Abstract: 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, e.g. peak oxygen consumption. Moreover, CPET has dramatically increased the mass of information obtainable from a relatively simple and inexpensive procedure such as exercise testing, furnishing an all-round vision of the systems involved in both O2 transport from air to mitochondria and its utilization, and making it possible to identify the link(s) limiting exercise capacity in the individual patient. However, during the last 20 years the use of CPET for prognostic purposes (mainly in chronic heart failure patients) has overshadowed its application for the
functional evaluation of cardiac patients, indeed its original one. This paper aims to provide professionals with an up-to-date review of the scientific rationale sustaining the use of CPET for functional evaluation of cardiac patients in both the clinical and research settings. Readers interested in the use of CPET for prognostic stratification of patients with cardiac disease (in particular, chronic heart failure) are referred to previously published reviews.

Suggested Reviewers:
STANDARDS FOR THE USE OF CARDIOPULMONARY EXERCISE TESTING FOR FUNCTIONAL EVALUATION OF CARDIAC PATIENTS

A Report from the Exercise Physiology Section of the European Association of Cardiovascular Prevention and Rehabilitation

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1. 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, e.g. peak oxygen consumption (peakVO$_2$) (1-3). Moreover, CPET has dramatically increased the mass of information obtainable from a relatively simple and inexpensive procedure such as exercise testing, furnishing an all-round vision of the systems involved in both O$_2$ transport from air to mitochondria and its utilization, and making it possible to identify the link(s) limiting exercise capacity in the individual patient. However, during the last 20 years the use of CPET for prognostic purposes (mainly in chronic heart failure patients) has overshadowed its application for the functional evaluation of cardiac patients, indeed its original one. This paper aims to provide 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 (Table 1). Readers interested in the use of CPET for prognostic stratification of patients with cardiac disease (in particular, chronic heart failure) are referred to previously published reviews (4). The parameters described in this report are obtainable either from ramp incremental or step constant-power CPET, as specified in the respective paragraphs.
2. Use of cardiopulmonary exercise testing for evaluation of O2 transport and utilization efficiency

2.1. Ventilatory anaerobic threshold

During incremental exercise, an energy requirement is reached above which blood lactate concentration increases at a progressively steeper rate (5). This is due to anaerobic glycolysis activation, which occurs as the oxygen supply rate is not rapid enough to reoxidize cytosolic NADH + H\(^+\) (6). Almost all of the H\(^+\) generated in the cell from lactic acid (La) dissociation is buffered by bicarbonate according to the following reaction:

\[
\text{H}^+ \text{La}^- + \text{HCO}_3^- \rightleftharpoons \text{H}_2\text{O} + \text{CO}_2 + \text{La}^- 
\]

Such production of CO\(_2\), in excess of that produced by aerobic metabolism (excess CO\(_2\)), makes the CO\(_2\) production (VCO\(_2\)) vs. VO\(_2\) 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 (7), and is a reliable index of aerobic fitness used for training prescription in both normal subjects and cardiac patients, especially for sustainable submaximal work (8,9). Inter-individual variance, exercise protocol (e.g. fast vs. slow work rate increments, step vs. ramp protocols) (10), blood sampling source (e.g. venous, capillary, arterial, arterialized) (11), and type of exercise (e.g. running, swimming, cycling, rowing, etc.) (12) can all affect blood lactate kinetics.
By measuring at the mouth gas exchange modifications induced by metabolic changes, the ‘ventilatory anaerobic threshold’ (VAT) can be determined analyzing the slope of the VCO$_2$ vs. VO$_2$ (plotted on equal scales) relationship during ramp incremental exercise (V-slope method) (13). Based on the above, VAT is the point of transition of the VCO$_2$ vs. VO$_2$ 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$_2$ produced above VAT increases ventilatory drive, which keeps the ventilation (VE) vs. VCO$_2$ relationship linear and the end-tidal CO$_2$ pressure (P$_{ET}$CO$_2$) value constant (i.e. the subject does not hyperventilate with respect to the volume of CO$_2$ metabolically produced). However, an inversion of the VE vs. VO$_2$ relationship behavior (increase vs. initial decrease, i.e. hyperventilation with respect to O$_2$) is observed above VAT; this makes both the VE vs. VO$_2$ ratio and end-tidal O$_2$ pressure (P$_{ET}$O$_2$) increase, in the presence of a still decreasing or constant VE/VCO$_2$ and P$_{ET}$CO$_2$.

VAT is thus identifiable with the nadir of the VE vs. VO$_2$ relationship (Fig. 1 - lower panel) and with the point where P$_{ET}$O$_2$ begins to increase (2). In the final phase of ramp incremental exercise, hyperventilation does occur also with respect to CO$_2$ (respiratory compensation point), making VE/VCO$_2$ increase and P$_{ET}$CO$_2$ decrease (14) (Fig. 1).

VAT is usually expressed as a VO$_2$ value relative to predicted VO$_{2max}$, the lower limit of normality being 40% of predicted VO$_{2max}$ (15). In the vast majority of healthy subjects, VAT occurs at around 50-60% of VO$_{2max}$ (Table 2); in trained endurance athletes, VAT can reach intensities as high as 80% of their VO$_{2max}$ (16).

All cardiac diseases affecting the O$_2$ transport chain (typically chronic heart failure) can determine a pathologic VAT (i.e. <40% predicted VO$_{2max}$) (17), as can deconditioning following bed rest for cardiac events, even in the presence of normal left ventricular
systolic function (18). However, when expressed relative to measured peakVO$_2$ (and not to predicted VO$_{2\text{max}}$), VAT will still occur at around 50-60% of peakVO$_2$ in most cardiac patients, with a trend towards higher percentages of peakVO$_2$ in patients with chronic heart failure (6,15,17,19). Of note, VAT may be not detectable in a variable percentage of patients (20), and especially in those with chronic heart failure due to exercise oscillatory ventilation and/or shortness of exercise time.

2.2. VO$_{2\text{max}}$

Maximal oxygen uptake (VO$_{2\text{max}}$) is a parameter which describes the maximal amount of energy obtainable by aerobic metabolism per unit of time (aerobic power). VO$_2$ 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$_2$ is the arterio-venous O$_2$ content difference. In healthy subjects, VO$_{2\text{max}}$ is mostly limited by cardiac output rather than by peripheral factors (21), its value however being influenced by several parameters, such as arterial O$_2$ content, fractional distribution of cardiac output to exercising muscles, and muscle ability to extract O$_2$; recent data also indicate a possible role of a central nervous system governor (22). VO$_{2\text{max}}$ attainment is evidenced by failure of VO$_2$ to increase despite increasing work rate (23). However, flattening of the VO$_2$ vs. power relationship is not seen often in routine clinical practice, and so a more realistic goal is to assess peakVO$_2$ rather than VO$_{2\text{max}}$. PeakVO$_2$ is defined as the highest VO$_2$, averaged over a 20- to 30-second period, achieved at presumed maximal effort during an incremental exercise test,
and may or may not equal VO\textsubscript{2max}, even if available evidence suggests that these two concepts are substantially analogous (24). In any case, peakVO\textsubscript{2} describes patients’ exercise tolerance far more reliably than exercise duration or peak power (25). Achievement of truly maximal effort (and thus of reliable VO\textsubscript{2max} values) can be assumed in the presence of one or more of the following criteria (26):

- failure of VO\textsubscript{2} and/or heart rate to increase with further increases in work rate
- peak respiratory exchange ratio $\geq 1.10 - 1.15$
- post-exercise blood lactate concentration $\geq 8 \text{ mmol/dl}$
- rating of perceived exertion $\geq 8$ (on the 10-point Borg scale)

Normal values of VO\textsubscript{2max} depend on age and sex, and are influenced by body size, level of physical activity, and genetic endowment (27). VO\textsubscript{2max} is measured in liters or milliliters of O\textsubscript{2} per minute, or in milliliters of O\textsubscript{2} per kilogram of body weight per minute. The highest values of VO\textsubscript{2max} are reported in endurance athletes (94 ml/kg/min) (28). VO\textsubscript{2max} declines on average by 10% per decade after the age of 30, due to decreasing maximal heart rate, stroke volume, blood flow to skeletal muscle, and skeletal muscle aerobic potential with age (29). VO\textsubscript{2max} is also 10 to 20% greater in males than in females of comparable age (30), because of higher hemoglobin concentration and greater muscle mass and stroke volume in males. Several formulas based on age and body dimensions are available for VO\textsubscript{2max} prediction in sedentary men and women, the most detailed recommendation being provided by Wasserman et al. (15) (Table 2).
Many cardiovascular diseases can affect VO$_{2\text{max}}$/peakVO$_2$. Namely, all pathologies impairing CO response to exercise will determine some degree of reduction of peakVO$_2$ with respect to predicted VO$_{2\text{max}}$. For example, peakVO$_2$ is classically reduced with respect to age- and sex-matched normal subjects in patients with chronic heart failure (17), but is also lower than normal in patients with preserved left ventricular function entering a rehabilitation program after recent cardiac surgery (31), due to bed rest-induced deconditioning. When possible, determination of peakVO$_2$ in patients referred for cardiac rehabilitation is a cornerstone for rational exercise prescription and evaluation of training efficacy (32,33).

2.3. Critical power

Critical power represents the highest power sustainable in conditions of both VO$_2$ and lactate steady-state (34), overlapping, as such, the concept of maximal lactate steady-state, i.e. the highest power sustainable in conditions of stable blood lactate concentration (35). 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 (36), situated between VAT and peakVO$_2$ powers as assessed during incremental ramp CPET.

From a mathematical standpoint, critical power corresponds to the power asymptote of the hyperbolic relationship linking power and duration of constant-power exercise (34). The determination of critical power requires the performance of 4 to 5 constant-power exercise tests in the above-VAT threshold effort intensity domains (see paragraph 2.4.), with relative intensities ranging between 70% and 120% of peak power reached during an incremental ramp exercise test (34); the critical power is then obtained by fitting a
quadratic hyperbola on the obtained power vs. 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 CPET has been described (37). If these data were confirmed, a single and easy-to-perform test - CPET - would provide operators with all the parameters describing O₂ transport and utilization system efficiency, i.e. anaerobic threshold, critical power, and peakVO₂.

Critical power has been evaluated by several authors in sedentary young normal subjects, revealing repeatable values around 65-70% of peak power (or 25-30% of ΔVAT-peakVO₂ power) (Table 2) at incremental exercise testing, with a steady-state VO₂ mean value corresponding to 70-80% of peakVO₂ (34,36). Elderly subjects show critical power values similar to those of young subjects when expressed relative to peak power, but with higher relative steady-state VO₂ mean values (around 80-90% of peakVO₂), demonstrating a broadening of the high-intensity domain of effort probably aimed at preservation of habitual activities performance in steady-state, non fatiguing metabolic conditions (38). Of note, similarly to the other O₂ transport and utilization system efficiency descriptors, also critical power is increased by aerobic training (39).

No data are currently available on critical power in cardiac patients. However, there is information suggesting that chronic heart failure patients perform their habitual activities at absolute and relative intensities higher than the individual VAT (40). This underlines the need for studies addressing critical power in this population.
2.4. \( VO_2 \) on-kinetics

During constant-power exercise below anaerobic threshold (moderate-intensity effort domain), three phases of \( VO_2 \) on-kinetics are classically described in human physiology (41-43): phase I, during which the \( VO_2 \) increase would rely mostly on pulmonary blood flow (i.e. CO) increment in the presence of an unchanging C(a-v)\( O_2 \); phase II, characterized by a mono-exponential \( VO_2 \) increase mainly reflecting skeletal muscle \( VO_2 \) consumption, as described by C(a-v)\( O_2 \) widening; and phase III, i.e. steady-state attainment (Fig. 3). As \( VO_2 \) does not reach instantaneously its steady-state value at step exercise onset, during phase I and II an \( O_2 \) deficit accumulates, defined as the cumulative difference between steady-state \( VO_2 \) level and \( VO_2 \) levels throughout the on-response (Fig. 3); the \( O_2 \) deficit will be larger the greater the recourse to anaerobic energy sources (alactic and lactic) and body \( O_2 \) stores before steady-state attainment (43,44). Above anaerobic threshold and up to critical power (high-intensity effort domain), it is still possible to reach a \( VO_2 \) steady-state for constant-power efforts (see paragraph 2.3.), even if in this intensity domain an additional, delayed-onset \( VO_2 \) component ('slow component') adds to the expected steady-state \( VO_2 \) value according to the below-VAT \( VO_2 \) vs. power (W) relationship (43,45,46). 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 \( VO_2 \) vs. W points, or with an incremental ramp CPET, by fitting a linear function to the breath-by-breath below-VAT \( VO_2 \) vs. W data, excluding from the fitting window the initial non-increasing or poorly increasing \( VO_2 \) period (47,48); the \( VO_2 \) vs. W slope values obtained with the above two methods have been shown to be superimposable (48). Beyond critical power (very-high intensity effort domain), a steady-state is no longer
attainable, and the VO$_2$ slow component makes VO$_2$ increase inexorably up to VO$_{2\text{max}}$ (43,46).

The presence of the VO$_2$ slow component introduces some methodological caveats about VO$_2$ on-response evaluation in the high- and very-high intensity domains; for this reason, VO$_2$ on-kinetics are usually assessed during moderate-intensity effort, and can thus be evaluated also in subjects unable to exercise maximally. In this context, phase I is described in terms of its amplitude and duration and the monoexponential VO$_2$ increase during phase II through its time constant (i.e. the time needed to reach 63% of the steady-state value) (Fig. 3).

VO$_2$ on-kinetics becomes more prolonged with age (Table 2), as demonstrated by increasing values of its mean response time (i.e. the time constant of the whole VO$_2$ on-response, involving both phase I and II) (Fig. 3) (49), which is due to modifications of the O$_2$ transport and utilization system during the aging process described in paragraph 2.2. Moreover, aerobic training affects the VO$_2$ on-kinetics similarly to the other descriptors of aerobic performance efficiency by shortening the phase II time constant (50), i.e. making the system adapt more rapidly to changes of loading conditions.

Cardiac disease can affect VO$_2$ on-kinetics mainly by reducing O$_2$ delivery to exercising skeletal muscles. This is evidenced by a prolonged phase II time constant in patients with coronary artery disease and lone atrial fibrillation with respect to normal subjects (51,52) and is confirmed by the finding of improved VO$_2$ on-kinetics after percutaneous transluminal coronary angioplasty (53). A significant prolongation of phase II time constant is also observed in patients with chronic heart failure (54), whose pathophysiologic picture affects several steps of the O$_2$ transport/utilization system (see
paragraph 6.3.), whereas a shortening of phase II time constant is observed in these patients after left ventricular assist device implantation (55).

2.5. VO$_2$ off-kinetics

During the resting recovery phase after constant-power moderate-intensity exercise, the O$_2$ debt contracted during the O$_2$ deficit accumulation is paid by a VO$_2$ in excess of the resting level (Fig. 3) (6,56); the same phenomenon is observed during recovery from an incremental exercise test. Such O$_2$ uptake is necessary for the re-phosphorylation of creatine in skeletal muscles and, later, conversion of lactate to pyruvate and other mechanisms (57,58). VO$_2$ during recovery fits an exponential function, and can be described by the time constant of the VO$_2$ off-response or its T$_{1/2}$, i.e. the time necessary for VO$_2$ to decrease by 50% from its peak effort value (59). The more efficient the O$_2$ delivery to, and O$_2$ utilization by, exercising skeletal muscles, the faster this time is; hence it is shorter in athletes and longer in deconditioned subjects (60).

After an incremental ramp exercise test, the average T$_{1/2}$ value in normal subjects ranges between 60 and 90 seconds (Table 2), and would appear to become more prolonged with advancing age, although no conclusive data are available on age-induced VO$_2$ off-kinetics modifications (59,61,62). T$_{1/2}$ is largely independent of exercise intensity, at least as long as it remains greater that 75% of the maximum (59); this can be particularly interesting in subjects who stop exercising before peak effort because of symptoms, poor motivation, or fear and in whom peakVO$_2$ is underestimated. Thus, a low peakVO$_2$ in the presence of normal VO$_2$ recovery kinetics suggests submaximal effort; conversely, a long T$_{1/2}$ reinforces the value of a low peakVO$_2$. 
All pathologies affecting the O$_2$ transport chain from ambient air to exercising skeletal muscle are expected to influence the post-exercise VO$_2$ behaviour. Indeed, several authors have shown that the kinetics of VO$_2$ recovery both after constant-power submaximal and incremental maximal exercise testing are slowed in patients with congenital heart disease and chronic heart failure (59,61-64); data for post-myocardial infarction patients are less clear (65,66).

3. Use of cardiopulmonary exercise testing for evaluation of ventilation efficiency and control

3.1. VO$_2$ vs. ventilation relationship - the oxygen uptake efficiency slope

The oxygen uptake efficiency slope (OUES) represents the rate of increase of VO$_2$ in response to a given VE during incremental exercise, indicating how effectively oxygen is extracted and taken into the body (67). 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$_2$ (y-axis) vs. the logarithm of VE (x-axis) during exercise, i.e. VO$_2$ = a log$_{10}$ VE + b, where a is the OUES and b is the intercept (67). The logarithmic transformation of VE is aimed at linearizing the otherwise curvilinear relation of VO$_2$ vs. VE, so making the OUES theoretically
independent of the patient-achieved effort level. Several studies have tested this hypothesis (67-75), showing either equal or slightly higher or lower submaximal vs. maximal OUES values, which thus outweigh the substantially larger differences in peakVO₂ 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 (68-70,71,72,75-77), and is easily calculated by a simple mathematical formula, thus improving intra- and interobserver measurement variability and objectivity (78). In healthy subjects, OUES has been investigated in children (67) and adults (69,70,73). Age-adjusted OUES values can be predicted using the gender-specific equations by Hollenberg et al. (69) (Table 2).

In patients with coronary artery disease, OUES is significantly reduced (71,75,76). However, patients who have undergone percutaneous transluminal coronary angioplasty with or without prior myocardial infarction have significantly higher OUES values compared to patients after coronary artery bypass grafting (75). This may be explained by a higher disease severity, pre- 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 to those in normal sinus rhythm (75); this is likely due to the impact of decreased oxygen delivery on the working muscles in patients with atrial fibrillation due to lower stroke volume and cardiac output response during exercise (79). In chronic heart failure, the OUES is reduced in proportion to disease severity (69,71,72,77) (see paragraph 6.3.).

Physical training has been shown to increase OUES in both coronary artery disease and chronic heart failure patients (75,77), suggesting that, after training, a given oxygen
uptake is achieved with a lower ventilatory cost. This OUES increase may be due to a reduced metabolic acidosis and/or ventilatory response at submaximal effort intensities. The training-induced changes of OUES parallel those of peakVO$_2$ (75,77), showing that OUES is sensitive to improvements in exercise tolerance. OUES would therefore appear to be clinically useful to monitor changes in exercise performance and effects of physical training, particularly in patients who can only perform submaximal exercise.

3.2. Ventilation vs. VCO$_2$ relationship - the VE vs. VCO$_2$ slope

Despite a manifold increase in VCO$_2$ and VO$_2$ during incremental exercise, the ventilatory control mechanisms normally keep arterial CO$_2$ tension (PaCO$_2$) and pH remarkably constant over a wide range of metabolic rates. The slope of the relationship between VE and VCO$_2$ describes the ventilatory efficiency during effort, showing the amount of air that must be ventilated to eliminate one litre of CO$_2$. The basic information given by the VE vs. VCO$_2$ slope is incorporated in the modified alveolar equation (80):

$$VE = 863 \times \frac{VCO_2}{PaCO_2} \times (1 - \frac{V_D}{V_T})$$

where $V_D$ and $V_T$ are volume of pulmonary dead space and tidal volume, respectively. If PaCO$_2$ is driven down by a high ventilatory drive from peripheral chemoreceptors and/or $V_D/V_T$ is high, the VE vs. VCO$_2$ slope increases; a low $V_T$ with respect to a normal anatomic dead space or an abnormally high physiological dead space are potential sources of high $V_D/V_T$ (81). Another proposed cause of increased ventilatory drive during exercise is effort-induced muscle metaboreflex (ergoreflex) overactivation (82). Of note, during incremental exercise VE and VCO$_2$ are linearly related until VE
increases disproportionately to VCO₂ (respiratory compensation point - see paragraph 2.1.). There is still controversy about whether the VE vs. VCO₂ slope should be calculated across the overall exercise data or only up to the respiratory compensation point; while its assessment until this point is the logical one from a physiological standpoint, calculation over the whole exercise period seems to increase the VE vs. VCO₂ slope prognostic value in chronic heart failure patients (83).

Normal values of VE vs. VCO₂ slope range between 20 and 30, with an intercept on the VE axis of some 4-5 l/min due to a reduction of VD/Vₜ ratio after the start of exercise and/or early exercise hyperventilation. The VE vs. VCO₂ slope is affected by age, showing increasing values with increasing age (84) (Table 2). A higher than normal VE vs. VCO₂ slope may be of undeterminable origin (primary hyperventilation) or due to hypoxia or respiratory or cardiac diseases that can stimulate VE (secondary hyperventilation). Conversely, a downward displacement of the VE vs. VCO₂ slope occurs when the PaCO₂ set point is raised, i.e. in primary alveolar hypoventilation syndrome (impaired ventilatory chemoreflex function).

In patients with coronary artery disease (previous myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery by-pass grafting, and significant chronic coronary stenosis), the VE vs. VCO₂ slope has been shown to be higher the lower the peakVO₂ is (85). This could be due to 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 vs. VCO₂ slope has been found to be increased also in patients with congenital heart disease, probably due to an altered VD/Vₜ ratio in this population (86,87). Finally, a
high VE vs. VCO₂ slope is frequently observed in chronic heart failure and is associated with the severity of disease (88,89) (see paragraph 6.3.), bearing an adverse prognostic significance (90).

3.3. Exercise oscillatory ventilation

Periodic breathing oscillations of VO₂, VCO₂, 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 (91). 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 (92-95). 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) (96).

EOV has been defined in different ways. Kremser et al.’s (92) 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. Leite et al.’s (97) description is based on the following criteria: 1) three or more regular oscillations (i.e. clearly distinguishable from inherent data noise); 2) regularity, so-defined when the standard deviation of three consecutive cycle lengths (time between 2 consecutive nadirs) is within 20% of the average; 3) minimal average amplitude of VE oscillation equal to 5 litres (peak value minus the average of two in-between
consecutive nadirs). Of note, the detection of VAT is often masked by the presence of EOV (94).

Among cardiac patients, EOV during exercise testing has been specifically detected in those with chronic heart failure (see paragraph 6.3.), 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 (91).

4. Use of cardiopulmonary exercise testing for evaluation of central hemodynamics

4.1. $VO_2$ and cardiac output

As already shown in paragraph 2.2., $VO_2$ is the product of CO times C(a-v)$O_2$. In the systemic circulation, $O_2$ content increases during exercise above VAT because of an increase in hemoglobin which is mainly due to the oncotic effect of increased intracellular lactate concentration (98,99). In the pulmonary artery, $O_2$ content diminishes progressively throughout the entire exercise; below anaerobic threshold, this is due to a reduction of $PO_2$ and above anaerobic threshold to both a shift in the oxyhemoglobin dissociation curve (Bohr effect) and a reduction of $PO_2$ (100). 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 subjects, 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 (101,102). Alternatively, stroke volume at peak exercise can be estimated through the oxygen pulse, which is $VO_2$/heart rate - i.e. 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, stroke volume in ml can then be calculated as $(\text{oxygen pulse/15}) \times 100$, where oxygen pulse is in ml/beat (23); however, this estimation must be used with caution in non perfectly normal and motivated subjects.

Few data are available as to normal CO values during effort. A frequently used formula based on the cardiac index vs. VO$_2$ relationship during incremental exercise (103) has been adapted for its estimation by converting cardiac index into CO values (104) (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 chronic heart failure 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 (105). 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 (106). However, rather than CO estimation during exercise, its direct non-invasive determination by means of CO$_2$ rebreathing or inert gas methods (107) together with VO$_2$ measurement might be a major advance in 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. 4) (108). This plot helps to discriminate between exercise limitation due to 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 chronic heart failure patients, in whom both a normal and reduced CO response during
effort has been described in the presence of a reduced peakVO$_2$ (104,109,110). Moreover, the role of anaemia in functional capacity impairment can be precisely calculated as well (111). As each hemoglobin (Hb) gram carries 1.34 ml of O$_2$, and since at peak exercise Hb desaturation is about 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$_2$ due to anaemia at peak effort. For example, if peak CO is 7.0 l/min, i.e. 70 dl/min, and hemoglobin is 10 g/dl, the amount of VO$_2$ lacking due to anaemia is 15 (normal Hb) - 10 (observed Hb) x 70 = 350 ml/min. Obviously, this 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.

4.2. Circulatory power

Cardiac power, the product of CO and central aortic (or mean arterial) pressure, is one of the most powerful indexes of cardiac systolic function (112-114). This is due to the fact that the heart and proximal vascular system are closely coupled and that, 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 (115). For cardiac pumping capability determination during effort, cardiac power can be assessed non-invasively by using the CO$_2$ rebreathing or inert gas methods to measure CO (116-119). The ‘circulatory power’ is a cardiac power surrogate obtainable from CPET, calculated as peakVO$_2$ multiplied by peak systolic blood pressure (120). As such, circulatory power represents
the triple product of CO x C(a-v)O₂ (from the Fick equation) x systolic blood pressure. For circulatory power to closely estimate cardiac power, there should not be a great difference in C(a-v)O₂ at peak exercise in either normal subjects or cardiac patients, which is usually the case (101,102,121-123). 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 non-invasive 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 peakVO₂, depend on age, sex, body mass, and training level. Considering 25 to 40 ml/kg/min as normal values for peakVO₂ and 150 to 220 mmHg for peak systolic blood pressure, normal values of peak circulatory power between 3500 and 8800 mmHg x ml/kg/min are obtained (Table 2). The highest values are found in athletes and in hypertensives with preserved systolic function. Patients with chronic heart failure generally have less than 3000 mmHg, and values <1800 mmHg 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 peakVO₂ as a percentage of predicted VO₂max (124).

Circulatory power is an interesting parameter for functional evaluation of cardiac patients as it summarizes heart rate, stroke volume, blood pressure, and C(a-v)O₂ responses to exercise (all of which can be altered in several cardiac pathophysiological conditions, in particular chronic heart failure), even though it does not allow to
distinguish between them as to relative responsibility for exercise capacity impairment. Vasodilators and beta-blockers may alter peakVO₂ and systolic blood pressure in opposite ways but the final interaction between drug therapy and functional and prognostic value of circulatory power has not been thoroughly evaluated yet (125).

5. Use of cardiopulmonary exercise testing for evaluation of exercise relative intensity

The VO₂ reserve (VO₂R) is the difference between resting and peakVO₂, and, as it describes the O₂ used during exercise in addition to basal consumption, is considered a direct measure of the exercise load or energy expenditure (126,127). As a consequence, the percentage of VO₂R (%VO₂R) is now considered the gold standard for estimation, prescription, and monitoring of exercise relative intensity (128), 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 paragraph 2.4.) (129).

Similarly to VO₂R, 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 heart rate reserve (%HRR) has been found to be substantially equivalent to %VO₂R, and not to percentage of VO₂ max (%VO₂ max) (126,127,130). Indeed, %HRR has been found to be equivalent to %VO₂ max in children and adolescents (131); on the contrary, in adults there is a discrepancy between %HRR and %VO₂ max, which decreases with increasing exercise intensity and seems to be inversely related to subjects’ fitness (126,127). The equivalence between
%HRR and %VO₂R has been observed also in elite endurance athletes (132); of note, particularly in trained subjects, there seems to be a better prediction of %VO₂R from %HRR for running than for arm exercise (133). Moreover, in patients with type 2 diabetes, %HRR was found to be an excellent descriptor of %VO₂R regardless of the presence of autonomic neuropathy (134). This finding is consistent with those in patients with previous myocardial infarction both on and off beta-blocking therapy (135), in whom an ergometric test without respiratory gas analysis would thus be sufficient for exercise relative intensity assessment. However, in patients with chronic heart failure (independently of beta-blocking therapy) a considerable uncertainty in prediction of %VO₂R on the basis of %HRR has been observed (136); carrying out a CPET in individual chronic heart failure patients seems thus advisable for exercise relative intensity determination and in order to avoid training stimulus inadequacy or excessive exercise-related risk.

As far as minimal aerobic training stimulus intensity is concerned, analysis of available studies supports the use of 45%VO₂R as a minimal effective intensity threshold for fitter subjects (peakVO₂ >40 ml/kg/min) and 30%VO₂R for those with a peakVO₂ <40 ml/kg/min (137); moreover, guidelines recommend a minimal intensity of 40%VO₂R to elicit improvements in aerobic fitness of less fit subjects, 50%VO₂R for the physically active, and up to 85%VO₂R for highly fit subjects (138). In patients with coronary artery disease, 45%VO₂R is the minimum intensity recommended for improving aerobic fitness (32); such a relative intensity is higher than that suggested for less fit normal individuals, since most cardiac patients do not reach their maximal effort and thus intensity prescription is based on peakVO₂ and not VO₂max. In any case, in agreement with the lower fitness-lower training intensity
principle (139), relative intensities as low as 23%VO$_2$R (140), and probably even lower (141), have proved to be effective in chronic heart failure patients. From such a low-to moderate-intensity domain of exercise, 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, i.e. critical power (see paragraph 2.3.). 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 chronic heart failure (142,143).

6. Use of cardiopulmonary exercise testing for functional evaluation of specific populations

6.1. 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 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$_2$ and oxygen pulse compared with non-ischemic controls (144). Moreover, symptomatic
patients had significantly lower values of the same parameters and a higher reduction of left ventricular ejection fraction at peak effort compared to the silent ischemia group (144). In another study (145), patients with exercise-induced ischemia presented peakVO$_2$ and oxygen pulse values similar to those of patients with normal perfusion studies; however, patients with extensive transient perfusion defects had a lower peak oxygen pulse than those with lower exercise-induced ischemia. Decreased VAT VO$_2$ has also been consistently shown to be related to the presence (144,145-148) and the extent of myocardial ischemia (149).

The ischemia-induced reduction in stroke volume can also decrease the VO$_2$ vs. W rise (150) and increase to some extent O$_2$ deficit values, which in turn could slow the VO$_2$ off-kinetics. Based on the above considerations, CPET has also been used for myocardial ischemia diagnostic purposes. Belardinelli et al. (151) 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$_2$ vs. W slope and oxygen pulse increase as a consequence of worsening myocardial contraction during ischemia. Bussotti et al. (146) also demonstrated a significant flattening of VO$_2$ vs. W 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. Also the presence of a “hump” morphology (i.e. a transient convex bulge at around 1 min of the VO$_2$ off-kinetics) has been shown to identify exercise-induced ischemia with 57% sensitivity and 97% specificity among patients with anterior Q-wave myocardial infarction (152); such phenomenon could be due to 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 3.

6.2. Patients with recent coronary and valvular surgery

After recent coronary and/or valvular surgery, exercise testing is performed mostly in order 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) (153-156); moreover, exercise testing and aerobic training have been recently confirmed to be safe early after heart valve surgery and coronary artery bypass grafting (157). 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 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, anaemia, sinus tachycardia, atrial fibrillation (in about 40% of patients), transient postoperative left ventricular dysfunction, and global fatigue (156,158). 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 peakVO₂ (31). 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 (159). Moreover, heart rate is often higher than after coronary artery bypass grafting (due to absence of systematic beta-blocker therapy and/or higher incidence of atrial fibrillation) and no formula allows to calculate the heart rate at the anaerobic threshold, which is often used as a target during the training sessions. Le Tourneau et al. (160) 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 peakVO₂ in either the valve repair or replacement group; these results were confirmed by Kim et al. (161). By contrast, a recent study in early post-mitral valve repair patients (162) 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, peakVO₂, peak power, peak oxygen pulse, and chronotropic reserve improved significantly. These results confirmed those of Douard et al. (163), who observed a significant increase of peakVO₂ 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 limits. Changes in CPET parameters induced by recent coronary and valvular surgery are summarized in Table 3.

6.3. Patients with chronic heart failure

A reduced ability to perform aerobic exercise is the hallmark of the chronic heart failure (CHF) pathophysiologic picture (17), related to changes in both peripheral (skeletal muscle, endothelium, regional blood flow, and reflex cardiopulmonary control systems) and central (lung and heart) links of the O$_2$ transport chain from ambient air to the skeletal muscle (164-165). These changes promote a vicious cycle of deterioration involving catabolic drive and reflex neurohormonal overactivation (166,167), which may lead to disease progression and functional deterioration. As a consequence, in CHF peakVO$_2$ is typically reduced with respect to age-matched normal subjects when computed either in absolute (l/min) or weighted terms (ml/kg/min), or as percent of predicted VO$_{2max}$, and its reduction is proportional to the severity of the syndrome (17,168). Together with peakVO$_2$, also all the other descriptors of O$_2$ transport and utilization system efficiency are lowered. 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 (19). 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$_2$ vs. W slope and a prolongation of both VO$_2$ on- and off-kinetics in moderate-intensity constant-power effort and of VO$_2$ off-kinetics after incremental exercise have been described.
and, in addition to VAT, provide useful submaximal descriptors of O\textsubscript{2} transport/utilization system efficiency. Patients with CHF and permanent atrial fibrillation show peakVO\textsubscript{2} values even lower than those of CHF patients in sinus rhythm, but with VAT occurring at a higher percentage of peakVO\textsubscript{2} (169). CPET also reveals an increased ventilation at comparable absolute submaximal and maximal levels of effort in CHF patients with respect to age-matched normal subjects (88). As a consequence, the VE vs. VCO\textsubscript{2} slope is usually increased (170,171), testifying to a reduced ventilatory efficiency which may be improved by aerobic training (170). Such ventilatory inefficiency is further evidenced by a decrease of the OUES with respect to age-matched normal subjects (71,72,77). Among the causes of the increased ventilatory response to exercise, a reduced oxygen-diffusing capacity due to an impairment of alveolar-arterial oxygen transfer has been suggested (172), although O\textsubscript{2} transfer is preserved and arterial O\textsubscript{2} desaturation during exercise is rare in otherwise uncomplicated CHF (173). An increase in dead space ventilation can be advocated because of a mismatching of ventilation relative to pulmonary perfusion of the high alveolar ventilation vs. low alveolar perfusion type (88). Another likely mechanism explaining the excessive exercise ventilation of CHF patients is an exaggerated ergoreflex response originating in the exercising skeletal muscles during effort (170), in the context of a generalized myopathy with early acidotic response: this may explain also the sympathetic hyper-responsiveness present in this syndrome (171). Also EOV has been described in a variable percentage (20-60\%) of CHF patients, associated with poor exercise capacity and severe prognosis (173,174). It has been attributed to the interaction of altered hemodynamic and neurohormonal regulatory factors (173,175),
even if recent data seem to depict an even more complex pathophysiologic picture (176).

CPET can also be used to monitor the effects of cardiac resynchronization therapy by biventricular pacing on CHF exercise pathophysiology; recent data show that improvements of aerobic function and ventilation-perfusion mismatching are most evident in those patients with the lowest pre-implantation peakVO$_2$ (177). Moreover, CPET has been used for functional evaluation of CHF patients after left ventricular assist device implantation, demonstrating a significant short-term peakVO$_2$ improvement (178,179). Finally, CPET can describe both functional impairment and prognosis of patients with diastolic heart failure (180). Changes in CPET parameters induced by CHF are summarized in Table 3.

6.4. **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$_2$ and VO$_2$ at VAT) improve significantly during the first two years after HTx, remaining however around 60-70% of the age- and sex-related reference values (181,182).

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 heart rate reserve during incremental exercise (i.e. chronotropic incompetence), that persist for many years following HTx (181). 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 (183-185). Second, due to irreversible pre-transplant 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 exercise capacity after HTx (186). 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 (187). It has been shown that improvements in exercise capacity after exercise training in HTx are highly correlated to 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 (188). Moreover, during the progression of CHF a specific myopathy develops, that 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 decreased muscle strength (189). As for endothelial dysfunction, these muscular adaptations can be reversed with exercise training and correlate closely to the observed improvements in exercise capacity (190). Due to these muscular metabolic changes, both on- and off-kinetics of VO₂ during constant-power moderate-intensity exercises are delayed in HTx patients (191,192).

Finally, ventilatory efficiency (expressed both as VE vs. VCO₂ slope and OUES) improves during the first years following HTx, remaining however impaired and
reaching values comparable to 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 (192,193). Changes of CPET parameters induced by HTx are summarized in Table 3.

7. Conclusions

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 paper 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 functional evaluation in the individual patient, namely, exercise tolerance assessment, training prescription, treatment efficacy evaluation, investigation of exercise-induced adaptations of the $O_2$ 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 due to 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.
8. Acknowledgements

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Figure legends

Figure 1. Upper panel. VCO₂ as a function of VO₂ during ramp incremental exercise (V-slope plot). The point where the VCO₂ vs. VO₂ 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 due to possible hyperventilation during these periods.

Lower panel. Ventilatory equivalents for O₂ (VE/VO₂) and CO₂ (VE/VCO₂) as a function of power (W) during ramp incremental exercise. The nadir of the VE/VO₂ relationship (full line) is the VAT, whereas that of the VE/VCO₂ relationship (dotted line) is the respiratory compensation point (RCP).

Figure 2. Time as a function of power for five constant-power exercise tests (1 = 50% of Δ ventilatory anaerobic threshold-peak VO₂ power, 2 = 70% of Δ ventilatory anaerobic threshold-peak VO₂ power, 3 = 90% of Δ ventilatory anaerobic threshold-peak VO₂ power, 4 = 100% peak VO₂ power, 5 = 120% peak VO₂ power). The power asymptote of the hyperbolic relationship is the critical power (CP).

Figure 3. VO₂ on- and off-kinetics during constant-power moderate-intensity exercise test. Black line shows mono-exponential fitting of phase II alone, gray line mono-exponential fitting of the whole VO₂ on- and off-response. See text for further details.
Figure 4. Cardiac output as a function of arterio-venous content $O_2$ difference ($C(a-v)O_2$) with superimposed VO$_2$ isophlets (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 subject (N, black arrow) and a patient with chronic heart failure (CHF, white arrow).
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 $O_2$ transport and utilization system efficiency (ventilatory, hemodynamic, and metabolic components)
### Table 2

#### Normal values

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>NORMAL VALUES</th>
<th>FORMULAE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VO$_2$ at VENTILATORY ANAEROBIC THRESHOLD</strong>&lt;sup&gt;(15)&lt;/sup&gt; &lt;br&gt; (ml/min)</td>
<td>&gt;40% predicted VO$_2$max 40-60% peakVO$_2$</td>
<td>/</td>
</tr>
<tr>
<td><strong>CRITICAL POWER</strong>&lt;sup&gt;(22)&lt;/sup&gt; &lt;br&gt; (W)</td>
<td>65-70% of peak power 25-30% of ΔVAT-peak power</td>
<td>/</td>
</tr>
</tbody>
</table>
| VO$_2$max<sup>(15)</sup> <br> (ml/min) | * | **
| * | M | F |
| 20 yrs | 3246 (43.3) | 1996 (33.3) |
| 30 yrs | 2967 (39.6) | 1821 (30.3) |
| 40 yrs | 2688 (35.8) | 1646 (27.4) |
| 50 yrs | 2409 (32.1) | 1471 (24.5) |
| 60 yrs | 2130 (28.4) | 1296 (21.6) |
| 70 yrs | 1851 (24.7) | 1121 (18.7) |
| 80 yrs | 1572 (21.0) | 945 (15.7) |
| **VO$_2$ ON-KINETICS MEAN RESPONSE TIME**<sup>(48)</sup> <br> (sec) | 30 - 44 yrs | 34 - 43 |
| | 45 - 59 yrs | 44 - 53 |
| | 60 - 80 yrs | 54 - 67 |
| **VO$_2$ OFF-KINETICS $T_{1/2}$**<sup>(58)</sup> <br> (sec) | 60±20 ¶ | / |
| **O$_2$ UPTAKE EFFICIENCY SLOPE**<sup>(68)</sup> <br> ([ml/min]/[l/min]) | M § | F § |
| 50-59 yrs | 2647 - 2407 | 1773 - 1630 |
| 60-69 yrs | 2380 - 2140 | 1615 - 1472 |
| 70-80 yrs | 2113 - 1846 | 1457 - 1300 |
| **VE vs. VCO$_2$ SLOPE**<sup>(83)</sup> | M | F |
| 20-39 yrs | 23.4 - 25.7 | 26.8 - 28.3 |
| 40-59 yrs | 25.8 - 28.1 | 28.4 - 29.9 |
| 60-80 yrs | 28.2 - 30.6 | 30.0 - 31.6 |
| **PEAK CARDIAC OUTPUT**<sup>(185)</sup> <br> (ml/min) | / | 5 × peakVO$_2$ + 3 # |
| **PEAK CIRCULATORY POWER** <br> (mmHg × ml/kg/min) | M | F |
| 20-39 yrs | 8600 - 7000 | 6660 - 5600 |
| 40-59 yrs | 7050 - 5680 | 5480 - 4400 |
| 60-80 yrs | 5630 - 4200 | 4320 - 3140 |

VAT, ventilatory anaerobic threshold; M, males; F, females; BSA, body surface area.

* values are calculated for men of 75 kg and women of 60 kg weight - values in brackets are ml/kg/min; ** formula for normal weight subjects - reference 14 reports also formulae for under- and overweight subjects; ¶ value for VO$_2$ off-kinetics after incremental exercise; § values are calculated for men of 1.9 m$^2$ and women of 1.65 m$^2$ BSA; # peakVO$_2$ in ml/min for 20-50 year-old males; ° values are calculated for VO$_2$max values reported above and peak systolic blood pressure of 200 mmHg.
Table 3

Cardiopulmonary exercise testing parameters in special populations

<table>
<thead>
<tr>
<th></th>
<th>EXERCISE-INDUCED ISCHEMIA</th>
<th>RECENT CORONARY OR VALVULAR SURGERY</th>
<th>RECENT OR PREVIOUS HEART TRANSPLANTATION</th>
<th>CHRONIC HEART FAILURE</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>VO₂ at VENTILATORY ANAEROBIC THRESHOLD</em></td>
<td>N or ↓ *</td>
<td>N or ↓</td>
<td>↓</td>
<td>↓ or ↓↓</td>
</tr>
<tr>
<td>CRITICAL POWER</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>PEAK VO₂</td>
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<td>N or ↓</td>
<td>↓</td>
<td>↓ or ↓↓</td>
</tr>
<tr>
<td>VO₂ ON-KINETICS MEAN RESPONSE TIME</td>
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<td>N or ↓ ?</td>
<td>↓</td>
<td>↓ or ↓↓</td>
</tr>
<tr>
<td>VO₂ OFF-KINETICS T₁/₂</td>
<td>N or ↓ **</td>
<td>N or ↓ ?</td>
<td>↓</td>
<td>↓ or ↓↓</td>
</tr>
<tr>
<td>O₂ UPTAKE EFFICIENCY SLOPE</td>
<td>N ?</td>
<td>N or ↓ ?</td>
<td>↓</td>
<td>↓ or ↓↓</td>
</tr>
<tr>
<td>VE vs.VCO₂ SLOPE</td>
<td>N ?</td>
<td>N or ↑ ?</td>
<td>↑</td>
<td>↑ or ↑↑</td>
</tr>
<tr>
<td>EXERTIONAL OSCILLATORY VENTILATION</td>
<td>Absent</td>
<td>?</td>
<td>Absent ?</td>
<td>May be present §</td>
</tr>
<tr>
<td>PEAK CARDIAC OUTPUT</td>
<td>↓</td>
<td>N or ↓ ?</td>
<td>↓</td>
<td>↓ or ↓↓</td>
</tr>
<tr>
<td>PEAK CIRCULATORY POWER</td>
<td>↓ ?</td>
<td>N or ↓ ?</td>
<td>↓ ?</td>
<td>↓ or ↓↓</td>
</tr>
</tbody>
</table>

N, normal; ?, not enough data available; ↓, reduced or shortened; ↓↓, severely reduced or shortened; ↑, increased or prolonged; ↑↑, markedly increased or prolonged.

* depending on exercise level with respect to ischemic threshold; ** possible ‘Hump’ phenomenon; § usually detectable in 10-12% of patients.
Figure 1

\[ \text{VO}_2 (\text{l/min}) = \frac{\text{VE}}{\text{VO}_2} \]

\[ \text{VCO}_2 (\text{l/min}) = \frac{\text{VE}}{\text{VCO}_2} \]
Figure 3

Figure showing the changes in VO$_2$ (l/min) over time with differentiated phases labeled as Phase I, Phase II, and Phase III. The graph highlights the transition from Exercise to Recovery and marks key points such as Basal VO$_2$, Steady-state VO$_2$, O$_2$ deficit, and O$_2$ debt. The x-axis represents Time (s) ranging from 0 to 120, and the y-axis represents VO$_2$ (l/min) ranging from 0 to 1.0.