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Statement

Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation Part I: Definition of cardiopulmonary exercise testing parameters for appropriate use in chronic heart failure

Task Force of the Italian Working Group on Cardiac Rehabilitation Prevention (Gruppo Italiano di Cardiologia Riabilitativa e Prevenzione GICR) endorsed by the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology*

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Cardiopulmonary exercise testing (CPET) provides a global assessment of the integrated response to exercise involving the pulmonary, cardiovascular, haematopoietic, neuropsychological, and skeletal muscle systems. This information cannot be obtained through investigation of the individual organ systems in isolation. The non-invasive, dynamic physiological overview permits the evaluation of both submaximal and peak exercise responses, providing the physician with relevant information for clinical decision making. The use of CPET in management of the chronic heart failure patient is increasing with the understanding that resting pulmonary and cardiac function testing cannot reliably predict exercise performance and functional capacity and that, furthermore, overall health status and prognosis are predicted better by indices of exercise tolerance than by resting measurements. Our aim is to produce a statement which provides recommendations on the interpretation and clinical application of CPET in heart failure, based on contemporary scientific knowledge and technical advances: the focus is on clinical indications, issues of standardization, and interpretative strategies for CPET. *Eur J Cardiovasc Prev Rehabil* 13:150–164 © 2006 The European Society of Cardiology

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Introduction

The purpose of this statement from the Gruppo Italiano di Cardiologia Riabilitativa (GICR) endorsed by Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology is to produce a comprehensive, conceptually balanced document on the use of cardiopulmonary exercise testing (CPET) in patients with chronic heart failure (CHF) due to left ventricular dysfunction.

CPET is a well-established tool applied in several clinical entities [1], and significant overlapping exists in the exercise responses of patients with different respiratory and cardiac diseases, the indication, performance and interpretation are peculiar in patients with CHF.

The aim is to produce a statement that provides recommendations on the interpretation and clinical application of CPET in CHF, based on contemporary scientific knowledge and technical advances: the focus is on clinical indications, issues of standardization, and interpretative strategies for CPET. Accordingly, this document is presented in eight sections: (1)

*See appendix for details.
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definitions of CPET; (2) indications for CPET in CHF; (3) safety; (4) equipment; (5) exercise protocols; (6) modality of performance; (7) data reporting; and (8) interpretation.

The intended audience for this document includes those who perform clinical CPET, and those who use the results of CPET to assist in clinical decision-making and in the prescription of exercise training programmes. Particular emphasis has been given to a description of the indications and applications of CPET in the diagnostic process, including prognosis, risk stratification and therapeutic monitoring of CHF patients.

For editorial purposes, this statement has been divided in three parts, where the first includes the definition, the second the modality, and the third the interpretation of the test.

The GICR *Ad Hoc* Task Force on Cardiopulmonary Exercise Testing included a group of acknowledged experts with a broad range of clinical and research expertise and conceptual approaches to the topic. In this document, recommendations are based on best available evidence, current prevailing scientific knowledge and expert opinion. There is an increasing demand for diagnostic and prognostic tools to stratify risks, to provide informed decision making in the timing and choice of appropriate therapeutic options (including drug, device and surgical interventions) and rehabilitation programmes in CHF. CPET provides reproducible indices of exercise limitation, cardiac and pulmonary function and, as such, it offers a useful means for both risk stratification and selection of therapeutic approaches. Increasing use of CPET has been fuelled by advances in technology, including the development of automated exercise systems with enhanced data acquisition and management and subject-monitoring capabilities, combined with scientific advances in exercise physiology and increased awareness of the importance of the integrated response in clinical assessment [2].

To achieve optimal use of this test in clinical practice, clarification of conceptual issues and standardization of CPET practices are necessary [3]. CPET use is still very limited since it is considered a complex methodology requiring a high level of organization and skilled processes. Our aim is to increase awareness and use of CPET, by showing that useful information provided by this technique is achievable and of value in multiple clinical settings.

Definitions of CPET

CPET provides a global assessment of the integrated response to exercise, allowing a comprehensive evaluation of the pulmonary, cardiovascular, haematopoietic, neuropsychological, and skeletal muscle systems. This non-invasive, dynamic, physiological assessment permits the evaluation of both submaximal and peak exercise responses. It involves the measurement of respiratory gas exchange: oxygen uptake (V_{O_2}), carbon dioxide output (V_{CO_2}) and minute ventilation (VE), in addition to monitoring electrocardiographic signals, blood pressure and pulse oximetry, typically during a symptom-limited maximal progressive exercise tolerance test. Under steady-state (equilibrium) conditions, V_{O_2} and V_{CO_2} measured at the mouth are equivalent to the total body O_2 consumption and CO_2 production.

The clinical meaning and importance of the respiratory gas exchange parameters with the derived indices are discussed below.

Oxygen uptake (V_{O_2})

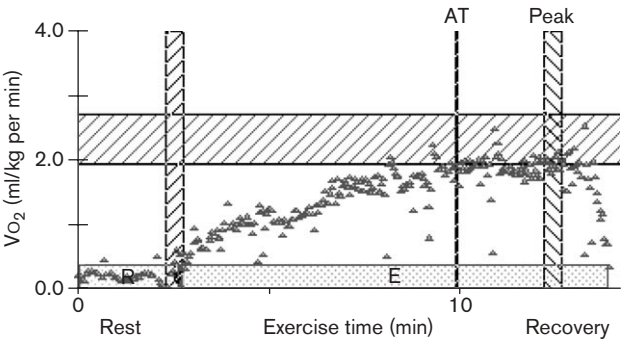
During exercise the relationship between work output, V_{O_2}, heart rate (HR), and cardiac output (CO) is approximately linear (Fig. 1). V_{O_2} is determined by cellular O_2 consumption and by the rate of O_2 transport. V_{O_2} can be computed from blood flow and O_2 extraction by the tissues (distance between capillary and mitochondria), as expressed in the Fick equation [see also the section on CO_2 output (V_{CO_2}) below]:

$$V_{CO_2} = CO \times [C(A-V)O_2 diff] \quad (1)$$

$$V_{O_2} = HR \times SV \times [C(A-V)O_2 diff] \quad (2)$$

where SV is stroke volume, while $C(A-V)O_2$diff is arteriovenous O_2 difference. Several factors can influence O_2 uptake: (1) oxygen-carrying capacity of the blood (which is determined by the available haemoglobin (Hb), the Hb–O_2 saturation/dissociation curve which shifts with temperature, C_{O_2} and pH); (2) cardiac function

Fig. 1



Oxygen uptake (V_{O_2})–exercise time relationships during maximal exercise in a patient with moderate chronic heart failure. AT, anaerobic threshold; E, exercise.

(HR, SV); (3) regional and local distribution of peripheral blood flow; (4) extraction by the tissues (capillary density, mitochondrial density and function, adequacy of perfusion, and tissue diffusion). The same factors determining V_{O_2} in normal patients also determine the response in CHF patients.

V_{O_2}–work rate relationship (V_{O_2}/WR)

Normally, V_{O_2} increases linearly as external work (power output) increases (Fig. 2). The accurate determination of the external work rate in watts [or kilopound metres (kpm) per min] allows the determination of this relationship. Cycle ergometry allows an accurate measurement of the external work. The slope of V_{O_2} versus external work rate reflects the metabolic conversion of chemical potential energy to mechanical work and the mechanical ability of the musculoskeletal system. The slope determined from the rate of change in V_{O_2} divided by the rate of change in external work during incremental exercise testing on a cycle ergometer (V_{O_2}/WR) is normally about 10–11 ml/min per watt [2] and is independent of sex, age and height.

A reduction in V_{O_2}/WR relationship most often indicates alteration in the metabolism of the skeletal muscles and/or inadequacies of O_2 transport, as may occur with diseases of the heart, lungs or circulation. Thus this pattern is not specific for diseases of the heart (such as CHF), but is also present in diseases of other organs and systems. It may also reflect errors in calibration. Nevertheless, since V_{O_2}/WR can also be assessed during submaximal exercise, it may provide important prognostic information in CHF patients [4].

In patients with severe CHF, the slope of V_{O_2}/WR can be decreased to 7 or 8 ml/min per watts (Fig. 2) [5]. This is the reason why it is mandatory to measure V_{O_2} in CHF patients and not to derive it from peak work-rate, based on various formula established in normal subjects in whom the slope is relatively constant. The decrease of slope is probably related to altered kinetics of cardiac output increase and/or peripheral oxygen extraction.

In patients undergoing submaximal graded exercise, the V_{O_2}/WR slope provides some insights: a normal slope suggests a non-cardiac cause to stopping exercise, a decreased slope suggests circulatory failure. However, at the individual level, this slope exhibits high variability, limiting its use. Its prognostic role has been suggested [6].

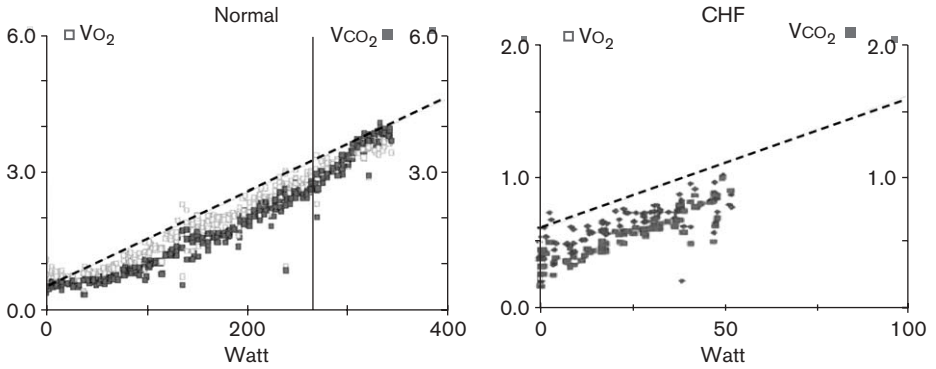
$V_{O_{2max}}$–$V_{O_{2peak}}$

Based on the above-stated principles [equations (1) and (2)], it derives that as V_{O_2} increases with increasing external work, the determinants of V_{O_2} approach maximal values, and as each factor approaches its relative limits (e.g. SV, HR or tissue oxygen extraction) the V_{O_2}/WR slope begins to plateau. Achieving a clear plateau in V_{O_2} has traditionally been used as the best evidence of $V_{O_{2max}}$ (Fig. 3).

V_{O_2} can increase from a resting value of about 3.5 ml/kg per min (about 250 ml/min in an average individual) to $V_{O_{2max}}$ values about 15 times the resting value (30–50 ml/kg per min). $V_{O_{2max}}$ is considered reduced when below 80% of predicted values.

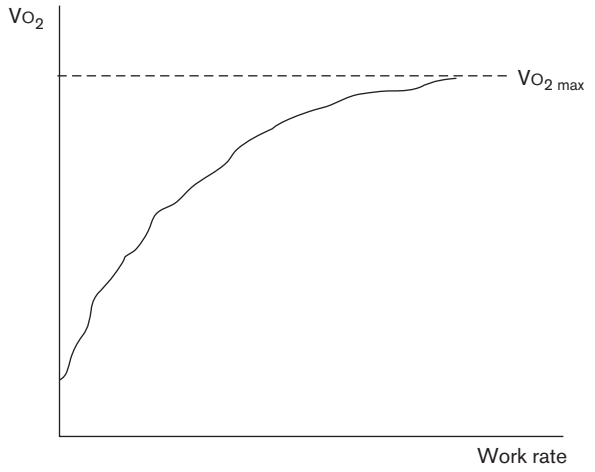
$V_{O_{2max}}$ is the best index of aerobic capacity and the gold standard for cardiorespiratory fitness. It represents the maximal achievable level of oxidative metabolism involving large muscle groups. However, in clinical testing situations, a clear plateau may not be achieved because of earlier occurrence of intolerable symptoms limiting exercise [7], when only V_{O_2} at peak exercise can be measured ($V_{O_{2peak}}$). Consequently, $V_{O_{2peak}}$ is often used

Fig. 2



V_{O_2} and V_{CO_2}-work rate relationships in a normal subject (Normal) and in a patient with chronic heart failure (CHF).

Fig. 3



Estimation of maximal oxygen uptake ($V_{O_{2max}}$).

Table 1 Predictors of exercise intolerance ($V_{O_{2peak}}$) or increased ventilatory response to exercise in chronic heart failure (CHF) (modified from Piepoli *et al.* [12])

	Number of patients	*r*	*P*
Skeletal muscle changes			
Muscle atrophy	15	−0.48	<0.01
Muscle strength	10	0.40	<0.001
Fibre type			
I (%)	22	−0.81	<0.01
IIb (%)	22	0.68	<0.01
Mitochondrial volume density	60	0.56	<0.001
Oxidative enzymatic activity	11	0.68	<0.05
PCr rate depletion on exercise	25	−0.62	<0.01
Autonomic changes			
Muscle ergoreflex	123	−0.53	<0.005
Peripheral chemoreflex	123	−0.33	<0.05
Central chemoreflex	123	−0.58	<0.003
Carotid baroreflex	123	0.52	<0.02
LF-HRV	123	0.60	<0.001
Pulmonary changes			
Lung diffusion (TLCO)	40	0.62	<0.001
Inspiratory capacity	51	0.71	<0.001
PCWP	51	−0.43	<0.01
Aortic wall elasticity	78	0.39	<0.04
RVEF >35	67	0.40	<0.01
LVEF	763	0.19	NS

LF-HRV, low-frequency fluctuation of heart rate variability; LVEF, RVEF, left and right ventricular ejection fraction, respectively; NS, not significant; PCr, phosphocreatine; PCWP, pulmonary capillary wedge pressure; TLCO, lung transfer capacity for carbon monoxide.

as an estimate for $V_{O_{2max}}$. For practical purposes, $V_{O_{2max}}$ and $V_{O_{2peak}}$ are currently used interchangeably, although they express different physiological measures [8].

Aerobic capacity should be measured directly because its estimation from resting indices, work rate, or submaximal exercise protocols is limited by physiological mechanisms and methodological inaccuracies, and as such is unreliable [8]. In turn, direct measurement of $V_{O_{2max}}$ is reliable and reproducible in normal subjects [9,10] and in CHF patients [11]. The main determinants of normal $V_{O_{2max}}$ or $V_{O_{2peak}}$ are genetic factors and quantity of exercising muscle. $V_{O_{2max}}$ and $V_{O_{2peak}}$ are also dependent on age, sex and body size, and can be affected by training. Decreases in $V_{O_{2max}}$ or $V_{O_{2peak}}$ are general indicators of reduced exercise capacity [12] (Table 1). Underlying causes of exercise limitation are determined, in turn, by inspecting the pattern of the responses of the other variables.

Contrary to observations in athletes or fit subjects, what is measured at the end of exercise in a CHF patient is not a plateau of $V_{O_{2max}}$, the patients stop early because of fatigue or dyspnoea. Therefore, before interpreting the value of $V_{O_{2peak}}$, it is necessary to be sure that the test has been maximal or submaximal, and can be considered valid.

A reduced $V_{O_{2peak}}$ is the starting point in the evaluation of reduced exercise tolerance. In fact, reduction in $V_{O_{2peak}}$ may have several causes: it may reflect problems with oxygen transport (cardiac output, O_2-carrying capacity of the blood), pulmonary limitation (mechanical, control of breathing or gas exchange), oxygen extraction at the tissues (tissue perfusion, tissue diffusion), neuromuscular or musculoskeletal limitations, and, of course, poor effort. In addition, in patients, perceptual responses (symptoms) rather than a physiological process, as defined in the Fick equation, may be responsible for a low $V_{O_{2peak}}$.

In CHF, $V_{O_{2max}}$ and $V_{O_{2peak}}$ are reduced when computed either as absolute terms (l/min), or weighted terms (ml/kg per min), or as percentage of normal (with respect to the predetermined values in relation to age, sex and body mass index). They constitute one of the best independent prognostic indices [13] (see Part III: Interpretation). Their assessment allows risk stratification, the choice of the therapeutic regimen and the relative response (pharmacological and non-pharmacological).

Kinetics of V_{O_2} recovery after exercise

At recovery, V_{O_2} decreases exponentially after a graded exercise (Fig. 1). The half-time of V_{O_2} recovery ($T_{1/2}$) has been shown to be 60–80 s in normal subjects after graded exercise. The kinetics of V_{O_2} is prolonged with the severity of heart failure. Patients with a $V_{O_{2peak}} < 10$–12 ml/kg per min may need 3 min to decrease their V_{O_2} by 50%. This is probably related to the slow kinetics of reconstitution of the energetic stores after exercise. This V_{O_2}-off kinetics has the advantage of being only minimally influenced by the level of exercise; therefore, in case of submaximal exercise (at least when > 50% of $V_{O_{max}}$), the V_{O_2}-off kinetics can be used to analyse the degree of impairment of circulatory function [14]. A normal V_{O_2}-off with a low $V_{O_{2peak}}$ suggests submaximal

exercise. Various groups have also shown that the half-time of V_{O_2} recovery has prognostic value [15].

CO_2 output (V_{CO_2})

During exercise, V_{CO_2} is determined by factors similar to those that govern O_2 uptake: cardiac output, CO_2-carrying capacity of the blood, and tissue exchange are major determinants. However, because CO_2 is much more soluble in tissues and blood, V_{CO_2} measured at the mouth is more strongly dependent on ventilation than is V_{O_2}. For example, before the beginning of exercise, if psychogenic hyperventilation is present, measured V_{CO_2} is higher than V_{O_2}.

During short-duration exercise, glycogen is used primarily by the muscles for energy, and the relation between O_2 consumption and CO_2 production is almost equimolar. As such, during progressive exercise V_{CO_2} increases nearly as much as does V_{O_2} over the lower work rate range, with an average V_{CO_2} versus V_{O_2} relationship of slightly less than 1.0 [2].

There is typically a relatively sharp change in slope toward the midrange of the V_{O_2} response [anaerobic threshold (AT), determined by V-slope method] (Fig. 4). This results in a steeper, but typically quite linear, profile over the upper work rate range. The steeper slope reflects the CO_2 generated in excess of that produced by aerobic metabolism, due to bicarbonate buffering of increased lactic acid production at these high work rates. With anaerobic metabolism, V_{CO_2} increases as a result of the chemical reaction between hydrogen ions (H^+, from lactate) and dissolved CO_2:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O \qquad (3)$$

As tissue lactate production increases [H^+], the reaction is driven to the right, producing extra CO_2 above that produced aerobically. The excess CO_2 may also come from reduction in the body CO_2 stores as a result of hyperventilation (manifested as arterial hypocapnia). Since the VE is closely proportionally coupled to V_{CO_2} during exercise, it is useful to analyse VE in relation to V_{CO_2}. It is also important to measure CO_2 output accurately, as it is the basis for the calculation of several derived variables, including (1) the respiratory exchange ratio, (2) the ratio between physiological dead space and tidal volume (VD/VT), and (3) alveolar ventilation.

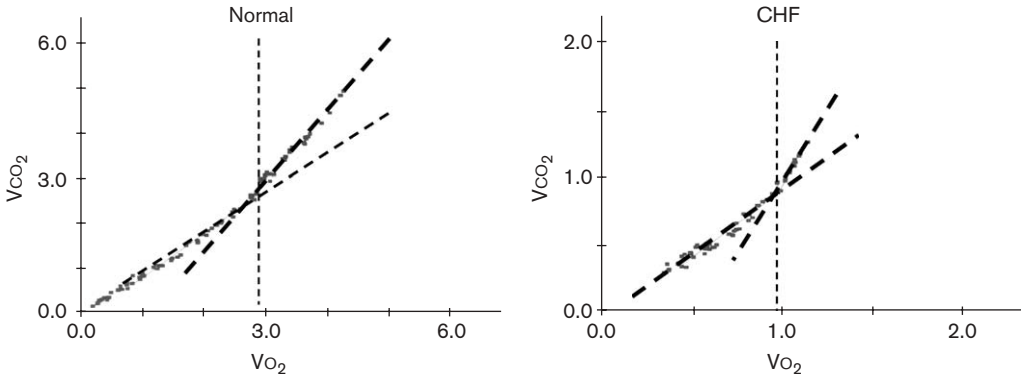
The mechanisms that govern V_{CO_2} rise in normal patients are also active in CHF patients. However, for the same amount of V_{CO_2} produced, the CHF patient presents a higher VE, and therefore the slope of the relationship of VE in relation to V_{CO_2} is significantly steeper: the reference value of 34 is typically surmounted (see the section on Ventilation, below).

Respiratory exchange ratio (V_{CO_2}/V_{O_2})

The ratio of V_{CO_2}/V_{O_2} is called the gas exchange ratio or respiratory exchange ratio (RER). Under steady-state conditions, the RER equals the respiratory quotient (RQ), the value of which is determined by the fuels used for metabolic processes. The term 'RQ' is often reserved for expressing events at the tissue level, which is difficult to measure and is not determined during clinical exercise testing. The term 'RER' is usually measured by gas exchange at the mouth.

In steady-state conditions, an RQ of 1.0 indicates metabolism of primarily carbohydrates, whereas an RQ of less than 1.0 indicates a mixture of carbohydrates with fat (RQ about 0.7) or protein (RQ about 0.8). In a true steady state, the blood and gas transport systems are keeping pace with tissue metabolism; thus, the RER can be used as a rough index of metabolic events (RQ).

Fig. 4



Anaerobic threshold in a normal subject (Normal) and in a patient with chronic heart failure (CHF).

However, above the anaerobic threshold an RER greater than 1.0 could also be caused by CO_2 derived from lactic acid or by hyperventilation, because of the 20-fold or more higher tissue solubility of CO_2 compared with O_2, and due to the fact that HCO_3^- and proteins are significant forms of transport for CO_2 in body tissues, whereas the only significant form of transport for O_2 is by combination with haemoglobin.

This index provides an indication of the level of exercise performed during CPET: in cases where a value above 1.1 is not reached the test is usually considered submaximal [8]. If the patient stops before reaching this value, limiting factors other than cardiac ones should be considered. This information may provide important prognostic value in CHF: an impaired exercise tolerance (reflected by $V_{O_{2peak}} < 10$ ml/kg per min) reached during maximal CPET test (with RQ value > 1.1 at peak exercise) is associated with a high mortality rate [13].

Anaerobic threshold (AT)

The AT, also known as the lactate threshold, lactic acid threshold, gas exchange threshold, or ventilatory threshold, is the point at which VE increases disproportionately relative to V_{O_2} and work. It represents the theoretical point during incremental exercise when muscle tissue switches over to anaerobic metabolism as an additional source: lactic acid begins to accumulate, it is buffered in the serum by the bicarbonate system, resulting in increased CO_2 excretion, which causes reflex hyperventilation. It is considered an estimator of the onset of metabolic acidosis caused predominantly by the increased rate of rise of arterial lactate during exercise, according to equation (3).

The AT is referenced to the V_{O_2} at which this change occurs and is expressed as a percentage of the predicted value of $V_{O_{2max}}$ (%$V_{O_{2max}}$ predicted). It occurs at 50–60% predicted $V_{O_{2max}}$ in normal, untrained individuals.

Work below AT encompasses most activities of daily living. It is reduced in most patients with important cardiovascular disease. An increase in AT with training can greatly enhance an individual's capacity to perform sustained submaximal activities, with consequent improvement in quality of life.

The difference in the terminology used to describe this transition reflects the controversy that exists regarding the physiological mechanisms underlying the increases in muscle and blood [lactate] that occur at the AT. Although the classic views concerning the assessment of the AT have been supported [16,17], others have continued to question this viewpoint [18,19]. If different muscle groups reach anaerobic metabolism at different times, the transition will be smooth and a distinct point, the AT, may be difficult to determine accurately.

Mechanisms

Controversies exist concerning the processes at the origin of AT: it is possible that both an imbalance between oxygen delivery versus oxidative capacity and the pattern of muscle fibre recruitment, contribute to the increase in lactic acid as exercise intensity increases. Concerning the latter mechanism, muscle fibres vary in the balance of oxidative versus glycolytic enzymes, that is, 'aerobic' versus 'anaerobic' metabolism. At low exercise intensities, fibres that are primarily oxidative are recruited, but as intensity increases, fibres that rely primarily on glycolytic pathways are activated, thus increasing the output of lactic acid [18–20].

However, anaerobiosis at the cellular level and increased arterial lactate occur above and below a critical arterial oxygen pressure (P_{O_2}), which suggests that other factors (i.e. glycolytic enzymes) may also be involved [18]. Studies using venous blood lactate measurements were consistent with a continuous development of acidosis, rather than a sudden onset of blood lactate accumulation during progressive exercise [21].

As such, the term AT should be used in a descriptive sense. The relative contribution of the different sources of lactic acid may also vary with disease. For example, in heart failure not only reduced oxygen delivery, but also alteration in muscle fibre composition and metabolism are present, so that, as exercise intensity increases, the rate of rise in V_{O_2} starts to decline and the rate of rise in lactate increases earlier than in normal individuals [12,22].

Regardless of mechanism, the increase in lactic acid, which appears in the blood as exercise intensity increases, has important physiological consequences. First, the build-up in lactic acid reduces the pH of both blood and interstitial fluid which, in turn, could ultimately compromise cellular function. Secondly, the reduced pH, and other events related to the change in pH, likely stimulate ventilation as the body attempts to buffer the increased acid by decreases in arterial CO_2 pressure (P_{CO_2}). Thirdly, the reduced pH allows a rightward shift on the Hb/O_2 dissociation curve, which increases O_2 delivery to the muscles (the so-called 'Bohr effect'). Indeed, at the end of the capillary bed of the working muscles P_{O_2} remains constant while O_2 saturation decreases [23]. Because lactic acid build-up affects cellular function, the magnitude of the rise in lactate and the pattern of rise in lactate relative to change in V_{O_2} during exercise may be a useful indicator in exercise testing. Also, the earlier lactate build-up occurs, the lower the long-term sustainable V_{O_2}.

Clinical applications

The AT demarcates the upper limit of a range of exercise intensities that can be accomplished almost entirely

aerobically. Whereas work rates below the AT can be sustained essentially indefinitely, a progressive increase in work rate above AT is associated with a progressive decrease in exercise tolerance [24]. In normal individuals, the AT occurs at about 50–60% $V_{O_{2max}}$ predicted in sedentary individuals, with a wide range of normal values extending from 35 to 80% [25]. The AT determination is age, modality and protocol specific.

AT determination is helpful as an indicator of level of fitness, for exercise prescription, and to monitor the effect of physical training [26]. When the AT is not reached, as in some patients with severe chronic obstructive airway disease [27], or cannot be determined from the ventilatory response, as in presence of an oscillatory pattern, an exercise prescription can still be established by using as a reference a percentage of peak work rate, $V_{O_{2max}}$ or HR [28].

A reduction in AT, as in $V_{O_{2peak}}$, is non-specific: it occurs in a wide spectrum of clinical conditions/diseases and, as such, has limited discriminatory ability in distinguishing between different clinical entities. Values below 40% of predicted $V_{O_{2max}}$ may indicate a cardiac, pulmonary (desaturation) or other limitations in O_2 supply to the tissues, or underlying mitochondrial abnormality (e.g. muscle dysfunction in cardiopulmonary diseases, mitochondrial myopathies).

Measurements

Several methods are available for AT determination and include invasive (lactic acid and standard bicarbonate) and non-invasive determinations [ventilatory equivalents method [VE/V_{O_2}, VE/V_{CO_2}, end-tidal expiratory oxygen pressure (PET_{O_2}), and end-tidal expiratory CO_2 pressure ($PETCO_2$)], V-slope method, and modified V-slope method] (Fig. 5).

Although of scientific and physiological importance, invasive methods have little applicability in clinical practice. Clinically, increasing lactic acidosis can be determined non-invasively by observing the pattern of change in V_{CO_2} and VE relative to V_{O_2} as exercise intensity increases.

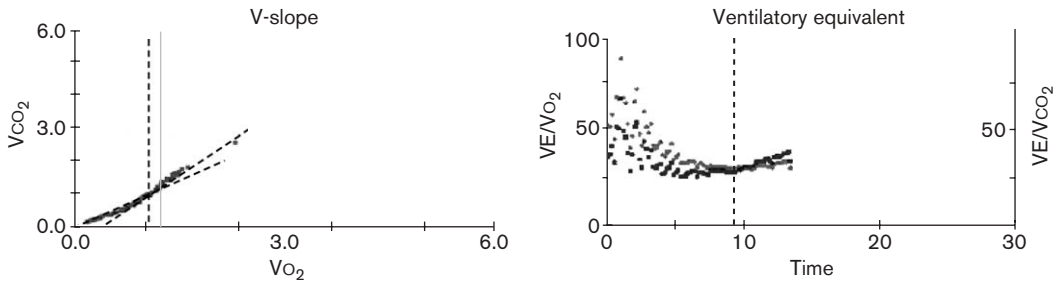
Ventilatory equivalents The ventilatory equivalents method involves the simultaneous analysis of multiple variables (VE/V_{O_2}, VE/V_{CO_2}, PET_{O_2}, and PET_{CO_2}). The AT is then defined by the following events, all of which occur roughly simultaneously: the V_{O_2} value at which VE/V_{O_2} and PET_{O_2} reach a nadir and thereafter begin to rise consistently, coinciding with an unchanged VE/V_{CO_2} and PET_{CO_2} (Fig. 5).

V-slope The AT is identified as the V_{O_2} at which the change in slope of the relationship of V_{CO_2} to V_{O_2} occurs. V_{CO_2} increases as a relatively linear function of V_{O_2} early in an incremental exercise protocol and this slope is termed S_1. As exercise intensity increases, there is a subsequent increase in the slope, referred to as S_2. To confirm that this change of slope is not occasioned by hyperventilation, monitoring ventilatory equivalents and $PETCO_2$ is necessary. Consequently, the ventilatory equivalents for O_2 and end-tidal O_2 reach their nadir and begin to rise in concert with the S_1–S_2 transition, without an increase in the ventilatory equivalent for CO_2 and/or decrease in end-tidal P_{CO_2} (Figs 4 and 5).

Modified V-slope Due to the complexity of its assessment, the original V-slope method proposed by Beaver and coworkers [29] has been replaced in most conventional systems by a simplified approach. The modified V-slope method, in turn, determines the point of the change in slope of the relationship of V_{CO_2} versus V_{O_2} and defines the V_{O_2} above which V_{CO_2} increases faster than V_{O_2} without hyperventilation [16].

When using these methods to detect anaerobic threshold, it should be kept in mind that there is a good correlation, but not necessarily a firm physiological link, between ATs determined invasively and non-invasively, and that unusual breathing pattern responses to exercise (such

Fig. 5



Estimation of the anaerobic threshold according to the modified V-slope method and to the ventilatory equivalent.

as oscillatory breathing) can adversely impact AT determination.

Because inappropriate increases in V_{CO_2} disproportionate to increases in metabolic rate (V_{O_2}) due to acute hyperventilation invalidate the non-invasive determination of the AT, it is recommended that both V-slope and ventilatory equivalents methods be used together ('dual methods approach') as the RER approximates 1.0, to more accurately determine the AT non-invasively [30].

In CHF a typical reduction in the values of AT is associated with the fall in exercise tolerance. Its computation has been proposed not only as adjunctive information, but also complementary to $V_{O_{2max}}$ because it measures the sustainable O_2 uptake and is an objective parameter of cardiopulmonary exercise capacity that can be derived from submaximal exercise testing. Therefore it is independent of influences such as reduced patient motivation as well as premature termination of exercise by the examiner. Conventionally AT values below 40% of the predicted maximal value of $V_{O_{2max}}$ are considered abnormal [2]. More recent data have proposed a threshold value of $V_{O_2} < 11$ ml/kg per min as a negative prognostic indicator [31,32].

However, in the most advanced stages of the syndrome, such as class III or IV of the New York Heart Association (NYHA) functional classification, quite often a clear value of AT is not identifiable, mainly in the presence of oscillations. The AT is independent of a patient's motivation. When detected, a normal AT with a low $V_{O_{2peak}}$ suggests submaximal exercise. Because of problems of determination, the AT has never supplanted the $V_{O_{2peak}}$ as a marker of functional capacity or prognosis in CHF patients. During most of the daily activity, and in some cases even at rest, patients' metabolism is near to, or even above, the AT [33].

Ventilation

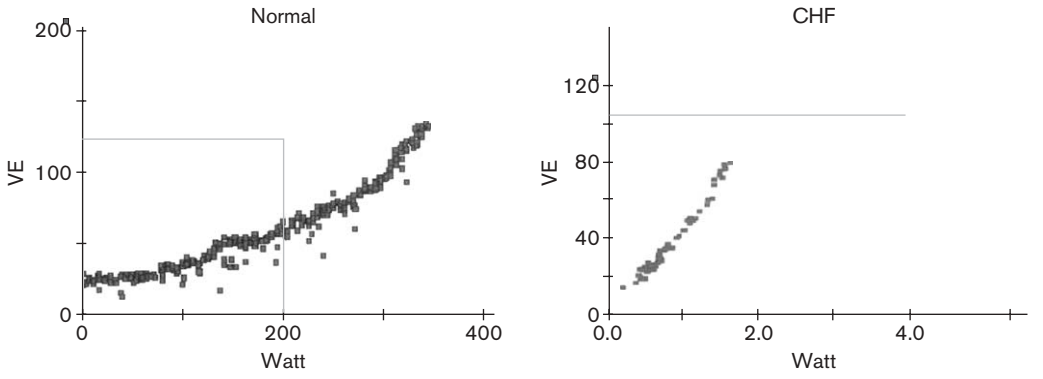
Increased ventilation (VE) during exercise is one of the primary means by which homeostatically controlled arterial blood gases and acid–base status is regulated under conditions of the augmented metabolic demands of exercising muscles (Fig. 6). Although the mechanisms that couple VE to gas exchange (metabolic demands) during exercise are not completely understood, several indicators of the ventilatory response to exercise may assess the normality or adequacy of the ventilatory response.

The most common ventilatory indices assessed during exercise include changes in total minute ventilation (VE) and breathing pattern (tidal volume, VT, and respiratory frequency, *f*), along with assessment of ventilatory reserve. Less commonly evaluated are changes in ventilatory timing (inspiratory time, TI, expiratory time, TE, and total time, Ttot) and changes in tidal volume relative to specific lung volumes (e.g. VT/VC).

More recently, changes in inspiratory capacity (IC) and a more thorough assessment of ventilatory constraint to exercise have also been utilized. Because ventilation is a balance between optimization of the mechanics of breathing and maintenance of gas exchange, many of the ventilatory indices express these combined elements, such as the efficiency of ventilation (VE versus V_{O_2} or V_{CO_2}) (Fig. 7).

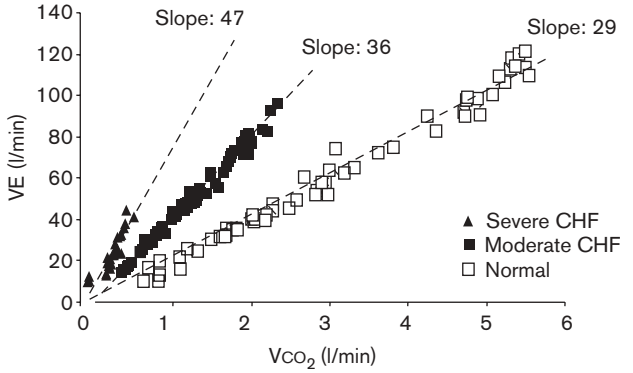
The rise in VE with exercise is associated with an increase in both depth (VT) and frequency of breathing (*f*). In health, VT increases are primarily responsible for rises in ventilation during low levels of exercise. As exercise progresses, both VT and *f* increase until 70–80% of peak exercise; thereafter *f* predominates. VT usually plateaus at 50–60% of vital capacity (VC); however, there is considerable variation.

Fig. 6



Ventilation (VE)–work rate relationship in a normal subject (Normal) and in a patient with chronic heart failure (CHF).

Fig. 7



Relationship between ventilation (VE) and carbon dioxide production (VE/V_{CO_2} slope). CHF, chronic heart failure.

In patients with CHF an altered ventilatory pattern has been described even in the resting state. Spirometric studies show a reduced forced VC and reduced total lung capacity, with a relatively preserved forced expiratory vital capacity [34–36]. This overall restrictive pattern of the lung has been attributed to increased parenchymal lung stiffness [37] due to interstitial oedema and consecutive fibrosis, and possibly to a compressive effect from cardiomegaly [38]. It is notable that the reduction in total lung capacity is related to pulmonary capillary wedge pressure [39,40] and the abnormalities are reversible, at least in part, by medical treatment [41] or heart transplantation [42,43], suggesting that they are likely to be attributable to fluid imbalances rather than permanent changes such as fibrosis.

In keeping with this concept, in the congestive state, CHF results in an abnormal increase in pulmonary capillary wedge pressures, predisposing the lungs to the early development or aggravation of interstitial oedema [44,45], which results in an abnormal dynamic reduction in lung compliance during exercise. These abnormalities lead to a breathing pattern during exercise that is characterized by a low tidal volume and an increased respiratory rate.

Furthermore, the direct impact of cardiomegaly as a compressive force upon the lungs should not be forgotten, since it was observed that over two-thirds of improvement in vital capacity after heart transplantation could be attributed to a simple reduction in cardiac size [46]. Despite the presence of restrictive respiratory changes, ventilatory capacity does not seem to limit exercise performance in CHF patients, who show an increase of ventilation during exercise that is about twice that of normal control subjects [22,47].

The ventilatory capacity can be estimated by multiplying the forced expiratory volume in one second (FEV_1) by the assumed highest respiratory rate (usually 35–40), which gives the theoretically achievable minute ventilation, which is referred to as the maximum voluntary ventilation (MVV) [48]. To assess whether the ventilatory capacity is limiting exercise gas exchange, the MVV is related to actual maximum minute ventilation measured at peak exercise (peakVE/MVV). This ratio is about 0.6–0.8 for normal individuals but can increase in patients with obstructive or restrictive lung disease or in trained athletes as pulmonary capacity reduces or circulatory and muscular gas exchange capacity increases. Some precaution should be used when evaluating the VE/MVV relationship in patients with poor motivation [49]. In CHF the peak VE/MVV ratio is reduced compared to that of normal patients [47]; this may arise from reduction of muscular and circulatory gas exchange capacity.

It is worthwhile mentioning that for the same amount of V_{CO_2} produced, the CHF patient presents an higher VE, and therefore the slope of the relationship of VE in relation to V_{CO_2} is significantly steeper. Several contributing factors have been investigated to explain the origin of this high ventilatory drive. Higher blood levels of metabolic factors resulting from abnormal muscle metabolism (e.g. lactate, hydrogen ion, adenosine, prostaglandin) may trigger the ventilatory centres of the medulla, either directly and/or indirectly via stimulation of peripheral and central chemoreflexes and muscle ergoreflex [50]. A positive feedback may come from the general activation of the sympathetic drive and/or the reduction in the vagal tone, together with impairment of the carotid baroreflex, all changes present in CHF syndrome [51]. Regardless of the mechanism, the elevation of the VE/V_{CO_2} slope is typical of CHF and is associated with poor prognosis, even in patients with relatively preserved exercise capacity, namely $V_{O_{2peak}}$.

Pulmonary diffusion capacity

Gas diffusion is described by Fick's law:

$$V_G = k \times A/d \times \alpha/\sqrt{M} \times \Delta p \qquad (4)$$

where V_G is the rate of diffusion of gas, k is a constant (temperature dependent), A is the membrane area, d is the thickness of the membrane, α is the solubility of the gas, M is the molecular mass of the gas and ΔP is the difference in pressure of the gas across the membrane. Accordingly, the alveolar diffusion rate is proportional to alveolar area, solubility and molecular mass of O_2 and CO_2 and mean alveolo-capillary difference in the pressures of O_2 and CO_2; and is inversely proportional to the thickness of the alveolo-capillary membrane. Because of its high solubility, CO_2 traverses the alveolo-capillary membrane about 23 times faster than O_2. Hence, any diffusion limitation of the lungs would primarily affect the diffusion of O_2 but not of CO_2. It can be anticipated

that a theoretical limitation of pulmonary diffusion that relevantly affects CO_2 diffusion must have led to an impairment of O_2 diffusion that would be incompatible with life.

Besides the size and characteristics of the alveolo-capillary membrane, O_2 diffusion depends on the capillary O_2 capacity (i.e. the ratio of O_2 uptake and the consecutive change in pressure of O_2). This depends on capillary blood volume, haemoglobin concentration and the reaction rate between O_2 and haemoglobin. The diffusion capacity of the lungs (D_L), therefore, has two determinants: conductance of the alveolo-capillary membrane resistance (D_M) and capillary blood volume (Qc), provided that haemoglobin concentration is normal. Consequently, the overall resistance to pulmonary diffusion can be described [52] as:

$$1/D_L = 1/D_M + 1/Qc. \quad (5)$$

In patients with CHF the diffusion capacity of the lung (D_L) is reduced and this correlates with heart failure severity [34,36]. The main contributor is a reduction in D_M [53], whereas capillary blood volume can be variable. This reduction in D_M results from interstitial oedema and fibrosis [54], both reversible. Treatment with angiotensin-converting enzyme (ACE) inhibitors and anti-aldosteronic drugs can improve diffusion capacity, which is paralleled by an improvement of the VE/V_{CO_2} and VD/VT ratios [55].

However, there is evidence that D_M remains low even years after heart transplantation [56]. The question of whether this reduction of diffusion capacity does contribute to exercise limitation and the enhanced ventilatory response to exercise in CHF is still an unresolved issue [57]. D_M closely correlates with peak oxygen uptake [58], but on the one hand, it has been shown that it may decreases during exercise, possibly as a result of the formation of interstitial oedema [59]. On the other hand, D_M may increase, but the extent of this increase is very limited and is accompanied by an increase in VC so that D_L remains constant [60].

However, diffusing capacity does not seem to limit alveolar oxygen consumption, that is, arterial hypoxaemia is not a typical finding in CHF [61]. Therefore, the correlations between diffusion capacity (or D_M) and markers of exercise capacity might not reveal a causal relationship but reflect a common determinant, namely poor haemodynamic response to exercise, with high left ventricular filling pressures and consecutive increases in pulmonary capillary pressure.

Pulmonary perfusion

The pulmonary circulation is characterized by a low vascular tone with a further reduction of pulmonary vascular resistance when blood flow increases [62]. This results in a low pulmonary artery pressure, which only mildly increases when cardiac output increases. Apart from this global haemodynamic characteristic, the regional distribution of blood flow within the lungs is tightly regulated by small pre-capillary resistance vessels. A major regulator of regional flow distribution is hypoxic vasoconstriction (Euler–Liljestrand mechanism); a fall in alveolar pressure of O_2 results in increased vascular tone and reduced blood flow through the related lung compartment [63,64]. This leads to a matching between pulmonary ventilation and perfusion, which minimizes intrapulmonary shunt (i.e. perfusion relatively large for the corresponding ventilation and therefore small alveolar spaces, favouring pulmonary-venous PO_2) and dead space ventilation (i.e. perfusion relatively small for the corresponding ventilation). Numerous vasodilators (nitric oxide, prostacyclin) [65–68] and vasoconstrictors (thromboxane, endothelin-1) [69–71] are involved in this regulatory process.

In CHF increased left ventricular filling pressures lead to pulmonary venous hypertension. This increase in pulmonary artery pressure is further augmented by an increase in pulmonary vascular resistance [62]. Haemodynamic studies in patients with mitral stenosis before and after mitral valve replacement show a prompt reduction in pulmonary vascular resistance after normalization of pulmonary venous pressures [72,73], which suggests that the increase in pulmonary vascular tone is a direct response to the increase in pulmonary venous pressures. The increase in vascular tone results from both an impairment of basal vasodilator activity and augmented vasopressor stimuli. It has been shown that the basal release of nitric oxide, a potent vasodilator [66], from the pulmonary vascular endothelium is reduced in patients with heart failure and secondary pulmonary hypertension [74–76], but can be stimulated by acetylcholine. There is reduced prostacyclin synthesis with a concomitant increase in the synthesis of thromboxane [69]. Endothelin-1 levels are elevated in heart failure and, in conjunction with the downregulation of pulmonary ET-B receptors, this produces pulmonary vasoconstriction [70,77].

These mechanisms lead not only to an increase in overall pulmonary vascular resistance, but also to an impairment of regional pulmonary blood flow distribution, as evident from scintigraphic studies [78]. This leads to an irregularity of pulmonary perfusion despite normal distribution of ventilation. This is referred to as pulmonary ventilation–perfusion mismatch. The failure to adequately reduce this mismatch during exercise may contribute to the low exercise capacity in patients with CHF [79].

Dead space ventilation

The theoretical volume of gas in the airways and the lungs, which does not contribute to gas exchange,

constitutes the dead space ventilation (VD). It can be divided into 'serial dead space' (previously called 'anatomical dead space') and 'alveolar dead space'. Serial dead space largely consists of the volume of the mouth, pharynx and large airways; its absolute volume might be relatively steady with time within any one patient. Alveolar dead space arises because perfusion of alveoli is insufficient for, or insufficiently well matched to, alveolar ventilation (VA); its absolute volume normally falls with exercise (if cardiac output rises sharply and in a well-distributed fashion). But alveolar dead space ventilation could also rise if cardiac output fails to rise adequately or becomes maldistributed.

VD/VT, the ratio between physiological dead space and tidal volume, constitutes an index of this mismatching between ventilation and perfusion, and it may be calculated according to the Bohr equation:

$$VD/VT = (P_{CO_2} - PET_{CO_2})/P_{CO_2} - VD\ valve/VT \quad (6)$$

where VD valve represents the mouthpiece and valve dead space volume. Non-invasive assessment of PCo_2 estimated by $PETco_2$, is not reliable and underestimates the real value, calculated by arterial sampling.

At rest the value of VD/VT ranges between 0.3 and 0.5, but on exercise it is reduced to 0.2. In patients with lung diseases, due to both ventilatory or perfusion abnormalities of the alveoli, this ratio is elevated at rest and does not fall on exercise [80].

Patients with CHF may fail to appropriately reduce their VD/VT ratio during exercise, which may contribute to exercise hyperpnoea [81]. Although the serial and alveolar components have not been measured directly, they both seem to be involved in this phenomenon. Patients with more severe heart failure had a more rapid and shallow breathing pattern, as well as an increased difference between end-tidal and arterial Pco_2, which suggests increased alveolar dead space. The increase in alveolar dead space has to arise from mechanisms that impede the improvement of ventilation/perfusion matching during exercise. The correlation of the VE/Vco_2 slope with severity of pulmonary hypertension [82] and cardiac output [83] suggests that pulmonary vasoconstriction and low pulmonary blood flow are potential contributors. Abnormal regulation of pulmonary vascular tone could lead to an uneven flow distribution through the lungs. Alternatively, assuming that the increase in cardiac output is a major facilitator of even blood flow distribution, a low cardiac output would lead to less of an improvement in blood flow distribution during exercise.

VE/Vco_2 slope

The VE/Vco_2 slope has emerged in recent years as a very popular parameter in patients with CHF and one of the most powerful CHF prognosticators [81,84,85]. During exercise, VE and Vco_2 are linearly related until the RER, where VE increases disproportionately to Vco_2. The slope of this relationship, before the RER, reflects the gain of chemoreceptors that triggers ventilation in response to changes in Pco_2 in the blood. The VE/Vco_2 slope has been related to increased pulmonary dead space, to the decrease of pulmonary blood flow, and to the activation of ergoreceptors originating from the muscle.

This slope is increased in CHF: normal values are between 20 and 30 while in CHF it can reach values around 80 (Fig. 7). The VE/Vco_2 is improved by training and by treatment. VE/Vco_2 slope appeared to better predict prognosis than peak Vo_2, particularly in two situations: (1) in the case of submaximal exercise; (2) in the case of beta-blocker therapy, where prognosis improves with treatment whereas peak Vo_2 generally remains unchanged or increases only slightly and VE/Vco_2 slope is decreased [86].

Whether the VE/Vco_2 slope should be calculated across the overall data or only until the RQ is still controversial [87]: using all points seems to increase the prognostic value [88].

Another slope, the oxygen uptake efficiency slope, relating linearly Vo_2 and the logarithm of VE during exercise, is another interesting parameter obtainable in cases of submaximal exercise [89]. It is decreased in heart failure.

Cardiac output

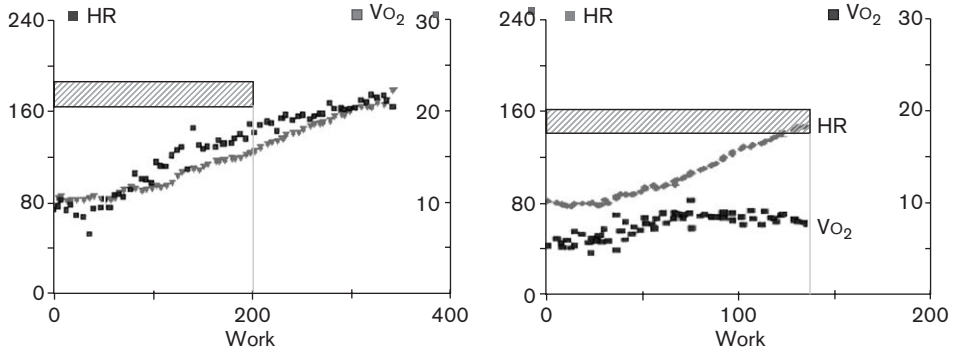
Cardiac output (CO) increases with exercise to support the increasing metabolic demands of the tissues. In normal subjects, according to the Fick equation [equation (1)], CO is a linear function of Vo_2 [90].

Increases in CO are initially accomplished by increases in SV and HR, and then at moderate to high-intensity exercise almost exclusively by increases in HR. The evaluation of HR response yields an estimation of cardiac function during exercise. The increase in cardiac output is largely driven by vagal withdrawal and by increases in either circulating or neurally produced catecholamines. Indirect measurement of cardiac function on exercise (HR, HR–Vo_2 relationship, O_2 pulse), assessed during CPET testing, has been proposed.

Heart rate (HR)

According to the Fick equation, it can be derived that HR measurement should be a simple guide to cardiac function during exercise, given the modest changes in SV. In healthy subjects, heart rate increases nearly linearly with increasing Vo_2 (Fig. 8). Increases in HR are initially mediated by a decrease in parasympathetic activity (vagal withdrawal) and, subsequently, almost exclusively

Fig. 8



Heart rate (HR)- and O_2 pulse–work rate relationships in a normal subject (Normal) and in a patient with chronic heart failure (CHF).

by increased sympathetic activity. Achievement of age-predicted values for maximal HR during exercise is often used as a reflection of maximal or near maximal effort, and presumably signals the achievement of $V_{O_{2max}}$. However, the use of this marker as a strict exercise end-point is not recommended [8]. Considerable variability (10–15 beats/min) within an age group is noted when available estimates of maximal HR are used, and as such, may complicate interpretation, as might the effects of bradycardic medication.

HR–V_{O_2} relationship

This relationship is often non-linear at low work rates for upright exercise, becoming relatively linear as work rate increases to maximum. It can be described by the slope and position of the regression line. The slope of the HR–V_{O_2} relationship is a function of the subject's SV and $C(A-V)O_2$ (see below). In the absence of anaemia, shunt, or hypoxia, the higher the SV, the lower the HR and, typically, its rate of change. HR at a given V_{O_2} is higher than normal in patients with lung disease, implying that SV must be lower, because cardiac output is similar to that of normal subjects. This may reflect deconditioning or relative unfitness, ventilatory limitation to exercise and, possibly, the haemodynamic consequences of dynamic hyperinflation. Patients with reduced O_2 delivery due to reduced O_2 content (hypoxaemia, anaemia, carboxyhaemoglobin, etc.), patients with abnormal O_2 utilization (metabolic myopathy), as well as patients with deconditioning, may also have an upward and steep HR–V_{O_2} relationship with (near) attainment of maximal heart rate.

Oxygen pulse (V_{O_2}/HR)

The ratio of V_{O_2} to HR is conventionally termed the 'oxygen pulse' and reflects the amount of O_2 extracted per heart beat. The O_2 pulse has been used as an estimator of stroke volume during exercise [2]; however, this remains controversial, especially in patients who desaturate. According to the modified Fick equation, the O_2 pulse is numerically equal to the product of SV and the arterial-to-mixed venous O_2 content difference, $C(A-V)O_2$.

The O_2 pulse normally increases with incremental exercise because of increases in both SV and O_2 extraction. At a near maximal/maximal work rate, in which $C(A-V)O_2$ is assumed to be maximal and relatively constant, the pattern of change of the O_2 pulse will represent the concomitant pattern of change of the SV, as long as the previous assumption is correct. The basic profile of the O_2 pulse over the range in which V_{O_2} increases linearly with HR appears to be hyperbolic, with a rapid rise at low work rates followed by a slow approach to an asymptotic value. A low, unchanging, flat O_2 pulse with increasing work rate may therefore be interpreted as resulting from a reduced SV, and/or as a failure for further skeletal muscle O_2 extraction, and/or occurrence of exercise-induced ischaemia. A low O_2 pulse therefore may reflect deconditioning, cardiovascular disease, and early exercise limitation due to ventilatory constraint, lung diseases or symptoms.

In CHF, impaired CO response on exercise is determined by alteration in all the above-mentioned indices. Chronotropic incompetence to exercise is charged with poor prognosis: the CHF patients with HR at peak exercise < 135 beats/min have a lower survival rate with respect to those with HR > 44 beats/min [31]. Similarly for the HR–V_{O_2} and oxygen pulse, down-slopes of these relationships are present in CHF: during exercise the progressive rise in HR is not adequately reflected by a proportional rise in V_{O_2}. However, these changes are not specific for CHF and many other factors may affect these patterns on exercise, for example, the presence of atrioventricular block or therapy (beta-blockade, calcium-channel blockers).

Blood pressure response

As exercise intensity increases, reflex control of distribution of cardiac output causes some characteristic changes in blood pressure and vascular resistance [91]. In working muscle, there are local mediators that cause intense vasodilation that increases blood flow to support metabolic demands. In addition, non-working muscles are vasoconstricted from reflex increases in sympathetic nerve activity [92]. The net result is a fall in systemic vascular resistance, but systolic blood pressure typically rises progressively with an increase in V_{O_2}. Diastolic blood pressure typically remains constant or may decline slightly if left heart function keeps up with the increases in cardiac output. Abnormal patterns of blood pressure response include excessive rise, reduced rise, or a fall.

An excessive rise in blood pressure is often seen in patients with known resting hypertension, but an abnormal rise with exercise in the face of normal resting blood pressure is also indicative of abnormal blood pressure control. If blood pressure does not increase with exercise, or in fact declines, a cardiac limitation or abnormality of sympathetic control of blood pressure is strongly suggested. If blood pressure falls as exercise intensity increases, the exercise test should be terminated immediately, as such a response could indicate serious abnormality such as heart failure, ischaemia, or restriction to blood flow, such as aortic stenosis, pulmonary vascular disease, or central venous obstruction.

Like the other indices of CO, the blood pressure response is impaired in CHF, with an impaired rise during progressive exercise. A systolic blood pressure value < 120 mmHg is associated with exercise intolerance ($VO_{2peak} \leq 14$ ml/kg per min) and reflects a poor prognosis [93]. The same limitations affecting the interpretation of the above indices of CO, also apply to the blood pressure response.

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Appendix

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