Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2011, **66**, pages 111–123 doi:10.1111/j.1365-2044.2010.06604.x

REVIEW ARTICLE

Controversies in the physiological basis of the 'anaerobic threshold' and their implications for clinical cardiopulmonary exercise testing

J. G. Hopker,[1] S. A. Jobson[2] and J. J. Pandit[3]

1 Lecturer, 2 Research Fellow, Centre for Sports Studies, University of Kent, Chatham Maritime, Chatham, Kent, UK
3 Consultant Anaesthetist, Nuffield Department of Anaesthetics, Senior Lecturer, Nuffield Department of Clinical Neurosciences and Fellow of St John's College, Oxford, UK

Summary

This article reviews the notion of the 'anaerobic threshold' in the context of cardiopulmonary exercise testing. Primarily, this is a review of the proposed mechanisms underlying the ventilatory and lactate response to incremental exercise, which is important to the clinical interpretation of an exercise test. Since such tests are often conducted for risk stratification before major surgery, a failure to locate or justify the existence of an anaerobic threshold will have some implications for clinical practice. We also consider alternative endpoints within the exercise response that might be better used to indicate a patient's capacity to cope with the metabolic demands encountered both during and following major surgery.

Correspondence to: Dr James Hopker
Email: j.g.hopker@kent.ac.uk
Accepted: 30 November 2010

The anaerobic threshold is a commonly used endpoint in cardiopulmonary exercise testing (CPX, also referred to as CPEX, CPET or CarPET) [1–3]. A recent review concluded that 'peak oxygen consumption and possibly anaerobic threshold are valid predictors of peri-operative morbidity' [4]. Cardiopulmonary exercise testing is purported to provide an objective evaluation of the body's response to 'stress', in the form of exercise-induced increases in oxidative demand. Anaesthetists (and sometimes cardiologists or surgeons) who usually conduct or supervise CPX tests therefore need to be familiar with the normal ventilatory and metabolic responses to exercise that are essential to interpretation. Since (as we shall show below) some of the fundamental physiology remains unclear, it follows that those who conduct the tests should interpret their results quite critically before applying them widely. Although the anaesthetic literature is replete with descriptions of the basic technique of CPX [5], it is sparser in discussion of the underlying physiology. This review is therefore primarily a physiological critique, but with clear bearing on clinical practice.

Cardiopulmonary exercise testing is suggested to provide an indication of the patient's ability to cope with the metabolic demands created by the planned insult of major surgery. Several endpoints in the exercise test have been proposed as important. For example, maximal aerobic capacity ($V_{O_{2max}}$) has been suggested to be useful, with a low $V_{O_{2max}}$ predicting higher peri-operative complication rates [6, 7]. However, $V_{O_{2max}}$ requires the patient to produce a maximal effort to exhaustion, which is difficult or inadvisable in some patients.

An 'anaerobic threshold' occurs at an exercise level below $V_{O_{2max}}$. The very broad idea is that the less 'fit' the patient, the earlier it is that anaerobic metabolism will occur during an exercise test [2, 7–10]. It has been suggested that a specific ventilatory anaerobic threshold (VAT, a concept we discuss further below) can be used to predict peri-operative complication rates (VAT $\leq$ 11 $ml.kg^{-1}.min^{-1}$) [3, 10] across a range of major surgeries [11].

However, using the anaerobic threshold can be problematic and it is debatable both whether there

exists a 'threshold' and also if it is 'anaerobic' [12–19]. Several terminologies (e.g. 'ventilatory threshold', 'ventilatory anaerobic threshold', 'individual anaerobic threshold', 'lactate threshold', 'onset of blood lactate accumulation' and the 'maximal lactate steady state') all appear to be used interchangeably but may in fact have very different meanings. With an absence of methodological standardisation, questions also remain over how best to measure anaerobic threshold. If substantiated, all these concerns cast doubt upon the appropriateness of this measure to guide clinical practice. Nevertheless, despite these uncertainties, the anaerobic threshold continues to be widely used.

In this review, we critically discuss (i) what is conventionally understood by the term 'anaerobic threshold', (ii) whether there is, in fact, a 'threshold' (discernible using either ventilatory or lactate measurement criteria), and (iii) the nature of the ventilatory response to exercise.

What is commonly understood by the term 'anaerobic threshold'?

The answer to this question must be provided in physiological terms. If an individual performs an incremental exercise test where the work rate is progressively increased, O_2 uptake (V_{O_2}) increases in strict proportion to the rising work rate to fuel aerobic muscle contraction (Fig. 1). However, a point is reached where aerobic metabolism alone cannot supply the energy needed for the ever-increasing work rate and then the contribution from anaerobic metabolism becomes significant: lactic acid is released into the circulation as a product of glycolysis. Under these circumstances, V_{O_2} measurement alone will no longer account for all of the energy used by the muscle. Consequently, the anaerobic threshold has been conventionally defined as 'the work rate or oxygen consumption just below that point at which metabolic acidosis and associated changes in gas exchange occur' [20]. Production and excretion of CO_2 (V_{CO_2}), however, do not rise in strict proportion to the rise in work rate (Fig. 1). Up to a certain point, they are linearly related, but beyond a certain work rate (which is said to be the same point at which lactate production becomes significant) there is an 'extra' output of CO_2 (Fig. 1). The generally accepted explanation for this 'excess' CO_2 production, offered by Wasserman, Beaver and colleagues [20–23] (but as we shall see below, disputed by others), is as follows. Bicarbonate (HCO_3^-) is the main buffer for lactate in muscles and the neutralising reaction between the two yields CO_2, which is subsequently excreted by the lungs and is detected as an increased V_{CO_2} at the mouth. This extra CO_2 is therefore (according to these authors) of 'non-metabolic' origin.

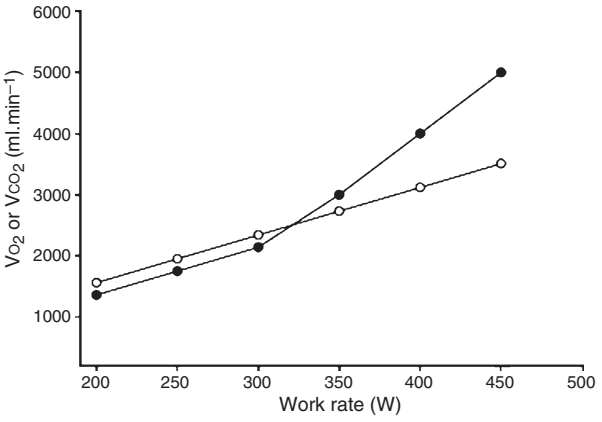

Figure 1 Volume of oxygen consumption (V_{O_2}) and volume of carbon dioxide produced (V_{CO_2}) plotted as a function of work rate for an exercising subject. Note the linear increase in V_{O_2} (○), but a biphasic increase in V_{CO_2} (●).

Changes in ventilatory control are also relevant. At low work rates, minute ventilation (V_E) is strictly proportional to the work rate (and therefore also to V_{O_2} and to V_{CO_2}). Above the point ascribed as the anaerobic threshold, however, V_E exceeds these proportionalities (Fig. 2): there is thus 'extra' ventilation in excess of V_{O_2} but broadly matching V_{CO_2} (Fig. 1). This break-point in the ventilatory response is generally seen at work rates of 47–64% of $V_{O_{2max}}$ in healthy untrained individuals [23]. It is tempting to think that the break-points in V_{CO_2} (Fig. 1) and in V_E (Fig. 2) are causally related, but we will discuss this in more detail later in the article.

In summary, the anaerobic threshold is commonly described by reference either to a blood lactate change (lactate anaerobic threshold, LAT) or to ventilatory gas exchange data, (ventilatory anaerobic threshold, VAT). Intuitively, it is felt that the points of the lactate and anaerobic thresholds should be the same.

Locating the ventilatory anaerobic threshold

The break-points referred above in the ventilatory and gas exchange responses form the basis for approaches to locate the anaerobic threshold point. The methods employed have undergone several refinements over the years. Initially, it was suggested that the point at which

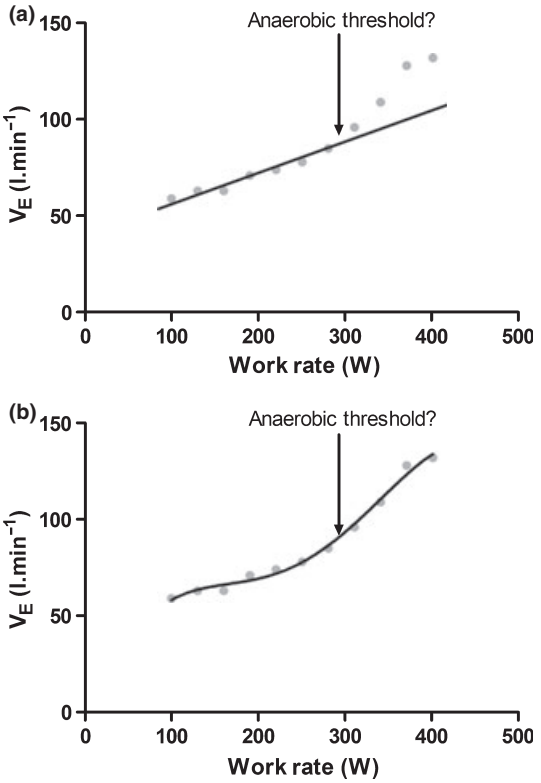

Figure 2 (a) Illustration of the ventilation (V_E) vs work rate relationship during an incremental exercise test (cycle ergometer) in an example subject. The V_E increases as work rate on the ergometer increases by 20 W every minute. Each data point represents 10 s averaged breath-by-breath data. It is possible to plot a bilinear relationship (but the bilinear plot does not fit some data points well). The break point could be said to represent an 'anaerobic threshold'. (b) The same data as 2a, but a non-linear plot now fits all the data much better, where a discrete break-point is not evident.

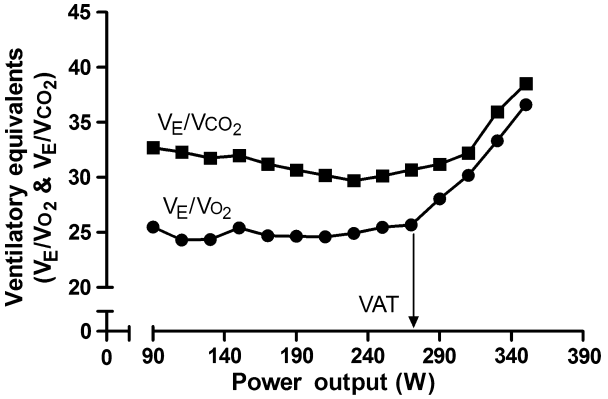

Figure 3 (a) The data in Fig. 2 re-plotted using the ratios of ventilation/volume of oxygen consumed (V_E/V_{O_2}) and ventilation/volume of carbon dioxide production (V_E/V_{CO_2}) vs. power output. These ratios remain relatively constant during the exercise test, until the point at which the V_E/V_{O_2} ratio increases (which can be assigned as the VAT). At this point, the ratio V_E/V_{CO_2} remains relatively constant and rises at a later point in the exercise test. The work rate at the VAT using VE/VO_2 ratio is represented by the arrow; the grey box illustrates the period of 'isocapnic buffering'. RCP, respiratory compensation point.

the slope of the V_E-work rate relationship abruptly increased (Fig. 2a), could be used [20, 24]. However, it became apparent that the plot of V_E against work rate (or time) in an incremental test was not strictly bilinear (which would make it easy to model and identify the 'break-point') but rather curvilinear (where V_E rises smoothly with no single break-point; Fig. 2b).

To overcome this limitation and more directly to take account of the concept of 'excess CO_2 production', Wasserman et al. plotted the ratio V_E/V_{O_2} and the ratio V_E/V_{CO_2} against work rate [23] (Fig. 3). These ratios were termed 'ventilatory equivalents' for O_2 and CO_2, respectively, and they found that a break-point could be identified more clearly using V_E/V_{O_2}.

Above the VAT identified using the break-point in V_E/V_{O_2} ratio is a region where V_E/V_{CO_2} ratio remains relatively constant (Fig. 3) and where, by definition, arterial P_{CO_2} also remains relatively constant. This area of the graph is termed the region of 'isocapnic buffering' [23]: the implication here is that the lactic acid produced is being buffered by HCO_3^- (to generate the 'excess' CO_2). At work rates higher than this, lactic acid production overwhelms blood buffers, the pH of blood declines and this constitutes an extra drive to ventilation. The ratio V_E/V_{CO_2} thus rises. Some authors have argued that this second change (termed the 'respiratory compensation point') should define the anaerobic threshold [14, 25, 26], so it is a matter of debate as to which of these two break-points (i.e. in V_E/V_{O_2} or in V_E/V_{CO_2}) should properly constitute the true 'anaerobic threshold' [25].

Another common method used to determine the anaerobic threshold is the 'V-Slope' method [21]. One way of conceptualising this method is to consider that a straight line is fitted to the plot of V_{CO_2} vs V_{O_2} using data obtained from both the early and later portions of an incremental exercise test. Anaerobic threshold is defined as the point where the slopes of these two lines intersect (Fig. 4). There exist several mathematical approaches to performing the calculations [27]. One potential limitation is of course the number of data points or range used to plot the two respective slopes

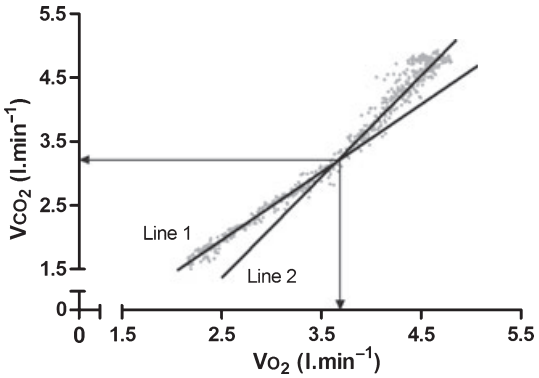

Figure 4 The V-Slope method for determining AT 4. The figure shows the same data set as that in Fig. 3. Here, the volume of carbon dioxide produced (V_{CO_2}) is plotted against the volume of oxygen consumed (V_{O_2}) data from which a regression line for both the lower (line 1) and upper (line 2) parts of the curve is subsequently drawn. The inflection point of the relationship is established from the intersection of the two regression lines. Arrows represent the respective values for V_{O_2} and V_{CO_2} at the putative anaerobic threshold.

(i.e. the gradient of each slope and intersect will depend on the number of data points used in the calculation). Nevertheless, Beaver et al. [21] have suggested that the results are relatively insensitive to this effect.

Despite using all these methods, VAT is not always immediately discernible in practice in all subjects and there appears significant variability between independent reviewers when identifying the VAT in the same data sets across a range of different methods [19, 28]. For example, three different methods of calculating the V-slope resulted in VAT estimates using the same data of 886, 1178 and 1793 ml.kg^{-1}.min^{-1} for one subject and 2027, 3196 and 2900 ml.kg^{-1}.min^{-1} for another (i.e. a range of ~58–102% of the lowest estimate) [27]. When the V-slope method is assessed for repeatability in the same subjects over a 6-week period without any training, it shows coefficients of variation of 12–17% and correlation coefficients of as low as 0.65 (compared with the highly repeatable $V_{O_{2max}}$, μ which shows correlation coefficients of ~0.96) [29].

Poor agreements of this type may occur because some of the assumptions on which these methods of identification of the anaerobic threshold are based may themselves be flawed. Recall that these methods assume the notion of 'excess CO_2' produced as a result of HCO_3^- buffering of lactate. If this were not the case, then the basis of these tests would in turn be undermined. Indeed, it appears that: (i) HCO_3^- is not the main buffer in muscle; (ii) buffering of lactate by HCO_3^- in any case does not produce excess CO_2; and (iii) the disproportionate rise in V_E above the point commonly termed 'anaerobic threshold' is not due to the purported excess V_{CO_2} also occurring above this point; rather the opposite: the excess minute ventilation causes the excess V_{CO_2} (and as we shall see below, something else causes the excess V_E). We will elaborate these points below:

Bicarbonate is not the main buffer in muscle

Beaver et al. [21] estimated that ~92% of lactate is buffered by HCO_3^-, and Wasserman et al. [20] further proposed that the concentrations of HCO_3^- and lactate mirror each other, such that as the magnitude of one rises, that of the other declines in a 1:1 ratio (perhaps aided by an antiport transport system in the muscle fibre membrane [23]). These observations were taken to support the hypothesis of HCO_3^- buffering.

However, detailed work by Hultman and Sahlin [30] estimates the HCO_3^- contribution to buffering to be just ~16%. In muscle, buffers such as protein histidine residues (31%), phosphocreatine (29%), phosphate (8%) and carnosine (4%) are collectively more important. Furthermore, no antiport has been found and lactate movement occurs via monocarboxylate transporters which act as symports not antiports [31].

Buffering of lactate by bicarbonate does not produce 'excess' carbon dioxide

Peronnet and Aguilaniu [32] explained elegantly why, even if lactates were buffered in the main by HCO_3^-, no excess CO_2 would result. The simple reason for this is that HCO_3^- is formed in the first place by dissolution of CO_2 in blood: any subsequent decomposition of HCO_3^- back into CO_2 does not result in any excess CO_2, but rather the same quantity of CO_2 that dissolved in the first place (In other words, the laws of mass balance hold and there is no net creation of extra CO_2 during neutralising reactions by HCO_3^-).

Hyperventilation causes the rise in V_{CO_2}, rather than vice versa

The standard interpretation proposes that the purported excess V_{CO_2} (Fig. 1) itself acts as a stimulus to V_E above the so-called anaerobic threshold (Fig. 2). We discuss below, in more detail, the mechanisms and reflexes involved in the control of breathing during exercise, but one problem with this suggestion is that the body possesses no receptors to detect V_{CO_2} so it is unclear how an increase in V_E would be brought

about. Secondly, it is well established that simple voluntary hyperventilation can increase V_{CO_2} measured at the mouth transiently (e.g. for 2–3 min). Because incremental exercise is a series of short-lived, step-increases in work rate, such a transient effect could recur over the whole course of the exercise test. Thus, it seems that the 'excess V_{CO_2}' may simply be a consequence of the increased minute ventilation (itself brought about by other factors) rather than by any excess production due to buffering. And if that is the case, then it follows that any measurement methods (such as V_E/V_{CO_2} or V-slope) based upon the assumption that CO_2 production increases due to buffering, may in turn be prone to error.

Locating the lactate anaerobic threshold

Given the problems inherent in the techniques of identifying a VAT, measuring blood lactate itself might enable more robust identification. However, identifying a 'LAT' leads to its own problems.

Numerous studies have supported the very plausible link between muscle hypoxia and lactate production [33]. Blood lactate increases more when cardiac output is impaired [34, 35] and also when hypoxic gas mixtures are inspired during exercise. Conversely, breathing hyperoxic mixtures attenuates the exercise-induced increase in blood lactate [36, 37]. However, these lines of evidence do not confirm the occurrence of tissue hypoxia as a key trigger for lactate production. There are contrary observations, to which we now turn.

First, it is the accumulation of blood lactate (suggesting the rate of lactate production has exceeded its removal from muscle and/or blood), not simply the production of any lactate, that should be considered to represent the body's response above the anaerobic threshold. Lactate production has been shown to occur within a single muscle even at rest [38–40] and under fully aerobic conditions at low exercise levels [14, 41, 42], although lactate does not start to accumulate at this point. The term 'anaerobic' is therefore arguably a misnomer, as muscle hypoxia is not required for lactate production to occur [41, 42]. Rather, it might be that the capacity for lactate removal exceeds the rate of lactate production by the muscle [41]. These processes of production and removal are continuous and the balance of these determines whether lactate accumulates [41]. As lactate production increases with, for example, incremental exercise, so too does lactate sequestration. Since these two processes occur gradually and at different times in each muscle fibre or muscle unit, the aggregate effect on blood lactate levels is unlikely to be discrete but a smooth change over time as exercise intensity increases (Fig. 5; i.e. not all tissue units reach their maximum limit for lactate sequestration at exactly the same time) [16, 18, 19, 28, 42].

Another problem is that factors unrelated to exercise also control lactate production. For example, adrenaline (which can be released during normal exercise) has itself been shown to cause an increase in blood lactate concentration [26, 42, 43], whereas β-blockade reduces blood lactate accumulation [44]. Similarly, recruitment of type-II muscle fibres with increasing work rate causes an increase in blood lactate production regardless of ambient P_{O_2} [45].

In summary, anaerobic metabolism does occur with heavy exercise and lactate does accumulate as a consequence, but a clear time-point at which this occurs is not easily discernible.

The tight link between ventilation and metabolism: key role for carotid bodies in the shape of the V_E response

Central to understanding the exercise test – and therefore to understanding the anaerobic threshold concept – is the nature of the ventilatory response. Yet this is an aspect sparsely discussed in the anaesthetic literature. The physiological basis of this response is one of the oldest (and yet incompletely resolved) questions in physiology. The properties of the individual elements of the respiratory control system in isolation (e.g. the peripheral and central chemoreceptors, various chemo- and mechano-receptors in

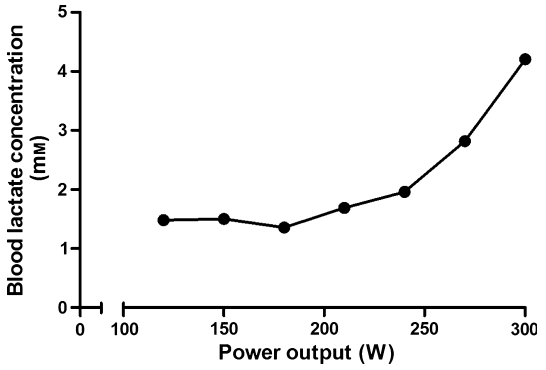

Figure 5 The smooth relationship between blood lactate production and exercise intensity in an experimental subject. Like the ventilatory response with incremental exercise (see Fig. 2b), there is no clear threshold point.

muscles and joints, the efferent control system of the intercostal muscles and diaphragm, the central neuronal structures in the brainstem) are well-described. However, what is less clear is how these elements work together to regulate ventilation so precisely to the work rate, such that arterial blood gas levels and pH are kept constant at low-to-moderate work rates.

Since arterial P_{O_2}, P_{CO_2} and pH are unchanged from their resting levels, it was assumed that the peripheral chemoreceptors (i.e. carotid bodies in humans) were not active during such low-to-moderate levels of exercise, but in fact they are more active than at rest. This is evidenced by administering hypoxic gases to individuals whose V_E can be observed to rise by a greater magnitude during exercise than at rest [46].

Carotid body stimuli during exercise

Physiologists realised that if the factor raising the activity of the carotid bodies was a chemical released into the bloodstream in proportion to the work performed, it would constitute an ideal mechanism to link ventilation to metabolism. Asmussen and Nielsen called this (yet unknown) substance 'Factor X' [47]. Substances such as catecholamines [48] or adenosine [49] have been proposed as candidates, and Paterson et al. [50] persuasively argued that arterial plasma K^+ (whose levels reach ~8 mM in heavy exercise) fulfilled many of the criteria required of a Factor X. The observation that arterial blood gas levels may oscillate rapidly around a (constant) mean value led to the notion that such oscillations (their amplitude or frequency) may relate to the level of work done and form a drive to breathe [51].

However, a key result against such a blood-borne drive to ventilation is the finding that when metabolites from the working muscles are prevented from entering the bloodstream (e.g. by the use of tourniquets) [52], V_E still matches the increase in metabolism. Therefore, 'neural drives' such as the activity of proprioceptors in joints or muscle spindles may be more important in maintaining the tight link between ventilation and metabolism.

Doubts about the 'neural' drive to breathing in exercise; the concept of redundancy of the system

However, in paraplegic subjects (in whom the connection between muscles made to work by direct electrical stimulation and the central nervous system is disrupted), not only is the link between ventilation and metabolism maintained, but the activity of the carotid bodies is also increased, just as it is in exercise in 'able-bodied' subjects [53–55]. If neither blood-borne signals to breathe, nor those carried via afferent nerves are essential to the ventilatory response, then what is left?

One suggestion is that the respiratory control system demonstrates considerable 'redundancy' [56]. Because the homeostasis of blood gases and pH is so important, and because exercise is such a common and necessary state for the organism, the body has evolved several ways of ensuring the tight link between ventilation and metabolism, such that loss of any one mechanism through disease or injury means that other mechanisms 'fill in' or compensate instantaneously to yield a near-normal response.

The nature of the ventilatory response at high intensity exercise

If determining the physiology underlying the ventilatory response to exercise at low-to-moderate levels was problematic, the nature of the response at the higher levels of exercise appeared (for a time at least) clearer. Wasserman et al. [57] demonstrated that individuals after carotid body resection (an old treatment for the breathlessness of asthma) lost the biphasic or curvilinear ventilatory response to incremental exercise. The relationship between V_E and work rate in these patients became essentially linear (Fig. 6). They argued that as these patients did not have peripheral arterial chemoreceptors, they were unable to detect changes in pH caused by accumulation of lactic acid and, therefore, they lost the extra drive to ventilation that normally accompanied heavy exercise. These subjects had 'lost' their VAT but had retained a LAT. Wasserman et al. concluded that intact carotid bodies were responsible for the break-point (or curvilinearity) in the ventilatory response. Since a break-point is central to the idea of the 'anaerobic threshold', it followed that the carotid bodies were key to this concept.

However, the details of this simple explanation were questioned by Hagberg et al. [58] and Paterson et al. [59], who observed that patients with myophosphorylase deficiency (McArdle's disease) exhibit a biphasic (curvilinear) ventilatory response to incremental exercise even though they cannot produce lactate. Paterson et al. [59], noted that the rise in plasma K^+ during the exercise test paralleled the ventilatory response and that both K^+ and V_E patterns were similarly curvilinear. Thus, although the carotid bodies were likely to be

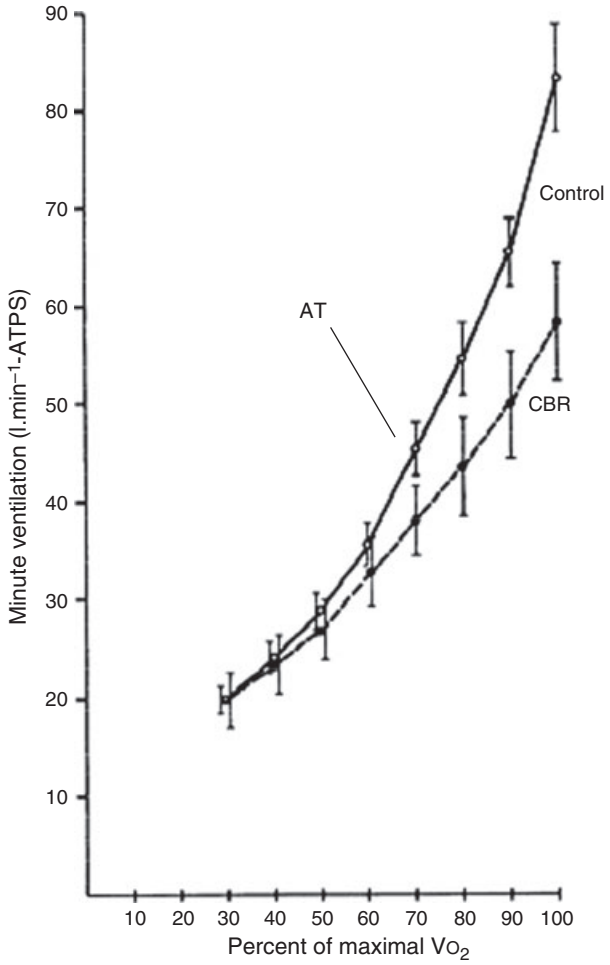

Figure 6 In normal subjects (solid line) incremental exercise yields a 'bilinear' relationship in which an anaerobic threshold (AT) may be identified. With carotid body resection (CBR; dotted lines), no such break-point is discernible and the relationship between ventilation (V_E) and volume of oxygen consumption (V_{O_2}) is more linear. Error bars are ± SEM (copied from Wasserman et al. [57] *Journal of Applied Physiology*, 1975, *Am Physiol Soc*, used with permission).

responsible for the unique shape of the ventilatory response, it was arguably K+, rather than lactate, that acted as the relevant stimulus. In contrast to patients with carotid body resection, McArdle's patients had 'lost' their LAT, yet retained a VAT. Clearly, lactate is not necessary to generate a biphasic or curvilinear ventilatory response, but are even the carotid bodies (regardless of the stimulus acting upon them) needed?

Wasserman et al. [57] had 'silenced' the carotid bodies by surgical removal to convert a biphasic or curvilinear ventilatory response into a linear one. However, silencing them by other means (breathing high O_2 mixtures or infusion of dopamine in healthy subjects) did not have the same effect [60–62]. This suggests that these organs are not essential for the shape of the ventilatory response. The system is again displaying its characteristic of 'redundancy' in generating a normal response even when individual components are removed or silenced.

Furthermore, if lactate accumulation underlies the anaerobic threshold, and in turn underlies the ventilatory response, then we might expect the time-point of the LAT to correspond to that of the VAT. Yet Hambrecht et al. [63] discovered a discrepancy in oxygen uptake at the LAT vs VAT. Dickhuth et al. [64] found the VAT to occur at a higher exercise intensity than the LAT. Chicharro et al. [65] showed significant differences between LAT and VAT when plotted against either heart rate, work rate or V_{O_2}, during incremental cycling exercise. Overall, studies find that the correlation coefficient between VAT and LAT can be as low as 0.53 [18]. This dissociation of LAT and VAT suggests that the two events are independent and therefore governed by different underlying physiological processes [17].

Critique of the anaerobic threshold notion: a summary

Table 1 summarises the main tenets of the conventional views of the anaerobic threshold and also the main counter-arguments to these.

Implications of the physiology for clinical exercise testing

Cardiopulmonary exercise testing machines generate a value for the 'anaerobic threshold' (usually using one of the gas exchange methods described above) and the notion is integral to almost all training programmes and courses. Indeed, several clinical studies have found that using an anaerobic threshold serves as a useful predictor of patient outcome, with a cut-off of precisely 11 $ml.kg^{-1}.min^{-1}$ suggested [3, 10]. Carlisle et al. [66] measured the VAT of 130 patients before abdominal aortic aneurysm repair. Multivariate analysis demonstrated that their VAT correlated significantly with postoperative survival. Significant correlations between VAT and postoperative survival rate have also been shown by Older et al. [10], who investigated 187 elderly patients undergoing major abdominal surgery. In patients with a VAT of < 11 $ml.kg^{-1}.min^{-1}$ ($n = 55$), 10 died of cardiovascular causes (18%),

Table 1 Summary of the central tenets of the 'anaerobic threshold hypothesis' (first column) and the main criticisms or counter-arguments to these tenets (second column).

Central tenets of 'anaerobic threshold hypothesis' during incremental exercise	Criticisms and counter-arguments
V_E response exhibits a break-point (i.e. it is bilinear with respect to measures of work rate)	V_E response is curvilinear, such that no single break-point can be identified
Break-point in V_E response is due to lactate	Curvilinear V_E response retained even in absence of lactate generation (eg, McArdle's disease): arterial plasma K^+ may be more important in generating the shape of the V_E response
Break-point in V_E response is due to intact, functioning carotid bodies (so is lost when they are surgically removed)	Curvilinear V_E response retained even when carotid bodies silenced (eg, using hyperoxia or dopamine infusion)
'Excess' V_{CO_2} is due to buffering of lactate by HCO_3^-	Buffering of lactate by HCO_3^- is limited (other muscle buffers more important) Even if it occurs, it does not release any 'excess' CO_2; rather only the same CO_2 as created HCO_3^- in the first place
'Excess' V_{CO_2} causes the disproportionate rise in V_E relative to work rate at high work rates	There are no receptors for detecting V_{CO_2} It is the disproportionate rise in V_E relative to work rate at high work rates that causes the apparent 'excess' V_{CO_2} Other mechanisms cause the disproportionate rise in V_E relative to work rate at high work rates (e.g. rise on arterial plasma K^+)
The anaerobic threshold is reliably identified by various techniques including break-points in profiles of V_E, lactate, V_{O_2}, V_{CO_2}, ventilatory equivalents, isocapnic buffering, etc	The various techniques yield very different values for purported anaerobic threshold, with poor repeatability and inter-observer or inter-algorithm agreement There is often a choice of several purported break-points, such as the 'ventilatory anaerobic threshold' vs the 'respiratory compensation point' vs the lactate anaerobic threshold, and so on
Lactate response exhibits a break-point (i.e. is bilinear with respect to measures of work rate)	Lactate is produced even during aerobic conditions at rest The lactate response is curvilinear, such that no single break-point can be identified
Anaerobic threshold measured using ventilatory or gas exchange criteria matches that using lactate measurements	Ventilatory or gas exchange profiles do not match the lactate profile
Adverse clinical outcomes correlate with a specific (low) value of anaerobic threshold	Associations of adverse clinical outcomes with a specific (low) value of anaerobic threshold are spurious, and not all trials confirm the association There are other, more appropriate measures within the exercise response that may have stronger associations, and that need further research

V_E, minute ventilation; V_{O_2}, oxygen consumption; V_{CO_2}, carbon dioxide production.

whereas in patients with a VAT of > 11 $ml.kg^{-1}.min^{-1}$ (n = 132), only one died of cardiovascular causes (0.8%), $p < 0.001$.

How can this be so, given the real physiological uncertainties around the concept of an 'anaerobic threshold'? One possibility is that these 'positive' findings arise by chance in relatively small studies. Not all trials confirm the positive correlations. For example, Nagamatsu et al. [67] investigated 91 patients before radical oesophagectomy and found no relationship between the VAT and postoperative complication rate. Similarly, Forshaw et al. [68] found no significant difference between the VAT of the patients (n = 78) who did and did not suffer complications following oesophagectomy ($p = 0.07$). A second possibility is that the interventions of anaesthetists during surgery may in some way differ between those with higher vs lower anaerobic thresholds, making more likely a significant relationship between pre-operative testing and postoperative outcomes. A third possibility is that there are two distinct patient populations. In one subgroup (e.g. those suffering cardiac dysfunction [69]) there is a pre-existing abnormality of the macrocirculation that can be worsened by major surgery, leading

to tissue hypoxia. The onset of anaerobic metabolism during exercise might reflect these macrocirculatory limitations rather well. However, in the other subgroup, the macrocirculation is normal but major surgery elicits an inflammatory response predominantly affecting the microcirculation and cellular function, leading to tissue hypoxia by different mechanisms. Exercise testing might reflect this situation less well. If the proportions of patients in these categories vary between the different trials, this may explain why some trials show positive results and some do not. A final possibility relates to the nature of the measurement being performed. The method embedded in CPX identifies a break-point in the ventilatory or gas exchange response. Although somewhat arbitrary, the methods do very crudely identify a time-point somewhere near to when the non-linearity in respiratory responses becomes pronounced. Whether or not this is because of anaerobic metabolism is irrelevant, but what is important is that the non-linearity becomes pronounced at a somewhat earlier time-point in those who are 'unfit' vs those who are 'fit'. Thus, it is feasible that applying the concept of the anaerobic threshold sometimes (or even often) 'works', albeit for the 'wrong' reasons. Approaches can be crude yet still work in practice (e.g. pH vs the more sophisticated Stewart analysis of acid–base disorders) [70].

Alternative endpoints within the exercise test

Although it is possible to continue to use the anaerobic threshold point as an empirical measure, without taking account of any of the physiological controversies outlined above, it would be more progressive to identify a more appropriate end-point, perhaps more clearly reflecting the two possible patient subgroups alluded to above. We suggest two: metabolic efficiency and the oxygen pulse.

An efficient use of oxygen during the process of aerobic energy production might be an important factor for survival [71, 72]. If a patient was, in a general sense, 'metabolically efficient', the reduced availability of oxygen both during and after surgery would have a lower impact than it would in a patient who was less efficient. Thus, rather than trying to identify a discrete point that may signify the limit of a patient's aerobic metabolism (i.e. $\dot{V}O_{2max}$ or VAT or LAT) it might be more pertinent to assess how well a patient is able to cope with prolonged tissue hypoxia. A simple exercise efficiency test [73] performed as part of pre-operative screening could be used, in which 'gross efficiency' is defined as the ratio of work accomplished (or power output on the cycle ergometer) divided by energy expended. This last entity can be estimated from calculating the energy expenditure for a given $\dot{V}O_2$, related to the known respiratory quotient from gas exchange data. For a reliable measurement of gross efficiency, gas measurement should occur under steady state conditions for at least 4 min [74], which is perhaps clinically preferable to the exhaustive exercise of an incremental test. A high pedal cadence can erroneously suggest low efficiency [75–78], so a standardised cadence must be used when conducting repeated measurements of efficiency in the same individual. Future studies should seek to test the hypothesis that such metabolic efficiency might provide a more powerful predictor of post-surgical outcome than those endpoints currently used for this purpose.

Evaluation of the 'oxygen pulse' might also provide valuable information during CPX testing. Oxygen pulse is the volume of O_2 taken up by the pulmonary blood during the period of a heartbeat [79], often using data from an incremental exercise test. It is derived from a re-arrangement of the Fick equation:

$$CO = SV \times HR = \dot{V}O_2/(CaO_2 - CvO_2)$$

$$O_2\text{pulse} = (\dot{V}O_2/HR) = SV \times (CaO_2 - CvO_2)$$

Thus a reduced O_2 pulse with exercise implies a reduced stroke volume response (e.g. cardiac dysfunction) or a reduced ability to extract O_2 from the blood (as in microcirculatory dysfunction) [79]. Oxygen pulse displays a characteristic bilinear pattern; initially a linear rise with exercise intensity, which later flattens. In disease, both the slope of the initial rise and the point and degree of flattening are more pronounced (Fig. 7).

The submaximal O_2 pulse has been shown to effectively risk stratify heart disease patients [80] and so may negate the need for maximal testing associated with the determination of $\dot{V}O_{2max}$.

Finally, relatively little work has been undertaken on the recovery period after exercise, which may better reflect processes that occur with recovery after major surgery than does an incremental exercise test (which creates a transition into exercise). In cardiology, it has been recognised that recovery of heart rate after exercise is an independent predictor of survival [81], and respiratory measurements made in the post-exercise period are insightful of control mechanisms

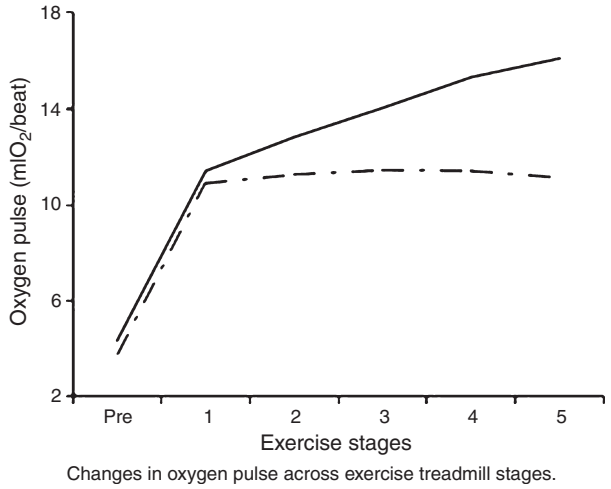

Figure 7 The relationship between O_2 pulse and increasing exercise intensity. Pattern A (—) illustrates a normal trace; Pattern B (-·-·) shows the response in a patient with cardiac disease. Reproduced from Lim et al. [79] with permission.

in physiology [82]. However, it remains to be explored whether gas exchange kinetics in this phase might predict postoperative outcomes [83].

Conclusion

The concept of the anaerobic threshold is more indeterminate and the methods of locating it are more complex than they may superficially at first appear. Rather than try to refine further the methods of locating exactly a putative 'anaerobic threshold', we suggest that the important research question is to establish which of the alternative endpoints (that have a more robust physiological basis) best predicts clinical outcomes. This question may be answerable, in part, by re-analysis of some existing data. In future, the best approach to assessing how well a patient might cope with the insult of major surgery is likely to be a (short) battery of fitness assessments as part of a pre-operative screening, perhaps including exposure to modest hypoxia. This last approach will require more sophisticated clinical exercise laboratories than are generally available, to deliver and monitor hypoxic gas mixtures. Clinical decisions may thereby become less reliant on the concept of an elusive entity.

Competing interests

JJP is an Editor of *Anaesthesia* and this manuscript has undergone an additional external review as a result. No external funding and no competing interests declared.

References

1 Gitt AK, Wasserman K, Kilkowski C, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation* 2002; **106**: 3079–84.
2 Nugent AM, Riley M, Megarry J, O'Reilly MJ, MacMahon J, Lowry R. Cardiopulmonary exercise testing in the preoperative assessment of patients for repair of abdominal aortic aneurysm. *Irish Journal of Medical Science* 1998; **167**: 238–41.
3 Older P, Hall A, Hader R. Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. *Chest* 1999; **116**: 355–62.
4 Smith TB, Stonell C, Purkayastha S, Paraskevas P. Cardiopulmonary exercise testing as a risk assessment method in non cardio-pulmonary surgery: a systematic review. *Anaesthesia* 2009; **64**: 883–93.
5 Ridgway ZA, Howell SJ. Cardiopulmonary exercise testing: a review of methods and applications in surgical patients. *European Journal of Anaesthesiology* 2010; **10**: 858–65.
6 Beckles MA, Spiro SG, Colice GL, Rudd RM. The physiologic evaluation of patients with lung cancer being considered for resectional surgery. *Chest* 2003; **123**: 105–14.
7 Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991; **83**: 778–86.
8 Epstein SK, Freeman RB, Khayat A, Unterborn JN, Pratt DS, Kaplan MM. Aerobic capacity is associated with 100-day outcome after hepatic transplantation. *Liver Transplantation* 2004; **10**: 418–24.
9 Nagamatsu Y, Yamana H, Fujita H, et al. The simultaneous evaluation of preoperative cardiopulmonary functions of oesophageal cancer patients in the analysis of expired gas with exercise testing. *Nippon Kyobu Geka Gakkai Zasshi* 1994; **42**: 2037–40.
10 Older P, Smith R, Courtney P, Hone R. Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. *Chest* 1993; **104**: 701–4.
11 Kothmann E, Danjoux G, Owen SJ, Parry A, Turley AJ, Batterham AM. Reliability of the anaerobic threshold in cardiopulmonary exercise testing of patients with abdominal aortic Aneurysms. *Anaesthesia* 2009; **64**: 9–13.
12 Brooks GA. Anaerobic threshold: review of the concept and direction for future research. *Medicine and Science in Sports and Exercise* 1985; **17**: 22–31.
13 Brooks GA. Response to Davis' manuscript. *Medicine and Science in Sports and Exercise* 1985; **17**: 19–21.

14 Davis JA. Anaerobic threshold: review of the concept and directions for future research. *Medicine and Science in Sports and Exercise* 1985; **17**: 6–18.
15 Davis JA. Response to Brooks' manuscript. *Medicine and Science in Sports and Exercise* 1985; **17**: 32–4.
16 Myers J, Ashley E. Dangerous curves: a perspective on exercise, lactate and the anaerobic threshold. *Chest* 1997; **111**: 787–95.
17 Walsh ML, Banister EW. Possible mechanisms of the anaerobic threshold. *Sports Medicine* 1988; **5**: 269–302.
18 Gladden LB, Yates JW, Stremel RW, Stamford BA. Gas exchange and lactate anaerobic thresholds: inter- and intra-evaluator agreement. *Journal of Applied Physiology* 1985; **58**: 2082–9.
19 Yeh MP, Gardner RM, Adams TD, Yanowitz FG, Crapo RO. 'Anaerobic threshold': problems of determination and validation. *Journal of Applied Physiology* 1983; **55**: 1178–86.
20 Wasserman K, Whipp BJ, Koyal SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. *Journal of Applied Physiology* 1973; **35**: 236–43.
21 Beaver WL, Wasserman KW, Whipp BJ. A new method for detecting an anaerobic threshold by gas exchange. *Journal of Applied Physiology* 1986; **60**: 2020–7.
22 Wasserman K, McIlroy MB. Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. *American Journal of Cardiology* 1964; **14**: 844–52.
23 Wasserman K. Determinants and detection of anaerobic threshold and consequences of exercise above it. *Circulation* 1987; **76**(Suppl. VI): V1–29.
24 Hughson RL, Weisiger KH, Swanson GD. Blood lactate concentration increases as a continuous function in progressive exercise. *Journal of Applied Physiology* 1987; **62**: 1975–81.
25 Chicharro JL, Hoyos J, Lucia A. Effects of endurance training on the isocapnic buffering and hypocapnic hyperventilation phases in professional cyclists. *British Journal of Sports Medicine* 2000; **34**: 450–5.
26 Simon J, Young JL, Blood DK, Segal KR, Case RB, Gutin B. Plasma lactate and ventilatory thresholds in trained and untrained cyclists. *Journal of Applied Physiology* 1986; **60**: 777–81.
27 Magalung UL, Grant JB. Determination of gas exchange threshold by nonparametric regression. *American Journal of Respiratory and Critical Care Medicine* 1995; **151**: 98–106.
28 Powers SK, Dodd S, Garner R. Precision of ventilatory and gas exchange alterations as a predictor of the anaerobic threshold. *European Journal of Applied Physiology* 1984; **52**: 173–7.
29 Wisen AGM, Wohlfart B. A refined technique for determining the respiratory gas exchange responses to anaerobic metabolism during progressive exercise – repeatability in a group of healthy men. *Clinical Physiology and Functional Imaging* 2004; **24**: 1–9.
30 Hultman E, Sahlin K. Acid-base balance during exercise. *Exercise and Sports Science Reviews* 1980; **8**: 41–128.
31 Thomas C, Perrey S, Lambert K, Hugon G, Mornet D, Mercier J. Monocarboxylate transporters, blood lactate removal after supramaximal exercise, and fatigue indexes in humans. *Journal of Applied Physiology* 2005; **98**: 804–9.
32 Peronnet F, Aguilaniu B. Lactic acid buffering, non-metabolic CO_2 and exercise hyperventilation: a critical reappraisal. *Respiratory Physiology and Neurobiology* 2006; **25**: 4–18.
33 Hill AV, Lupton H. Muscular exercise and the supply and utilization of oxygen. *Quarterly Journal of Medicine* 1923; **16**: 135–71.
34 Myers J, Froelicher VF. Hemodynamic determinants of exercise capacity in chronic heart failure. *Annals of Internal Medicine* 1991; **115**: 377–86.
35 Linnarson D, Karlsson J, Fagraeus N, Saltin B. Muscle metabolites and oxygen deficit with exercise in hypoxia and hyperoxia. *Journal of Applied Physiology* 1974; **36**: 399–402.
36 Hughes RL, Clode M, Edwards RHT, Goodwin TJ, Jones NL. Effect of inspired O_2 on cardiopulmonary and metabolic exercise responses in man. *Journal of Applied Physiology* 1968; **24**: 336–47.
37 Brooks GA. Current concepts in lactate exchange. *Medicine and Science in Sports and Exercise* 1991; **23**: 895–906.
38 Gladden LB. Muscle as a consumer of lactate. *Medicine and Science in Sports and Exercise* 2000; **32**: 764–71.
39 Stainsby WN, Sumners C, Andrew GM. Plasma catecholamines and their effect on blood lactate and muscle lactate output. *Journal of Applied Physiology* 1984; **57**: 321–5.
40 Stainsby WN, Brechue WF, O'Drobinak DM. Regulation of muscle lactate production. *Medicine and Science in Sports and Exercise* 1991; **23**: 907–11.
41 Connett RJ, Gayeski TEJ, Honig GR. Lactate accumulation in fully aerobic, working dog gracilis muscle. *American Journal of Physiology* 1984; **246**: hl20–8.
42 Dennis SC, Noakes TD, Bosch AN. Ventilation and blood lactate increase exponentially during incremental exercise. *Journal of Sports Sciences* 1992; **10**: 437–49.
43 Stainsby WN, Sumners C, Eitzman PD. Effects of catecholamines on lactic acid output during progressive working contractions. *Journal of Applied Physiology* 1985; **59**: 1809–14.
44 Issekutz B. Effect of beta-adrenergic blockade on lactate turnover in exercising dogs. *Journal of Applied Physiology* 1984; **56**: 1754–9.
45 Spurway NC. Aerobic exercise, anaerobic exercise and the lactate threshold. *British Medical Bulletin* 1992; **48**: 569–91.
46 Pandit JJ, Robbins PA. The ventilatory effects of sustained isocapnic hypoxia during exercise in humans. *Respiration Physiology* 1991; **86**: 393–404.

47 Asmussen E, Nielsen M. Studies on the regulation of respiration in heavy work. *Acta Physiologica Scandinavica* 1946; **12**: 171–88.
48 Bracken RM, Linnane DM, Brooks S. Alkalosis and the plasma catecholamine response to high-intensity exercise in man. *Medicine and Science in Sports and Exercise* 2005; **37**: 227–33.
49 Watt AH, Reid PF, Stephens MR, Routledge PA. Adenosine-induced respiratory stimulation in man depends on site of infusion. Evidence for an action on the carotid body? *British Journal of Clinical Pharmacology* 1987; **23**: 486–90.
50 Paterson DJ, Robbins PA, Conway J. Changes in arterial plasma potassium and ventilation during exercise in man. *Respiration Physiology* 1989; **78**: 323–30.
51 Linton RAF, Miller R, Cameron IR. Role of P_{CO2} oscillations and chemoreceptors in ventilatory response to inhaled and infused CO_2. *Respiration Physiology* 1997; **29**: 201–10.
52 Leonard B, Mitchell JH, Mizuno M, Rube N, Saltin B, Secher NH. Partial blockade and cardiovascular responses to static exercise in man. *Journal of Physiology* 1985; **359**: 365–79.
53 Adams L, Garlick J, Guz A, Murphy K, Semple SJG. Is the voluntary control of exercise in man necessary for the ventilatory response. *Journal of Physiology* 1984; **355**: 71–83.
54 Pandit JJ, Bergstrom E, Frankel HL, Robbins PA. Increased hypoxic sensitivity during exercise in man: are neural afferents necessary? *Journal of Physiology* 1994; **477**: 169–75.
55 Pandit JJ, Robbins PA. Acute ventilatory responses to hypoxia during voluntary and electrically-induced leg exercise in man. *Journal of Physiology* 1994; **477**: 161–8.
56 Cunningham DJC, Robbins PA, Wolff CB Integration of respiratory responses to changes in alveolar partial pressures of CO_2 and O_2 and in arterial pH. In: Cherniack NS, Widdicombe BJG, eds. *Handbook of Physiology, Sect. 3. The Respiratory System.* Bethesda, MD: American Physiological Society, 1986: 475–528.
57 Wasserman K, Whipp BJ, Koyal SN, Cleary MG. Effect of carotid body resection on ventilatory and acid-base control during exercise. *Journal of Applied Physiology* 1975; **39**: 354–8.
58 Hagberg JM, Coyle EF, Carroll JE, Miller JM, Martin WH, Brooke MH. Exercise hyperventilation in patients with McArdle's disease. *Journal of Applied Physiology* 1982; **52**: 991–4.
59 Paterson DJ, Friedland JS, Bascom DA, et al. Changes in arterial K+ and ventilation during exercise in normal subjects and subjects with McArdle's syndrome. *Journal of Physiology* 1990; **429**: 339–48.
60 Henson LC, Ward DS, Whipp BJ. Effect of dopamine on ventilatory response to incremental exercise in man. *Respiration Physiology* 1992; **89**: 209–24.
61 Hogan MC, Cox RH, Welch HG. Lactate accumulation during incremental exercise with varied inspired oxygen fraction. *Journal of Physiology* 1983; **55**: 1134–40.
62 Pandit JJ, Robbins PA. Respiratory effects of breathing high oxygen during incremental exercise. *Advances in Experimental Medicine and Biology* 2002; **499**: 331–6.
63 Hambrecht R, Niebauer J, Fiehn E, et al. Effect of an acute beta-adrenergic blockade on the relationship between ventilatory and plasma lactate threshold. *International Journal of Sports Medicine* 1995; **16**: 219–24.
64 Dickhuth HH, Yin L, Niess A, et al. Ventilatory, lactate-derived and catecholamine thresholds during incremental treadmill running: relationship and reproducibility. *International Journal of Sports Medicine* 1999; **20**: 122–7.
65 Chicharro JL, Perez M, Vaquero AF, Lucia A, Legido JC. Lactic threshold versus ventilatory threshold during ramp test on a cycle ergometer. *Journal of Sports Medicine and Physical Fitness* 1997; **37**: 117–21.
66 Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *British Journal of Surgery* 2007; **94**: 966–9.
67 Nagamatsu Y, Shima I, Yamana H, Fujita H, Shirouzu K, Ishitake T. Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with squamous cell carcinoma of the thoracic esophagus. *Journal of Thoracic and Cardiovascular Surgery* 2001; **121**: 1064–8.
68 Forshaw MJ, Strauss DC, Davis AR, et al. Is cardiopulmonary exercise testing a useful test before esophagectomy? *Annals of Thoracic Surgery* 2008; **85**: 294–9.
69 Groban L, Kitzman D. Diastolic function: a barometer of cardiovascular risk? *Anaesthesiology* 2010; **112**: 1303–6.
70 Sirker AA, Rhodes A, Grounds RM, Bennett ED. Acid-base physiology: the 'traditional' and the 'modern' approaches. *Anaesthesia* 2002; **57**: 348–56.
71 Van Esbroeck C, Eve T, Hubons A. Evaluation of tissue oximetry in peri-operative monitoring of colorectal surgery. *British Journal of Surgery* 1992; **79**: 584–7.
72 Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet* 2002; **360**: 219–23.
73 Hopker J, Passfield L, Coleman D, Jobson S, Edwards L, Carter H. The effects of training on gross efficiency in cycling: a review. *International Journal of Sports Medicine* 2009; **30**: 845–50.
74 Chuang ML, Ting H, Otsuka T, et al. Aerobically generated CO_2 stored during early exercise. *Journal of Applied Physiology* 1999; **87**: 1048–58.
75 Chavarren J, Calbet JAL. Cycling efficiency and pedalling frequency in road cyclists. *European Journal of Applied Physiology* 1999; **80**: 555–63.

76 Hagberg J, Mullin J, Giese M, Spitznagel E. Effect of pedalling rate on submaximal exercise responses of competitive cyclists. *Journal of Applied Physiology* 1981; **51**: 447–51.
77 Marsh AP, Martin PE. The association between cycling experience and preferred and most economical cadences. *Medicine and Science in Sports and Exercise* 1993; **25**: 1269–74.
78 Ettema G, Loras HW. Efficiency in cycling: a review. *European Journal of Applied Physiology* 2009; **106**: 1–14.
79 Lim JG, McAveney TJ, Fleg JL, et al. Oxygen pulse during exercise is related to resting systolic and diastolic left ventricular function in older persons with mild hypertension. *American Heart Journal* 2005; **150**: 941–6.
80 Vijay NK, MacCarter D, Washam M, Jantz R, Gilmet K. Submaximal oxygen pulse as a new risk stratifier. *Journal of Cardiac Failure* 2006; **12**: S15.
81 Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *New England Journal of Medicine* 1999; **341**: 1351–7.
82 Clement ID, Pandit JJ, Bascom DA, Robbins PA. Ventilatory chemoreflexes at rest following a brief period of heavy exercise in man. *Journal of Physiology* 1996; **495**: 875–84.
83 Pandit JJ, Robbins PA. The effect of exercise on the development of respiratory depression during sustained isocapnic hypoxia in humans. *Respiration* 1997; **64**: 86–95.