

## Review

# Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association of Cardiovascular Prevention and Rehabilitation

Alessandro Mezzani<sup>a</sup>, Piergiuseppe Agostoni<sup>b</sup>, Alain Cohen-Solal<sup>d</sup>, Ugo Corrà<sup>a</sup>, Anna Jegier<sup>f</sup>, Evangelia Koudi<sup>g</sup>, Sanja Mazic<sup>h</sup>, Philippe Meurin<sup>e</sup>, Massimo Piepoli<sup>c</sup>, Attila Simon<sup>i</sup>, Christophe Van Laethem<sup>j</sup> and Luc Vanhees<sup>k</sup>

<sup>a</sup>S. Maugeri Foundation, Veruno Scientific Institute, Cardiology Division, Veruno (NO), <sup>b</sup>Centro Cardiologico Monzino, Institute of Cardiology, University of Milan, Milan, <sup>c</sup>Heart Failure Department, Cardiology Unit, Guglielmo da Saliceto Hospital, Piacenza, Italy, <sup>d</sup>Department of Cardiology, University Denis Diderot-Hospital Lariboisiere, Assistance Publique-Hôpitaux de Paris, Paris, <sup>e</sup>Les Grands Prés, Cardiac Rehabilitation Center, Villeneuve Saint Denis, France, <sup>f</sup>Department of Sports Medicine, Medical University, Lodz, Poland, <sup>g</sup>Laboratory of Sports Medicine, Aristotle University, Thessaloniki, Greece, <sup>h</sup>Institute of Medical Physiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia, <sup>i</sup>State Hospital for Cardiology, Balatonfüred, Hungary, <sup>j</sup>Cardiovascular Center, Onze Lieve Vrouw Ziekenhuis, Aalst and <sup>k</sup>Department of Rehabilitation Sciences-Biomedical Sciences, KU Leuven, Leuven, Belgium

Received 6 November 2008 Accepted 4 January 2009

Cardiopulmonary exercise testing (CPET) is a methodology that has profoundly affected the approach to patients' functional evaluation, linking performance and physiological parameters to the underlying metabolic substratum and providing highly reproducible exercise capacity descriptors. This study provides professionals with an up-to-date review of the rationale sustaining the use of CPET for functional evaluation of cardiac patients in both the clinical and research settings, describing parameters obtainable either from ramp incremental or step constant-power CPET and illustrating the wealth of information obtainable through an experienced use of this powerful tool. The choice of parameters to be measured will depend on the specific goals of functional evaluation in the individual patient, namely, exercise tolerance assessment, training prescription, treatment efficacy evaluation, and/or investigation of exercise-induced adaptations of the oxygen transport/utilization system. The full potentialities of CPET in the clinical and research setting still remain largely underused and strong efforts are recommended to promote a more widespread use of CPET in the functional evaluation of cardiac patients. *Eur J Cardiovasc Prev Rehabil* 00:000-000 © 2009 The European Society of Cardiology

European Journal of Cardiovascular Prevention and Rehabilitation 2009, 00:000-000

**Keyword:** anaerobic threshold, cardiac disease, cardiopulmonary exercise testing, critical power, functional evaluation, oxygen consumption, ventilation

Correspondence to Dr Alessandro Mezzani, MD, S. Maugeri Foundation, Veruno Scientific Institute, IRCCS, Cardiology Division, Laboratory for the Analysis of Cardiorespiratory Signals, Via per Revislate 13, Veruno (NO) 28010, Italy  
Tel: +39 322 884711; fax: +39 322 830294; e-mail: amezzani@fsm.it  
A. M. and L. V. are current and past Chair, respectively, of the Exercise Physiology Section of the European Association of Cardiovascular Prevention and Rehabilitation.

Experts panel: S. Adamopoulos, Onassis Cardiac Surgery Center, 2nd Department of Cardiology, Athens, Greece; S. Gielen, Department of Cardiology, University of Leipzig, Leipzig Heart Center, Leipzig, Germany; M. Metra, Section of Cardiovascular Diseases, Department of Experimental and Applied Medicine, University of Brescia, Brescia, Italy; J-P. Schmid, Department of Cardiology, Cardiovascular Prevention and Rehabilitation, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland

## Introduction

Cardiopulmonary exercise testing (CPET) is a methodology that has profoundly changed the approach to patients' functional evaluation, linking performance and physiological parameters to the underlying metabolic substratum and providing highly reproducible exercise capacity descriptors, for example, peak oxygen uptake (peakVO<sub>2</sub>) [1-3]. Moreover, CPET has dramatically increased the mass of information obtainable from a

**Table 1 Aims of cardiac patients functional evaluation**

Reproducible assessment of patient's exercise capacity
Prescription of endurance training intensity
Evaluation of response to endurance training
Evaluation of response to therapeutic interventions (drugs, ventricular resynchronization, etc.) affecting exercise capacity
Evaluation of the O <sub>2</sub> transport and utilization system efficiency (ventilatory, hemodynamic, and metabolic components)

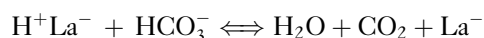
relatively simple and inexpensive procedure such as exercise testing, furnishing an all-round vision of the systems involved in both O<sub>2</sub> transport from air to mitochondria and its utilization, and making it possible to identify the link(s) limiting the exercise capacity in the individual patient. However, during the last 20 years, the use of CPET for prognostic purposes [mainly in chronic heart failure (CHF) patients] has overshadowed its application for the functional evaluation of cardiac patients, indeed its original one. This report aims to provide professionals with an up-to-date review of the rationale sustaining the use of CPET for the functional evaluation of cardiac patients in both clinical and research settings (Table 1), describing parameters obtainable either from ramp incremental or step constant-power CPET, as specified in the respective paragraphs.

Finally, as treatment of the use of CPET for differentiation of cardiac versus pulmonary causes of dyspnea and/or impaired exercise capacity is not a specific goal of this report, readers interested in this topic are referred to previously published reviews [4], as are those interested in the use of CPET for prognostic stratification of patients with cardiac disease (in particular, CHF) [5].

## Use of cardiopulmonary exercise testing for the evaluation of O<sub>2</sub> transport and utilization efficiency

### Ventilatory anaerobic threshold

During incremental exercise, an energy requirement is reached above which blood lactate concentration increases at a progressively steeper rate [6]. This is because of anaerobic glycolysis activation, that occurs as the oxygen supply rate is not rapid enough to reoxidize cytosolic NADH + H<sup>+</sup> [7]. Almost all of the H<sup>+</sup> generated in the cell from lactic acid (La) dissociation is buffered by bicarbonate according to the following reaction:



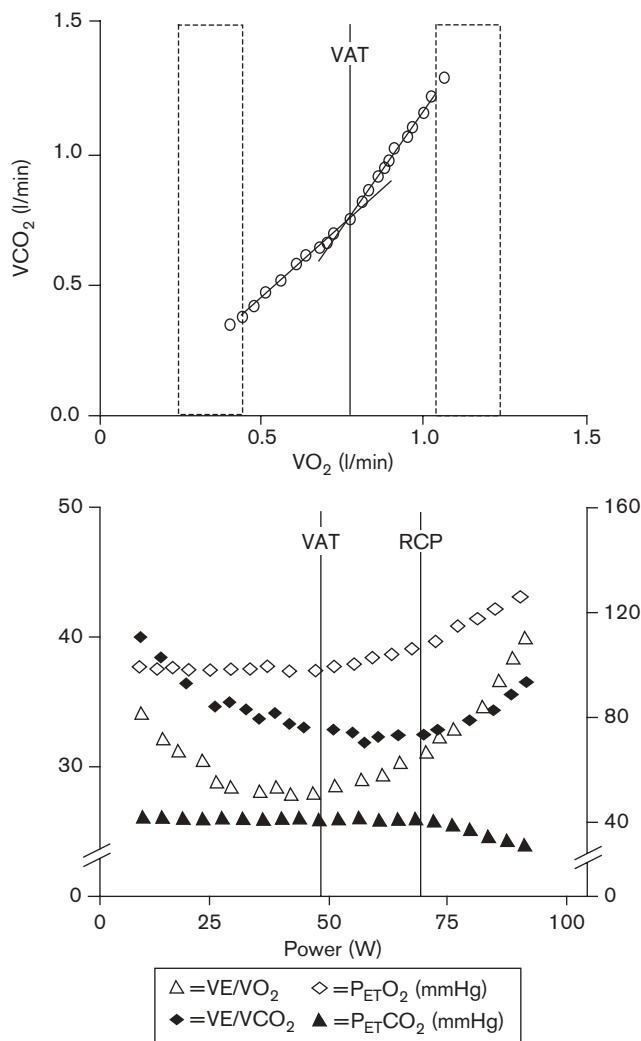
Such a production of CO<sub>2</sub>, in excess of that produced by aerobic metabolism (excess CO<sub>2</sub>), makes the CO<sub>2</sub> production (VCO<sub>2</sub>) versus VO<sub>2</sub> relationship become steeper. This has been labeled 'anaerobic threshold' or also 'aerobic threshold' or 'first lactate turn point', with some terminology disagreement in the scientific literature [8], and is a reliable index of aerobic fitness used for training prescription in both normal individuals and

cardiac patients, especially for sustainable submaximal work [9,10]. Interindividual variance, exercise protocol (e.g. fast versus slow work rate increments, step versus ramp protocols) [11], blood sampling source (e.g. venous, capillary, arterial, arterialized) [12], and type of exercise (e.g. running, swimming, cycling, rowing, etc.) [13] can all affect blood lactate kinetics.

By measuring gas exchange modifications induced by metabolic changes at the mouth, the 'ventilatory anaerobic threshold' (VAT) can be determined analyzing the slope of the VCO<sub>2</sub> versus VO<sub>2</sub> (plotted on equal scales) relationship during ramp incremental exercise (V-slope method) [14], where VAT is the point of transition of the VCO<sub>2</sub> versus VO<sub>2</sub> slope from less than 1 (activation of aerobic metabolism alone) to greater than 1 (anaerobic plus aerobic metabolism) (Fig. 1, upper panel). Moreover, the excess CO<sub>2</sub> produced above VAT increases ventilatory drive, which keeps the ventilation (VE) versus VCO<sub>2</sub> relationship linear and the end-tidal CO<sub>2</sub> pressure (P<sub>ET</sub>CO<sub>2</sub>) value constant (i.e. the individual does not hyperventilate with respect to the volume of CO<sub>2</sub> metabolically produced). However, an inversion of the VE versus VO<sub>2</sub> relationship behavior (increase versus initial decrease, i.e. hyperventilation with respect to O<sub>2</sub>) is observed above VAT; this makes both the VE versus VO<sub>2</sub> ratio and end-tidal O<sub>2</sub> pressure increase, in the presence of a still decreasing or constant VE/VCO<sub>2</sub> and P<sub>ET</sub>CO<sub>2</sub>. VAT is thus also identifiable with the nadir of the VE versus VO<sub>2</sub> relationship and with the point where end-tidal O<sub>2</sub> pressure begins to increase [2] (Fig. 1, lower panel). In the final phase of exercise, hyperventilation does occur also with respect to CO<sub>2</sub> (respiratory compensation point), making VE/VCO<sub>2</sub> increase and P<sub>ET</sub>CO<sub>2</sub> decrease [15] (Fig. 1- lower panel). VAT is usually expressed as a VO<sub>2</sub> value relative to predicted maximal oxygen uptake (VO<sub>2max</sub>), the lower limit of normality being 40% of predicted VO<sub>2max</sub> [16]. In the vast majority of healthy individuals, VAT occurs at approximately 40–60% of VO<sub>2max</sub> (Table 2); in trained endurance athletes, VAT can reach intensities as high as 80% of their VO<sub>2max</sub> [23].

All cardiac diseases affecting the O<sub>2</sub> transport chain (typically CHF) can determine a pathologic VAT (i.e. < 40% predicted VO<sub>2max</sub>) [24], as can deconditioning following bed rest for cardiac events, even in the presence of normal left ventricular systolic function [25]. However, when expressed relative to measured peakVO<sub>2</sub> (and not to predicted VO<sub>2max</sub>), VAT will still occur at approximately 40–60% of peakVO<sub>2</sub> in most cardiac patients, with a trend toward higher percentages of peakVO<sub>2</sub> in patients with CHF [7,16,24,26]. Notably, VAT may be not detectable in a variable percentage of patients [27], and especially in those with CHF because of exercise oscillatory VE and/or shortness of exercise time.

Fig. 1



Upper panel: CO<sub>2</sub> production (VCO<sub>2</sub>) as a function of oxygen uptake (VO<sub>2</sub>) during ramp incremental exercise (V-slope plot). The point where the VCO<sub>2</sub> versus VO<sub>2</sub> slope increases in steepness is the ventilatory anaerobic threshold (VAT). The initial and final phases of exercise data (dotted rectangles) are usually excluded from the analysis because of possible hyperventilation during these periods. Lower panel: ventilatory equivalents for O<sub>2</sub> (VE/VO<sub>2</sub>) and CO<sub>2</sub> (VE/VCO<sub>2</sub>) and end-tidal O<sub>2</sub> (P<sub>ET</sub>O<sub>2</sub>) and CO<sub>2</sub> (P<sub>ET</sub>CO<sub>2</sub>) pressures as a function of power (W) during ramp incremental exercise. The nadir of VE/VO<sub>2</sub> and the breakpoint of P<sub>ET</sub>O<sub>2</sub> is the VAT, whereas the nadir of VE/VCO<sub>2</sub> and the breakpoint of P<sub>ET</sub>CO<sub>2</sub> is the respiratory compensation point (RCP).

### Maximal oxygen uptake

VO<sub>2max</sub> is a parameter which describes the maximal amount of energy obtainable by aerobic metabolism per unit of time (aerobic power). VO<sub>2</sub> is defined by the Fick equation:

$$VO_2 = CO \times C(a-v)O_2$$

where CO is cardiac output and C(a-v)O<sub>2</sub> is the arteriovenous O<sub>2</sub> content difference. In healthy individuals, VO<sub>2max</sub> is mostly limited by CO rather than by peripheral

factors [28], its value, however, being influenced by several parameters, such as arterial O<sub>2</sub> content, fractional distribution of CO to exercising muscles, and muscle ability to extract O<sub>2</sub>; recent data also indicate a possible role of a central nervous system governor [29]. VO<sub>2max</sub> attainment is evidenced by failure of VO<sub>2</sub> to increase despite increasing work rate [30]. However, flattening of the VO<sub>2</sub> versus power relationship is not seen often in routine clinical practice, and therefore a more realistic goal is to assess peakVO<sub>2</sub> rather than VO<sub>2max</sub>. PeakVO<sub>2</sub> is defined as the highest VO<sub>2</sub>, averaged over a 20 to 30-s period, achieved at presumed maximal effort during an incremental exercise test, and may or may not be equal to VO<sub>2max</sub>, even if available evidence suggests that these two concepts are substantially analogous [31]. In any case, peakVO<sub>2</sub> describes patients' exercise tolerance far more reliably than exercise duration or peak power [32]. Achievement of truly maximal effort (and thus of reliable VO<sub>2max</sub> values) can be assumed in the presence of one or more of the following criteria [33]:

- (1) Failure of VO<sub>2</sub> and/or heart rate to increase with further increases in work rate.
- (2) Peak respiratory exchange ratio (VCO<sub>2</sub>/VO<sub>2</sub>) ≥ 1.10–1.15.
- (3) Postexercise blood lactate concentration ≥ 8 mmol/dl.
- (4) Rating of perceived exertion ≥ 8 (on the 10-point Borg scale).

Normal values of VO<sub>2max</sub> depend on age and sex, and are influenced by body size, level of physical activity, and genetic endowment [34]. VO<sub>2max</sub> is measured in liters or milliliters of O<sub>2</sub> per minute, or in milliliters of O<sub>2</sub> per kilogram of body weight per minute. The highest values of VO<sub>2max</sub> are reported in endurance athletes (94 ml/kg per min) [35]. VO<sub>2max</sub> declines on average by 10% per decade after the age of 30, because of decreasing maximal heart rate, stroke volume, blood flow to skeletal muscle, and skeletal muscle aerobic potential with age [36]. VO<sub>2max</sub> is also 10 to 20% greater in males than in females of comparable age [37], because of higher hemoglobin (Hb) concentration and greater muscle mass and stroke volume in males. Several formulae based on age and body dimensions are available for VO<sub>2max</sub> prediction in sedentary men and women, the most detailed recommendation being provided by Wasserman *et al.* [16] (Table 2).

Many cardiovascular diseases can affect VO<sub>2max</sub>/peakVO<sub>2</sub>. Namely, all pathologies impairing CO response to exercise will determine some degree of reduction of peakVO<sub>2</sub> with respect to predicted VO<sub>2max</sub>. For example, in patients with CHF peakVO<sub>2</sub> is classically reduced with respect to age-matched and sex-matched normal individuals [24], but is also lower than normal in patients with preserved left ventricular function entering a rehabilitation program after recent cardiac surgery [38], because of

**Table 2 Normal values**

Parameters	Normal values			Formulae
VO <sub>2</sub> at VAT (ml/min) [16]	> 40% predicted VO <sub>2max</sub> , 40–60% peakVO <sub>2</sub>			–
Critical power (W) [17]	65–70% of peak power, 25–30% of ΔVAT – peak power			–
VO <sub>2max</sub> (ml/min) [16]	Age (years)	M <sup>a</sup>	F <sup>a</sup>	Sedentary men <sup>b</sup> [50.72–(0.372 × age)] × weight Sedentary women <sup>b</sup> [22.78–(0.17 × age)] × (weight + 43)
	20	3246 (43.3)	1996 (33.3)	
	30	2967 (39.6)	1821 (30.3)	
	40	2688 (35.8)	1646 (27.4)	
	50	2409 (32.1)	1471 (24.5)	
	60	2130 (28.4)	1296 (21.6)	
	70	1851 (24.7)	1121 (18.7)	
	80	1572 (21.0)	945 (15.7)	
VO <sub>2</sub> on-kinetics mean response time (s) [18]	30–44	34–43		Sedentary men (0.67 × age) + 13.9
	45–59	44–53		
	60–80	54–67		
VO <sub>2</sub> off-kinetics T <sub>1/2</sub> (s) [19]		60 ± 20 <sup>c</sup>		–
O <sub>2</sub> uptake efficiency slope [(ml/min)/(l/min)] [20]		M <sup>d</sup>	F <sup>d</sup>	Sedentary men <sup>d</sup> Sedentary women <sup>d</sup>
	50–59	2647–2407	1773–1630	1.320–(26.7 × age) + (1.394 × BSA)
	60–69	2380–2140	1615–1472	
	70–80	2113–1846	1457–1300	1.175–(15.8 × age) + (841 × BSA)
VE versus VCO <sub>2</sub> slope [21]		M	F	Sedentary men (0.12 × age) + 21 Sedentary women (0.08 × age) + 25.2
	20–39	23.4–25.7	26.8–28.3	
	40–59	25.8–28.1	28.4–29.9	
	60–80	28.2–30.6	30.0–31.6	
Peak cardiac output (l/min) [22]		–		
Peak circulatory power (mmHg × ml/kg per min)		M <sup>f</sup>	F <sup>f</sup>	5 × peakVO <sub>2</sub> + 3 <sup>e</sup> –
	20–39	8600–7000	6660–5600	
	40–59	7050–5680	5480–4400	
	60–80	5630–4200	4320–3140	

BSA, body surface area; F, females; M, males; peakVO<sub>2</sub>, peak oxygen consumption; T<sub>1/2</sub>, time necessary for VO<sub>2</sub> to decrease by 50% from its peak effort value; VAT, ventilatory anaerobic threshold; VO<sub>2max</sub>, maximal oxygen uptake. <sup>a</sup>Values are calculated for men of 75 kg and women of 60 kg weight, values in brackets are ml/kg per min. <sup>b</sup>Formula for normal weight individuals, Ref. [16] also reports formulae for underweight and overweight individuals. <sup>c</sup>Value for VO<sub>2</sub> off-kinetics after incremental exercise. <sup>d</sup>Values are calculated for men of 1.9 m<sup>2</sup> BSA and women of 1.65 m<sup>2</sup> BSA. <sup>e</sup>PeakVO<sub>2</sub> in liters/minute for 20–50 year old males. <sup>f</sup>Values are calculated for VO<sub>2max</sub> reported above and peak systolic blood pressure of 200 mmHg.

bed rest-induced deconditioning. When possible, determination of peakVO<sub>2</sub> in patients referred for cardiac rehabilitation is a cornerstone for rational exercise prescription and evaluation of training efficacy [39,40].

**Critical power**

Critical power represents the highest power sustainable in conditions of both VO<sub>2</sub> and lactate steady state [17], overlapping, as such, the concept of maximal lactate steady state, that is, the highest power sustainable in conditions of stable blood lactate concentration [41]. As aerobic exercise is usually performed in steady-state conditions, the critical power is a crucial (though quite neglected) marker of the upper limit of sustainable aerobic training intensity [42], situated between VAT and peakVO<sub>2</sub> powers as assessed during ramp incremental CPET.

From a mathematical standpoint, critical power corresponds to the power asymptote of the hyperbolic relationship linking power and duration of the constant-power exercise [17]. The determination of critical power requires the performance of four to five constant-power exercise tests in the above-VAT threshold effort intensity domains (see section ‘VO<sub>2</sub> on-kinetics’), with relative intensities ranging between 70 and 120% of peak power reached during an incremental ramp exercise test [17]; the critical power is then obtained by fitting a rectangular

hyperbola on the obtained power versus duration points (Fig. 2). Such a procedure is of course not feasible in the routine clinical setting; however, the existence of a very close correlation between critical power and power at respiratory compensation point during ramp incremental CPET has been described [43]. If these data were confirmed, a single and easy-to-perform test, CPET, would provide operators with all the parameters describing O<sub>2</sub> transport and utilization system efficiency, that is, anaerobic threshold, critical power, and peakVO<sub>2</sub>.

Critical power has been evaluated by several authors in sedentary young normal individuals, revealing repeatable values around 65–70% of peak power (or 25–30% of ΔVAT – peakVO<sub>2</sub> power) (Table 2) at incremental exercise testing, with a steady-state VO<sub>2</sub> mean value corresponding to 70–80% of peakVO<sub>2</sub> [17,42]. Elderly individuals show critical power values similar to those of young individuals when expressed relative to peak power, but with higher relative steady-state VO<sub>2</sub> values (approximately 80–90% of peakVO<sub>2</sub>), demonstrating a broadening of the high-intensity domain of effort, probably aimed at preservation of habitual activities performance in steady-state, nonfatiguing metabolic conditions [44]. Notably, similar to the other O<sub>2</sub> transport and utilization system efficiency descriptors, critical power is also increased by aerobic training [45].

No data are currently available on critical power in cardiac patients. However, there is information suggesting that CHF patients can perform their habitual activities at absolute and relative intensities higher than the individual VAT [46]. This underlines the need for studies addressing critical power in this population.

### VO<sub>2</sub> on-kinetics

During the constant-power exercise below the anaerobic threshold (moderate-intensity effort domain), three phases of VO<sub>2</sub> on-kinetics are classically described in human physiology [47–49]: phase I, during which the VO<sub>2</sub> increase would rely mostly on pulmonary blood flow (i.e. CO) increment in the presence of an unchanging C(a–v)O<sub>2</sub>; phase II, characterized by a monoexponential VO<sub>2</sub> increase mainly reflecting skeletal muscle VO<sub>2</sub> consumption, as described by C(a–v)O<sub>2</sub> widening; and phase III, that is, steady-state attainment (Fig. 3). As VO<sub>2</sub> does not reach instantaneously its steady-state value at step exercise onset, during phase I and phase II an O<sub>2</sub> deficit accumulates, defined as the cumulative difference between steady-state VO<sub>2</sub> level and VO<sub>2</sub> levels throughout the whole on-response (Fig. 3); the O<sub>2</sub> deficit will be larger the greater the recourse to anaerobic energy sources (alactic and lactic) and body O<sub>2</sub> stores before steady-state attainment [49,50]. Above anaerobic threshold and up to critical power (high-intensity effort domain), it is still possible to reach a VO<sub>2</sub> steady state for constant-power efforts (see section ‘Critical power’), even if in this intensity domain an additional, delayed-onset VO<sub>2</sub> component (‘slow component’) adds to the expected steady-state VO<sub>2</sub> value according to the below-

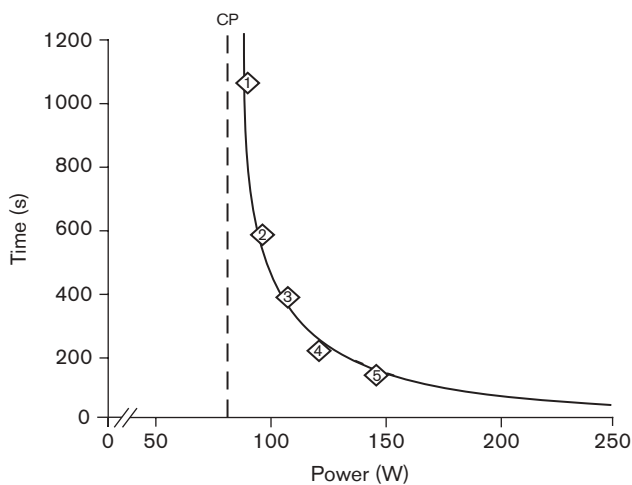
VAT VO<sub>2</sub> versus power relationship [49,51,52]. The latter can be determined either by performing multiple constant-power exercise tests at different below-VAT powers and then fitting a linear relationship on the obtained VO<sub>2</sub> versus power points, or with an incremental ramp CPET, by fitting a linear function to the breath-by-breath below-VAT VO<sub>2</sub> versus power data, excluding from the fitting window the initial nonincreasing or poorly increasing VO<sub>2</sub> period [53,54]; the VO<sub>2</sub> versus power slope values obtained with the above two methods have been shown to be superimposable [54]. Beyond critical power (very high-intensity effort domain), a steady state is no longer attainable, and the VO<sub>2</sub> slow component makes VO<sub>2</sub> increase inexorably up to VO<sub>2max</sub> [49,51,52].

The presence of the VO<sub>2</sub> slow component introduces some methodological caveats about VO<sub>2</sub> on-response evaluation in the high-intensity and very-high-intensity domains [51,52]; for this reason, VO<sub>2</sub> on-kinetics is more easily assessed during moderate-intensity effort, and can thus be evaluated also in individuals unable to exercise maximally. In this context, phase I is described in terms of its amplitude and duration, whereas the monoexponential VO<sub>2</sub> increase during phase II through its time constant (i.e. the time needed to reach 63% of the steady-state value), fitted on the VO<sub>2</sub> data starting from the phase I to phase II transition [49] (Fig. 3).

VO<sub>2</sub> on-kinetics in the moderate-intensity effort domain becomes more prolonged with age (Table 2), as demonstrated by increasing values of both its mean response time (i.e. the time constant of the whole VO<sub>2</sub> on-response, involving both phase I and phase II, fitted on the VO<sub>2</sub> data from time=0 of the exercise phase, see Fig. 3) [18] and phase II time constant [55], which is because of modifications of the O<sub>2</sub> transport and utilization system during the aging process described in the section ‘Maximal oxygen uptake’. Moreover, aerobic training affects the VO<sub>2</sub> on-kinetics similarly to the other descriptors of aerobic performance efficiency by shortening both the mean response time and the phase II time constant [56], that is, making the system adapt more rapidly to changes of loading conditions.

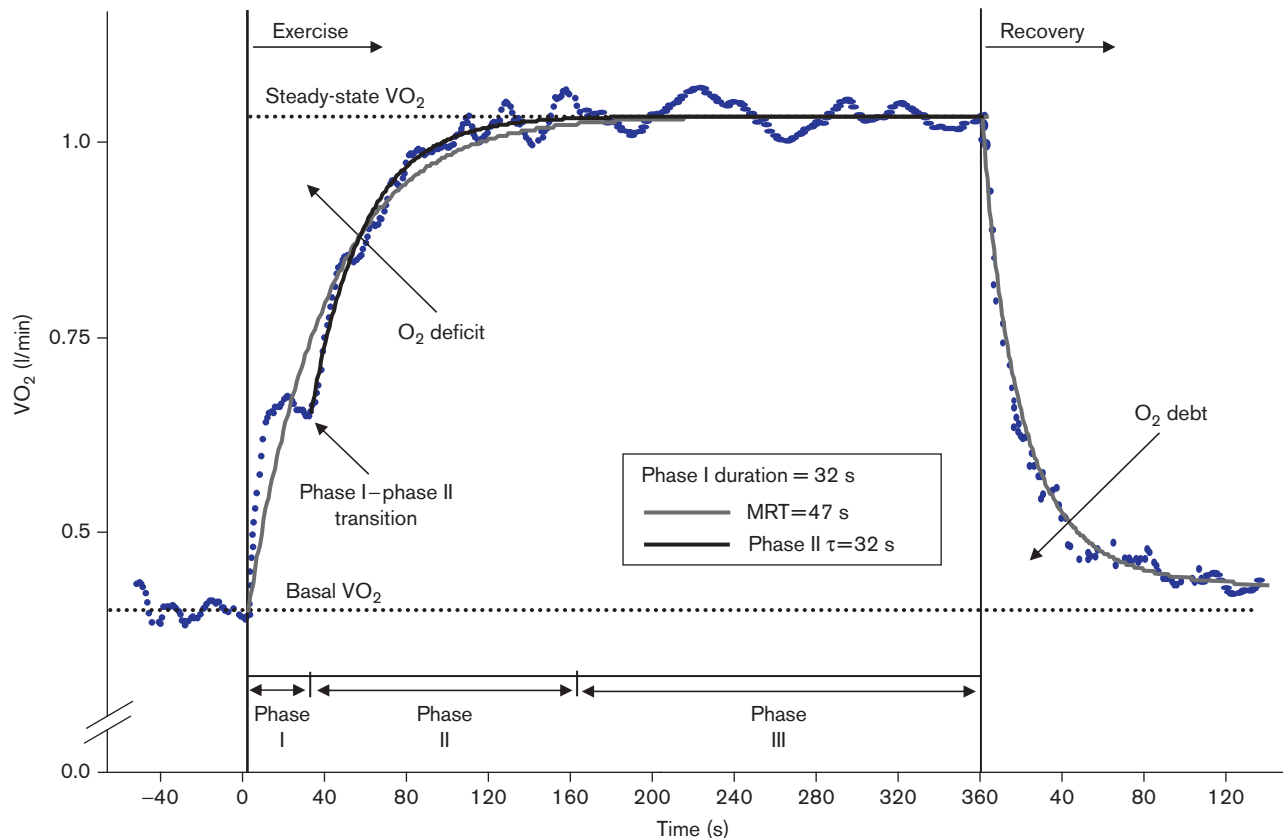
Cardiac disease can affect VO<sub>2</sub> on-kinetics in the moderate-intensity effort domain mainly by reducing O<sub>2</sub> delivery to exercising skeletal muscles. This is evidenced by a prolonged mean response time in patients with coronary artery disease and lone atrial fibrillation with respect to normal individuals [57,58], and is confirmed by the finding of improved VO<sub>2</sub> on-kinetics after percutaneous transluminal coronary angioplasty [59]. A significant prolongation of mean response time is also observed in patients with CHF [60], whose pathophysiology affects several steps of the O<sub>2</sub> transport/utilization system (see section ‘Patients with chronic heart failure’), whereas a

Fig. 2



Time as a function of power (W) for five constant-power exercise tests (1 = 50% of  $\Delta$  ventilatory anaerobic threshold (VAT) – peak oxygen consumption (peakVO<sub>2</sub>) power, 2 = 70% of  $\Delta$  VAT – peakVO<sub>2</sub> power, 3 = 90% of  $\Delta$  VAT – peakVO<sub>2</sub> power, 4 = 100% peakVO<sub>2</sub> power, 5 = 120% peakVO<sub>2</sub> power). The power asymptote of the hyperbolic relationship is the critical power (CP).

Fig. 3



Oxygen uptake ( $\text{VO}_2$ ) as a function of time during constant-power moderate-intensity exercise. Black line shows monoexponential fitting of  $\text{VO}_2$  on-kinetics phase II starting from phase I to phase II transition, gray line monoexponential fitting of the whole  $\text{VO}_2$  on-response and off-response. The  $\text{O}_2$  deficit is calculated as the cumulative difference between steady-state  $\text{VO}_2$  level and the whole  $\text{VO}_2$  on-response (gray line). See text for further details. MRT, mean response time.

shortening of mean response time is observed in these patients after left ventricular assist device implantation [61].

### **$\text{VO}_2$ off-kinetics**

During the resting recovery phase after constant-power moderate-intensity exercise, the  $\text{O}_2$  debt contracted during the  $\text{O}_2$  deficit accumulation is paid by a  $\text{VO}_2$  in excess of the resting level (Fig. 3) [7,62]; the same phenomenon is observed during recovery from an incremental exercise test. Such an  $\text{O}_2$  uptake is necessary for the rephosphorylation of creatine in skeletal muscles and, later, conversion of lactate to pyruvate and other mechanisms [63,64].  $\text{VO}_2$  during recovery fits an exponential function, and can be described by the time constant of the  $\text{VO}_2$  off-response or its  $T_{1/2}$ , that is, the time necessary for  $\text{VO}_2$  to decrease by 50% from its peak effort value [19]. The more efficient the  $\text{O}_2$  delivery to, and  $\text{O}_2$  utilization by, exercising skeletal muscles, the faster this time is; hence, it is shorter in athletes and longer in deconditioned patients [65].

After an incremental ramp exercise test, the average  $T_{1/2}$  value in normal individuals ranges between 60 and 90 s (Table 2), and would seem to become more prolonged with advancing age, although no conclusive data are available on age-induced  $\text{VO}_2$  off-kinetics modifications [19,66,67].  $T_{1/2}$  is largely independent of exercise intensity, at least as long as it remains greater than 75% of the maximum [19]; this can be particularly interesting in individuals who stop exercising before peak effort because of symptoms, poor motivation, or fear and in whom peak  $\text{VO}_2$  is underestimated. Thus, a low peak  $\text{VO}_2$  in the presence of normal  $\text{VO}_2$  recovery kinetics suggests submaximal effort; conversely, a long  $T_{1/2}$  reinforces the value of a low peak  $\text{VO}_2$ .

All pathologies affecting the  $\text{O}_2$  transport chain from ambient air to exercising skeletal muscle are expected to influence the postexercise  $\text{VO}_2$  behavior. Indeed, several authors have shown that the kinetics of  $\text{VO}_2$  recovery both after the constant-power and the incremental exercise testing are slowed in patients with congenital

heart disease and CHF [19,66–69]; data for post-myocardial infarction patients are less clear [70,71].

### Use of cardiopulmonary exercise testing for the evaluation of ventilation efficiency and control

#### VO<sub>2</sub> versus ventilation relationship: the oxygen uptake efficiency slope

The oxygen uptake efficiency slope (OUES) represents the rate of increase of VO<sub>2</sub> in response to a given VE during incremental exercise, indicating how effectively oxygen is extracted and taken into the body [72]. OUES is mainly influenced by the onset of lactic acidosis (which depends on the distribution of blood to the working muscles), muscle mass, oxygen extraction and utilization, and the physiologic pulmonary dead space (which in turn is affected by lung perfusion and structural integrity), thus incorporating cardiovascular, musculoskeletal, and respiratory function into a single index.

OUES is determined from the linear relation of VO<sub>2</sub> (*y*-axis) versus the logarithm of VE (*x*-axis) during exercise, that is,  $VO_2 = a \log_{10} VE + b$ , where 'a' is the OUES and 'b' is the intercept [72] (Fig. 4, upper panel). The logarithmic transformation of VE is aimed at linearizing the otherwise curvilinear relation of VO<sub>2</sub> versus VE, thus making the OUES theoretically independent of the patient-achieved effort level. Several studies have tested this hypothesis [20,72–79], showing either equal or slightly higher or lower submaximal versus maximal OUES values, which thus outweigh the substantially larger differences in peakVO<sub>2</sub> measurements observed in the case of premature termination of the exercise test. The feasibility and repeatability of OUES determination is superior to that of VAT [20,73–76,79–81], and is easily calculated by a simple mathematical formula, thus improving intraobserver and interobserver measurement variability and objectivity [82]. In healthy individuals, OUES has been investigated in children [72] and adults [20,74,77]. Age-adjusted OUES values can be predicted using the sex-specific equations by Hollenberg and Tager [20] (Table 2).

In patients with coronary artery disease, OUES is significantly reduced [75,79,81]. However, patients who have undergone percutaneous transluminal coronary angioplasty with or without prior myocardial infarction have significantly higher OUES values compared with patients after coronary artery bypass grafting [79]. This may be explained by a higher disease severity, preoperative and postoperative deconditioning, and the impact of chest surgery on lung perfusion and structural integrity in the latter group. Furthermore, OUES is impaired in coronary artery disease patients with atrial fibrillation as compared with those in normal sinus rhythm [79]; this is likely because of the impact of decreased oxygen delivery

on the working muscles in patients with atrial fibrillation, owing to lower stroke volume and CO response during exercise [83]. In CHF, the OUES is reduced in proportion to disease severity [20,75,76,81] (see section 'Patients with chronic heart failure' and Fig. 4, upper panel).

Physical training has been shown to increase OUES in both coronary artery disease and CHF patients [79,81], suggesting that, after training, a given oxygen uptake is achieved with a lower ventilatory cost. This OUES increase may be because of a reduced metabolic acidosis and/or ventilatory response at submaximal effort intensities. The training-induced changes of OUES parallel those of peakVO<sub>2</sub> [79,81], showing that OUES is sensitive to improvements in exercise tolerance. OUES would therefore seem to be clinically useful to monitor changes in exercise performance and effects of physical training, particularly in patients who can only perform submaximal exercise.

#### Ventilation versus VCO<sub>2</sub> relationship: the VE versus VCO<sub>2</sub> slope

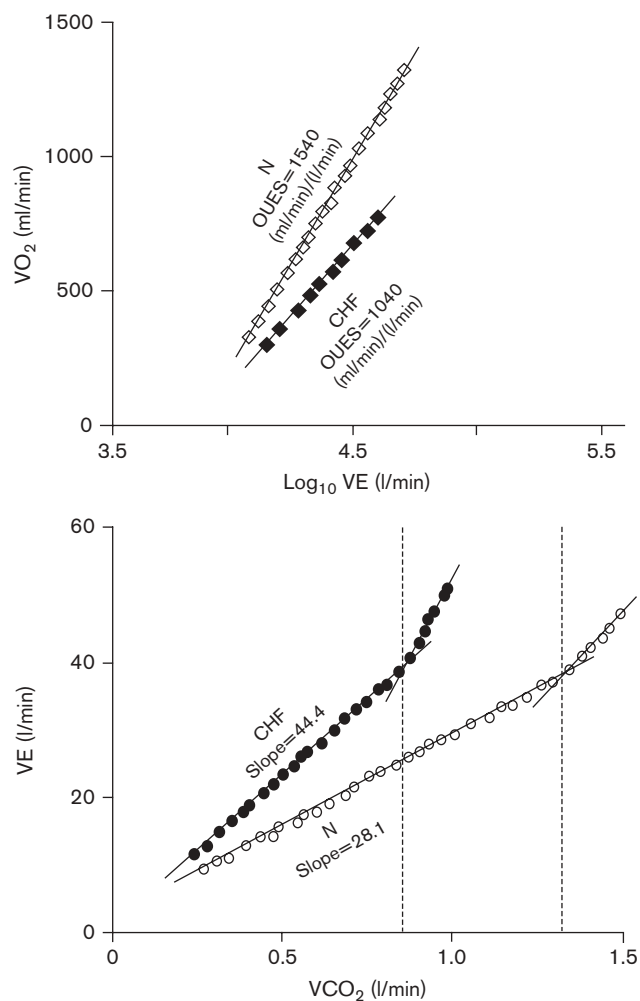
Despite a manifold increase in VCO<sub>2</sub> and VO<sub>2</sub> during incremental exercise, the ventilatory control mechanisms normally keep arterial CO<sub>2</sub> tension (PaCO<sub>2</sub>) and pH remarkably constant over a wide range of metabolic rates. The slope of the relationship between VE and VCO<sub>2</sub> describes the ventilatory efficiency during effort, showing the amount of air that must be ventilated to eliminate 1 l of CO<sub>2</sub> (Fig. 4, lower panel). The basic information given by the VE versus VCO<sub>2</sub> slope is incorporated in the modified alveolar equation [84]:

$$VE = 863 \times VCO_2 / PaCO_2 \times (1 - V_D / V_T)$$

where  $V_D$  and  $V_T$  are volume of pulmonary dead space and tidal volume, respectively.

If PaCO<sub>2</sub> is driven down by a high ventilatory drive from peripheral chemoreceptors and/or  $V_D/V_T$  is high, the VE versus VCO<sub>2</sub> slope increases; a low  $V_T$  with respect to a normal anatomic dead space and/or an abnormally high physiological dead space are potential sources of high  $V_D/V_T$  [85]. Another proposed cause of increased ventilatory drive during exercise is effort-induced muscle metaboreflex (ergoreflex) overactivation [86]. Notably, during incremental exercise VE and VCO<sub>2</sub> are linearly related until VE increases disproportionately to VCO<sub>2</sub> (respiratory compensation point, see section 'Ventilatory anaerobic threshold'). There is still controversy about whether the VE versus VCO<sub>2</sub> slope should be calculated across the overall exercise data or only up to the respiratory compensation point; although its assessment until this point is the logical one from a physiological standpoint, calculation over the whole exercise period seems to

Fig. 4



Upper panel: oxygen uptake ( $VO_2$ ) as a function of ventilation (VE) logarithm during ramp incremental exercise in a normal individual (N) and a CHF patient. The slope of the relationship is the oxygen uptake efficiency slope (OUES). Lower panel: VE as a function of  $CO_2$  production ( $VCO_2$ ) during ramp incremental exercise in an N and a patient with chronic heart failure (CHF). Vertical broken lines represent the respiratory compensation point. A reduced ventilatory efficiency is present in CHF, as witnessed by a shallower OUES and a steeper VE versus  $VCO_2$  slope, respectively, when compared with normal individuals.

increase the VE versus  $VCO_2$  slope prognostic value in CHF patients [87].

Normal values of the VE versus  $VCO_2$  slope range between 20 and 30, with an intercept on the VE axis of some 4–5 l/min because of a reduction of  $V_D/V_T$  ratio after the start of exercise and/or early exercise hyperventilation. The VE versus  $VCO_2$  slope is affected by age, showing increasing values with increasing age [21] (Table 2). A higher than normal VE versus  $VCO_2$  slope may be of undeterminable origin (primary hyperventilation) or because of hypoxia or respiratory or cardiac diseases that can stimulate VE (secondary hyperventila-

tion). Conversely, a downward displacement of the VE versus  $VCO_2$  slope occurs when the  $PaCO_2$  set point is raised, that is, in primary alveolar hypoventilation syndrome (impaired ventilatory chemoreflex function).

In patients with coronary artery disease (previous myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and significant chronic coronary stenosis), the VE versus  $VCO_2$  slope has been shown to be higher the lower the peak  $VO_2$  is [88]. This could be because of a marked sympathetic overactivity and neurohormonal imbalance in these patients, causing an exaggerated ventilatory response to exercise and/or to exercise-induced ischemia, causing a mismatch between CO response to exercise and increasing work rate and a consequent metabolic acidosis. The VE versus  $VCO_2$  slope has been found to be increased also in patients with congenital heart disease, probably because of an altered  $V_D/V_T$  ratio in this population [89,90]. Finally, a high VE versus  $VCO_2$  slope is frequently observed in CHF patients (Fig. 4, lower panel) and is associated with the severity of disease [90–92] (see section ‘Patients with chronic heart failure’).

#### Exercise oscillatory ventilation

Periodic breathing oscillations of  $VO_2$ ,  $VCO_2$ , and VE may be present in humans during spontaneous breathing while awake (both at rest and during exercise) and during sleep, and their presence is usually associated with an underlying pathological condition [94]. Exercise-induced oscillatory ventilation (EOV) is a slow, prominent, consistent (rather than random) fluctuation of VE during incremental exercise that may be evanescent or transient and has several distinct patterns. It has been observed throughout the entire exercise protocol, or only during early or peak exercise [95–98]. The origin of these oscillations is unclear, and several mechanisms have been proposed, which may be conveniently grouped into ventilatory (i.e. instability in the feedback ventilatory control system) and hemodynamic (i.e. pulmonary blood flow fluctuations) [99].

EOV has been defined in different ways. Kremser *et al.*'s [95] definition relies on the presence of cyclic fluctuations in VE lasting longer than 66% of the exercise protocol, with an amplitude of more than 15% of the average value at rest, and increasing in the transition from rest to light exercise and diminishing during heavy exercise (Fig. 5). Leite *et al.*'s [100] description is based on the following criteria: (i) three or more regular oscillations (i.e. clearly distinguishable from inherent data noise); (ii) regularity, so-defined when the standard deviation of three consecutive cycle lengths (time between two consecutive nadirs) is within 20% of the average; and (iii) minimal average amplitude of VE oscillation equals to 5 l (peak value minus the average of

two in-between consecutive nadirs). Notably, the detection of VAT is often masked by the presence of EOV [97].

Among cardiac patients, EOV during exercise testing has been specifically detected in those with CHF (see section 'Patients with chronic heart failure'), and associated with cyclic changes in arterial  $O_2$  and  $CO_2$  tensions; the magnitude of EOV during exercise is correlated with the severity of heart failure [99].

## Use of cardiopulmonary exercise testing for the evaluation of central hemodynamics

### $VO_2$ and cardiac output

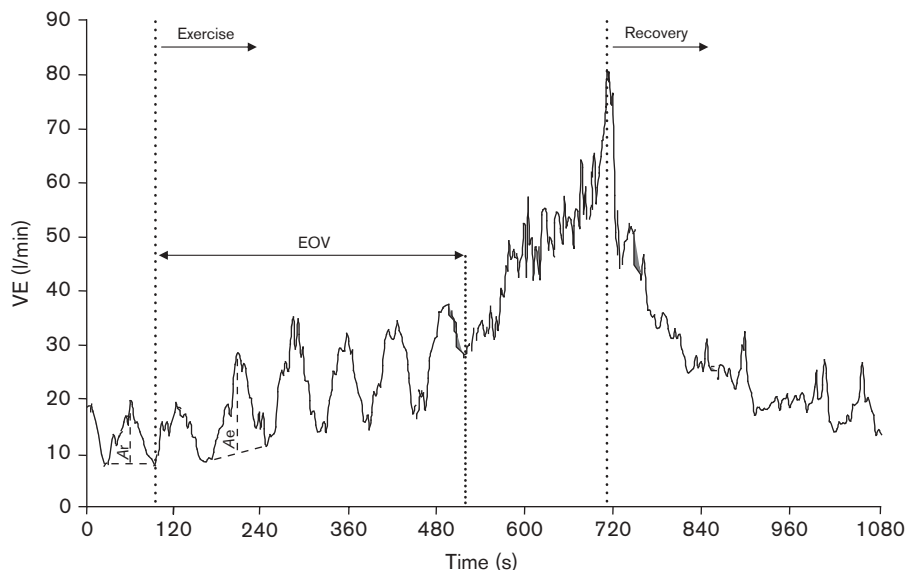
As already shown in the section 'Maximal oxygen uptake',  $VO_2$  is the product of CO times  $C(a-v)O_2$ . In the systemic circulation,  $O_2$  content increases during incremental exercise above VAT because of an increase in Hb, which is mainly because of the oncotic effect of increased intracellular lactate concentration [101,102]. In the pulmonary artery,  $O_2$  content diminishes progressively throughout the entire exercise; below anaerobic threshold, this is because of a reduction of arterial  $O_2$  tension ( $PaO_2$ ) and above anaerobic threshold of both a shift in the oxyhemoglobin dissociation curve (Bohr effect) and a reduction of  $PaO_2$  [103]. As a consequence,  $C(a-v)O_2$  increases linearly with progression of work rate, and its value is relatively fixed at anaerobic threshold and peak effort in normal individuals, which makes  $C(a-v)O_2$  at a given relative intensity of effort predictable, and CO indirectly assessable according to the Fick equation, when the corresponding absolute  $VO_2$  value is known

[104,105]. Alternatively, stroke volume at peak exercise can be estimated through the oxygen pulse, which is  $VO_2/\text{heart rate}$ , that is, stroke volume multiplied by  $C(a-v)O_2$ ; assuming normal values of arterial  $O_2$  content and  $C(a-v)O_2$  at peak effort, peak stroke volume in milliliter can then be calculated as  $(\text{peak oxygen pulse}/15) \times 100$ , where oxygen pulse is in milliliters per beat [30]; however, this estimation must be used with caution in nonperfectly normal and motivated individuals.

Few data are available as to normal CO values during effort. A frequently used formula based on the cardiac index versus  $VO_2$  relationship during incremental exercise [106] has been adapted for CO estimation by converting cardiac index into CO values [22] (Table 2). This formula estimates the lower limit of normality for CO increase at a given  $VO_2$  (i.e. energy expenditure) value in young to middle-aged healthy males.

In CHF patients,  $C(a-v)O_2$  has a lower variability at VAT than at peak exercise, allowing more reliable CO estimates at such exercise intensity [107]. Indeed, estimated CO at VAT has been shown to independently predict multivessel coronary artery disease and the combined end point of cardiac death, reinfarction, and clinically driven revascularization in patients with recent acute myocardial infarction and reduced left ventricular ejection fraction [108]. However, rather than CO estimation during exercise, its direct noninvasive determination by means of  $CO_2$  rebreathing or inert gas methods [109] together with  $VO_2$  measurement might

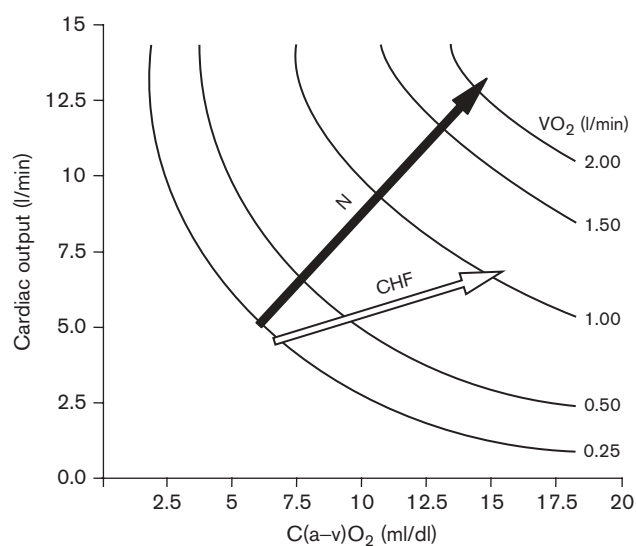
Fig. 5



Ventilation (VE) as a function of time during ramp incremental exercise in a patient with chronic heart failure. An oscillatory VE pattern is present both at rest and during exercise. Exertional oscillatory ventilation (EOV) is defined as cyclic fluctuations in VE lasting at least 66% of the exercise period, with an amplitude of fluctuations during exercise ( $A_e$ )  $> 15\%$  of the average value at rest ( $A_r$ ). For further details, see Ref. [95].

be a major advance in the evaluation of cardiac patients, allowing to calculate the  $C(a-v)O_2$  and to build the  $CO/C(a-v)O_2/VO_2$  plot (Fig. 6) [110]. This plot helps to discriminate between exercise limitation because of altered left ventricle pump function or other causes, mainly muscle deconditioning; indeed, for corresponding  $VO_2$  values, in the former case  $CO$  increase is limited in the presence of a maximal widening of the  $C(a-v)O_2$ , whereas in the latter  $CO$  increase is greater with a lesser widening of the  $C(a-v)O_2$ . This can be useful in CHF patients, in whom both a normal and reduced  $CO$  response during effort has been described in the presence of a reduced peak  $VO_2$  [22,111,112]. Moreover, the role of anemia in functional capacity impairment can be precisely calculated as well [113]. As each Hb gram carries 1.34 ml of  $O_2$ , and as at peak exercise Hb desaturation is approximately 70%, each gram of Hb delivers to the muscle about 1 ml of  $O_2$ . In normal conditions, Hb is 15 g/dl, and, if peak  $CO$  (dl/min) is known, one can easily estimate the amount of missing  $VO_2$  owing to anemia at peak effort. For example, if peak  $CO$  is 7.0 l/min, that is, 70 dl/min, and Hb is 10 g/dl, the amount of  $VO_2$  lacking because of anemia is  $15$  (normal Hb)  $- 10$  (observed Hb)  $\times 70 = 350$  ml/min. Such a calculation is possible only if patients are normoxic, have no cardiac shunt, and the exercise is performed at sea level. This information can be very useful when planning a training intervention in the cardiac rehabilitation setting.

Fig. 6



Cardiac output as a function of arteriovenous content  $O_2$  difference [ $C(a-v)O_2$ ] during ramp incremental exercise, with superimposed oxygen uptake ( $VO_2$ ) isopleths [cardiac output/ $C(a-v)O_2/VO_2$  plot]. Arrows show the variations of cardiac output,  $C(a-v)O_2$ , and  $VO_2$  during ramp incremental exercise for a normal individual (N, black arrow) and a patient with chronic heart failure (CHF, white arrow).

### Circulatory power

Cardiac power, the product of  $CO$  and central aortic (or mean arterial) pressure, is one of the most powerful indices of cardiac systolic function [114–116]. This is because the heart and proximal vascular system are closely coupled and for two similar  $CO$  responses to exercise or to any stress, the ability – as opposed to inability – to sustain an optimal pressure testifies to a higher efficiency of the cardiac pump. Indeed, it has been shown that an impaired blood pressure response during exercise is associated with cardiac dysfunction and poor outcome [117]. For cardiac pumping capability determination during effort, cardiac power can be assessed noninvasively by using the  $CO_2$  rebreathing or inert gas methods to measure  $CO$  [118–121]. The ‘circulatory power’ is a cardiac power surrogate obtainable from CPET, calculated as peak  $VO_2$  multiplied by peak systolic blood pressure [122]. As such, circulatory power represents the triple product of  $CO \times C(a-v)O_2$  (from the Fick equation)  $\times$  systolic blood pressure. For circulatory power to closely estimate cardiac power, there should not be a great difference in  $C(a-v)O_2$  at peak exercise in either normal individuals or cardiac patients, which is usually the case [104,105,123–125]. Moreover, systolic blood pressure and mean arterial pressure should increase in parallel during exercise. In any case, given the inconsistency of diastolic blood pressure manual recording during exercise, systolic blood pressure measurement is more reliable than mean blood pressure in a noninvasive laboratory setting. Finally, unlike invasive assessment of cardiac power, never possible at truly peak exercise, circulatory power can be easily assessed at maximal effort during incremental exercise testing.

The normal values of peak circulatory power have not been extensively assessed and, like peak  $VO_2$ , depend on age, sex, body mass, and training level. Considering 25–40 ml/kg per min as normal values for peak  $VO_2$  and 150–220 mmHg for peak systolic blood pressure, normal values of peak circulatory power between 3500 and 8800 mmHg  $\times$  ml/kg per min are obtained (Table 2), the highest being found in athletes and in hypertensive patients with preserved systolic function. Patients with CHF generally have values less than 3000 mmHg  $\times$  ml/kg per min, and values less than 1800 mmHg  $\times$  ml/kg per min seem to be associated with a very-high short-term risk requiring aggressive treatment, such as in the case of heart transplantation. Circulatory power can also be calculated expressing peak  $VO_2$  as a percentage of predicted  $VO_{2max}$  [126].

Circulatory power is an interesting parameter for the functional evaluation of cardiac patients as it summarizes heart rate, stroke volume, blood pressure, and  $C(a-v)O_2$  responses to exercise (all of which can be altered in several cardiac pathophysiological conditions, in particular

CHF), although it does not allow to distinguish between them as to relative responsibility for the exercise capacity impairment. Vasodilators and  $\beta$ -blockers may alter peak $\text{VO}_2$  and systolic blood pressure in opposite ways, but the final interaction between drug therapy and circulatory power has not been thoroughly evaluated yet [127].

### Use of cardiopulmonary exercise testing for the evaluation of exercise relative intensity

The  $\text{VO}_2$  reserve ( $\text{VO}_{2R}$ ) is the difference between resting and peak $\text{VO}_2$ , and, as it describes the  $\text{O}_2$  used during exercise in addition to basal consumption, is considered a direct measure of the exercise load or energy expenditure [128,129]. As a consequence, the percentage of  $\text{VO}_{2R}$  ( $\%\text{VO}_{2R}$ ) is now considered the gold standard for estimation, prescription, and monitoring of exercise relative intensity [130], even if limited by possible poor correspondence to exercise intensity as defined by physiological descriptors of effort intensity domains (i.e. VAT and critical power, see section ' $\text{VO}_2$  on-kinetics') [131].

Similar to  $\text{VO}_{2R}$ , heart rate reserve (HRR) is defined as the difference between basal and peak heart rate. In healthy sedentary (on both cycle ergometry and treadmill exercise) and in obese adults, the percentage of HRR ( $\%\text{HRR}$ ) has been found to be substantially equivalent to  $\%\text{VO}_{2R}$ , and not to the percentage of  $\text{VO}_{2\text{max}}$  ( $\%\text{VO}_{2\text{max}}$ ) [128,129,132]. Indeed,  $\%\text{HRR}$  has been found to be equivalent to  $\%\text{VO}_{2\text{max}}$  in children and adolescents [133]; in contrast, in adults there is a discrepancy between  $\%\text{HRR}$  and  $\%\text{VO}_{2\text{max}}$ , which decreases with increasing exercise intensity and seems to be inversely related to individuals' fitness [128,129]. The equivalence between  $\%\text{HRR}$  and  $\%\text{VO}_{2R}$  has been observed also in elite endurance athletes [134]; notably, particularly in trained individuals, there seems to be a better prediction of  $\%\text{VO}_{2R}$  from  $\%\text{HRR}$  for running than for arm exercise [135]. Moreover, in patients with type 2 diabetes,  $\%\text{HRR}$  was found to be an excellent descriptor of  $\%\text{VO}_{2R}$  regardless of the presence of autonomic neuropathy [136]. This finding is consistent with those in patients with previous myocardial infarction both on and off  $\beta$ -blocking therapy [137], in whom an incremental ergometric test without respiratory gas analysis would thus be sufficient for exercise relative intensity assessment. However, in patients with CHF (independently of  $\beta$ -blocking therapy), a considerable uncertainty in prediction of  $\%\text{VO}_{2R}$  on the basis of  $\%\text{HRR}$  has been observed [138]; carrying out a CPET in individual CHF patient thus seems advisable for exercise relative intensity determination and to avoid training stimulus inadequacy or excessive exercise-related risk.

Regarding minimal aerobic training stimulus intensity, analysis of available studies supports the use of 45% $\text{VO}_{2R}$

as a minimal effective intensity threshold for fit individuals (peak $\text{VO}_2 > 40$  ml/kg per min) and 30% $\text{VO}_{2R}$  for those with a peak $\text{VO}_2$  less than 40 ml/kg per min [139]. Moreover, guidelines recommend a minimal intensity of 40% $\text{VO}_{2R}$  to elicit improvements in aerobic fitness of less fit individuals, 50% $\text{VO}_{2R}$  for the physically active, and up to 85% $\text{VO}_{2R}$  for highly fit individuals [140].

In patients with coronary artery disease, 45% $\text{VO}_{2R}$  is the minimum intensity recommended for improving aerobic fitness [39]; such a relative intensity is higher than that suggested for less fit normal individuals, as most cardiac patients do not reach their maximal effort and thus intensity prescription is based on peak $\text{VO}_2$  and not  $\text{VO}_{2\text{max}}$ . In any case, in agreement with the lower fitness-lower training stimulus intensity principle [141], relative intensities as low as 23% $\text{VO}_{2R}$  [142], and probably even lower [143], have proved to be effective in CHF patients. From such a low-to-moderate intensity domain, aerobic training stimulus relative intensity can be increased according to individual needs in the high-intensity domain, up to the physiologic limit of aerobic steady-state performance, that is, critical power (see section ' $\text{VO}_2$  on-kinetics'). Once exercise-related risk has been thoroughly assessed, such a training intensity can safely be prescribed also in cardiac patients, both with stable coronary artery disease and preserved left ventricular systolic function or CHF [144,145].

The reported increase in peak $\text{VO}_2$  after a period of aerobic training in normal individuals ranges between 10 and 25%, whereas in cardiac patients it has been found to vary between 7 and 54%, with comparable increases described for  $\text{VO}_2$  at VAT [146,147]. However, a great discrepancy exists between different studies as to training-induced peak $\text{VO}_2$  and  $\text{VO}_2$  at VAT changes, probably because of differences in study populations, individuals' or patients' baseline exercise capacity, and training stimulus intensity and duration. Physiological and performance parameters obtainable from CPET, and useful for aerobic training prescription and monitoring, are summarized in Table 3.

### Use of cardiopulmonary exercise testing for the functional evaluation of specific populations

#### Patients with exercise-induced ischemia

CPET can be useful to detect exercise-induced myocardial ischemia, especially among patients with resting ECG abnormalities. Narrowing of the great epicardial coronary arteries does not let adequate blood flow to the myocardium during effort, which increases the myocardial  $\text{O}_2$  need by increasing heart rate, blood pressure, and contractility. Exercise-induced myocardial ischemia is followed by decreased contractility and development of new regional wall-motion abnormalities; these, in turn, can result in decreasing stroke

volume and CO and, consequently, reduced oxygen delivery to the periphery above the ischemic threshold. Indeed, patients with exercise-induced silent or symptomatic ischemia have been found to have lower peakVO<sub>2</sub> and oxygen pulse compared with nonischemic controls [148]. Moreover, symptomatic patients had significantly lower values of the same parameters and a higher reduction of left ventricular ejection fraction at peak effort compared with the silent ischemia group [148]. In another study [149], patients with exercise-induced ischemia presented peakVO<sub>2</sub> and oxygen pulse values similar to those of patients with normal perfusion; however, patients with extensive transient perfusion defects had a lower peak oxygen pulse than those with lower exercise-induced ischemia. Decreased VAT VO<sub>2</sub> has also been consistently shown to be related to the presence [148–152] and the extent [153] of myocardial ischemia.

The ischemia-induced reduction in stroke volume can also decrease the VO<sub>2</sub> versus power rise [154] and increase to some extent O<sub>2</sub> deficit values, which in turn could slow the VO<sub>2</sub> off-kinetics. Based on the above considerations, CPET has also been used for myocardial ischemia diagnostic purposes. Belardinelli *et al.* [155] showed that CPET improves significantly the diagnostic accuracy of standard ECG stress test for detecting exercise-induced myocardial ischemia, demonstrating a flattening of both VO<sub>2</sub> versus power slope and oxygen pulse increase as a consequence of worsening myocardial contraction during ischemia (Fig. 7). Bussotti *et al.* [150] also demonstrated a significant flattening of VO<sub>2</sub> versus power slope above anaerobic threshold in patients with exercise-induced silent ST-segment depression and presence of great coronary artery narrowing, as compared with patients with ST-segment depression but without coronary artery stenosis. In addition, the presence of a 'hump' morphology (i.e. a transient convex bulge at approximately 1 min of the VO<sub>2</sub> off-kinetics) has been shown to identify exercise-induced ischemia with 57% sensitivity and 97% specificity among patients with

anterior Q-wave myocardial infarction [156]; such phenomenon could be because of a paradoxical increase of stroke volume after cessation of effort. Therefore, most pathophysiological factors linked to exercise-induced ischemia can be reliably measured by CPET, which should be used extensively for myocardial perfusion evaluation in patients with coronary artery disease, especially in the presence of an uninterpretable ECG during effort. In any case, it must be considered that a significant overlap of data exists among patients with and without ischemia; as a consequence, information derived from CPET should be integrated with other clinical and instrumental descriptors of exercise-induced myocardial ischemia. Changes of CPET parameters induced by myocardial ischemia are summarized in Table 4.

#### Patients with recent coronary and valvular surgery

After recent coronary and/or valvular surgery, exercise testing is performed mostly to evaluate exercise tolerance, prescribe individualized training programs, look for residual ischemia and/or exercise-induced arrhythmias, and evaluate prognosis (mostly after coronary artery bypass grafting) [157–160]. Moreover, exercise testing and aerobic training have been recently confirmed to be safe early after heart valve surgery and coronary artery bypass grafting [161]. CPET adds to conventional ergometry the possibility of measuring more precisely patients' exercise capacity and providing a sound physiological basis for exercise training prescription, in a population of patients with sometimes significantly impaired exercise performance. Indeed, early after cardiac surgery many factors can contribute to a drop of the exercise capacity with respect to the preoperative level: ventilatory impairment (from atelectasia, pleural effusion, and/or phrenic nerve injury), congestive heart failure, reduction of ribs and sternal mobility, anemia, sinus tachycardia, atrial fibrillation (in about 40% of patients), transient postoperative left ventricular dysfunction, and global fatigue [160,162]. Indeed, among patients entering a rehabilitation program after a recent acute cardiac event those with recent coronary artery bypass graft have been found to have the lowest peakVO<sub>2</sub> [38].

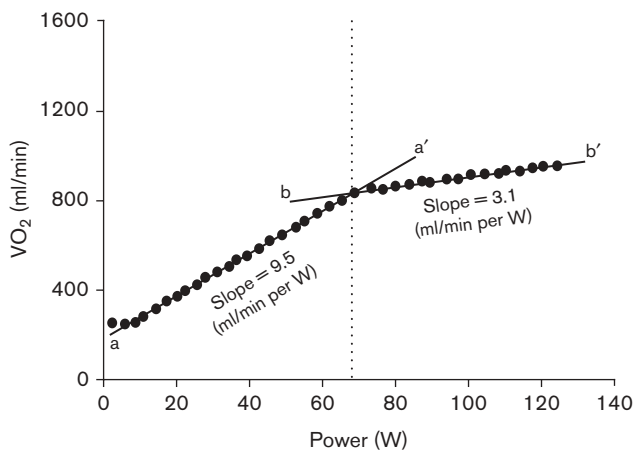
**Table 3** Cardiopulmonary exercise testing physiological and performance parameters useful for aerobic exercise training prescription and monitoring

	Physiological	Performance
Intensity		
Absolute	VO <sub>2</sub> at VAT HR at VAT VO <sub>2</sub> at critical power HR at critical power PeakVO <sub>2</sub> HR at peakVO <sub>2</sub>	Power at VAT Critical power Peak power
Relative	%VO <sub>2</sub> R at VAT %HRR at VAT %VO <sub>2</sub> R at critical power %HRR at critical power	

%HRR, percentage of heart rate reserve; %VO<sub>2</sub>R, percentage of VO<sub>2</sub> reserve; HR, heart rate; VAT, ventilatory anaerobic threshold; VO<sub>2</sub>, oxygen uptake.

Exercise tolerance may be even more impaired after heart valve surgery, as physiological hemodynamic conditions are not fully restored by valve replacement or repair. All prostheses are more or less stenotic, and this may result in a hemodynamically significant stenosis during exercise, mostly after mitral valve replacement but probably also in the presence of prosthesis/patient size mismatch after aortic valve replacement [163]. Moreover, heart rate is often higher than after coronary artery bypass grafting (because of absence of systematic β-blocking therapy and/or higher incidence of atrial fibrillation) and no formula allows the calculation of the heart rate at the anaerobic threshold, which is often used as a target during the

Fig. 7



Oxygen uptake ( $VO_2$ ) as a function of power during ramp incremental exercise in a patient with coronary artery disease. The transition (dotted line) from a normal increase in  $VO_2$  (a–a' slope) to an increase in  $VO_2$  lower than 3.9 ml/min/W (b–b' slope) is considered a marker of the onset of myocardial ischemia. For further details, see Ref. [155].

**Table 4** Cardiopulmonary exercise testing parameters in special populations

	Exercise-induced ischemia	Recent coronary or valvular surgery	Recent or previous heart transplantation	Chronic heart failure
$VO_2$ at VAT	N or ↓ <sup>a</sup>	N or ↓	↓	↓ or ↓↓
Critical power	?	?	?	?
Peak $VO_2$	↓	N or ↓	↓	↓ or ↓↓
$VO_2$ on-kinetics mean response time	N or ↓ <sup>a</sup>	N or ↓?	↓	↓ or ↓↓
$VO_2$ off-kinetics $T_{1/2}$	N or ↓ <sup>b</sup>	N or ↓?	↓	↓ or ↓↓
$O_2$ uptake efficiency slope	N ?	N or ↓?	↓	↓ or ↓↓
VE versus $VCO_2$ slope	N ?	N or ↑?	↑	↑ or ↑↑
Exertional oscillatory ventilation	Absent	?	Absent?	May be present <sup>c</sup>
Peak cardiac output	↓	N or ↓?	↓	↓ or ↓↓
Peak circulatory power	↓?	N or ↓?	↓?	↓ or ↓↓

?, not enough data available; ↓, reduced or shortened; ↓↓, severely reduced or shortened; ↑, increased or prolonged; ↑↑, markedly increased or prolonged; N, normal; VAT, ventilatory anaerobic threshold;  $VCO_2$ ,  $CO_2$  production; VE, ventilation;  $VO_2$ , oxygen uptake; <sup>a</sup>Depending on exercise level with respect to ischemic threshold. <sup>b</sup>Possible 'hump' phenomenon. <sup>c</sup>Usually detectable in 10–12% of patients.

training sessions. Le Tourneau *et al.* [164] investigated the functional effects of surgical correction of mitral regurgitation by mitral valve replacement or repair in the absence of cardiac rehabilitation. Patients underwent CPET before and 216 ± 80 days after surgery (i.e. after healing of all transient postoperative complications); surprisingly, mitral regurgitation correction did not lead to an overall improvement of peak $VO_2$  in either the valve repair or replacement group; these results were confirmed by Kim *et al.* [165]. In contrast, a recent study in early postmitral valve repair patients [166] showed that

a CPET performed 21 ± 10 days after surgery allowed to prescribe an exercise aerobic training driven by the measured heart rate at VAT; after completion of the training period, peak $VO_2$ , peak power, peak oxygen pulse, and chronotropic reserve improved significantly. These results confirmed those of Douard *et al.* [167], who observed a significant increase of peak $VO_2$  after a 3-month aerobic training period driven by CPET results in patients having undergone mitral balloon valvuloplasty for mitral stenosis. In summary, early after coronary and especially valvular heart surgery, the spontaneous exercise capacity improvement is weak and CPET allows the prescription of an efficient training program focused on the patient's physiological limitations. Changes in CPET parameters induced by recent coronary and valvular surgery are summarized in Table 4.

### Patients with chronic heart failure

A reduced ability to perform aerobic exercise is the hallmark of the CHF pathophysiologic feature [24], related to changes in both peripheral (skeletal muscle, endothelium, regional blood flow, and reflex cardiopulmonary control systems) and central (lung, heart, and Hb content of arterial blood) links of the  $O_2$  transport chain from ambient air to the skeletal muscle [168–170]. These changes promote a vicious cycle of deterioration involving catabolic drive and reflex neurohormonal over-activation [170,171], which may lead to disease progression and functional deterioration. As a consequence, in CHF patients peak $VO_2$  is typically reduced with respect to age-matched normal individuals when computed either in absolute (l/min) or weighted terms (ml/kg per min), or as percent of predicted  $VO_{2max}$ , and its reduction is proportional to the severity of the syndrome [24,172]. Together with peak $VO_2$ , also all the other descriptors of  $O_2$  transport and utilization system efficiency are altered. For example, a reduction in the values of  $VO_2$  at VAT, a parameter derived from submaximal work rate and therefore independent of patient motivation, has been classically described [26]. However, in the most advanced stages of the syndrome a clear VAT is often not identifiable, particularly in the presence of EOV. Consistent with the above findings, also a reduction in the  $VO_2$  versus power slope and a prolongation of both  $VO_2$  on-kinetics and off-kinetics in moderate-intensity constant-power effort and of  $VO_2$  off-kinetics after incremental exercise have been described [19,60] and, in addition to VAT, provide useful submaximal descriptors of  $O_2$  transport/utilization system efficiency. Patients with CHF and permanent atrial fibrillation show peak $VO_2$  values even lower than those of CHF patients in sinus rhythm, but with VAT occurring at a higher percentage of peak $VO_2$  [173].

CPET also reveals an increased VE at comparable absolute submaximal levels of effort in CHF patients

with respect to age-matched normal individuals [91]. As a consequence, the VE versus VCO<sub>2</sub> slope is usually increased [174,175] (Fig. 4, lower panel), testifying to a reduced ventilatory efficiency, which may be improved by aerobic training [174]. Such ventilatory inefficiency is further evidenced by a decrease of the OUES with respect to age-matched normal individuals [20,76,81] (Fig. 4, upper panel). Among the causes of the increased ventilatory response to exercise, a reduced oxygen-diffusing capacity because of an impairment of alveolar-arterial oxygen transfer has been suggested [176], although O<sub>2</sub> transfer is preserved and arterial O<sub>2</sub> desaturation during exercise is rare in otherwise uncomplicated CHF [177]. An increase in dead space VE can be advocated because of a mismatching of VE relative to pulmonary perfusion of the high alveolar VE versus low alveolar perfusion type [91]. Another likely mechanism explaining the excessive exercise VE of CHF patients is an exaggerated ergoreflex response originating in the exercising skeletal muscles during effort [174], in the context of a generalized myopathy with early acidotic response: this may explain also the sympathetic hyper-responsiveness present in this syndrome [175]. In addition, EOV has been described in a variable percentage (20–60%) of CHF patients (Fig. 5), associated with poor exercise capacity and severe prognosis [177,178]. It has been attributed to the interaction of altered hemodynamic and neurohormonal regulatory factors [177,179], even if recent data seem to depict an even more complex pathophysiological feature [180].

CPET can also be used to monitor the effects of cardiac resynchronization therapy by biventricular pacing on CHF exercise pathophysiology [181], also when upgrading from right ventricular to biventricular pacing [182]. Moreover, CPET has been used for the functional evaluation of CHF patients after left ventricular assist device implantation, demonstrating a significant short-term peakVO<sub>2</sub> improvement [183,184]. Finally, CPET can describe both functional impairment and prognosis of patients with diastolic heart failure [185]. Changes in CPET parameters induced by CHF are summarized in Table 4.

#### **Patients with recent or previous heart transplantation**

Despite a successful replacement of the failing heart and a recovery of cardiac function, most heart transplant (HTx) recipients experience a persistent impairment in maximal exercise capacity. Indices of maximal and submaximal aerobic exercise capacity (peakVO<sub>2</sub> and VO<sub>2</sub> at VAT) improve significantly during the first 2 years after HTx, remaining, however, around 60–70% of the age-related and sex-related reference values [186,187].

Several mechanisms, both central and peripheral, may account for this finding. First, surgical-induced cardiac

denervation results in a decreased peak heart rate, a delayed heart rate response, and a decreased HRR during incremental exercise (i.e. chronotropic incompetence), which persist for many years after HTx [186]. It has been proposed that the observed chronotropic incompetence, together with cyclosporin-induced diastolic dysfunction, is the major cause of exercise intolerance in HTx recipients; however, recent data obtained in paced and physically trained HTx patients question this hypothesis [188–190]. Second, because of irreversible pretransplant damage of the alveolar-capillary membrane, chronic administration of immunosuppressive drugs, and cytomegalovirus infection, pulmonary diffusion capacity is impaired in most HTx recipients; it is still under debate whether an impaired pulmonary diffusion capacity is a major factor in the limitation of the exercise capacity after HTx [191]. Third, blood flow and oxygen distribution to the skeletal muscles are impaired after HTx. Several authors have demonstrated a decreased capillary density and vascular dysfunction with persistent endothelial dysfunction in the skeletal muscle of HTx patients [192]. It has been shown that improvements in the exercise capacity after exercise training in HTx are highly correlated with improvements in skeletal muscle endothelial function and not to alterations in cardiac or pulmonary function, implying a major role of endothelial function in the observed exercise capacity impairment [193]. Moreover, during the progression of CHF a specific myopathy develops, which persists after HTx and is even worsened by the administration of corticosteroids and cyclosporin, inducing muscle atrophy and a further decrease in oxidative capacity; these detrimental changes result in an inefficient muscle metabolism and a decreased muscle strength [194]. As for endothelial dysfunction, these muscular adaptations can be reversed by exercise training and correlate closely with the observed improvements in exercise capacity [195]. Owing to these muscular metabolic changes, both on-kinetics and off-kinetics of VO<sub>2</sub> during constant-power moderate-intensity exercise are delayed in HTx patients [196,197].

Finally, ventilatory efficiency (expressed both as OUES and VE versus VCO<sub>2</sub> slope) improves during the first years after HTx, remaining, however, impaired and reaching values comparable with those observed in moderate CHF. The increased ventilatory response to exercise may be caused by sustained increases in peripheral chemoreceptor sensitivity and increased muscle metaboreflex activity in response to locally produced metabolites during effort [197,198]. Changes of CPET parameters induced by HTx are summarized in Table 4.

#### **Conclusion**

CPET is a methodology now widely available throughout the world and supported by an impressive body of scientific evidence in several different clinical fields.

This study emphasizes the opportunities that CPET offers for the functional evaluation of cardiac patients, illustrating the wealth of information obtainable through an experienced use of this powerful tool. The choice of parameters to measure will depend on the specific goals of the functional evaluation in the individual patient, namely, exercise tolerance assessment, training prescription, treatment efficacy evaluation, investigation of exercise-induced adaptations of the O<sub>2</sub> transport/utilization system (whether of single links or the whole system), etc. However, the full potentialities of CPET in the clinical and research setting still remain largely underused because of inertia of the cardiologic world in the face of a demanding methodology from the cultural standpoint. Strong efforts are needed to promote a more widespread use of CPET in the functional evaluation of cardiac patients.

## Acknowledgements

The authors are grateful to Rosemary Allpress for her careful revision of the English manuscript. There are no conflicts of interest.

## References

- 1 Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. *Principles of exercise testing and interpretation: including pathophysiology and clinical applications*. Philadelphia: Lippincott Williams & Wilkins; 2005.
- 2 ERS Task Force, Palange P, Ward SA, Carlsen KH, Casaburi R, Gallagher CG, Gosselink R, et al. Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 2007; **29**:185–209.
- 3 Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, et al.; American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Nursing. Assessment of functional capacity in clinical and research settings. A Scientific Statement From the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation* 2007; **116**:329–343.
- 4 Gay SE, Weisman IM, Flaherty KR, Martinez FJ. Cardiopulmonary exercise testing in unexplained dyspnea. In: Weisman IM, Zeballos RJ, editors. *Clinical exercise testing*. Basel: Karger; 2002. pp. 81–88.
- 5 Task Force of the Italian Working Group on Cardiac Rehabilitation and Prevention (Gruppo Italiano di Cardiologia Riabilitativa e Prevenzione, GICR); Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation Part III: Interpretation of cardiopulmonary exercise testing in chronic heart failure and future applications. *Eur J Cardiovasc Prev Rehabil* 2006; **13**:485–494.
- 6 Hill AV, Long CNH, Lupton H. Muscular exercise, lactic acid and the supply and utilization of oxygen. *Proc R Soc Lond* 1924; **96**:438–475.
- 7 Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Physiology of exercise. In: Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ, editors. *Principles of exercise testing and interpretation: including pathophysiology and clinical applications*. Philadelphia: Lippincott Williams & Wilkins; 2005. pp. 10–65.
- 8 Binder RK, Wonisch M, Corrà U, Cohen-Solal A, Vanhees L, Saner H, et al. Methodological approach to the 1st and 2nd lactate threshold in incremental cardiopulmonary exercise testing. *Eur J Cardiovasc Prev Rehabil* 2008; **15**:726–734.
- 9 Meyer T, Lucia A, Earnest CP, Kindermann W. A conceptual framework for performance diagnosis and training prescription from submaximal gas exchange parameters-theory and application. *Int J Sports Med* 2005; **26** (Suppl 1):S38–S48.
- 10 Goodman LS, McKenzie DC, Taunton JE, Walters MB. Ventilatory threshold and training heart rate in exercising cardiac patients. *Can J Sport Sci* 1988; **13**:220–224.
- 11 McLellan TM. Ventilatory and plasma lactate response with different exercise protocols: a comparison of methods. *Int J Sports Med* 1985; **6**:30–35.
- 12 Yeh MP, Gardner RM, Adams TD, Yanowitz FG, Crapo RO. Anaerobic threshold: problems of determination and validation. *J Appl Physiol* 1983; **55**:1178–1186.
- 13 Davis JA, Vodak P, Wilmore JH, Vodak J, Kurtz P. Anaerobic threshold and maximal aerobic power for three modes of exercise. *J Appl Physiol* 1976; **41**:544–550.
- 14 Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; **60**:2020–2027.
- 15 Meyer T, Faude O, Scharhag J, Urhausen A, Kindermann W. Is lactic acidosis a cause of exercise induced hyperventilation at the respiratory compensation point? *Br J Sports Med* 2004; **38**:622–625.
- 16 Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Normal values. In: Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ, editors. *Principles of exercise testing and interpretation: including pathophysiology and clinical applications*. Philadelphia: Lippincott Williams & Wilkins; 2005. pp. 160–182.
- 17 Hill DW. The critical power concept. *Sports Med* 1993; **16**:237–254.
- 18 Babcock MA, Paterson DH, Cunningham DA, Dickinson JR. Exercise on-transient gas exchange kinetics are slowed as a function of age. *Med Sci Sports Exerc* 1994; **26**:440–446.
- 19 Cohen-Solal A, Laperche T, Morvan D, Geneves M, Caveziel B, Gourgon R. Prolonged kinetics of recovery of oxygen consumption after maximal graded exercise in patients with chronic heart failure. Analysis with gas exchange measurements and NMR spectroscopy. *Circulation* 1995; **91**:2924–2932.
- 20 Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol* 2000; **36**:194–201.
- 21 Neder JA, Nery LE, Peres C, Whipp BJ. Reference values for dynamic responses to incremental cycle ergometry in males and females aged 20 to 80. *Am J Respir Crit Care Med* 2001; **164**:1481–1486.
- 22 Chomsky DB, Lang CC, Rayos GH, Shyr Y, Yeoh TK, Pierson RN III, et al. Haemodynamic exercise testing. A valuable tool in the selection of cardiac transplantation candidates. *Circulation* 1996; **94**:3176–3183.
- 23 Joyner MJ, Coyle EF. Endurance exercise performance: the physiology of champions. *J Physiol* 2008; **586**:35–44.
- 24 Solal AC, Chabernaud JN, Gourgon R. Comparison of oxygen uptake during bicycle exercise in patients with chronic heart failure and in normal subjects. *J Am Coll Cardiol* 1990; **16**:80–85.
- 25 Capelli C, Antonutto G, Kenfack MA, Cautero M, Lador F, Moia C, et al. Factors determining the time course of VO<sub>2</sub>(max) decay during bedrest: implications for VO<sub>2</sub>(max) limitation. *Eur J Appl Physiol* 2006; **98**:152–160.
- 26 Metra M, Raddino R, Dei Cas L, Visioli O. Assessment of peak oxygen consumption, lactate and ventilatory thresholds and correlation with resting and exercise hemodynamic data in chronic congestive heart failure. *Am J Cardiol* 1990; **65**:1127–1133.
- 27 Cohen-Solal A, Aupetit JF, Gueret P, Kolsky H, Zannad F. Can anaerobic threshold be used as an end-point for therapeutic trials in heart failure? Lessons from a multicentre randomized placebo-controlled trial. The VO<sub>2</sub> French Study Group. *Eur Heart J* 1994; **15**:236–241.
- 28 Saltin B, Calbet JA. Point: in health and in a normoxic environment, VO<sub>2</sub>max is limited primarily by cardiac output and locomotor muscle blood flow. *J Appl Physiol* 2006; **100**:744–745.
- 29 Noakes TD. Testing for maximum oxygen consumption has produced a brainless model of human exercise performance. *Br J Sports Med* 2008; **42**:551–555.
- 30 Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Measurements during integrative cardiopulmonary exercise testing. In: Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ, editors. *Principles of exercise testing and interpretation: including pathophysiology and clinical applications*. Philadelphia: Lippincott Williams & Wilkins; 2005. pp. 76–110.
- 31 Day JR, Rossiter HB, Coats EM, Skasick A, Whipp BJ. The maximally attainable VO<sub>2</sub> during exercise in humans: the peak vs. maximum issue. *J Appl Physiol* 2003; **95**:1901–1907.
- 32 Myers J. Applications of cardiopulmonary exercise testing in the management of cardiovascular and pulmonary disease. *Int J Sports Med* 2005; **26** (Suppl 1):S49–S55.
- 33 Howley ET, Basset DR Jr, Welch HG. Criteria for maximal oxygen uptake: review and commentary. *Med Sci Sports Exerc* 1995; **27**:1292–1301.
- 34 Rivera MA, Pérusse L, Simoneau JA, Gagnon J, Dionne FT, Leon AS, et al. Linkage between a muscle-specific CK gene marker and VO<sub>2max</sub> in the HERITAGE family study. *Med Sci Sports Exerc* 1999; **31**:698–701.

- 35 Astrand P-O, Rodahl K. Physical training. In: Astrand P-O, Rodahl K, editors. *Textbook of work physiology. Physiological bases of exercise*. New York: McGraw Hill Book Company; 1986. pp. 412–485.
- 36 Betik AC, Hepple RT. Determinants of  $\text{VO}_{2\text{max}}$  decline with aging: an integrated perspective. *Appl Physiol Nutr Metab* 2008; **33**:130–140.
- 37 Astrand I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand* 1960; **49** (Suppl 169):1–9.
- 38 Ades PA, Savage PD, Brawner CA, Lyon CE, Ehrman JK, Bunn JY, et al. Aerobic capacity in patients entering cardiac rehabilitation. *Circulation* 2006; **113**: 2706–2712.
- 39 Swain DP, Franklin BA. Is there a threshold intensity for aerobic training in cardiac patients? *Med Sci Sports Exerc* 2002; **34**:1071–1075.
- 40 Nieuwland W, Berkhuyzen MA, Van Velthuisen DJ, Rispen P. Individual assessment of intensity-level for exercise training in patients with coronary artery disease is necessary. *Int J Cardiol* 2002; **84**:15–20.
- 41 Billat VL, Sirvent P, Py G, Koralsztein JP, Mercier J. The concept of maximal lactate steady state: a bridge between biochemistry, physiology and sport science. *Sports Med* 2003; **33**:407–426.
- 42 Poole DC, Ward SA, Gardner GW, Whipp BJ. Metabolic and respiratory profile of the upper limit for prolonged exercise in man. *Ergonomics* 1988; **31**:1265–1279.
- 43 Dekker J, Baron B, Dupont L, Vanvelcenaher J, Pelayo P. Maximal lactate steady state, respiratory compensation threshold and critical power. *Eur J Appl Physiol* 2003; **89**:281–288.
- 44 Neder JA, Jones PW, Nery LE, Whipp BJ. The effect of age on the power/duration relationship and the intensity-domain limits in sedentary men. *Eur J Appl Physiol* 2000; **82**:326–332.
- 45 Jenkins DG, Quigley BM. Endurance training enhances critical power. *Med Sci Sports Exerc* 1992; **24**:1283–1289.
- 46 Faggiano P, D'Aloia A, Gualeni A, Lavatelli A, Giordano A. Assessment of oxygen uptake during the 6-minute walking test in patients with heart failure: preliminary experience with a portable device. *Am Heart J* 1997; **134**:203–206.
- 47 Linnarsson D. Dynamics of pulmonary gas exchange and heart rate changes at start and end of exercise. *Acta Physiol Scand* 1974; **415** (Suppl):1–68.
- 48 Whipp BJ, Ward S. Physiological determinants of pulmonary gas exchange kinetics during exercise. *Med Sci Sports Exerc* 1990; **22**:62–71.
- 49 Whipp BJ, Ward SA, Rossier HB. Pulmonary  $\text{O}_2$  uptake during exercise: conflating muscular and cardiovascular responses. *Med Sci Sports Exerc* 2005; **37**:1574–1585.
- 50 Di Prampero PE. Energetics of muscular exercise. *Rev Physiol Biochem Pharmacol* 1981; **89**:143–222.
- 51 Gaesser GA, Poole DC. The slow component of oxygen uptake kinetics in humans. *Exerc Sport Sci Rev* 1996; **24**:35–70.
- 52 Whipp BJ. Domains of aerobic function and their limiting parameters. In: Steinacker JM, Ward SA, editors. *The physiology and pathophysiology of exercise tolerance*. New York: Plenum Press; 1996. pp. 83–89.
- 53 Hansen JE, Casaburi R, Cooper DM, Wasserman K. Oxygen uptake as related to work rate increment during cycle ergometer exercise. *Eur J Appl Physiol* 1988; **57**:140–145.
- 54 Whipp BJ, Davis JA, Torres F, Wasserman K. A test to determine parameters of aerobic function during exercise. *J Appl Physiol* 1981; **50**:217–221.
- 55 DeLorey DS, Kowalchuk JM, Paterson DH. Effect of age on  $\text{O}_2$  uptake kinetics and the adaptation of muscle deoxygenation at the onset of moderate-intensity cycling exercise. *J Appl Physiol* 2004; **97**:165–172.
- 56 Jones AM, Koppo K. Effects of training on  $\text{VO}_2$  kinetics and performance. In: Jones AM, Poole DC, editors. *Oxygen uptake kinetics in sport, exercise and medicine*. London: Routledge; 2005. pp. 373–397.
- 57 Koike A, Yajima T, Adachi H, Shinizu N, Kano H, Sugimoto K, et al. Evaluation of exercise capacity using submaximal exercise at a constant work rate in patients with cardiovascular disease. *Circulation* 1995; **91**:1719–1724.
- 58 Lok NS, Lau CP. Oxygen uptake kinetics and cardiopulmonary performance in lone atrial fibrillation and the effects of sotalol. *Chest* 1997; **111**:934–940.
- 59 Adachi H, Koike A, Niwa A, Sato A, Takamoto T, Marumo F, et al. Percutaneous transluminal coronary angioplasty improves oxygen uptake kinetics during the onset of exercise in patients with coronary artery disease. *Chest* 2000; **118**:329–335.
- 60 Sietsema KE, Ben-Dov I, Zhang YY, Sullivan C, Wasserman K. Dynamics of oxygen uptake for submaximal exercise and recovery in patients with chronic heart failure. *Chest* 1994; **105**:1693–1700.
- 61 Feldman CM, Khan SN, Slaughter MS, Sobieski M, Graham JD, Eaheart B, et al. Improvement in early oxygen uptake kinetics with left ventricular assist device support. *ASAIO J* 2008; **54**:406–411.
- 62 Meakins T, Long C. Oxygen consumption, oxygen debt and lactic acid in circulatory failure. *J Clin Invest* 1927; **4**:273–293.
- 63 Margaria R, Edwards H, Dill D. The possible mechanisms of contracting and paying the oxygen debt and the role of lactic acid in muscular contraction. *Am J Physiol* 1933; **106**:689–715.
- 64 Harris R, Edwards R, Hultman E, Nordesjo L, Nyland B, Sahlin K. The time course of phosphoril-creatine resynthesis during recovery of the quadriceps muscle in man. *Pflügers Arch* 1976; **367**:137–142.
- 65 Hagberg JM, Hickson RC, Ehsani AA, Holloszy JO. Faster adjustment to and recovery from submaximal exercise in the trained state. *J Appl Physiol* 1980; **48**:218–224.
- 66 Degroote P, Millaire A, Decoulet E, Nugue O, Guimier P, Ducloux G. Kinetics of oxygen consumption during and after exercise in patients with dilated cardiomyopathy: new markers of exercise intolerance with clinical implications. *J Am Coll Cardiol* 1996; **28**:168–175.
- 67 Nanas S, Nanas J, Kassiotis C, Nikolaou C, Tsaloglou E, Sakellariou D, et al. Early recovery of oxygen kinetics after submaximal exercise test predicts functional capacity in patients with chronic heart failure. *Eur J Heart Fail* 2001; **3**:685–692.
- 68 Giardini A, Donti A, Specchia S, Coutsoumbas G, Formigari R, Prandstaller D, et al. Recovery kinetics of oxygen uptake is prolonged in adults with an atrial septal defect and improves after transcatheter closure. *Am Heart J* 2004; **147**:910–914.
- 69 Giardini A, Specchia S, Coutsoumbas G, Donti A, Formigari R, Fattori R, et al. Impact of pulmonary regurgitation and right ventricular dysfunction on oxygen uptake recovery kinetics in repaired tetralogy of Fallot. *Eur J Heart Fail* 2006; **8**:736–743.
- 70 Sunagawa H, Honda S, Yoshii K, Mizoguchi Y, Fukuda S, Iwao H. Estimation of exercise capacity from oxygen consumption in the recovery phase of submaximal exercise. *Jpn Circ J* 1986; **50**:1309–1312.
- 71 Shimizu N, Koike A, Koyama Y, Kobayashi K, Marumo F, Hiroe M. Kinetics of pulmonary gas exchange during and while recovering from exercise in patients after anterior myocardial infarction. *Jpn Circ J* 1999; **63**:459–466.
- 72 Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol* 1996; **28**:1567–1572.
- 73 Baba R, Tsuyuki K, Kimura Y, Ninomiya K, Aihara M, Ebine K, et al. Oxygen uptake efficiency slope as a useful measure of cardiorespiratory functional reserve in adult cardiac patients. *Eur J Appl Physiol Occup Physiol* 1999; **80**:397–401.
- 74 Mourot L, Perrey S, Tordi N, Rouillon JD. Evaluation of fitness level by the oxygen uptake efficiency slope after a short-term intermittent endurance training. *Int J Sports Med* 2004; **25**:85–91.
- 75 Van Laethem C, Bartunek J, Goethals M, Nellens P, Andries E, Vanderheyden M. Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. *Am Heart J* 2005; **149**:175–180.
- 76 Davies LC, Wensel R, Georgiadou P, Cicoira M, Coats AJ, Piepoli MF, et al. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J* 2006; **27**:684–690.
- 77 Pichon A, Jonville S, Denjean A. Evaluation of the interchangeability of  $\text{VO}_{2\text{max}}$  and Oxygen Uptake Efficiency Slope. *Can J Appl Physiol* 2002; **27**:589–601.
- 78 Marinov B, Kostianev S. Exercise performance and oxygen uptake efficiency slope in obese children performing standardized exercise. *Acta Physiol Pharmacol Bulg* 2003; **27**:59–64.
- 79 Defoor J, Schepers D, Reybrouck T, Fagard R, Vanhees L. Oxygen uptake efficiency slope in coronary artery disease: clinical use and response to training. *Int J Sports Med* 2006; **27**:730–737.
- 80 Van Laethem C, Van de Veire N, De Sutter J, Bartunek J, De Backer G, Goethals M, et al. Prospective evaluation of the oxygen uptake efficiency slope as a submaximal predictor of peak oxygen uptake in aged patients with ischemic heart disease. *Am Heart J* 2006; **152**:297–315.
- 81 Van Laethem C, Van De Veire N, De Backer G, Bihija S, Seghers T, Cambier D, et al. Response of the oxygen uptake efficiency slope to exercise training in patients with chronic heart failure. *Eur J Heart Fail* 2007; **9**:625–629.
- 82 Baba R, Kubo N, Morotome Y, Iwagaki S. Reproducibility of the oxygen uptake efficiency slope in normal healthy subjects. *J Sports Med Phys Fitness* 1999; **39**:202–206.
- 83 Ueshima K, Myers J, Ribisl PM, Atwood JE, Morris CK, Kawaguchi T, et al. Hemodynamic determinants of exercise capacity in chronic atrial fibrillation. *Am Heart J* 1993; **125**:1301–1305.

- 84 Whipp BJ, Ward SA, Wasserman K. Ventilatory responses to exercise and their control in man. *Am Rev Respir Dis* 1984; **129** (Suppl): S17–S20.
- 85 Hsia CCW, Johnston RL Jr. Exercise physiology and lung diseases. In: Bone R, editor. *Comprehensive textbook of pulmonary and critical care medicine*. St Louis: Mosby-Yearbook; 1993. pp. 1–20.
- 86 Wensel R, Georgiadou P, Francis DP, Bayne S, Scott AC, Genth-Zotz S, et al. Differential contribution of dead space ventilation and low arterial pCO<sub>2</sub> to exercise hyperpnea in patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2004; **93**:318–323.
- 87 Tabet JY, Beauvais F, Thabut G, Tartiere JM, Logeart D, Cohen-Solal A. A critical appraisal of the prognostic value of the VE/VCO<sub>2</sub> slope in chronic heart failure patients. *Eur J Cardiovasc Prev Rehabil* 2003; **10**:267–272.
- 88 Van de Veire NR, Van Laethem C, Philippé J, De Winter O, De Backer G, Vanderheyden M, De Sutter J. VE/VCO<sub>2</sub> slope and oxygen uptake efficiency slope in patients with coronary artery disease and intermediate peakVO<sub>2</sub>. *Eur J Cardiovasc Prev Rehabil* 2006; **13**:916–923.
- 89 Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation* 2005; **112**:828–835.
- 90 Dimopoulos K, Okonko DO, Diller GP, Broberg CS, Salukhe TV, Babu-Narayan SV, et al. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. *Circulation* 2006; **113**:2796–2802.
- 91 Wasserman K, Zhang YY, Gitt A, Belardinelli R, Koike A, Lubarsky L, et al. Lung function and exercise gas exchange in chronic heart failure. *Circulation* 1997; **96**:2221–2227.
- 92 Johnston RL Jr. Gas exchange efficiency in congestive heart failure. *Circulation* 2000; **101**:2774–2776.
- 93 Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1997; **29**:1585–1590.
- 94 Khoo MC, Kronauer RE, Strohl KP, Slutsky AS. Factors inducing periodic breathing in humans: a general model. *J Appl Physiol* 1982; **53**:644–659.
- 95 Kremser CB, O'Toole MF, Leff AR. Oscillatory hyperventilation in severe congestive heart failure secondary to idiopathic dilated cardiomyopathy or to ischemic cardiomyopathy. *Am J Cardiol* 1987; **59**:900–905.
- 96 Ben-Dov I, Sietsema KE, Casaburi R, Wasserman K. Evidence that the circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure. *Am Rev Respir Dis* 1992; **145**:776–781.
- 97 Yajima T, Koike A, Sugimoto K, Miyahara Y, Marumo F, Hiroe M. Mechanism of periodic breathing in patients with cardiovascular disease. *Chest* 1994; **106**:142–146.
- 98 Feld H, Priest S. A cyclic breathing pattern in patients with poor left ventricular function and compensated: a mild form of Cheyne-Stokes respiration? *J Am Coll Cardiol* 1993; **21**:971–974.
- 99 Piepoli MF, Ponikowski PP, Volterrani M, Francis D, Coats AJ. Aetiology and pathophysiological implications of oscillatory ventilation at rest and during exercise in CHF. Do Cheyne and Stokes have an important message for modern-day patients with heart failure? *Eur Heart J* 1999; **20**:946–953.
- 100 Leite JJ, Mansur AJ, de Freitas HF, Chizola PR, Bocchi EA, Terra-Filho M, et al. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. *J Am Coll Cardiol* 2003; **41**:2175–2181.
- 101 Agostoni PG, Wasserman K, Guazzi M, Cattadori G, Palermo P, Marenzi G, et al. Exercise-induced hemoconcentration in heart failure due to dilated cardiomyopathy. *Am J Cardiol* 1999; **83**:278–280.
- 102 Perego GB, Marenzi M, Guazzi M, Sganzerla P, Assanelli E, Palermo P, et al. Contribution of PO<sub>2</sub>, P50, and Hb to changes in arteriovenous O<sub>2</sub> content during exercise in heart failure. *J Appl Physiol* 1996; **80**:623–631.
- 103 Agostoni PG, Wasserman K, Perego GB, Marenzi G, Guazzi M, Assanelli E, et al. Oxygen transport to muscle during exercise in chronic congestive heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997; **79**:29–33.
- 104 Stringer WW, Hansen JE, Wasserman K. Cardiac output estimated noninvasively from oxygen uptake during exercise. *J Appl Physiol* 1997; **82**:908–912.
- 105 Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Clinical applications of cardiopulmonary exercise testing. In: Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ, editors. *Principles of exercise testing and interpretation: including pathophysiology and clinical applications*. Philadelphia: Lippincott Williams & Wilkins; 2005. pp. 198–241.
- 106 Higginbotham M, Morris K, Williams R, Mc Hale P, Coleman E, Cobb F. Regulation of stroke volume during submaximal exercise and maximal upright exercise in normal man. *Circ Res* 1986; **58**:281–291.
- 107 Agostoni PG, Wasserman K, Perego GB, Guazzi M, Cattadori G, Palermo P, et al. Non-invasive measurement of stroke volume during exercise in heart failure patients. *Clin Sci* 2000; **98**:545–551.
- 108 Bigi R, Desideri A, Rambaldi R, Cortigiani L, Sponzilli C, Fiorentini C. Angiographic and prognostic correlates of cardiac output by cardiopulmonary exercise testing in patients with anterior myocardial infarction. *Chest* 2001; **120**:825–833.
- 109 Vanhees L, Defoor J, Schepers D, Brusselle S, Reybroeck T, Fagard R. Comparison of cardiac output measured by two automated methods of CO<sub>2</sub> rebreathing. *Med Sci Sports Exerc* 2000; **32**:1028–1034.
- 110 Agostoni P, Cattadori G, Apostolo A, Contini M, Palermo P, Marenzi G, et al. Non-invasive measurement of cardiac output during exercise by inert gas rebreathing technique: a new tool for heart failure evaluation. *J Am Coll Cardiol* 2005; **46**:1779–1781.
- 111 Metra M, Faggiano P, D'Aloia A, Nodari S, Gualeni A, Raccagni D, et al. Use of cardiopulmonary exercise testing with hemodynamic monitoring in the prognostic assessment of ambulatory patients with chronic heart failure. *J Am Coll Cardiol* 1999; **33**:943–950.
- 112 Wilson JR, Groves J, Rayos G. Circulatory status and response to cardiac rehabilitation in patients with heart failure. *Circulation* 1996; **94**:1567–1572.
- 113 Agostoni P, Cerino M, Palermo P, Magini A, Bianchi M, Bussotti M, et al. Exercise capacity in patients with beta-thalassaemia intermedia. *Br J Haematol* 2005; **131**:278–281.
- 114 Tan L. Cardiac pumping and prognosis in heart failure. *Lancet* 1986; **2**:1360–1363.
- 115 Kass D, Beyar R. Evaluation of contractile state by maximal ventricular power divided by the square of end-diastolic volume. *Circulation* 1991; **84**:1698–1708.
- 116 Cotter G, Milo-Cotter O, Kaluski E. Hemodynamic monitoring in acute heart failure. *Crit Care Med* 2008; **36** (Suppl):S40–S43.
- 117 Osada N, Chaitman BR, Miller LW, Yip D, Cishek MB, Wolford TL, et al. Cardiopulmonary exercise testing identifies low risk patients with heart failure and severely impaired exercise capacity considered for heart transplantation. *J Am Coll Cardiol* 1998; **31**:577–582.
- 118 Tan L, Bain R, Littler W. Assessing cardiac pumping capability by exercise testing and inotropic stimulation. *Br Heart J* 1989; **62**:20–25.
- 119 Lang CC, Karlin P, Hayte J, Levy WC, Lim TK, Mancini DM. Peak cardiac power, measured non-invasively, is a powerful predictor of mortality in chronic heart failure. *Circulation* 2007; **116** (Suppl II):II-505.
- 120 Williams SG, Cooke GA, Wright DJ, Parsons WJ, Riley RL, Marshall P, et al. Peak exercise cardiac power output; a direct indicator of cardiac function strongly predictive of prognosis in chronic heart failure. *Eur Heart J* 2001; **22**:1496–1503.
- 121 Lang CC, Karlin P, Hayte J, Tsao L, Mancini DM. Ease of noninvasive measurement of cardiac output coupled with peak VO<sub>2</sub> determination at rest and during exercise in patients with heart failure. *Am J Cardiol* 2007; **99**:404–405.
- 122 Cohen-Solal A, Tabet JY, Logeart D, Bourgoin P, Tokmakova M, Dahan M. A non-invasively determined surrogate of cardiac power ('circulatory power') at peak exercise is a powerful prognostic factor in chronic heart failure. *Eur Heart J* 2002; **23**:806–814.
- 123 Weber K, Kinasewitz G, Janicki J, Fishman A. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 1982; **65**:1213–1223.
- 124 Higginbotham MB, Morris KG, Conn EH, Coleman RE, Cobb FR. Determinants of variable exercise performance among patients with severe left ventricular dysfunction. *Am J Cardiol* 1983; **51**:52–60.
- 125 Sullivan M, Knight J, Higginbotham M, Cobb F. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. Muscle blood flow is reduced with maintenance of arterial pressure. *Circulation* 1989; **80**:769–781.
- 126 Scharf C, Merz T, Kiowski W, Oechslin E, Schalcher C, Brunner-La Rocca HP. Noninvasive assessment of cardiac pumping capacity during exercise predicts prognosis in patients with congestive heart failure. *Chest* 2002; **122**:1333–1339.
- 127 Tabet JY, Metra M, Thabut G, Logeart D, Cohen-Solal A. Prognostic value of cardiopulmonary exercise variables in chronic heart failure patients with or without beta-blocker therapy. *Am J Cardiol* 2005; **98**:500–503.
- 128 Swain DP, Leutholtz BC. Heart rate reserve is equivalent to %VO<sub>2</sub> reserve, not to VO<sub>2</sub>%. *Med Sci Sports Exerc* 1997; **29**:410–414.

- 129 Swain DP, Leutholtz BC, King ME, Haas LA, Branch JD. Relationships between % heart rate reserve and %VO<sub>2</sub> reserve in treadmill exercise. *Med Sci Sports Exerc* 1998; **30**:318–321.
- 130 Franklin BA, Whaley MH, Howley ET. General principles of exercise prescription. In: Franklin BA, Whaley MH, Howley ET, editors. *ACSM's guidelines for exercise testing and prescription*. Philadelphia: Lippincott Williams & Wilkins; 2000. pp. 137–164.
- 131 Meyer T, Gabriel HHW, Kindermann W. Is determination of exercise intensities as percentages of VO<sub>2max</sub> or HR<sub>max</sub> adequate? *Med Sci Sports Exerc* 1999; **31**:1342–1345.
- 132 Byrne NM, Hills AP. Relationships between HR and VO<sub>2</sub> in the obese. *Med Sci Sports Exerc* 2002; **34**:1419–1427.
- 133 Hui SS, Chan JW. The relationship between heart rate reserve and oxygen uptake reserve in children and adolescents. *Res Q Exerc Sport* 2006; **77**:41–49.
- 134 Lounana J, Campion F, Noakes T, Medelli J. Relationship between %HRmax, %HR reserve, %VO<sub>2max</sub> and VO<sub>2</sub> reserve in elite cyclists. *Med Sci Sports Exerc* 2007; **39**:350–357.
- 135 Rotstein A, Meckel Y. Estimation of VO<sub>2</sub> reserve from heart rate during arm exercise and running. *Eur J Appl Physiol* 2000; **83**:545–550.
- 136 Golberg SR, Swain DP, Vinik AI. Use of heart rate reserve and rating of perceived exertion to prescribe exercise intensity in diabetic autonomic neuropathy. *Diabetes Care* 2003; **26**:986–990.
- 137 Brawner CA, Keteyian SJ, Ehrman JK. The relationship of heart rate reserve to VO<sub>2</sub> reserve in patients with heart disease. *Med Sci Sports Exerc* 2002; **34**:418–422.
- 138 Mezzani A, Corrà U, Giordano A, Cafagna M, Adriano EP, Giannuzzi P. Unreliability of the % VO<sub>2</sub> reserve versus % heart rate reserve relationship for aerobic effort relative intensity assessment in chronic heart failure patients on or off-beta-blocking therapy. *Eur J Cardiovasc Prev Rehabil* 2007; **14**:92–98.
- 139 Swain DP, Franklin BA. VO<sub>2</sub> reserve and the minimal intensity for improving cardiorespiratory fitness. *Med Sci Sports Exerc* 2002; **34**:152–157.
- 140 Pollock M, Gaesser G, Butcher J, Despres J-P, Dishman R, Franklin B, et al. ACSM Position Stand: The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc* 1998; **30**:975–991.
- 141 Durstine JL, Painter P, Franklin BA, Morgan D, Pitetti KH, Roberts SO. Physical activity for the chronically ill and disabled. *Sports Med* 2000; **30**:207–219.
- 142 Belardinelli R, Georgiou D, Scocco V, Barstow TJ, Purcaro A. Low intensity exercise training in patients with chronic heart failure. *J Am Coll Cardiol* 1995; **26**:975–982.
- 143 Demopoulos L, Bijou R, Fergus I, Jones M, Strom J, LeJemtel TH. Exercise training in patients with severe congestive heart failure: enhancing peak aerobic capacity while minimizing the increase in ventricular wall stress. *J Am Coll Cardiol* 1997; **29**:597–603.
- 144 Rognmo Ø, Hetland E, Helgerud J, Hoff J, Slørdahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil* 2004; **11**:216–222.
- 145 Roveda F, Middlekauff HR, Rondon MU, Reis SF, Souza M, Nastari L, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. *J Am Coll Cardiol* 2003; **42**:854–860.
- 146 Jones AM, Carter H. The effects of endurance training on parameters of aerobic fitness. *Sports Med* 2000; **29**:373–386.
- 147 Hansen D, Dendale P, Berger J, Meeusen R. Rehabilitation in cardiac patients. What do we know about training modalities? *Sports Med* 2005; **35**:1063–1084.
- 148 Klainman E, Kusniec J, Stern J, Fink G, Farbstein H. Contribution of cardiopulmonary indices in the assessment of patients with silent and symptomatic ischemia during exercise testing. *Int J Cardiol* 1996; **53**:257–263.
- 149 Munhoz EC, Hollanda R, Vargas JP, Silveira CW, Lemos AL, Hollanda RM, et al. Flattening of oxygen pulse during exercise may detect extensive myocardial ischemia. *Med Sci Sports Exerc* 2007; **39**:1221–1226.
- 150 Bussotti M, Apostolo A, Andreini D, Palermo P, Contini M, Agostoni P. Cardiopulmonary evidence of exercise-induced silent ischemia. *Eur J Cardiovasc Prev Rehabil* 2006; **13**:249–253.
- 151 Meyer K, Samek A, Pinchas A, Baier M, Betz P, Roskamm H. Relationship between ventilation threshold and onset of ischemia in ECG during stress testing. *Eur Heart J* 1995; **26**:623–630.
- 152 Fortini A, Bonechi F, Taddei T, Gensini GF, Malfanti PL, Neri Serneri GG. Anaerobic threshold in patients with exercise-induced myocardial ischemia. *Circulation* 1991; **83** (Suppl):11–50.
- 153 Zafir N, Fink G, Klainman E, Sulkes J, Spitzer S. Relation between aerobic capacity and extent of myocardial ischemia in patients with normal cardiac function. *Am Heart J* 1999; **138**:1088–1092.
- 154 Itoh H, Tajima A, Koike A, Osada N, Maeda T, Kato M, et al. Oxygen uptake abnormalities during exercise in coronary artery disease. In: Wasserman K, editor. *Cardiopulmonary exercise testing and cardiovascular health*. Armonk: Futura Publishing Company; 2002. pp. 165–172.
- 155 Belardinelli R, Lacalaprice F, Carle F, Minnucci A, Cianci G, Perna G, et al. Exercise-induced myocardial ischemia detected by cardiopulmonary exercise testing. *Eur Heart J* 2003; **24**:1304–1313.
- 156 Takaki H, Sakuragi S, Nagaya N, Suzuki S, Goto Y, Sato T, et al. Postexercise VO<sub>2</sub> hump phenomenon as an indicator for inducible myocardial ischemia in patients with acute anterior myocardial infarction. *Int J Cardiol* 2006; **111**:67–74.
- 157 Butchart EG, Gohlke-Bärwolf C, Antunes MJ, Tornos P, De Caterina R, Cormier B, et al.; Working Groups on Valvular Heart Disease, Thrombosis, and Cardiac Rehabilitation and Exercise Physiology, European Society of Cardiology. Recommendations for the management of patients after heart valve surgery. *Eur Heart J* 2005; **26**:2463–2471.
- 158 American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease); Society of Cardiovascular Anesthesiologists, Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al. ACC/AHA 2006 Guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice Guidelines (Writing Committee to Develop Guidelines on Patients with Valvular Heart Disease). *Circulation* 2006; **114**:e84–e231.
- 159 Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, et al. ACC/AHA guidelines for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol* 1997; **30**:260–315.
- 160 Sellier P, Chatellier G, D'Agrosa-Boiteux MC, Douard H, Dubois C, Goepfert PC, et al.; Investigators of the PERISCOP study. Use of non-invasive cardiac investigations to predict clinical endpoints after coronary bypass graft surgery in coronary artery disease patients: results from the prognosis and evaluation of risk in the coronary operated patient (PERISCOP) study. *Eur Heart J* 2003; **24**:916–926.
- 161 Pavy B, Iliou MC, Meurin P, Tabet JY, Corone S. Safety of exercise training for cardiac patients. Results of the French registry of complications during cardiac rehabilitation. *Arch Intern Med* 2006; **166**:2329–2334.
- 162 Weissman C. Pulmonary function after cardiac and thoracic surgery. *Anesth Analg* 1999; **88**:1272–1279.
- 163 De Carlo M, Milano A, Musumeci G, Tartarini G, Biadi O, Benedetti M, et al. Cardiopulmonary testing in patients with 21 mm St Jude medical aortic stenosis. *J Heart Valve Dis* 1999; **8**:522–528.
- 164 Le Tourneau T, de Groot P, Millaire A, Foucher C, Savoye C, Pigny P, et al. Effect of mitral valve surgery on exercise capacity, ventricular ejection fraction and neurohormonal activation in patients with severe mitral regurgitation. *J Am Coll Cardiol* 2000; **36**:2263–2269.
- 165 Kim HJ, Ahn SJ, Park SW, Cho BR, Sung J, Hong SH, et al. Cardiopulmonary exercise testing before and one year after mitral valve repair for severe mitral regurgitation. *Am J Cardiol* 2004; **93**:1187–1189.
- 166 Meurin P, Iliou MC, Ben Driss A, Pierre B, Corone S, Cristofini P, Tabet JY; Working Group of Cardiac Rehabilitation of the French Society of Cardiology. Early exercise training after mitral valve repair: a multicentric prospective French study. *Chest* 2005; **128**:1638–1644.
- 167 Douard H, Chevalier L, Labbe L, Choussat A, Broustet JP. Physical training improves exercise capacity in patients with mitral stenosis after balloon valvuloplasty. *Eur Heart J* 1997; **18**:464–469.
- 168 Wilson JR, Martin JL, Schwartz D, Ferraro N. Exercise intolerance in patients with chronic heart failure: role of impaired nutritive flow to skeletal muscle. *Circulation* 1984; **69**:1079–1087.
- 169 Sullivan MJ, Cobb FR. Central hemodynamic response to exercise in patients with chronic heart failure. *Chest* 1992; **101** (Suppl):340S–346S.
- 170 Clark AL, Poole-Wilson PA, Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol* 1996; **28**:1092–1102.
- 171 Floras JS. Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. *J Am Coll Cardiol* 1993; **22**:72A–84A.
- 172 Weber KT, Janicki JS, McElroy PA. Determination of aerobic capacity and the severity of chronic cardiac and circulatory failure. *Circulation* 1987; **76** (6 Pt 2):VI40–VI45.

- 173 Agostoni P, Emdin M, Corrà U, Veglia F, Magri D, Tedesco CC, *et al.* Permanent atrial fibrillation affects exercise capacity in chronic heart failure patients. *Eur Heart J* 2008; **29**:2367–2372.
- 174 Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P, Coats AJ. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. *Circulation* 1996; **93**:940–952.
- 175 Tumminello G, Guazzi M, Lancellotti P, Piérard LA. Exercise ventilation inefficiency in heart failure: pathophysiological and clinical significance. *Eur Heart J* 2007; **28**:673–678.
- 176 Puri S, Baker BL, Dutka DP, Oakley CM, Hughes JM, Cleland JG. Reduced alveolar capillary membrane diffusing capacity in chronic heart failure. Its pathophysiological relevance and relationship to exercise performance. *Circulation* 1995; **91**:2769–2774.
- 177 Clark AL, Coats AJ. Usefulness of arterial blood gas estimations during exercise in patients with chronic heart failure. *Br Heart J* 1994; **71**: 528–530.
- 178 Corrà U, Giordano A, Bosimini E, Mezzani A, Piepoli M, Coats AJ, *et al.* Oscillatory ventilation during exercise in patients with chronic heart failure. Clinical correlates and prognostic implications. *Chest* 2002; **121**: 1572–1580.
- 179 Ponikowski P, Anker D, Chua TP, Francis D, Banasiak W, Coats AJS, *et al.* Oscillatory breathing pattern during wakefulness in patients with chronic heart failure—Clinical implications and role of augmented peripheral chemosensitivity. *Circulation* 1999; **100**:2418–2424.
- 180 Agostoni P, Apostolo A, Albert RK. Mechanisms of periodic breathing during exercise in patients with chronic heart failure. *Chest* 2008; **133**:197–203.
- 181 Wasserman K, Sun XG, Hansen JE. Effect of biventricular pacing on the exercise pathophysiology of heart failure. *Chest* 2007; **132**:250–261.
- 182 Leclercq C. Upgrading from right ventricular pacing to biventricular pacing in pacemaker patients with chronic heart failure: Heart failure. *Heart* 2008; **94**:102–107.
- 183 De Jonge N, Kirkels H, Lahpor JR, Klöpping C, Hulzebos EJ, de la Rivière AB, *et al.* Exercise performance in patients with end-stage heart failure after implantation of a left ventricular assist device and after heart transplantation: an outlook for permanent assisting? *J Am Coll Cardiol* 2001; **37**: 1794–1799.
- 184 Maybaum S, Mancini D, Xydas S, Starling RC, Aaronson K, Pagani FD, *et al.* LVAD Working Group. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. *Circulation* 2007; **115**:2497–2505.
- 185 Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol* 2005; **46**:1883–1890.
- 186 Braith RW, Edwards DG. Exercise following heart transplantation. *Sports Med* 2000; **30**:171–192.
- 187 Givertz MM, Hartley LH, Colucci WS. Long-term sequential changes in exercise capacity and chronotropic responsiveness after cardiac transplantation. *Circulation* 1997; **96**:232–237.
- 188 Scott CD, Omar I, McComb JM, Dark JH, Bexton RS. Long-term pacing in heart transplant recipients is usually unnecessary. *Pacing Clin Electrophysiol* 1991; **14**:1792–1796.
- 189 Squires RW, Leung TC, Cyr NS, Allison TG, Johnson BD, Ballman KV, *et al.* Partial normalization of the heart rate response to exercise after cardiac transplantation: frequency and relationship to exercise capacity. *Mayo Clin Proc* 2002; **77**:1295–1300.
- 190 Richard R, Verdier JC, Duvallet A, Rosier SP, Leger P, Nignan A, *et al.* Chronotropic competence in endurance trained heart transplant recipients: heart rate is not a limiting factor for exercise capacity. *J Am Coll Cardiol* 1999; **33**:192–197.
- 191 Braith RW, Limacher MC, Mills RM Jr, Leggett SH, Pollock ML, Staples ED. Exercise-induced hypoxemia in heart transplant recipients. *J Am Coll Cardiol* 1993; **22**:768–776.
- 192 Schaefer A, Piquard F, Doutreleau S, Mettauer B, Epailly E, Eisenmann B, *et al.* Reduced exercise capacity is associated with reduced nitric oxide production after heart transplantation. *J Thorac Cardiovasc Surg* 2001; **122**:821–822.
- 193 Schmidt A, Pleiner J, Bayerle-Eder M, Wiesinger GF, Rödler S, Quittan M, *et al.* Regular physical exercise improves endothelial function in heart transplant recipients. *Clin Transplant* 2002; **16**:137–143.
- 194 Schaufelberger M, Eriksson BO, Lönn L, Rundqvist B, Sunnerhagen KS, Swedberg K. Skeletal muscle characteristics, muscle strength and thigh muscle area in patients before and after cardiac transplantation. *Eur J Heart Fail* 2001; **3**:59–67.
- 195 Lampert E, Mettauer B, Hoppeler H, Charloux A, Charpentier A, Lonsdorfer J. Skeletal muscle response to short endurance training in heart transplant recipients. *J Am Coll Cardiol* 1998; **32**:420–426.
- 196 Grassi B, Marconi C, Meyer M, Rieu M, Cerretelli P. Gas exchange and cardiovascular kinetics with different exercise protocols in heart transplant recipients. *J Appl Physiol* 1997; **82**:1952–1962.
- 197 Nanas SN, Terrovitis JV, Charitos C, Papazachou O, Margari Z, Tsagalou EP, *et al.* Ventilatory response to exercise and kinetics of oxygen recovery are similar in cardiac transplant recipients and patients with mild chronic heart failure. *J Heart Lung Transplant* 2004; **23**:1154–1159.
- 198 Van Laethem C, Goethals M, Verstreken S, Walravens M, Wellens F, De Proft M, *et al.* Response of the oxygen uptake efficiency slope to orthotopic heart transplantation: lack of correlation with changes in central hemodynamic parameters and resting lung function. *J Heart Lung Transplant* 2007; **26**:921–926.