

Oxygen uptake kinetics in chronic heart failure: clinical and physiological aspects

H.M.C. Kemps, G. Schep, J. Hoogsteen, E.J.M. Thijssen, W.R. De Vries, M.L. Zonderland, P.A.F.M. Doevendans

One of the hallmark symptoms of patients with chronic heart failure (CHF) is exercise intolerance. Therefore, exercise testing has become an important tool for the evaluation and monitoring of heart failure. Whereas the maximal aerobic capacity (peak $\dot{V}O_2$) is a reliable indicator of the severity and prognosis of heart failure, submaximal exercise parameters may be more closely related to the ability to perform daily activities. As such, oxygen (O_2) uptake kinetics, describing the rate change of O_2 uptake during onset or recovery of submaximal constant-load exercise (O_2 onset and recovery kinetics, respectively), have been shown to be useful parameters for objectively evaluating the functional capacity of CHF patients. However, their evaluation in this population is not a routine part of daily clinical practice. Possible reasons for this include a lack of standardisation of the assessment methodology and a limited number of studies evaluating the clinical use of O_2 uptake kinetics in CHF patients. In addition, the pathophysiological

mechanisms underlying the delay in O_2 uptake kinetics in these patients are not completely understood. This review discusses the current literature on the clinical potency and physiological determinants of O_2 uptake kinetics in CHF patients and provides directions for future research. (*Neth Heart J* 2009;17:238-44.)

Keywords: chronic heart failure, exercise testing, oxygen uptake kinetics, time constant, mean response time

Chronic heart failure (CHF) can be defined as a clinical syndrome resulting from the inability of the heart to maintain sufficient cardiac output for adequate tissue oxygenation. As a consequence, CHF patients suffer from exercise intolerance. One of the main determinants of reduced exercise capacity in these patients is systolic and/or diastolic left ventricular dysfunction, which causes an impaired haemodynamic response to exercise.¹ Other pathophysiological mechanisms include an impaired muscle blood flow caused by increased vasoconstriction² and/or an impaired local vasodilatory capacity,³ muscle mitochondrial dysfunction,⁴ an exaggerated ventilatory response to exercise,⁵ and autonomic imbalance.⁶ Because resting indices of cardiac function⁷ and the level of perceived exercise intolerance⁸ correlate poorly with the exercise performance of these patients, exercise testing has become indispensable in the evaluation and monitoring of heart failure.

Exercise testing

Traditionally, maximal oxygen uptake ($\dot{V}O_2$ max) is considered the gold standard measure of aerobic fitness. In healthy individuals, $\dot{V}O_2$ max is usually defined as the point at which $\dot{V}O_2$ reaches a plateau despite a further increase in work rate during a symptom-limited exercise test. However, in CHF patients such a plateau in $\dot{V}O_2$ is rarely seen, suggesting that most of these patients do not attain a maximal exercise level during symptom-limited exercise testing. Therefore, the highest attainable $\dot{V}O_2$ in CHF patients is referred to

H.M.C. Kemps
J. Hoogsteen
E.J.M. Thijssen

Department of Cardiology, Máxima Medical Centre, Veldhoven, the Netherlands

G. Schep

Department of Sports Medicine, Máxima Medical Centre, Veldhoven, the Netherlands

W.R. De Vries

Rudolf Magnus Institute of Neuroscience, Section Rehabilitation and Sports Medicine, University Medical Center Utrecht, Utrecht, the Netherlands

M.L. Zonderland

University Medical Center Utrecht, Department of Medical Physiology, Division Heart & Lungs, Utrecht, the Netherlands

P.A.F.M. Doevendans

Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands

Correspondence to: H.M.C. Kemps

Department of Cardiology, Máxima Medical Centre,
PO Box 7777, 5500 MB, Veldhoven, the Netherlands
E-mail: h.kemps@wxs.nl

as peak $\dot{V}O_2$, rather than $\dot{V}O_{2\max}$. It has been demonstrated that peak $\dot{V}O_2$ is a reliable indicator of the severity of heart failure⁹ and a strong predictor of the prognosis in these patients.¹⁰ For the assessment of exercise performance in CHF patients, however, the use of peak $\dot{V}O_2$ has several limitations. First, the reliability of the assessment of this exercise parameter is hampered by the influence of the patients' motivation, the presence / absence of encouragement, and the criteria used to terminate the test. Second, as daily life mainly consists of repetitive submaximal activities, the maximal exercise capacity does not reflect the functional capacity of these patients very well. This may explain the relatively low sensitivity of peak $\dot{V}O_2$ for evaluating the efficacy of therapeutic interventions in heart failure.^{11,12} Therefore, there is a growing interest in submaximal exercise parameters to monitor changes in the functional capacity of CHF patients.

Frequently used submaximal exercise parameters are $\dot{V}O_2$ at the ventilatory threshold (VT) and the six-minute walking distance. The main limitation of the former is that it cannot be detected in a substantial number of CHF patients due to ventilatory irregularities.¹³ The value is also dependent on the exercise protocol used, making it difficult to compare figures from different centres.¹⁴ The six-minute walk test is well tolerated and easy to perform in CHF patients, but the outcome is substantially influenced by motivation and encouragement. More importantly, the usefulness of the six-minute walking distance to assess changes in functional capacity is limited by a significant learning effect.¹⁵ Other submaximal exercise variables that have been used to assess the functional capacity in CHF patients include the ventilatory response to incremental exercise, expressed as the $\dot{V}_E/\dot{V}CO_2$ slope or the oxygen uptake efficiency slope (OUES), and oxygen (O_2) uptake kinetics during and after constant-load exercise with an intensity below the VT (O_2 onset and O_2 recovery kinetics, respectively). Both $\dot{V}_E/\dot{V}CO_2$ slope¹⁶ and OUES¹⁷ have been shown to be sensitive to the effects of physical training in CHF patients. However, as the assessment of these parameters requires exercise exceeding the anaerobic threshold, they should be considered more as parameters of maximal effort. O_2 uptake kinetics during and after constant-load exercise below the VT represent a true measure of submaximal exercise capacity, but its clinical usefulness in CHF patients is not well established.

O_2 uptake kinetics

O_2 uptake kinetics describe the rate of change in $\dot{V}O_2$ during or after exercise. According to Fick's law (equation 1), $\dot{V}O_2$ is determined by cardiac output (\dot{Q}) and systemic O_2 extraction, which in turn is determined by arterial O_2 content and O_2 utilisation in the metabolising tissues. Therefore, O_2 onset and recovery kinetics can be considered to reflect the interaction of the cardiovascular, pulmonary, and metabolic systems during and after exercise.

Equation 1

$$\dot{V}O_2 = \dot{Q} * (CaO_2 - Cvo_2)$$

with $\dot{V}O_2$ = oxygen uptake (ml/min), \dot{Q} = cardiac output (l/min), CaO_2 = arterial oxygen content (ml/l) and Cvo_2 = mixed venous oxygen content (ml/l)

Assessment of O_2 uptake kinetics

O_2 onset kinetics

Figure 1 shows an example of the time course of $\dot{V}O_2$ during and after constant-load exercise below the VT. Classically, O_2 onset kinetics during submaximal constant-load exercise are considered to consist of three phases. Phase I, or the cardiodynamic phase, reflects a fast increase in $\dot{V}O_2$ of approximately 15 to 20 seconds as a consequence of an abrupt increase in pulmonary blood flow. Phase II reflects a mono-exponential increase in $\dot{V}O_2$, caused by an increase in cellular respiration at the skeletal muscle level. Phase III reflects a 'steady state' situation when exercise is performed below the VT, or a slow linear $\dot{V}O_2$ increase with exercise above the VT.¹⁸ Mathematically, O_2 onset kinetics during exercise below the VT in healthy individuals are well described by a simple mono-exponential model (equation 2), provided that phase I, which is functionally distinct from phase II, is omitted from the data.¹⁹

Equation 2

$$\dot{V}O_{2(t)} = \dot{V}O_{2\text{baseline}} + A * (1 - e^{-(t-Td)/\tau})$$

with A = $\dot{V}O_2$ -amplitude during exercise (ml/min), Td = time delay (sec) and τ = time constant (sec)

This model has several limitations when applied to CHF patients. First, as a consequence of a reduced

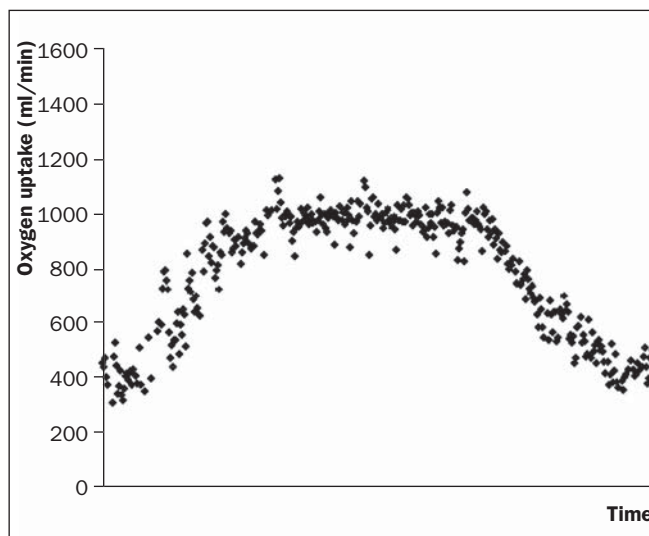


Figure 1. Breath-by-breath values of $\dot{V}O_2$ during and after a constant-load exercise test of six minutes at 50% of the maximal workload with a recovery period of five minutes in a patient with chronic heart failure.

ventilatory threshold, the exercise-related increase in $\dot{V}O_2$ is lower in CHF patients than in healthy subjects, and omitting phase I from the data leads to an even greater reduction of the $\dot{V}O_2$ amplitude. As pointed out by Lamarra et al., a relatively low $\dot{V}O_2$ amplitude results in a low accuracy of mono-exponential modelling of O_2 onset kinetics, due to a relatively high noise-to-signal ratio.²⁰ Second, the reliability of this method may be compromised by the typical ventilatory oscillations in CHF patients.²¹ Therefore, O_2 onset kinetics have also been assessed by the mean response time in CHF patients, using an algebraic method. This method involves calculating the cumulative sum of $\dot{V}O_2$ in excess of resting $\dot{V}O_2$. Subsequently, the O_2 deficit is calculated by subtracting this cumulative sum from the theoretical $\dot{V}O_2$ requirement (equation 3). The mean response time is calculated by dividing the O_2 deficit by the theoretical $\dot{V}O_2$ requirement (equation 4).²²

Equation 3

$$O_2 \text{ deficit} = t * \Delta \dot{V}O_2 - \Sigma \dot{V}O_2$$

with t = duration of constant-load test (min), $\Delta \dot{V}O_2$ = $\dot{V}O_{2 \text{ steady state}} - \dot{V}O_{2 \text{ baseline}}$ (ml/min) and $\Sigma \dot{V}O_2$ = cumulative sum of $\dot{V}O_2$ in excess of resting $\dot{V}O_2$ (ml)

Equation 4

$$\text{Mean response time} = O_2 \text{ deficit} / \Delta \dot{V}O_2$$

The accuracy and reproducibility of different methods to assess O_2 onset kinetics in CHF patients are not well established. Although previous studies suggested an acceptable reproducibility of mono-exponential modeling²³ and the algebraic method,²² intra-class correlations and limits of agreement were not mentioned. Therefore, we recently evaluated the accuracy and reproducibility of both methods in CHF patients.²⁴ It was shown that the goodness-of-fit of mono-exponential modelling was insufficient in a substantial number of patients. In addition, the reproducibility of both methods was too low to warrant their use for the assessment of effects of therapeutic interventions. Therefore, future studies should consider strategies to improve the reproducibility of O_2 onset kinetics through a reduction of the noise-to-signal ratio. This may be achieved by increasing the $\dot{V}O_2$ amplitude, e.g. by starting exercise from rest instead of unloaded cycling, or by averaging the $\dot{V}O_2$ responses from multiple exercise tests.²⁰ However, the latter approach is complicated and time-consuming, and therefore only suitable for research purposes, but not for daily clinical practice.

O₂ recovery kinetics

O_2 recovery kinetics after submaximal exercise are generally considered to follow a mono-exponential course (Equation 5) in both healthy subjects¹⁹ and CHF patients.^{25,26}

Equation 5

$$\dot{V}O_{2(t)} = \dot{V}O_{2 \text{ steady state}} - B * (1 - e^{-(t-Td)/\tau})$$

with B = $\dot{V}O_2$ -amplitude during exercise recovery (ml/min), Td = time delay (sec) and τ = time constant (sec)

In a recent study, we showed that the assessment of O_2 recovery kinetics following submaximal exercise by a mono-exponential model is feasible and reproducible in CHF patients.²⁴ By using the most optimal sampling interval (5 breaths) to calculate the time constant (τ), we showed that a change of at least 13 seconds in τ is needed to exceed the normal test-to-test variations.

Possible explanations for the higher reproducibility of O_2 recovery kinetics as compared with onset kinetics include fewer motion artefacts and a more stable breathing pattern during exercise recovery. Also, as ventilatory oscillations in CHF patients are most pronounced during the transition from rest to exercise,²⁷ they may have a greater influence on the reliability of the assessment of O_2 onset kinetics than O_2 recovery kinetics. Another explanation may be a lesser influence of a cardiodynamic phase (phase I) during exercise recovery, resulting in a higher $\dot{V}O_2$ amplitude that can be used for analysis of the data.

Clinical applications of O₂ uptake kinetics

In 1927 Meakins et al.²⁸ observed slower O_2 onset and recovery kinetics in a patient with circulatory failure as compared with a healthy subject. It was not until the 1990s that O_2 uptake kinetics were further evaluated as a potential instrument for objectively assessing the functional capacity of CHF patients. Most of these studies clearly demonstrated that O_2 onset kinetics during constant-load exercise below the VT are delayed in CHF patients, with slower O_2 uptake kinetics being associated with more fatigue due to a greater reliance on the anaerobic metabolism.^{22,23,25,29} Although less attention has been paid to exercise recovery, several studies showed that O_2 recovery kinetics after submaximal exercise^{22,25,26,30} are also prolonged in CHF patients, with the degree of the delay correlating with the functional impairment in these patients. An example of O_2 uptake kinetics in a CHF patient and a healthy subject of comparable age and body mass index is shown in figure 2.

Whether O_2 uptake kinetics are sensitive to the effects of therapeutic interventions in CHF patients is not well established. So far, preliminary studies with small sample sizes showed that O_2 onset kinetics may be useful in CHF patients to evaluate the effects of β -blocking agents,³¹ physical training,³² and heart transplantation.³³ To our knowledge, no studies have evaluated the clinical utility of O_2 recovery kinetics after submaximal exercise to assess the effect of therapeutic interventions in CHF patients.

In addition to grading functional impairments, O_2 uptake kinetics may also be used for risk stratification

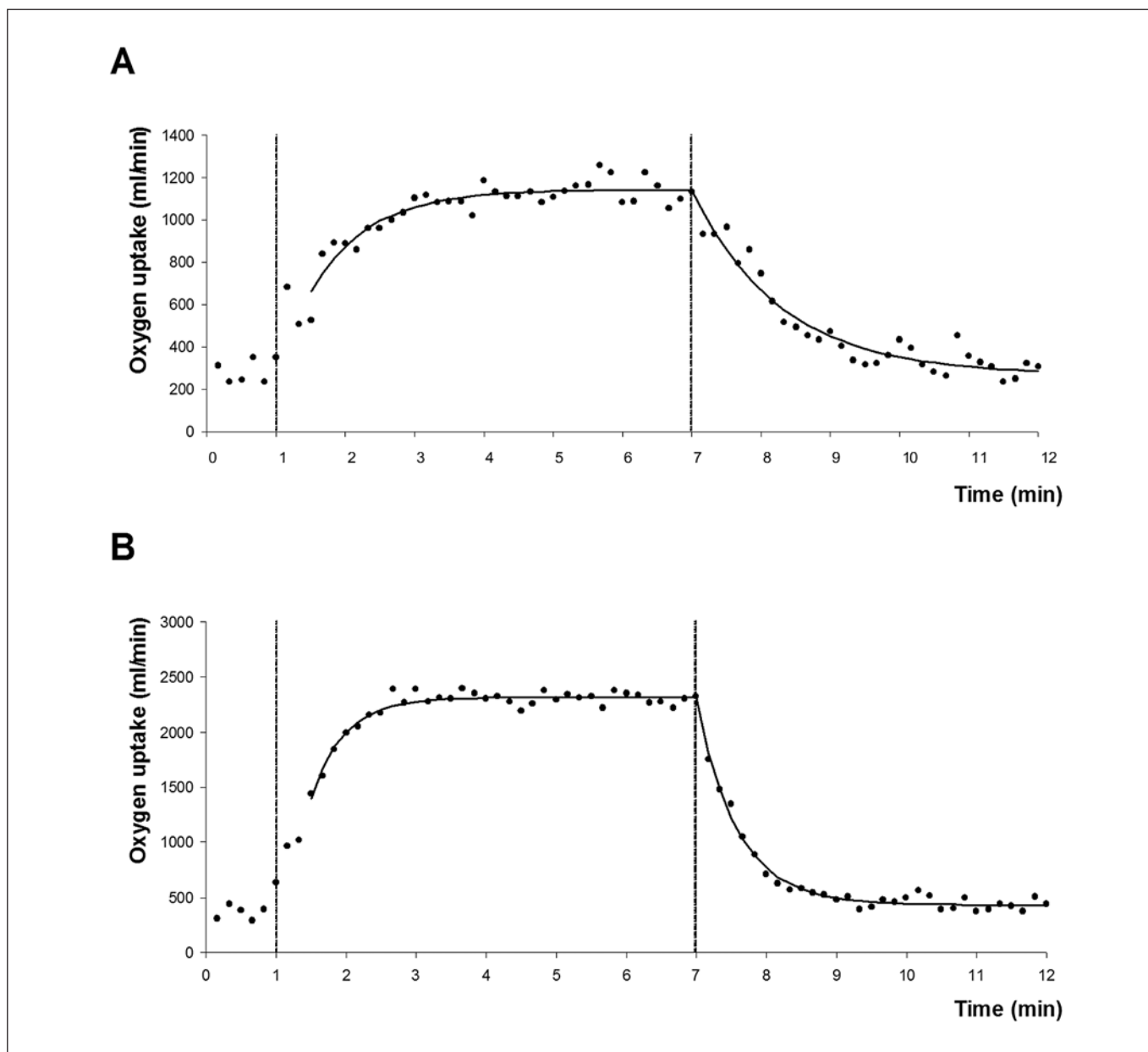


Figure 2. $\dot{V}O_2$ uptake kinetics during and after a constant-load exercise test of six minutes at 50% of the maximal workload with a recovery period of five minutes in a patient with chronic heart failure (A) and a healthy subject of comparable age and body mass index (B). $\dot{V}O_2$ data were averaged in ten-second intervals. The curved line represents the mono-exponential model fit. The first vertical line indicates onset of exercise and the second vertical line the end of exercise.

in CHF. $\dot{V}O_2$ onset kinetics during exercise below the VT were shown to be an independent predictor of mortality in CHF.^{34,35} The prognostic value of $\dot{V}O_2$ onset kinetics may even be superior to peak $\dot{V}O_2$.³⁵ However, studies with large numbers of patients are needed to confirm this finding. The prognostic value of $\dot{V}O_2$ recovery kinetics after submaximal exercise has not yet been evaluated.

In all of the above-mentioned studies, standardisation is lacking because different exercise protocols and calculation methods were used to assess $\dot{V}O_2$ uptake

kinetics in CHF patients. Therefore, before using $\dot{V}O_2$ uptake kinetics in clinical practice, it is of crucial importance to establish uniform assessment methods. To achieve this, more data are needed on the accuracy of the modelling techniques and exercise protocols currently being used in CHF patients. Furthermore, kinetic parameters should be investigated to discover which is best suited to serve various clinical purposes, such as assessment of prognosis or quantifying or predicting effects of therapeutic interventions (e.g. medication, physical training, cardiac resynchronisation therapy).

Physiological determinants of O₂ uptake kinetics

As mentioned before, O₂ uptake kinetics provide objective information on the ability of CHF patients to perform daily activities. Therefore, more knowledge of the physiological determinants of O₂ uptake kinetics may lead to a better understanding of the pathophysiological mechanisms causing functional impairments in these patients. This may eventually aid in the development of therapeutic approaches to improve the exercise capacity in CHF patients. Assessment of the physiological determinants of O₂ uptake kinetics may also be used to classify CHF patients better, allowing a more appropriate treatment selection. For example, patients who are mainly limited by peripheral derangements may benefit from physical training,³⁶ while patients with more pronounced circulatory dysfunction during exercise may be better candidates for treatments to improve the central haemodynamics, such as CRT³⁷ or heart transplantation.³⁸

Theoretically, changes in $\dot{V}O_2$ during or after exercise are determined by tissue oxygenation (O₂ delivery) and the speed at which O₂ can be used for oxidative metabolism (O₂ utilisation). O₂ delivery depends on O₂ transport and diffusion in the lungs, O₂ content of the blood, cardiac function, peripheral vasoconstriction, local vasodilatory capacity, capillary density, and diffusion of O₂ from the blood to the tissues. O₂ utilisation is determined by the number of mitochondria, which is influenced by muscle fibre type distribution in skeletal muscles, and mitochondrial enzyme activity. Several mechanisms contribute to a reduction in O₂ delivery in CHF: cardiac insufficiency, elevated vasoconstriction due to increased sympathetic activity,³⁹ elevated plasma angiotensin levels,² impaired nitric oxide-mediated vasodilatation,³ and a blunted redistribution of blood flow from the non-exercising tissues to the working skeletal muscles.⁴⁰ O₂ utilisation may be limited by mitochondrial dysfunction and / or a reduction in the number of mitochondria due to muscle atrophy or a shift in muscle fibre type distribution to type II fibres.⁴¹

O₂ onset kinetics

Whereas impairments in both O₂ delivery and O₂ utilisation may be present in CHF, the relative contribution of these factors to the delay in O₂ onset kinetics is not well established. Animal studies have previously demonstrated a delayed increase in muscle capillary blood flow⁴² and a more rapid decrease in muscle microvascular O₂ pressure during submaximal exercise in rats with heart failure,⁴³ suggesting a limitation of O₂ onset kinetics by O₂ delivery. This notion is supported by human studies showing that the delay in O₂ onset kinetics during submaximal exercise ergometry in CHF patients is associated with a delayed increase in cardiac output.^{44,45} Yet, studies evaluating the physiological determinants of O₂ uptake kinetics at a local muscle level showed that abnormalities in muscle metabolism are not associated with a reduced muscle blood flow during submaximal exercise

in CHF patients.^{4,46} The exercise protocols applied in these studies, however, involved small-muscle groups (calf and forearm muscles respectively) and, therefore, the results of these studies may not be representative for whole body exercise.

O₂ recovery kinetics

Data are even scarcer about the pathophysiological mechanisms underlying the delay in O₂ recovery kinetics in CHF. In an animal study, CHF was associated with a slower recovery of microvascular O₂ pressure following submaximal exercise than in healthy controls,⁴⁷ suggesting that submaximal exercise recovery in CHF is limited by O₂ delivery. In another study with rats, this delayed recovery of microvascular O₂ pressure was shown to be associated with a diminished vascular NO availability,⁴⁸ suggesting an important role for endothelial function in the delay of metabolic recovery in CHF. The results from human studies are conflicting. Toussaint et al. showed that a prolonged skeletal muscle metabolic recovery after submaximal exercise was associated with a reduction of reactive hyperaemic blood flow and postulated that local circulatory dysfunction is an important contributor to the prolonged metabolic recovery in these patients.⁴⁹ Yet, Hanada et al. found that muscle metabolic recovery following submaximal exercise was more delayed than muscle tissue re-oxygenation in CHF patients and concluded that metabolic recovery in these patients is mainly limited by O₂ utilisation.⁵⁰ Measurements of muscle metabolism and muscle perfusion / oxygenation were not performed simultaneously in either of the studies.

Conclusions

O₂ uptake kinetics at submaximal exercise are potentially useful to objectively assess the functional capacity of CHF patients. As O₂ recovery kinetics can be assessed more reliably than O₂ onset kinetics in CHF patients, they may be particularly valuable in clinical practice. Future studies should therefore evaluate the usefulness of these exercise parameters for clinical purposes such as assessment of prognosis and quantifying effects of therapeutic interventions aiming at an improvement of the exercise capacity of these patients (e.g. physical training and cardiac resynchronisation therapy).

Considering the pathophysiological background of the delay in O₂ uptake kinetics in CHF patients, more knowledge on this issue may be useful for the development of treatments and an improved classification of these patients, allowing for a more appropriate treatment selection. Whereas the results from animal studies suggest that the delay in O₂ onset and recovery kinetics in CHF patients is primarily caused by impairments in O₂ delivery to skeletal muscles, data from human studies are scarce and sometimes contradictory. Therefore, additional research is needed, preferably by performing simultaneous measurements of O₂ delivery and O₂ utilisation. ■

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