

Review

Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing

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Determination of an 'anaerobic threshold' plays an important role in the appreciation of an incremental cardiopulmonary exercise test and describes prominent changes of blood lactate accumulation with increasing workload. Two lactate thresholds are discerned during cardiopulmonary exercise testing and used for physical fitness estimation or training prescription. A multitude of different terms are, however, found in the literature describing the two thresholds. Furthermore, the term 'anaerobic threshold' is synonymously used for both, the 'first' and the 'second' lactate threshold, bearing a great potential of confusion. The aim of this review is therefore to order terms, present threshold concepts, and describe methods for lactate threshold determination using a three-phase model with reference to the historical and physiological background to facilitate the practical application of the term 'anaerobic threshold'. *Eur J Cardiovasc Prev Rehabil* 15:726–734 © 2008 The European Society of Cardiology

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Introduction

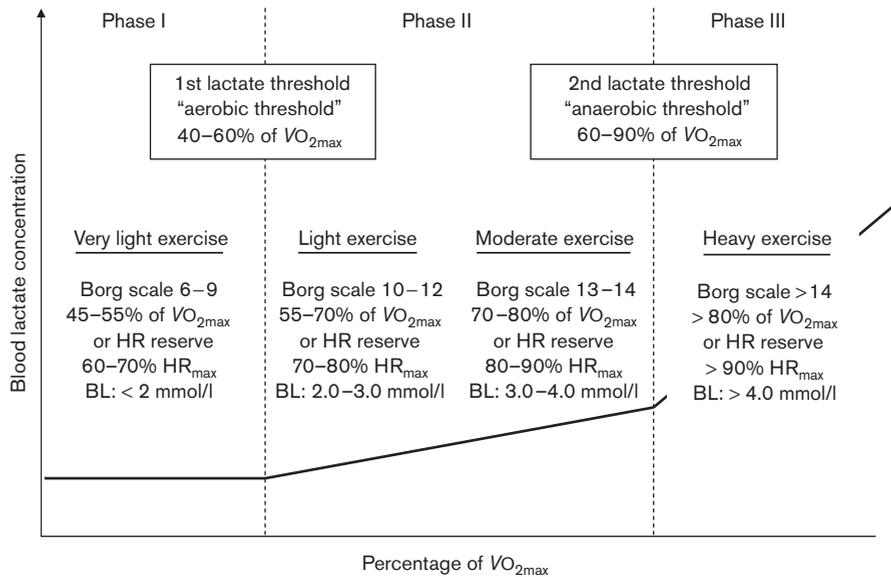
Exercise capacity is one of the most powerful predicting factors of life expectancy, both in patients with [1] and without cardiac disease [2]. Preventive strategies to avoid development or progression of heart disease aim to promote physical activity and to improve exercise performance. Prescribed exercise to reach these goals has to assure optimal efficacy and maximal safety, especially in patients with known cardiovascular diseases, where an exercise intensity above a critical level may have potential detrimental effects [3]. Structured exercise-based cardiac rehabilitation programmes have shown to be an effective approach to reduce mortality and morbidity in these patients [4].

The prescription of correct exercise intensity plays a decisive role [5] and is either related to a percentage of maximal exercise capacity, maximal heart rate or linked to the concept of the so-called 'lactate threshold' (LT). For the determination of the LT during exercise, basically two different methods are used: (i) direct invasive measurement of blood lactate (BL) or (ii) noninvasive measurement of the ventilatory and gas exchange response with indirect definition of the LT. These differences in the methodological approach have led to a contradictory nomenclature and controversy on the physiological basis of what is called the 'LT' and even more confusion and misunderstandings prevail concerning the noninvasive determination of the LT via changes of ventilation and gas exchange parameters during exercise [6–8].

The aim of this review is therefore to order terms, threshold concepts, and methods using a three-phase model [9].

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Fig. 1



The three-phase model according to Skinner *et al.* [9]: relation between blood lactate concentration (BL) and exercise intensity. HR, heart rate; VO_2 , oxygen consumption; Borg scale: subjective rating of perceived exertion.

Table 1 Threshold terms in a three-phase model of incremental exercise with a first and a second threshold of ventilatory/gas exchange, blood lactate/pH or heart rate response, ordered by the date of publication

First ('aerobic') threshold	Second ('anaerobic') threshold
Point of optimal ventilatory efficiency (PoW), Hollmann [14]	Aerobic-anaerobic threshold, Mader <i>et al.</i> [15]
Anaerobic threshold, Wasserman and McLlroy [16]; Wasserman [17]	Threshold of decompensated metabolic acidosis, Reinhard <i>et al.</i> [18]
Lactate threshold, Yoshida <i>et al.</i> [19]; Pendergast <i>et al.</i> [20]	Anaerobic threshold, Kindermann <i>et al.</i> [21]; Skinner and McLellan [9]
Aerobic threshold, Kindermann <i>et al.</i> [21]; Skinner and McLellan [9]	Onset of blood lactate accumulation, Sjödin and Jacobs [22]
Ventilatory anaerobic threshold, Orr <i>et al.</i> [23]; Simonton <i>et al.</i> [13]	Respiratory compensation point, Beaver <i>et al.</i> [24]; Wasserman <i>et al.</i> [25]
Ventilatory threshold, Reybrouck <i>et al.</i> [26]	Individual anaerobic threshold, Stegmann <i>et al.</i> [27]
Ventilatory break point, Brooks [6]	Heart rate deflection point, Conconi <i>et al.</i> [28]
Lactate break point, Brooks [6]	Second ventilatory threshold, McLellan [7]
First ventilatory threshold, McLellan [7]	Maximal lactate steady state, Heck <i>et al.</i> [29]
Gas exchange threshold, Yoshida <i>et al.</i> [30]	Terminal hyperventilation point, Simonton <i>et al.</i> [13]
First lactate turn point, Hofmann <i>et al.</i> [31]; Pokan <i>et al.</i> [3]	Ventilatory threshold 2, Ahmaidi <i>et al.</i> [32]
Change point in VO_2 , Zoladz <i>et al.</i> [33]	Heart rate threshold, Hofmann <i>et al.</i> [34]
Aerobic gas exchange threshold, Meyer <i>et al.</i> [35]	Heart rate turn point, Hofmann <i>et al.</i> [31]; Pokan <i>et al.</i> [36]
Aerobic lactate threshold, Meyer <i>et al.</i> [35]	Second lactate turn point, Hofmann <i>et al.</i> [31]; Pokan <i>et al.</i> [3]
	Critical lactate clearance point, Brooks [37]
	Anaerobic gas exchange threshold, Meyer <i>et al.</i> [35]
	Anaerobic lactate threshold, Meyer <i>et al.</i> [35]

Energy supply and lactic acid production during incremental exercise

The rise of BL concentration during stepwise increase of workload is best described using a model with two turning points instead of continuous [10] or single breakpoint models [11]. A number of studies have identified the existence of two ventilatory thresholds or LTs during exercise to exhaustion. From the physiological point of view, three phases of energy supply and two intersection points can be defined with increasing exercise intensity (Fig. 1) [3,9,12,13]. Numerous terms have been described for an early (first) threshold and a late (second) threshold (Table 1) [3,6,7,9,13,14–37].

According to Skinner and McLellan [9], it is suggested, that the first threshold is called the 'aerobic threshold' and the second the 'anaerobic threshold'.

Phase I

During the first phase of energy supply, greater oxygen extraction by the tissues is found resulting in a lower fraction of oxygen ($P_{ET}O_2$) in the expired air. On the opposite side, more carbon dioxide (CO_2) is produced and expired. Therefore, a linear increase in oxygen consumption (VO_2), CO_2 output and ventilation (V_E) is found. Increasing workload during the first phase of energy supply does not lead to a significant increase of the BL concentration.

Phase II

With increasing exercise intensity above a first LT the lactate production rate is higher than the metabolizing capacity in the muscle cell. Lactate will appear in the compartment of the blood and leads to an increase in the BL concentration. The concomitant increase in H^+ is buffered by bicarbonate (HCO_3^-) resulting in an increased production of CO_2 and a continuous rise in the CO_2 fraction of the expired air ($P_{ET}CO_2$). Centrally stimulated receptors integrating peripheral muscle and chemoreceptor afferences lead to a steeper increase of V_E , whereas the increase of V_{O_2} remains linear with increasing workload. The oxidative capacity of the whole system (i.e. nonworking muscles, liver, ventricular muscle mass) is sufficiently high to cope with the incoming lactate.

During steady-state exercise, this leads to an equilibrium in BL appearance and BL elimination. The highest workload, which can be performed for about 30 min without a systematic increase in the BL concentration, is called 'maximal lactate steady state' (MLSS) and reflects the gold standard for the determination of the second or 'anaerobic threshold' [6,38,39].

Phase III

With further increase in the workload above a second LT, the muscular lactate production rate exceeds the systemic lactate elimination rate. This leads to an exponential increase in the BL concentration during incremental exercise and a steady increase of the BL concentration (no steady state) during a constant workload test. A further nonlinear increase in V_{CO_2} , and more pronounced in V_E , is observed. At this point, hyperventilation cannot compensate adequately the rise in H^+ and there is a drop in $P_{ET}CO_2$.

Controversial terminology

The first descriptions of threshold concepts during cardiopulmonary exercise testing (CPX) arose from the need for rating physical fitness during submaximal exercise tests and from the observation of parameters with curvilinear slope patterns [8,40]. One of the first thresholds in noninvasive CPX was the 'point of optimal ventilatory efficacy' (phase I to II), presented by Hollmann [14]. Wasserman and McIlroy [16] introduced for the same turning point the term 'threshold of anaerobic metabolism', defined by an increase in the respiratory gas exchange ratio (RER) accompanied by a decrease in HCO_3^- . After their publication in 1973 [17], the term 'anaerobic threshold' became popular as an identifier for the first LT. The same term was, however, also used to describe the transition from phase II to III as proposed by Skinner and McLellan [9].

The use of synonymous terms for the first and second transition points caused considerable confusion in the

scientific world. Moreover, the initial concept of the anaerobic threshold as a demarcation of the work load (WL) above which the contracting muscles are not adequately supplied with oxygen [17], has been noticeably challenged [6]. Concerning BL kinetics, in the 1970s Mader [29,15] introduced the '4 mmol/l LT' and in 1981 Sjödín and Jacobs [22] proposed the term 'onset of BL accumulation'. Consequently, numerous other threshold denominations have appeared in the literature, which may be allocated to the first or second threshold (Table 1).

Until today, no widely accepted agreement on a nomenclature for these threshold concepts has been settled for the following reasons:

1. At no time point does the incremental exercise energy supply seem exclusively aerobic or anaerobic [41], so the terms themselves may be considered misnomers [6]
2. BL kinetics, ventilatory response and gas exchange patterns depend on exercise protocol (i.e. fast vs. slow WL increments, step vs. ramp protocol) [7], WL characteristics (e.g. running, swimming, cycling, rowing) [42] and source of blood sampling (venous, capillary, arterial, arterialised) [8,10]
3. Cause and effect relationship of invasive (e.g. lactate, pyruvate, pH, bicarbonate, epinephrine) and non-invasive (e.g. heart rate, ventilation, respiratory gas exchange) CPX parameters seems clear in some cases but a good statistical correlation does not necessarily imply a firm physiological link.

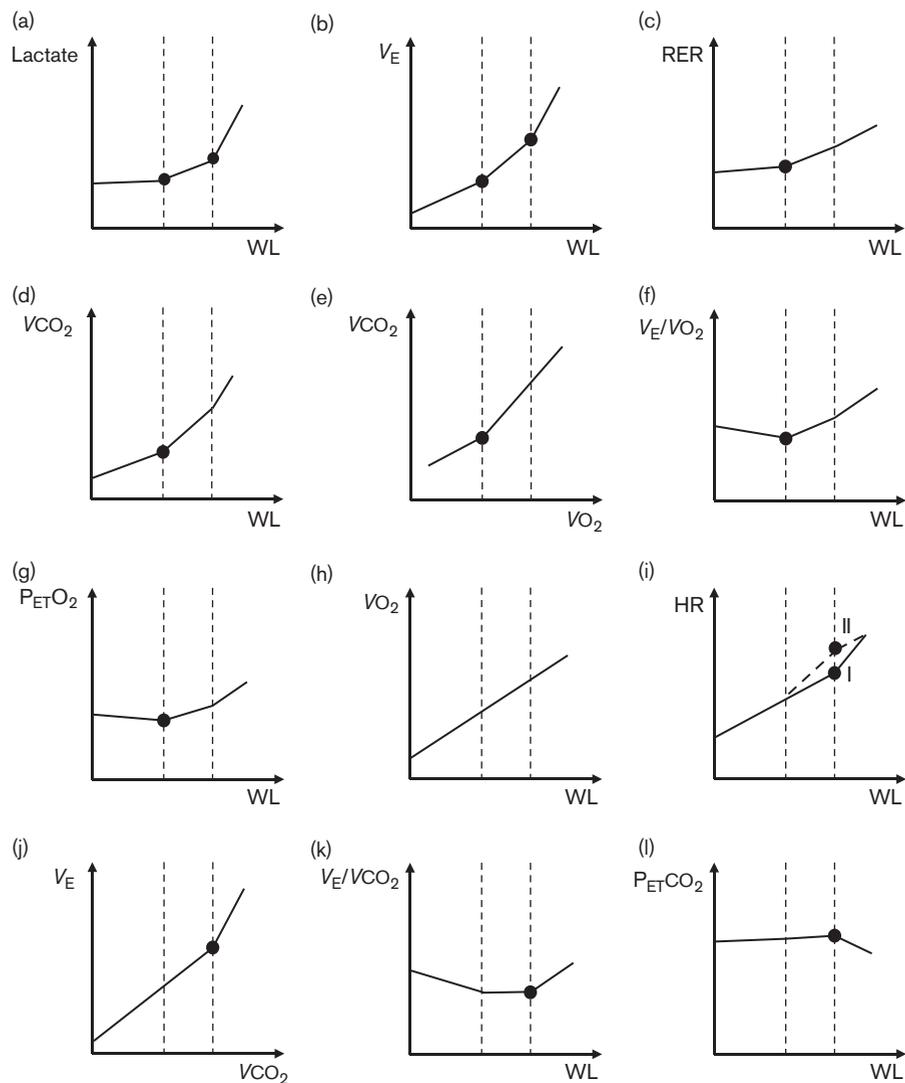
The three-phase model for the description of lactic acid changes and the corresponding respiratory gas exchange kinetics during an incremental exercise stress test are, however, particularly useful for the understanding of threshold determination. Additionally, the determination of a first and a second threshold fits the needs of exercise prescription particularly well. Therefore, we propose to use the three-phase model with the terms 'aerobic' and 'anaerobic threshold' or 'first' and 'second LT' in this setting.

Different approaches for determination of the first ('aerobic') and second ('anaerobic') threshold during incremental cardiopulmonary exercise test

In the following section, an overview of methods (Fig. 2) and terms (Table 1) is presented. Table 2 summarises the most useful methods for threshold determination.

Lactic acid versus workload BL concentration does not rise linearly with increasing WL, but shows a sudden sustained increase over resting levels at a certain individual exercise intensity. This first abrupt increase in BL [19] was widely used as a gold standard for noninvasive threshold

Fig. 2



Schematic representation of different methods for determination of 'lactate thresholds' during incremental exercise testing, applying a three-phase model with an first ('aerobic') and second ('anaerobic') threshold [9]. WL, work load, HR, heart rate.

determinations by ventilation or gas exchange parameters. A log-log transformation of BL versus $\dot{V}O_2$ [43] is a demonstrative way for the detection of this 'first lactate turn point', which may approximate BL levels around 2 mmol/l [21]. Fixation to an absolute BL concentration, however, is protocol dependent and it does not consider interindividual variance in resting BL levels nor does it reflect the LT as a flexion point [12] (Fig. 2a).

With increasing WL above the first LT the patient reaches a point at which lactate production equals maximal lactate clearance capacity. This was called the 'MLSS' [29] or 'onset of blood lactate accumulation' [22]. It reflects the WL threshold beyond which endurance exercise will not lead to a steady state and is used as an upper limit of intensity during endurance training.

Three-line regression concepts have incorporated the two LTs into one graph [11]. The 'second lactate turn point' was shown to correlate well with MLSS [38,39] and approximates a BL level of 4 mmol/l [29,15]. The important point in favor of this threshold fixation, however, seems the convenience of a whole number. Defining an 'individual anaerobic threshold' possibly better reflects the individual lactate level at the MLSS, which may significantly deviate from the 4 mmol/l level [27,32].

V_E versus workload The curve of minute V_E shows a curvilinear slope pattern with two break points. The first coincides with the 'aerobic threshold', the second with the 'anaerobic threshold' [9,13]. By drawing a tangent from the zero point to the minute ventilation and

Table 2 Most practical methods for first ('aerobic') and second ('anaerobic') threshold determination

First ('aerobic') threshold	Second ('anaerobic') threshold
Intersection of a two line regression of the V_{CO_2} versus V_{O_2} (V-slope) graph, with a change of the slope from less than one to greater than or equal to one (Figs 2e and 3a)	Inflection of V_E versus V_{CO_2} (respiratory compensation point) (Figs 2j and 4),
Nadir or first increase of V_E/V_{O_2} versus WL without a simultaneous increase in V_E/V_{CO_2} versus WL (Figs 2f and 3b)	Nadir or nonlinear increase of V_E/V_{CO_2} versus WL (Figs 2k and 3b)
Nadir or first rise of $P_{ET}O_2$, while $P_{ET}CO_2$ remains constant or is increasing (Figs 2g and 4b)	Deflection point of the end tidal $P_{ET}CO_2$ (Figs 2l and 4)

V_{CO_2} , carbondioxide consumption; $P_{ET}O_2$, fraction of oxygen in the expired air; $P_{ET}CO_2$, CO_2 -fraction of the expired air; V_{O_2} , oxygen consumption.

dropping a line on the abscissa (V_{O_2}) a 'point of optimal ventilatory efficiency' [14] was determined. The 'point of optimal ventilatory efficiency' reflects the point at which a maximum amount of oxygen can be taken up with a minimum of ventilation (Fig. 2b). In a multiline regression model [7,23] the first curvilinear rise in V_E is called the '(first) ventilatory threshold' (VT1). It reflects an increasing ventilatory drive because of excess CO_2 , stemming from the buffering of lactic acid by bicarbonate.

With increasing WL beyond 'VT' a second curvilinear rise in V_E may be observed. This second increase in ventilatory drive is also caused by increasing acidosis and by additional CO_2 stemming from lactic acid buffering [18]. The 'second ventilatory threshold' (VT2) [7,32] is demonstrated by the second break point in the three-line regression of V_E versus WL.

Respiratory gas exchange ratio versus workload The RER is the ratio of CO_2 output and O_2 uptake (V_{CO_2}/V_{O_2}). With steady-state conditions, the RER equals the respiratory quotient, which should be reserved for expressing events at the tissue level. The steepest part of a curve plotting RER against V_{O_2} was called the 'threshold of anaerobic metabolism' [16] but the initial concept of the anaerobic threshold has been widely questioned [6] and the same term is also in use for the second threshold [9,21] (Fig. 2c). The first threshold may also be defined at the point where the RER versus WL curve having been flat or rising slowly, changes to a more positive slope [24], with a value approaching, but remaining below 1.0 [44]. Fixation of the threshold at $RER = 1$ or at $RER \geq 1$ with sustained increase [45] renders conflicting correlations with other methods [13,46].

To the best of our knowledge, there is no validated breakpoint in the multiline regression analysis of the RER versus WL, which was correlated with the second threshold. Fixing the second threshold at a RER of 1.0 or slightly higher reflects no breakpoint whatsoever.

V_{CO_2} versus workload The H^+ ions of rising BL are buffered by bicarbonate causing an increase in CO_2 produced from the rapid dissociation of carbonic acid. This is reflected by a curvilinear increase of V_{CO_2} versus

WL [17] at the first threshold with a further increase at the second threshold (Fig. 2d).

V_{CO_2} versus V_{O_2} One of the most frequently used methods for the determination of the first threshold is the 'V-slope method' [24]. During the early WL increments in CPX, V_{CO_2} rises as a linear function of V_{O_2} , but as exercise intensity increases, a subsequent increase in this slope occurs (Figs 2e and 3a). Practically, the V_{CO_2} versus V_{O_2} curve is divided into two regions fitted by a two-line regression with the threshold at the intersection. Besides the two-line regression model, the threshold in this graph may be fixed to the point where the slope changes from a value of less than 1 to ≥ 1 or where a 45-degree (slope = 1) tangent touches the graph [47].

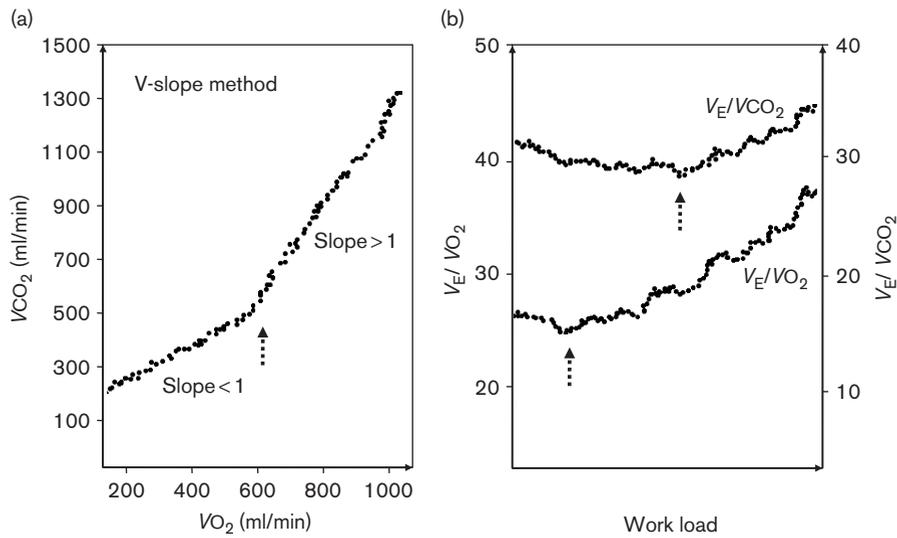
The V-slope method should not be referred to as the 'VT', however, because the V_E is an equal factor on both, the x-axis and y-axis, and does not account for the break point in the increase in the V-slope plot. The V-slope plot is a plot of increased moles of CO_2 output relative to moles of O_2 uptake and the threshold result of the addition of CO_2 to the venous blood.

V_E/V_{O_2} versus workload (Fig. 2f), *$P_{ET}O_2$ versus workload* (Figs 2g and 4b): $P_{ET}O_2$ decreases during the initial WL increments because of changes in the physiological dead space and tidal volume ratio. At the first threshold, when V_E increases out of proportion to V_{O_2} , $P_{ET}O_2$ reaches a minimum and increases thereafter. In other words, the V_E/V_{O_2} slope breaks with linearity and increases, whereas the V_E/V_{CO_2} slope first decreases and subsequently remains constant (Fig. 2k) [18,24]. Correspondingly, $P_{ET}O_2$ is noted to increase, whereas $P_{ET}CO_2$ does not change (Fig. 2l) [17].

As a three-line regression model of V_E versus WL shows an inflection at the second threshold while V_{O_2} remains linear, there is also a second inflection in V_E/V_{O_2} versus WL. This determination method, however, is barely realised.

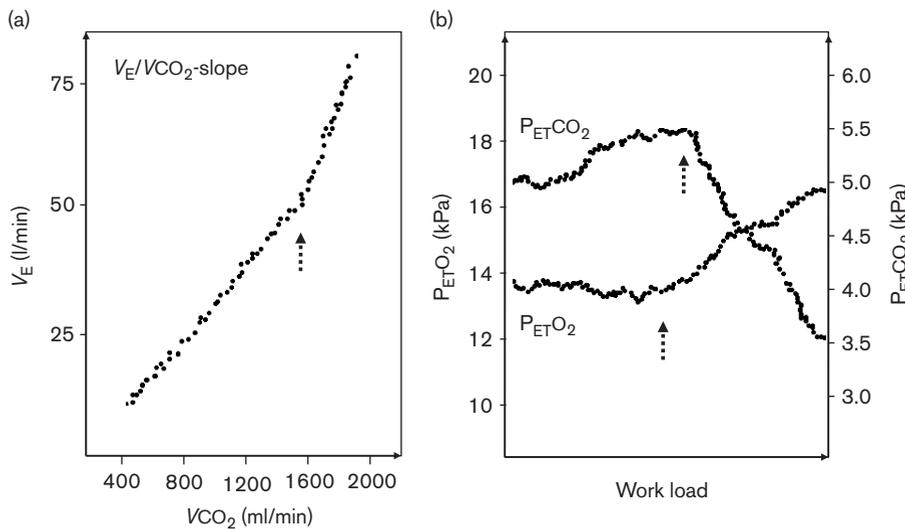
V_{O_2} versus workload V_{O_2} rises linearly with WL. During a ramp protocol, no breakpoint may be detected, but in a step protocol a delayed constant value may be observed

Fig. 3



(a) Determination of the first ('aerobic') threshold by the 'V-slope method'. (b) Determination of the first ('aerobic') threshold at the nadir of V_E/V_{O_2} and the second ('anaerobic') threshold at the nadir of V_E/V_{CO_2} .

Fig. 4



(a) Determination of the second ('anaerobic') threshold at the inflection of the V_E versus V_{CO_2} slope ('respiratory compensation point'). (b) Determination of the first ('aerobic') threshold at the nadir of fraction of oxygen (P_{ETO_2}) and the second ('anaerobic') threshold at the inflection of carbon dioxide fraction of the expired air (P_{ETCO_2}).

beyond the early threshold [48](Fig. 2h). This phenomenon was called 'Change Point in V_{O_2} ' [33]; however, the precise physiological mechanism responsible for the changing V_{O_2} pattern remains to be established [49].

Heart rate versus workload A deflection from linearity of the heart rate versus WL curve may be detected, called the

'Heart rate deflection point' [28]. This breakpoint occurs at the second threshold and not the first [50,36] (Fig. 2i). As this 'heart rate turn point' is not always found, it may not be regarded as a generalizable physiological variable. An upward flexion (I) may suggest a decline in left ventricular function [36], shown in most patients with coronary heart disease, whereas a deflection

(II) is rather a physiological phenomenon observed in approximately 85% of healthy adults at the second threshold [31].

V_E versus V_{CO_2} (Figs 2j and 4a), V_E/V_{CO_2} versus work load (Fig. 2k), P_{ETCO_2} versus work load (Figs 2l and 4b): To compensate for the decrease in blood pH beyond the second threshold, V_E increases out of proportion to V_{CO_2} . This inflection in the V_E versus V_{CO_2} slope has been called 'respiratory compensation point' [24]. It correlates with the second break point of the V_E versus WL graph (Fig. 2b). The point is thought to represent a relative hyperventilation because of metabolic acidosis. This threshold may be also determined by the minimal value in the V_E/V_{CO_2} versus WL relation (Fig. 2k) [13]. When no nadir is found, the threshold may be determined at the deflection point of P_{ETCO_2} versus WL (Fig. 2l and 4b).

Particularities of threshold determinations in different clinical entities

In patients with cardiovascular [51] or pulmonary [52] disease, early onset of lactic acid accumulation during CPX may impair accurate noninvasive determination of the transition from phase I to II [52,53]. This is manifested by the lack of a nadir but with rather a continuous rise in the V_E/V_{O_2} (Figs 2f and 5) from the early increments on. Consequently no inflection point of the P_{ETO_2} (Figs 2g and 5) may be observed.

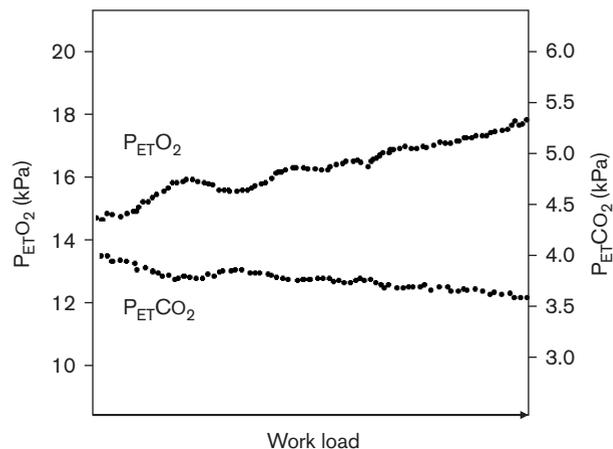
Patients with chronic heart failure will be more likely to present with an abnormal ventilatory response [54] (e.g. exercise oscillatory ventilation; Fig. 6) making threshold determinations based on breathing patterns prone to inaccuracy. In addition, respiratory compensation for the decrease in blood pH (phase II to III) may be affected in severely dyspnoeic patients who, however, hardly ever reach this exercise stage.

Likewise in patients with chronic obstructive pulmonary disease, lactic acidosis may occur early during CPX [52]. Furthermore, because of rapidly developing dyspnoea, chronic obstructive pulmonary disease patients may neither show a first (Figs 2b and 7) [55] nor a second LT [24] (Figs 2j and 7).

Patients with skeletal muscle mitochondrial disease may exhibit elevated BL levels at rest or with minimal exercise [56] associated with exaggerated ventilatory response [57]. Decreased oxidative capacity of the affected mitochondria causes shortening of the aerobic-anaerobic transition (phase II), making discrimination of the first from the second threshold difficult (Fig. 8).

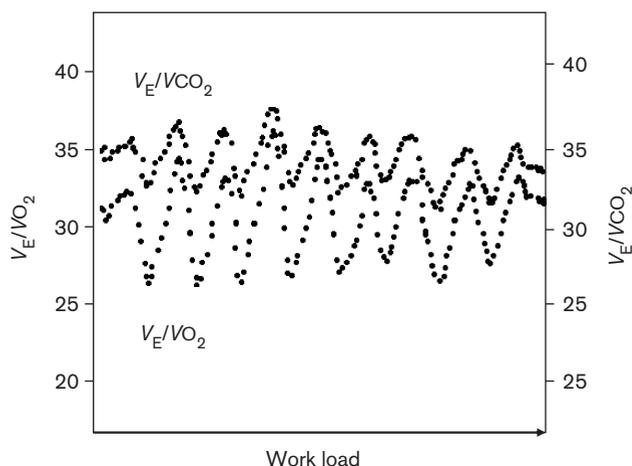
In patients with McArdle's disease, who do not produce lactic acid during exercise because of the lack of the muscle isoform of glycogen phosphorylase (myophos-

Fig. 5



Cardiopulmonary exercise testing of a 74-year-old man with ischaemic cardiopathy and heart failure (left ventricular ejection fraction 20%), showing a lack of a nadir but rather a continuous rise of fraction of oxygen (P_{ETO_2}) and decrease of carbon dioxide fraction of the expired air (P_{ETCO_2}) from the early stages of work load increments, indicating early onset of anaerobic metabolism. Furthermore, because of rapidly developing dyspnoea, no respiratory compensation point is discerned.

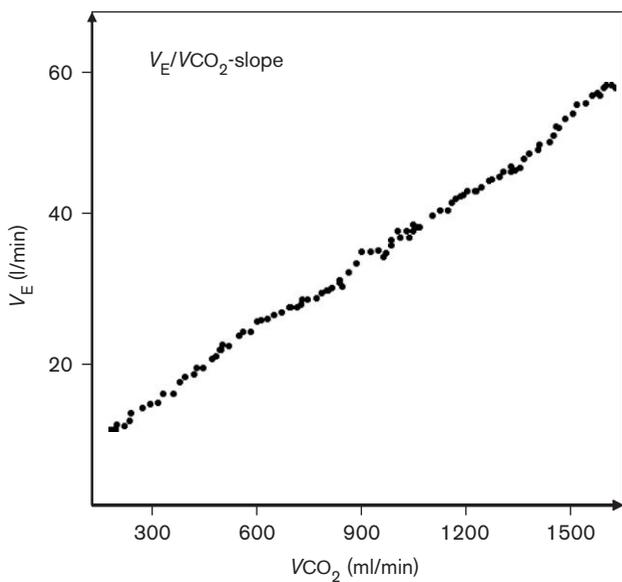
Fig. 6



Exercise oscillatory ventilation in a 61-year-old man with congestive heart failure (dilated cardiomyopathy, left ventricular ejection fraction 25%), precluding any reliable determination of any ventilatory threshold.

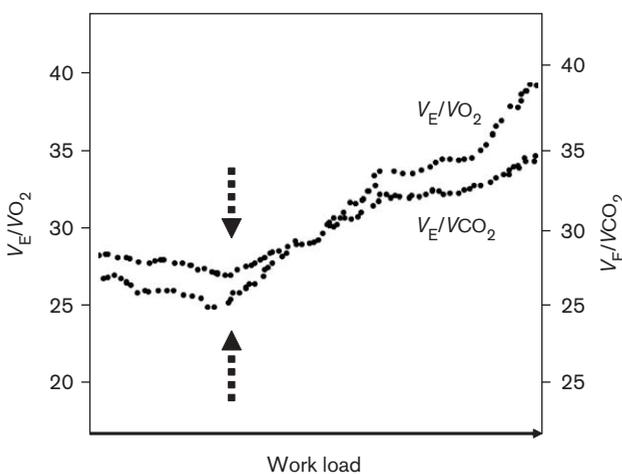
phorylase), no metabolic acidosis will occur during CPX [58]. Consequently, V_{CO_2} will not increase out of proportion to V_{O_2} and the RER will not rise above 1.0. The transition from phase I to II will hardly be discernible. A curvilinear increase in ventilation and a drop in P_{ETCO_2} may be observed because of hyperventilation, possibly caused by nonhumoral stimuli originating in the active muscles [58].

Fig. 7



Cardiopulmonary exercise testing of a 61-year-old man with respiratory exercise limitation because of severe obstructive pulmonary disease: no inflection ('respiratory compensation point') is discernible in the V_E/V_{CO_2} slope.

Fig. 8



Cardiopulmonary exercise testing of a 39-year-old man with respiratory chain defect mitochondriopathy. The nadir of both fraction of oxygen and carbon dioxide fraction of the expired air occur simultaneously making the distinction between the first and second threshold hardly possible.

In heart transplant recipients, the denervation of the graft alters heart rate response to exercise [59]. Chronotropic incompetence is an issue [60] and affects threshold determination based on heart rate character-

istics. Determination of the first threshold and second threshold, however, seems accurate [61].

Summary

Threshold names and concepts describing the changes of BL during CPX have been at the origin of extensive controversy in the scientific world. The aim of this review was to give an overview of the different concepts that have been described during the last decades, to order terms and to propose the three-phase model of lactic acid accumulation with a first ('aerobic') and a second ('anaerobic') threshold as the basis for further discussion. The advantage of this concept is the clear differentiation between two 'LTs' of different meaning and its applicability to exercise prescription, especially in cardiac patients with different degrees of functional impairment. Caution, however, remains to be taken when reporting about data measured at different 'LTs' to avoid mixing up methods. As scientists may use the same terms for different phenomena, it should only be used in combination with a statement about the method used for its determination.

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