphics Corporation) was used to perform breath-by-breath respiratory gas exchange analysis. Arterial pressure measurements were measured using a SunTech Tango device, specifically designed for exercise testing (SunTech Medical, Eynsham, Oxfordshire, UK).

While baseline data were noted, the test was explained to the patient, and an initial arterial pressure measurement recorded. The patient then commenced cycling at a rate of 60–70 rpm. During the first 3 min of exercise, no resistance was added to the cycle, to allow time for gas exchange to settle into a consistent pattern, and the patient to become used to the exercise. After 3 min, the exercise phase of the protocol commenced, with resistance added to the cycle flywheel in a linear fashion, hence increasing the patient's work rate in a smooth pattern.

The exercise protocol was determined by the age and general fitness of the patient, and varied from 5 to 20 W min^{-1} increase in work rate, with the majority of patients requiring a work rate of 10 W min^{-1} to complete the test within a 10 min period.

The test was terminated when a consistently rising value of the respiratory exchange ratio (the ratio of carbon dioxide production to oxygen uptake) >1.0 indicated that the AT had been passed. A sustained increase in respiratory exchange ratio >1.0 indicated that lactate production had commenced, due to the additional carbon dioxide production relative to oxygen consumption that occurs when lactate is buffered by bicarbonate. After the test was finished, the value of AT was obtained using the V-slope method.[8] A value for AT of 10.9 ml kg^{-1} min^{-1} or less was taken as a marker of an increased mortality risk based on previously published data in surgical patients.[5] [6]

The ventilatory equivalent for carbon dioxide (VE/VCO$_2$) was recorded as the value measured at the AT. A value of ≥34 was taken as indicative of higher risk, based on previously published data in heart failure patients.[9] We also analysed mortality of a subset of patients with a VE/VCO$_2$ of ≥42 as this had been shown to be associated with reduced mid-term survival in aortic surgery patients.[7]

Patients unable to complete the test to AT due to either fatigue or onset of dysrhythmia were treated as being at higher risk, and included in the AT <11 ml kg^{-1} min^{-1} group for analysis. Patients unable to complete the test to AT because of joint mobility problems were excluded from the analysis.

Clinical management

There were no rigid protocols for perioperative management, but test results were forwarded to surgeons and anaesthetists, with recommendations as to which patients were felt to be at particular risk, and therefore may benefit from invasive perioperative monitoring and postoperative high-dependency care if available.

Data recorded

Details of the patient's history and CPET results were stored on a secure Microsoft Access database (Microsoft Corporation, Redmond, WA, USA). Surgical outcomes were obtained from the hospital core patient database, and combined with the CPET database for analysis.

Outcome measures and statistics

Primary outcome measures were the relative risks of reduced AT, elevated ventilatory equivalent for carbon dioxide, or the presence of clinical cardiac risk factors [ischaemic heart disease (IHD), heart failure, diabetes, renal insufficiency, or cerebrovascular disease] on all-cause hospital mortality

Table 1 Preoperative data

	Risk factor present	Risk factor absent
Anaerobic threshold (AT)		
	AT $\leq$10.9 ml kg^{-1} min^{-1}	AT >10.9 ml kg^{-1} min^{-1}
Number of patients (%)	457 (54)	390 (46)
Age (mean, range)	73.1 (39–92)	68.8 (38–93)
Sex (M/F)	226/231	280/110
Ventilatory equivalent for carbon dioxide >34 (VE/VCO$_2$ >34)		
	VE/VCO$_2$ $\geq$34	VE/VCO$_2$ <34
Number of patients (%)	442 (51)	405 (49)
Age (mean, range)	73.8 (51–93)	68.2 (38–89)
Sex (M/F)	253/189	254/151
	VE/VCO$_2$$\geq$42	VE/VCO$_2$<42
Number of patients (%)	100 (12)	747 (88)
Cardiac risk factors (overall) expressed as number (%)		
	Present	Absent
Ischaemic heart disease	143 (17)	704 (83)
Renal insufficiency	40 (5)	807 (95)
Cerebrovascular disease	41 (5)	806 (95)
Heart failure	24 (3)	823 (97)
Diabetes	97 (11)	750 (89)
One or more cardiac risk factors	271 (32)	576 (68)
Patients with ischaemic heart disease (IHD)		
	History of IHD	No history of IHD
Age (mean, range)	73.6 (42–89)	70.6 (38–93)
Sex (M/F)	95/48	412/292

after surgery.[10] Relative risk was calculated with 95% confidence intervals, using the method described by Morris and Gardner.[11]

Ninety-day survival curves were calculated for reduced AT and elevated VE/VCO$_2$, and curves compared with log-rank analysis, and receiver-operator characteristic curves (ROC curves) were calculated for AT and VE/VCO$_2$ as predictors of hospital and 90 day mortality (Prism 5, Graphpad Software, La Jolla, CA, USA).

Differences in prevalence of patient characteristics were analysed with the χ^2 test (SPSS ver. 13.0, SPSS Inc., Chicago, IL, USA).

Results

Eight hundred and forty-seven patients were included in the analysis, comprising 843 patients who underwent surgery after pre-assessment and CPET to a successful AT measurement, and four patients who had been unable to achieve AT as a result of either frailty (two patients) or cardiac dysrhythmias (two patients). Five hundred and ninety-three patients underwent colorectal surgery and 254 underwent surgery for radical nephrectomy or cystectomy.

An additional 13 patients had surgery but had been unable to complete CPET due to mobility issues from osteoarthritis. These were excluded from analysis; one of these patients died.

Preoperative data

CPET variables

Patients with either a reduced AT or an increased VE/VCO$_2$ were significantly older than those with normal parameters (Table 1, P<0.001). Females were more likely to have a reduced AT compared with males (Table 1, P<0.001), but there was no significant sex difference in the distribution of VE/VCO$_2$ risk (Table 1, P=0.212).

Cardiac risk factors

Of the individual risk factors, only IHD was prevalent in sufficient numbers to reasonably allow further analysis. The patients with IHD were significantly older (P=0.001, Table 2).

Mortality after surgery

Hospital mortality

Eighteen patients died in hospital (2.1% mortality), 12 patients after colorectal surgery (2.0%) and six patients after major urological cancer surgery (2.4%). An AT of 10.9 ml kg^{-1} min^{-1} or less, a VE/VCO$_2$ of 34 or more, and a history of IHD were all associated with an increased relative risk for all-cause hospital mortality (Table 2). The overall presence of any one or more of the Lee's cardiac risk factors was not significantly associated with an increased risk of mortality. For patients with no documented history

Table 2 Postoperative mortality. NS, non-survivors; S, survivors

Surgical outcome	Risk factor present		Risk factor absent		Relative risk of non-survival (95% CI)
	NS	S	NS	S	
AT $\leq$10.9	16	441	2	388	6.8 (1.6–29.5)
VE/VCO$_2$ $\geq$34	15	427	3	402	4.6 (1.4–14.8)
VE/VCO$_2$ $\geq$42	5	95	13	734	2.9 (1.1–7.5)
$\geq$1 cardiac risk factors	8	263	10	566	1.7 (0.7–4.1)
Ischaemic heart disease (IHD)	7	136	11	693	3.1 (1.3–7.7)
Renal insufficiency	1	39	17	790	1.2 (0.2–6.6)
Cerebrovascular disease	1	40	17	789	1.2 (0.2–6.4)
Heart failure	0	24	18	805	0.0 (0.0–6.5)
Diabetes	1	96	17	733	0.45 (0.1–2.6)
Patients with one or more cardiac risk factors present					
AT$\leq$10.9	7	177	1	86	3.3 (0.5–20.6)
Patients with no known cardiac risk factors present					
AT$\leq$10.9	9	264	1	302	10.0 (1.7–61.0)
Patients with history of ischaemic heart disease					
AT$\leq$10.9	6	97	1	39	2.3 (0.4–14.7)
Patients with no history of ischaemic heart disease					
AT$\leq$10.9	10	344	1	349	9.9 (1.6–59.9)
Planned postoperative admission to high-dependency care (HDU)					
HDU	**Yes**	**No**			
AT$\leq$10.9	146	311			
AT$\geq$11	21	369			
Outcome of patients with AT <11 ml kg^{-1} min^{-1} by postoperative location					
	HDU	Ward			
Survivors	135	306			
Non-survivors	11	5			4.7 (1.7–13.2)

of cardiac risk factors, the relative risk of mortality was 10.0 (95% CI 1.7–61.0) for patients with an AT of 10.9 ml kg^{-1} min^{-1} or less (Table 2).

ROC analysis

The area under the curve (AUC) was 0.68 [95% CI (0.59–0.76) for AT and 0.69 (0.55–0.82) for VE/VCO$_2$ as predictors of hospital mortality] (Fig. 1). AT of 10.9 ml kg^{-1} min^{-1} or less, and VE/VCO$_2$ of 34 or more both had a sensitivity of 88% and specificity of 47% for hospital mortality.

Survival at 90 days

Thirty-five patients (4.1%) had died by 90 days after surgery. Survival at 90 days was significantly greater in patients with an AT of 11 or greater (P=0.034, Fig. 2), in patients with VE/VCO$_2$ <34 (P=0.021, Fig. 3), and in patients without IHD (P=0.02).

ROC analysis

The AUC was 0.60 [95% CI (0.52–0.68) for AT and 0.64 (0.54–0.73) for VE/VCO$_2$ (Fig. 4) as predictors of 90 day mortality]. AT of 10.9 ml kg^{-1} min^{-1} or less had a sensitivity of 71% and a specificity of 47%, while VE/VCO$_2$ of 34 or more had a sensitivity of 68% and specificity of 53% for 90 day

mortality. For a VE/VCO$_2$ of 42 or greater, sensitivity and specificity were 29% and 86%, respectively, for hospital mortality, and 21% and 88% for 90 day mortality.

Morbidity after surgery

AT influenced postoperative care, with significantly more patients in the low AT group being electively admitted HDU after surgery (P<0.001, Table 2). The hospital mortality in the group admitted to HDU was significantly higher (7.5% vs 1.6%, P=0.001).

Overall median length of hospital stay was lower in the group with AT 11 or greater (8 vs 9 days, P<0.001).

Discussion

Our results confirm that the use of a value of AT of 10.9 ml kg^{-1} min^{-1} or less appears justified as a practical basis for evaluating the risk of postoperative mortality after major abdominal surgery. This was despite an increased likelihood of postoperative high-dependency care in the low AT group.

These findings are in keeping with the first of Older's studies in which the group with AT of 10.9 ml kg^{-1} min^{-1} or less had an overall mortality rate of 18%, increasing to 42% in those patients with reduced AT and IHD.[5] For those patients with IHD who had an AT of 11 ml kg^{-1} min^{-1} or
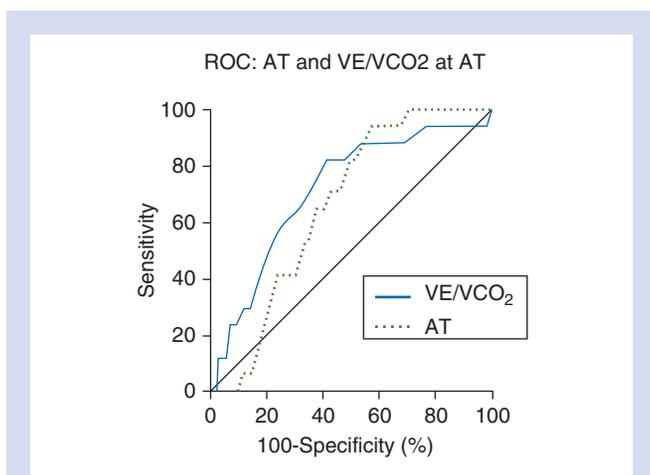
Fig 1 AT <11 and VE/VCO$_2$ >34 as predictors of hospital mortality: AUC 0.68 [95% CI (0.59–0.76) for AT, 0.69 (0.55–0.82) for VE/VCO$_2$].

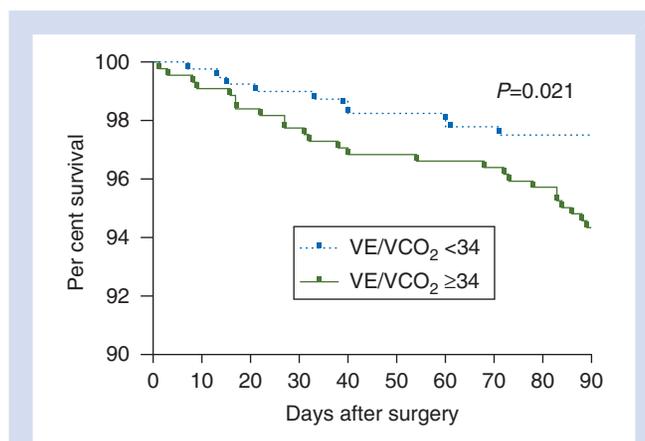**Fig 3** Kaplan–Meier curve for 90 day survival for VE/VCO$_2$ <34 compared with VE/VCO$_2$ >34. Survival at 90 days was significantly greater in patients with VE/VCO$_2$ <34 ($P=0.021$).
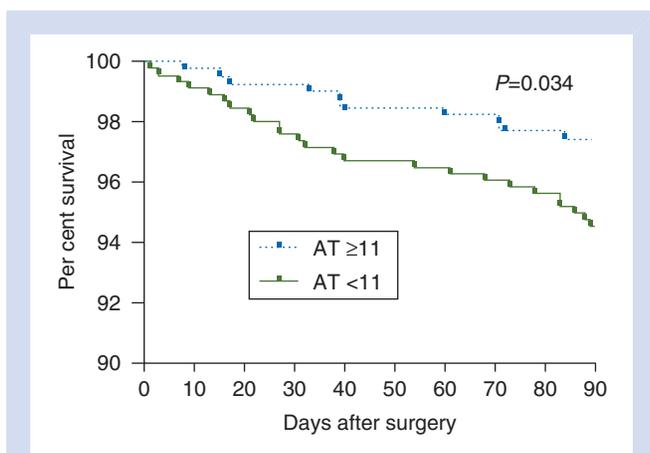

Fig 2 Kaplan–Meier curve for 90 day survival for AT ≥ 11 ml kg^{-1} min^{-1} compared with AT <11 ml kg^{-1} min^{-1}. Survival at 90 days was significantly greater in patients with an AT of 11 ml kg^{-1} min^{-1} or greater ($P=0.034$).
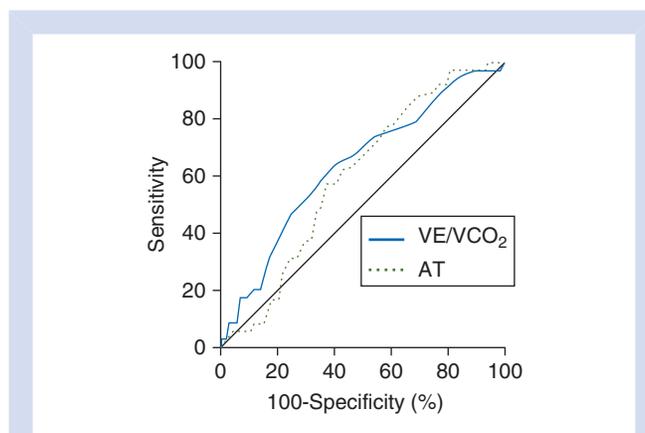

Fig 4 AT <11 and VE/VCO$_2$ >34 as predictors of 90 day mortality. AUC 0.60 [95% CI (0.52–0.68) for AT, 0.64 (0.54–0.73) for VE/VCO$_2$]

greater, mortality was only 4%, thus emphasizing the importance of functional capacity in determining risk, rather than just the presence of clinical disease. Since Older's original publication, there have been major changes in secondary prevention treatment for patients with IHD, in particular the prescribing of statins and β-blockers, for which there is some evidence that perioperative administration may reduce risk of cardiac-related death in certain high-risk groups.[12] [13] Of particular interest, however, is that the predictive benefit of CPET is just as apparent in those patients with no history of IHD, or any other cardiac risk factors. The implication is that clinical history cannot safely be used as a screening measure for selecting patients for CPET, in units where testing facilities may be limited.

A ventilatory equivalent for CO$_2$ (VE/VCO$_2$) of 34 or greater is also associated with an increased risk of hospital mortality.

In a study of patients undergoing aortic aneurysm surgery, the presence of ventilatory inefficiency as indicated by an elevated VE/VCO$_2$ value, in this case 43 or greater, was also predictive of decreased mid-term survival (median 35 months).[7] Our observations would suggest that in the non-vascular surgical population, relatively few patients (12%) have values of VE/VCO$_2$ this high. We decided to observe whether a value for VE/VCO$_2$ of 34 or greater confers additional risk, based on the findings in heart failure patients that combining a reduced AT with ventilatory inefficiency of this degree defines a group at increased risk of early death.[9] Fourteen of the 18 patients in our series who died had both reduced AT and elevated VE/VCO$_2$; therefore, we did not test for independence of these predictive variables, as it would appear that this is a high-risk combination representing severe impairment of functional capacity. Although the relative risk of this combination is the same as that of an AT <11 ml kg^{-1} min^{-1} (6.3 vs 6.5 respectively), the population sizes differ considerably (315 vs 468, respectively).

This has practical implications, as it more closely defines the group most likely to benefit from postoperative high-dependency where resources are limited.

Large-scale retrospective studies in patients undergoing non-cardiac surgery have suggested that a history of heart failure is more likely to lead to an adverse outcome than a history of coronary artery disease.[14] [15] CPET is often used to evaluate severity of disease in patients with a clinical diagnosis of heart failure, and an AT of 11 ml kg^{-1} min^{-1} or less is associated with New York Heart Association criteria classification of 2–3, indicating moderate disease.[16] The prevalence of diagnosed heart failure in our patient group was small at just 3%, yet the results from CPET suggest that the underlying prevalence of heart failure in our elderly surgical population is much higher, with 54% of patients recording an AT of <11 ml kg^{-1} min^{-1}. Although many of these patients with reduced AT do not have symptoms suggestive of cardiac disease, it is likely that preoperative CPET is identifying a group of patients that, while stable at rest and gentle activity, are not able to mount an appropriate cardiac response to severe stress, and hence are more likely to develop postoperative organ dysfunction.

The recently updated ACC/AHA Guidelines for assessing cardiac risk for non-cardiac surgery recognize the importance of accurate assessment of functional capacity in their algorithm.[10] However, the guidelines do not describe the role of CPET, but instead recommend a self-administered questionnaire, the Duke Activity Status Index.[17] Questionnaires are inevitably subjective, and dependent on accurate reporting by the patient. Recent studies have suggested that the Duke Activity Status Index is not a reliable predictor of the results of objectively tested functional capacity.[18] [19] Our data suggest that screening the complete population of elderly patients undergoing high-risk surgery for reduced AT and ventilatory inefficiency is likely to be a more reliable method of detecting the high-risk population than relying on a patient's history or their subjective assessment of exercise capacity.

The principle weakness of this study was the low incidence of the endpoint of all-cause mortality, which is reflected in the wide confidence intervals around the relative risks. Our hospital mortality rate of 2.0% for colorectal surgery places this cohort in a very low mortality category according to recent published data from the USA.[20] For this reason, we did not feel it appropriate to attempt to define new cut-off values for AT or VE/VCO$_2$ as predictors of postoperative mortality using ROC analysis, although this analysis confirms that both reduced AT and ventilatory inefficiency are significant predictors of hospital mortality. A much larger study population would be required to do this with any degree of confidence.

Visser and colleagues[21] have suggested that mortality at 90 days is the more realistic measure after colorectal surgery, with mortality for elective surgery being 1.4% at 30 days, increasing to 4.1% at 90 days in his series. In our series, 30 day mortality was 1.0%, half the in-hospital deaths occurring after this point, and 4.1% at 90 days, the same as in Visser and colleagues' series, and the difference in mortality between groups of patients with impaired functional capacity was maintained out to 90 days. Our data support Visser and colleagues' case for presenting 90 day mortality in studies of postoperative outcomes. AUC values at 90 days using ROC analysis were lower than for hospital mortality, implying other factors (such as disease progression) may have been implicated in some of the post-hospital, pre-90 day deaths.

We chose to measure all-cause mortality, rather than specifically trying to differentiate between cardiac and non-cardiac causes. In the first series of patients studied using CPET, the all-cause mortality was 7.5%, and that attributed to non-surgical causes was 5.9%, a relatively small difference.[5] In practice, making a true differentiation between surgical and non-surgical deaths can be problematic and subjective. Measuring all-cause hospital mortality as the endpoint avoids such controversies.

Further work is required to see if other, simpler, objective tests of functional capacity can provide equally informative but simpler alternatives to CPET. For patients undergoing oesophageal resection, a good result on a shuttle walk test is associated with a good outcome from the surgery itself,[19] but the overall range of data available from these simple tests is invariably limited. CPET has added value over simpler tests, in that it can also provide diagnostic evidence of the presence of IHD and its effect on myocardial wall function; indeed, it is more sensitive and specific than standard treadmill testing for this purpose.[22]

Work is required to evaluate whether the threshold values for AT are influenced by gender; our data show a disproportionate number of females in the low AT group. Work in patients with heart failure shows that the peak oxygen uptake associated with 85% 1 yr transplant-free survival was 11.5 ml kg^{-1} min^{-1} for men compared with 10.0 ml kg^{-1} min^{-1} for women.[23] Perhaps, female surgical patients have a lower AT threshold for being considered at risk.

In conclusion, we found that patients with reduced AT or impaired ventilatory efficiency are more likely to die after major intra-abdominal surgery, whether or not they have associated clinical cardiac risk factors. It would therefore seem inappropriate to select out a subpopulation for CPET on the basis of the presence of clinical risk factors alone, as most patients with reduced AT do not have such indicators.

Conflict of interest

None declared.

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