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ORIGINAL PAPER

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Peak oxygen uptake

Myth and truth about an internationally accepted reference value

Die maximale Sauerstoffaufnahme – Schein und Sein eines international anerkannten Referenzwertes

Zusammenfassung Dieser Beitrag beschäftigt sich kritisch mit der Durchführung von Messungen der maximalen Sauerstoffaufnahme (VO_2peak) bei Herzpatienten und hinterfragt deren angemessene Interpretation. Im ersten Abschnitt werden die häufigsten klinischen Anwendungen von VO_2peak-Messungen diskutiert: Abschätzung der funktionellen Kapazität sowie ihrer Veränderungen, Beurteilung der Notwendigkeit invasiver diagnostischer bzw. therapeutischer Maßnahmen, Bezugspunkt für Trainingsvorgaben und Prognosestellung. Der zweite Abschnitt befasst sich mit wichtigen methodischen Problemen und Einschränkungen, die anhand von wissenschaftlichen Studien illustriert sind. Schließlich werden Empfehlungen für möglichst aussagekräftige VO_2-peak-Messungen abgeleitet. Es wird deutlich, dass irreführende ergometrische Befunde möglich sind, wenn man sich nicht streng an solche Vorgaben hält. Dies kann zu Über- oder Unterschätzungen sowohl der Ausdauerleistungsfähigkeit als auch vermeintlicher Trainingseffekte führen.

Schlüsselwörter Training – Ergometrie – Herzinsuffizienz – Ausdauer – Methodik

Summary This article critically examines the execution of VO_2-peak testing in cardiac patients and questions their appropriate interpretation. In the first part, the most common clinical implications of VO_2peak measurements are discussed: assessment of (changes in) functional capacity, evaluation of the necessity of invasive diagnostic/therapeutic measures, reference for exercise prescriptions, determination of prognosis. In the second part, important methodological problems and constraints are addressed and illustrated by references to scientific studies. Finally, recommendations are given for meaningful VO_2peak testing. It is evident that failure to strictly follow such recommendations might result in misleading ergometric findings and, thus, in over- or underestimation of endurance capacity and/or training effects.

Key words Exercise – ergometry – heart failure – functional capacity – endurance – methodology

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Introduction

Since the first description of maximal oxygen uptake (VO_2max) as an indicator of endurance capacity [45] no other single parameter derived from cardiopulmonary exercise testing has gained such wide acceptance. The term VO_2peak is considered more appropriate when determined under circumstances that prevent the attainment of the "real" biological maximum which has been defined as a plateau in oxygen uptake despite increasing work rate [103]. A failure of VO_2 to "level off" might be due to cycle instead of treadmill ergometry or due to the early occurrence of limiting

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symptoms both of which are quite common in cardiologic settings. Although alternative measures like the anaerobic threshold [104, 106] exist, the vast majority of scientific publications utilizes VO_2peak as variable to assess functional capacity, document fitness changes, and to refer exercise (intensity) prescriptions. Even prognosis in cardiac disease and, thus, decisions about invasive therapeutic measures, e.g. heart transplantation, have been linked to the results of maximal ergometric testing [62]. However, there are certain methodological and subject/patient-bound sources of error in the determination of VO_2peak which might render its use unreliable when not accounted for. This overview aims to sensitize readers about important shortcomings of maximal ergometric variables which have to be considered during their interpretation. Some examples from the literature are given to illustrate the practical relevance of such matters. For the most part, examples are taken from studies in chronic heart failure (CHF) patients because in this population VO_2peak is considered to be of outstanding importance and, thus, very frequently determined within scientific investigations. However, the general statements and recommendations given here are also valid for other cardiac entities. It is the additional aim of this paper to enforce and popularize methodological necessities when conducting tests to accurately determine VO_2peak values. Although it is also possible to elicit VO_2peak during constant load tests, this article focuses on the more common incremental exercise protocols because they were considered to be much more prevalent.

Applications for the determination of VO_2peak

The determination of VO_2peak is widely considered to be valuable in determining endurance capacity in healthy subjects [77, 96] and to assist in the evaluation of a variety of cardiac diseases, most prominently in CHF [61, 94]. Acknowledging this, recent guidelines from several authorities include maximal exercise testing as an obligatory/recommended tool within the management of patient populations [19, 48, 91, 101]. Four main purposes of determining VO_2peak can be distilled: assessing (changes in) functional capacity, evaluating the necessity of invasive diagnostic/therapeutic measures, obtaining a reference for exercise prescriptions, determining prognosis.

Assessment of functional capacity

Whereas in healthy individuals VO_2peak is mainly considered as an indicator of (aerobic) endurance capacity [16] it is often – partly in concert with other variables – regarded as a descriptor of "functional capacity" in cardiac patients [10, 11, 106]. However, it is probably more appropriate to emphasize the correlation between high maximal ergometric measures (e.g. VO_2peak) and the ability to sustain submaximal exercise (i.e. endurance) because there are studies in CHF patients challenging a close "functional" link between performance in daily life, central hemodynamics, and VO_2peak [30–32, 37, 108]. Even the term "exercise capacity" does not adequately address what VO_2peak really reflects because there are certainly aspects of exercise (coordination, strength) which are surely important for patients but rarely measured by determining VO_2peak. The most appropriate description might be "maximal ergometric capacity".

In addition, several studies that used certain forms of physical training – mostly endurance stimuli – reported increases in VO_2peak [1, 11, 21, 39, 53]. But other authors cast doubt if small improvements in the clinical status – albeit meaningful for the single patient – are sufficiently reflected in detectable increases of VO_2peak [22]. Altogether, VO_2peak is not adequately addressed as "functional capacity" which is a more sophisticated term also covering other aspects of daily life. VO_2peak rather represents a global measure of endurance capacity which in cardiac patients might lack the sensitivity to detect tiny changes of the clinical state. Larger differences in cardiac performance will, nevertheless, be reflected appropriately.

Evaluation of the necessity to conduct invasive diagnostic/therapeutic measures

A disproportionally low peak VO_2 compared to what is expected for the given sex, age and training history (tables of normative values) is frequently regarded as an indicator of probable cardiovascular disease. In such cases, additional diagnostic measures are to be initiated. When cardiac volume is related to VO_2peak or to the peak oxygen pulse, a more sensitive parameter for the detection of early cardiac disease might result [90, 97]. However, the most momentous function of VO_2peak measurements for an individual patient is undoubtedly its role in determining the indication for heart transplantation in CHF [53]. With regard to prognosis, Mancini et al. calculated a VO_2peak of 14 $ml \cdot min^{-1} \cdot kg^{-1}$ as the cut-off point below which life expectancy after heart transplantation exceeds that without surgery [62]. Although the precise value of 14 $ml \cdot min^{-1} \cdot kg^{-1}$ has been questioned [82], an important role within the decision process about transplantation remained for VO_2peak. It has to be emphasized that prior to any such decision the attainment of optimal medical management is necessary. Particularly appropriate beta-blocker therapy seems mandatory [111].

Reference for exercise prescriptions

The large majority of training studies in cardiac patients used VO_2peak determinations as the reference for their exercise prescriptions [72], that is, percentages of VO_2peak were set as recommended intensities or upper margins for rehabilitative activities. However, not seldomly the precise way of transfering this value into training practice remained unclear. This remark refers to the necessity of deriving power outputs, velocities, or heart rates from percentages of VO_2peak which is, by definition, an *oxygen uptake*. Beneath differences in the exercise protocols (see below) time constants for oxygen uptake [40, 41] and heart rate [18] as well as interindividual variability in time constants [29] have to be considered and might introduce a large amount of variability. Additional variance is added by different degrees of effort spent by patients from this population (see below). Even in healthy subjects there exists evidence that fixed percentages of peak VO_2 (and peak heart rate) correspond to widely differing degrees of individual strain [70]. Therefore, it has been concluded that this concept of exercise prescription is invalid [51, 108, 109]. In cardiac patients, to our knowledge no systematic approach has been conducted to evaluate the % VO_2peak concept by means of constant load trials at given intensities. Altogether, there is much uncertainty about the individual cardiovascular and metabolic strain when prescribing an exercise intensity to cardiac patients with VO_2peak as the sole reference.

Determination of prognosis

Generally, VO_2peak is regarded as an important predictor of prognosis in CHF patients [61, 81]. This has been demonstrated by use of survival curves in relatively large patient samples [87, 94] although the prognostic power has been evaluated as satisfactory only below 10 and above 18 $ml \cdot min^{-1} \cdot kg^{-1}$ [87]. Mejhert et al. [67] extended this approach to other maximal gas exchange data. Even the superiority of peak VO_2 to some hemodynamic variables [94] and to submaximal ergometric indices [88] has been claimed. However, in the very recent past a combined view of VO_2peak and ventilatory parameters – particularly the ventilatory equivalent for carbon dioxide – has been propagated [36, 89, 92] and might hold future options. Recent evidence indicates that laboratory parameters from resting venous blood samples, namely natriuretic peptides, might give valuable prognostic information [34] and even an estimation of “functional capacity” [54]. However, the precision of such evaluations for the longitudinal patient evaluation has been questioned [73]. In summary, for the particular purpose of giving a prognosis in CHF (cardiac) patients, as yet no single ergometric parameter has been shown to be comparatively concise and valid as VO_2peak.

Methodological considerations

Obtaining accurate VO_2peak measurements requires the observation of several methodological constraints. These refer to exercise mode and protocol as well as to investigator attitude and documentation accuracy. The more these rules are violated, the less valid the resulting VO_2peak measurement will be.

Exercise mode

It is known for long that due to differences in active muscle mass certain modes of exercise can lead to variations in peak VO_2 [44]. This is usually reflected in corresponding differences in maximal heart rate, too. The most frequently investigated comparison is between treadmill and cycle ergometry. Peak measurements on a treadmill are about 10% higher irrespective of the tested population (summarized in [95], table on p 102). Although probably of smaller size, differences between supine, semi-supine and upright cycling do exist [14] – particularly pronounced in cardiac patients [74]. They have to be taken into account when interpreting VO_2peak data from such tests.

Exercise protocol

To ensure peak measurements, the protocol has to be designed in a way that it does not interfere with the patients’ ability to exercise maximally. There must be enough time for the oxygen consuming processes to increase, and exhaustion shall not interfere too early. Beneath severity of disease, information to be gathered to decide about an adequate starting load and the increment includes sex, age, medication, and training history. An often cited study arrived at the conclusion that 8–17 minutes is an appropriate duration [17]. However, when more closely examining the results in their n = 12 subjects and eliminating one obvious outlier, it reports that 8–12 minutes is a more precise evaluation – at least for cycle ergometry. This is in accordance with recommendations being made in reviews about this issue [57, 64, 107]. Another prerequisite for the realisation of peak VO_2 has more recently been addressed: the necessity of avoiding too large workload increments which might lead to premature cessations of exercise particularly in patients [79, 80]. The resulting ramp or ramp-like (short stages of ≤1 min) protocols share the additional advantage of delivering "smoother" curves for the gas exchange parameters [109] which enable easier detection of the anaerobic threshold.

Degree of effort

The degree of effort spent by the tested patients has an obvious influence on maximal ergometric variables. For scientific as well as clinical decisions it is not appropriate to rely on a subjective estimation alone – even when supplemented by a formalized patient rating [15]. Also, in the longitudinal approach the thorough documentation of objective criteria for the degree of effort is obligatory. In a cardiologic setting, maximally achieved heart rate (HR_{max}) is always available. In addition, when VO_2peak is determined directly, that is, not by use of (imprecise) estimation formulae, maximal respiratory exchange ratio (RER_{max}) and the presence of levelling off in VO_2 has to be assessed. Maximal blood lactate concentrations (La_{max}) can give additional information although their close physiological link to the RER might render them redundant for this particular purpose.

In healthy subjects, there is some evidence for the use of minimal (obligatory) values for the mentioned criteria when interpreting single exercise tests [28, 47, 64, 95]. Although levelling off in VO_2 is regarded as "most valid indicator" [64] for maximal effort, there are technical [83] as well as physiological [85, 86] arguments against its uncritical use. In addition, there exist different definitions for its presence [76, 100], and considerable percentages of healthy individuals do not reach a plateau at all [26, 28]. Particularly in cardiac patients these findings indicate a careful use of the levelling off phenomenon as a prerequisite for the assumption that maximal effort was reached. A plateau should preferably used as confirmation only.

Also, the application of HR_{max} criteria is not without problems. The most widely applied formulae are 220 minus age for treadmill exercise and 200 minus age for cycle exercise or, alternatively, percentages of their results [57]. However, there is evidence for a considerable inter-subject variability [59] which can render HR_{max} an unreliable criterion [23, 47]. The frequent use of beta-blockers in cardiac patients adds another source of (systematic) deviation from formula-predicted values.

RER_{max} and (if available) La_{max} are considered to be the most reliable indicators of maximal effort in healthy subjects [28]. Both parameters are closely linked and, thus, not independent of each other because RER values above 1.0 can only be reached due to the buffering of lactid acid which produces "excess" CO_2 (in addition to the metabolic CO_2). But there is no uniformity in recommendations for cut-off values which range between 1.0 [24] and 1.15 [49] for RER_{max} and 5.5 [25] and 10.0 $mmol \cdot l^{-1}$ [96] for La_{max}. It is commonly assumed that with increasing age (and with growing limitation due to disease) acidosis tolerance and, thus, maximal RER as well as maximal blood lactate decrease [47]. Therefore, cardiac patients cannot be expected to reach values as high as healthy or younger subjects. The attainment of an $RER_{max} \geq 1.0$ [56] and/or a $La_{max} \geq 6$ $mmol \cdot l^{-1}$ can be regarded as indicating sufficient effort although there are reports about higher RER values in CHF patients [12, 55, 99]. Some of the latter are peculiar as they would correspond to unbelievably high blood lactate concentrations in this patient population. They might have been erroneously measured in the immediate post-exercise time when VO_2 decreases abruptly whereas VCO_2 remains elevated due to the release of lactate from the working muscles.

The situation changes markedly when a longitudinal approach is applied, that is, when intra-individual comparisons are made over a period of time, e.g. for the assessment of the "clinical course". Under these circumstances, the objective degree of effort should be *comparable* (although subjectively maximal) as opposed to *sufficient* in the evaluation of a single test. This underlines the necessity of documenting all available data which describe the degree of effort. However, in a large number of scientific investigations no statements are given concerning any of the mentioned descriptors. A review of 41 training studies in CHF patients between 1988 and 2003 revealed that in 16 of these investigations no statement was given as to the degree of effort spent by the patients [72].

Example for sequelae of methodological unattentiveness

Training studies are most susceptible for different degrees of effort spent by the subjects of the training group during pre- and post-testing. There are at least three reasons for this potential inaccuracy:

1. Habituation of the subjects to physical effort (usually not present in control groups); the less fit the subjects are the more confounding is this factor.
2. Trained patients want to demonstrate their success to the investigator (exercise is not blindable!).

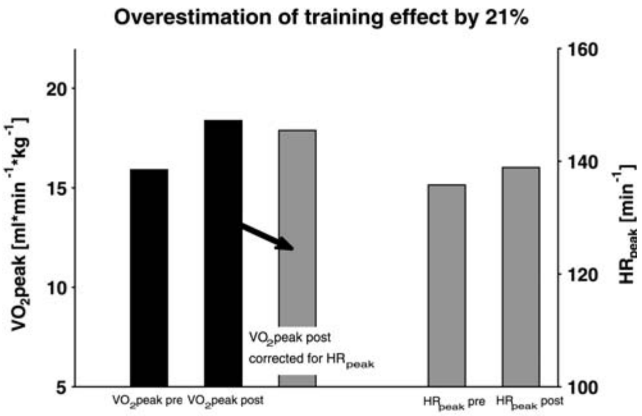

Fig. 1 Overestimation of the training effect in CHF patients. Data obtained from studies between 1988 and 2003 which reported VO_2peak as well as HR_{peak} [9–12, 21, 27, 39, 50, 53, 55, 60, 68, 84, 110]. VO_2peak at post-testing (after training) was "corrected" taking into account differences in HR_{peak} between pre- and post-testing. This was achieved by calculating $HR_{Reserve}$ (HR_{peak} minus HR_{rest}) for both testing dates and dividing post-testing VO_2peak by the ratio $HR_{Reserve}$ post : $HR_{Reserve}$ pre. When HR_{rest} was unavailable, a constant value of 60 min^{-1} was assumed. This assumption tends to diminish the error being made (the overestimation of the training effect) because after training rather lower than higher resting heart rates can be expected

3. Lacking investigator blinding (expectation higher for subjects known to belong to the training group).

The first two of these factors are unavoidable in any training study. However, we are not aware of investigations during which the physician who supervised the ergometric testing was reported to be blind to the randomization result. Whereas for scientifically sound determinations of echocardiographic measurements or submaximal gas exchange or lactate thresholds, blinded determinations from more than one rater are obligatory, nothing similar is established for studies that use VO_2peak as the criterion measure. To illustrate the sequelae of these shortcomings, all available training studies in CHF patients between 1988 and 2003 were screened. Only those reporting VO_2peak values as well as maximal heart rates were used for this calculation [9–12, 21, 27, 39, 50, 53, 55, 60, 68, 84, 110]. It can be shown that the "true" effect on endurance capacity was overestimated by approximately 20% (Fig. 1). We feel, it is tempting to believe that such an overestimation is even larger in studies without information about the degree of effort.

Other aspects

There will always be some otherwise unexplained ("biological") variability present for VO_2peak measurements in human beings. Therefore, even when accounting for all technical error – e.g. from the metabolic systems themselves [6, 75] or from temporal sampling strategy [46] – and using the most recent equipment, it cannot be expected to be completely free from measurement error [3]. Biological variability has been reported to be around 5% in trained healthy individuals [52] and can be reasonably expected to be higher in cardiac patients. Although the most adequate statistic for reliability investigations is a Bland-Altman plot [4], most such studies used mainly regression or correlation analyses [8, 58]. However, they almost uniformly documented some degree of intraindividual variability. Using another statistical approach in 15 moderately trained runners, Bagger et al. [7] arrived at the conclusion that the "critical difference" for VO_2peak was 7.1% in their study. That is, when interpreting changes in peak oxygen uptake, smaller differences cannot be reliably considered as "true" changes.

Scaling oxygen uptake to body dimensions by simply dividing it by the weight is not optimal [13, 43]. This statement refers to cross-sectional comparisons, that is, also to comparisons with normative values, as well as to the intraindividual course when considerable changes in body weight are present. It was shown that an exponent of 2/3 (for homogeneous groups with respect to age and height), or 3/4 (heterogeneous groups) is more appropriate [43]. Otherwise, the performance of heavier patients will be systematically underestimated. Such mathematical adjustments might seem sophisticated but they can reach relevance when cut-off values are used for clinical decisions [62].

It is not sufficiently precise to predict oxygen uptake from workloads [78, 93] or treadmill times [33]. Therefore, direct gas exchange measurements are necessary particularly in those patients with well-known alterations of their VO_2 – workload relationship [69]. Maximal attained workloads itself can represent an alternative in the evaluation of performance [42]. However, they require a standard exercise protocol for comparisons. Also, this has not been systematically assessed in cardiac patients.

The 6-minute walking test

It has to be emphasized that several of these points of criticism with regard to VO_2peak are similarly valid when other measures necessitating maximal patient effort are considered, e.g. the 6-minute walking test which was recently recommended as reasonable alternative to ergometric exercise testing [38]. In addition to the mentioned shortcomings of peak ergometric values, habituational and pacing strategy effects are likely to interfere with this self-paced walking test.

Such confounders can lead to performance variability of a size that can exceed worthwhile clinical effects. Therefore, particular attention has to be paid to similar degrees of effort spent and to changes in the velocity profile during 6 minutes of exercise. A habituation trial might be the best solution.

Alternative variables to be determined during exercise testing

Although sufficient safety of maximal exercise testing in cardiac patients seems well-evidenced [35, 98, 102] and validity of maximal ergometric variables is likely for several applications (see application section), the reported methodological constraints point to the necessity of searching for alternatives within the submaximal range. Beneath the anaerobic threshold [104, 105], there recently arose some supportive measures from a close inspection of gas exchange curves which might aid in clinical decision making. The ventilatory equivalent for carbon dioxide [36] together with the anaerobic threshold has been shown to have prognostic value in CHF. Also, the so called oxygen uptake efficiency slope (OUES) has been propagated as a useful measure for the description of disease severity [5] in cardiac patients. However, OUES simply represents another way of using oxygen uptake and ventilation within one ratio, and it is, thus, questionable if it is superior to using the ventilatory equivalent for oxygen.

Nevertheless, there exists a very simple alternative to VO_2peak for evaluating cardiac patients longitudinally: the HR curve. Provided medication remains constant and the testing time is the same, a uniform rightward shift from rest over the tested workloads can reliably be interpreted as indicating improved endurance capacity. Among others, Coats et al. [20] have used this approach to document training effects in CHF patients. However, the disadvantage remains that exercise prescription from the HR curve alone is difficult [108, 109]. Reference to the anaerobic threshold might be the most reliable and applicable solution for this purpose in cardiac patients [63, 65, 66] although there are only very few corresponding reports [71, 73].

Recommendations for an appropriate conduction and interpretation of ergometric testing for the determination of maximal oxygen uptake

It can be derived from the preceding sections that methodological requirements for a valid determination of VO_2peak are not easily met. A "checklist" for the conduction of VO_2peak tests is provided below and intended to facilitate meaningful results for the scientist as well as the practitioner.

- Each test should be carried out up to the (symptom-limited) maximum. Extrapolation from submaximal measurements should be avoided!
- All relevant properties of the exercise protocol have to be reported: cycle ergometer vs. treadmill, ramp vs. graded test, ramp increment, stage duration, stage increment, total test duration.
- A ramp or ramp-like (i.e. stages of short duration and small increment) exercise protocol of 8–12 minutes duration is most appropriate.
- All available criteria for the degree of effort shall be reported: HR_{max}, levelling off, RER_{max}, La_{max}, standardized subjective measures (e.g. Borg scale), investigator impression.
- An overall judgment should be made (and eventually documented) if maximal effort was reached by the tested subject/patient.
- When comparing results longitudinally in one individual, identical equipment and exercise protocols have to be used if ever applicable.
- Different degrees of maximal effort have to be taken into account.
- Results from tests with different test modes and exercise protocols can only be interpreted with caution.
- A biological variability of about 5% has to be expected, i.e. changes below this margin cannot be safely interpreted as real changes in a single subject.
- The most appropriate body weight reference is $kg^{2/3}$ instead of kg^1. This is particularly important when comparing subjects of widely different weights.

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