Soothing the sleeping giant: improving skeletal muscle oxygen kinetics and exercise intolerance in HFpEF

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Sarma S, Levine BD. Soothing the sleeping giant: improving skeletal muscle oxygen kinetics and exercise intolerance in HFpEF. J Appl Physiol 119: 734–738, 2015. First published June 5, 2015; doi:10.1152/japplphysiol.01127.2014.—Patients with heart failure with preserved ejection fraction (HFpEF) have similar degrees of exercise intolerance and dyspnea as patients with heart failure with reduced EF (HFrEF). The underlying pathophysiology leading to impaired exertional ability in the HFpEF syndrome is not completely understood, and a growing body of evidence suggests “peripheral,” i.e., noncardiac, factors may play an important role. Changes in skeletal muscle function (decreased muscle mass, capillary density, mitochondrial volume, and phosphorylative capacity) are common findings in HFrEF. While cardiac failure and decreased cardiac reserve account for a large proportion of the decline in oxygen consumption in HFrEF, impaired oxygen diffusion and decreased skeletal muscle oxidative capacity can also hinder aerobic performance, functional capacity and oxygen consumption (VO2) kinetics. The impact of skeletal muscle dysfunction and abnormal oxidative capacity may be even more pronounced in HFpEF, a disease predominantly affecting the elderly and women, two demographic groups with a high prevalence of sarcopenia. In this review, we 1) describe the basic concepts of skeletal muscle oxygen kinetics and 2) evaluate evidence suggesting limitations in aerobic performance and functional capacity in HFpEF subjects may, in part, be due to alterations in skeletal muscle oxygen delivery and utilization. Improving oxygen kinetics with specific training regimens may improve exercise efficiency and reduce the tremendous burden imposed by skeletal muscle upon the cardiovascular system.

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tive capacity for peripheral oxygen utilization to adapt to metabolic needs (17).

Little is known about the peripheral abnormalities that occur in HFpEF, whether defects are related to vascular dysfunction or driven by deficits in muscle oxidative capacity. The predominant emphasis of most pharmacologic trials and training studies is peak VO$_2$ as a gauge of interventional effectiveness. While peak VO$_2$ quantifies systemic maximal aerobic power and is useful as a primary outcome variable in HFpEF studies, it may not adequately quantify or detect regional changes in skeletal muscle oxygen uptake and utilization, i.e., VO$_2$ kinetics that reflect positive “vasculo-myofibrillar” remodeling. Increases in skeletal muscle mass, mitochondrial and capillary density, and phosphorylative efficiency are important mediators behind improvements in exertional tolerance. The magnitude and effect size of these changes may not be completely characterized by focusing solely on peak VO$_2$ response. Few patients engage in activities near peak VO$_2$, and understanding the cardiometabolic responses to activities of daily living may provide more practical insight into functional limitations. Defining and developing tools to quantify muscle oxidative metabolism could aid future studies in delineating the contribution of peripheral determinants to exercise limitations in HFpEF patients and identify new maladaptive pathways associated with the syndrome. In this review, we 1) describe the basic concepts of skeletal muscle oxygen kinetics or VO$_2$ kinetics and 2) evaluate evidence suggesting limitations in aerobic performance and functional capacity in HFpEF subjects may, in part, be due to alterations in skeletal muscle oxygen delivery and utilization. We believe VO$_2$ kinetics has potential application as both a “biomarker” of coupling efficiency between vascular beds and exercising muscle as well as a therapeutic target for intervention in HFpEF.

**Skeletal Muscle Oxidative Kinetics and Impairments in Disease States**

VO$_2$ kinetics provides an assessment of the rapidity with which the cardiovascular system can match the metabolic demands of exercising muscle beds. At the onset of exercise, there is a lag between adequate oxygen delivery and metabolic demand that is buffered to some degree by substrate level phosphorylation. To sustain aerobic activity, oxygen delivery needs to augment through both convective and diffusional processes. Under steady-state workloads in healthy individuals, increased blood flow (convective) to metabolically active muscle and close proximity of mitochondria to capillary beds (diffusion) leads to a rapid equilibrium between metabolic demand and oxygen supply.

VO$_2$ kinetics are characterized as the time required for oxygen supply to adequately match oxygen demand during fixed exercise below ventilatory threshold, and is typically measured by a breath-by-breath analysis of pulmonary oxygen uptake (34). Breath-by-breath measures of pulmonary VO$_2$ are plotted in the time domain and fitted by a monoeponential model: \( \text{VO}_2 = \text{VO}_2(b) + A \times [1 - e^{-(t-TD)/\tau}] \), where \( \text{VO}_2(b) \) is baseline or resting \( \text{VO}_2 \), \( A \) is the amplitude increase in \( \text{VO}_2 \), \( t \) is time, TD is the time delay prior to onset of exponential rise and \( \tau \) is the time to reach 63% of \( \text{VO}_2 \) plateau. At the onset of exercise, oxygen uptake increases in a hyperbolic manner and reaches a steady-state plateau within 3 min during light to moderate exercise (Fig. 1). The VO$_2$ kinetic response is quantified as mean response time (MRT) or time to reach 63% of the VO$_2$ plateau phase from rest assuming first order kinetics.

Prolonged or slowed VO$_2$ kinetics leads to an oxygen “deficit” that must be buffered by increased glycolysis and depletion of high-energy phosphate stores, primarily in the form of phosphocreatine, until oxygen delivery and utilization equilibrates for the imposed workload. A slow MRT causes a fall in intracellular myocyte pH, rapidly depletes phosphocreatine, and is indicative of inefficient coupling between oxygen demand and supply (24). Abnormalities in either tissue oxygen delivery or inability of exercising muscle to efficiently utilize oxidative phosphorylation can prolong MRT.

In healthy individuals, there is a rapid rise in muscle blood flow at the onset of exercise corresponding to an increase in vascular conductance. Initially, the rise in blood flow is driven primarily by the mechanical pumping action of exercising muscle followed by neural and metabolite-mediated vasodilation (10). This rapid early flux ensures adequate delivery of oxygen, and in young healthy subjects there are virtually no limitations in oxygen uptake kinetics due to limited muscle oxygen supply (5, 35). Rather, under normal conditions, metabolic or “mitochondrial inertia” of the respiratory electron transport system appears to be responsible for the hyperbolic delay in early oxygen uptake (29). In disease states, it is unknown whether limitations in VO$_2$ kinetics is due to decreased oxygen delivery or metabolic inertia, as these two facets of oxygen uptake can be difficult to distinguish experimentally.

Abnormalities in VO$_2$ kinetics correlate well with functional limitations and provide a more representative assessment of work necessary for activities of daily living than peak VO$_2$. (4)

In HFrEF, VO$_2$ kinetics have been shown to independently correlate with New York Heart Association class and HF mortality, reflecting the degree of cardiac impairment with advancing severity of HF (8). Therapies that improve cardiac output reserve (e.g., cardiac resynchronization therapy), can improve VO$_2$ kinetics via improved bulk delivery of oxygen to exercising muscles (33). Changes in VO$_2$ kinetics can be a helpful indicator of response to therapy and may even precede improvements in maximal VO$_2$ and exercise time (28, 32).

![Fig. 1. Oxygen consumption (\( \text{VO}_2 \)) kinetics for a fixed submaximal workload. Hatched area represents the \( \text{O}_2 \) deficit, the amount of work supplied by nonaerobic metabolism. Tau, or mean response time, is time to reach ~63% of plateau phase of \( \text{VO}_2 \) from rest. A longer tau for a given fixed workload leads to a larger \( \text{O}_2 \) deficit and increased reliance on phosphocreatine and anaerobic metabolism to supply energy during the period of oxygen debt.](http://jap.physiology.org/doi/10.1152/japplphysiol.01127.2014)
Slowed VO₂ kinetics can also be seen in conditions where cardiac output is not limited. A prolonged MRT can identify patients with metabolic myopathies such as McArdle’s disease, a glyogen storage disorder condition marked by inability to catabolize glycerol into glucose as well as patients with mitochondrial myopathies, extreme examples whereby impairments in oxygen utilization rather than cardiac delivery delay oxygen utilization (15). Both patients with McArdle’s disease and mitochondrial myopathies share similar phenotypes with respect to VO₂ kinetics, characterized by an inability to maximize aerobic respiration due to slowed oxidative metabolism.

Aging and fitness both affect VO₂ kinetics as well. With increasing age, there is an increase in MRT, but this effect appears to be mediated by underlying fitness (9). Older individuals who are fitter display kinetics that are similar to young individuals. However, the effect of aerobic training on VO₂ kinetic response appears to be attenuated in the elderly compared with the young, suggesting limitations to vasculo-myofibrillar remodeling with aging (26).

In addition to providing information on functional capacity, VO₂ kinetics correlate well to peak VO₂ and is not as effort dependent (3). For patients who are limited by noncardiopulmonary barriers to peak exercise (e.g., arthritis, back pain, and frailty), characterizing MRT may be clinically more practical and could help identify individuals with significantly impaired cardiorespiratory fitness. MRT can also be measured at relatively light workloads (~30% peak VO₂) where there is essentially no cardiac limitation to VO₂ kinetics, allowing for an “isolated” assessment of myofibrillar recruitment, muscle tissue oxygen delivery, and oxidative efficiency. Thus VO₂ kinetics can provide valuable insight into isolating and understanding the peripheral factors that contribute to exercise intolerance during activities of daily living. To date no studies have assessed changes in VO₂ kinetics in HFpEF, but a growing body of evidence suggests peripheral abnormalities in oxygen utilization rather than limitations in cardiac reserve play an important role in exertional intolerance.

Abnormalities in Skeletal Muscle Oxidative Function in HFpEF

The sine qua non of HFpEF has traditionally been cardiac diastolic dysfunction, leading to a rapid rise in ventricular filling pressures during activities (1). While there is no large degree of exertional intolerance is a result of exercise induced pulmonary edema, recent studies suggest abnormalities in peripheral oxygen uptake occur even during submaximal exercise, prior to the development of symptom limiting dyspnea. Work by our group and others have shown HFpEF patients have lower calculated AVO₂ difference (derived from the Fick equation) during exercise, which correlates to peak VO₂ more so than changes in cardiac output (7, 16, 17). The low AVO₂ difference is thought to arise from decreased muscle oxidative capacity, although impaired endothelial function and an inability to vasodilate in the presence of metabolic by-products likely also plays a role.

Discerning the relative contributions of impaired oxidative capacity vs. inadequate vasodilation to slowed oxygen kinetics is controversial. A number of studies of endothelial dysfunction in HFpEF have come to conflicting conclusions regarding the importance of vascular dysfunction and exercise intolerance. While higher levels of endothelial dysfunction are associated with worse overall disease prognosis (2), there appears to be minimal or no relation between endothelial function to exercise capacity (18) nor to improvements with exercise capacity with training (21). These studies suggest impairments in oxidative capacity, whether through changes in mitochondrial structure and function or alterations in muscle fiber subtype, may be the primary factor responsible for impaired functional capacity as represented by prolonged VO₂ kinetics.

By using 31-phosphate magnetic resonance spectroscopy to quantify large muscle energetics, HFpEF patients exhibit lower oxidative phosphorylation rates, increased anaerobic glycosis, and long recovery times to regenerate phosphocreatine compared with healthy sedentary age-matched controls (7). Consistent with this observation of decreased aerobic oxidative capacity, muscle biopsies of HFpEF patients display fewer type 1 fibers and lower capillary to fiber ratios (23). The paucity of type 1 fibers and capillary density around skeletal myofibrils both correlate to decreased peak VO₂. The diminished oxidative capacity of skeletal muscle presumably leads to impaired VO₂ kinetics in HFpEF patients (Fig. 2). The accrual of a large oxygen deficit at the onset of exercise could induce fatigability or impede transition to higher aerobic workloads.

The consequences of increased anaerobic metabolism and accumulation of glycolytic by-products on hemodynamic response is unknown. HFpEF patients display a hyperdynamic cardiac response to exercise with cardiac outputs higher than expected for a given VO₂ (7). This hyperdynamic response to exercise is comparable to patients with mitochondrial myopathies, suggesting a similar role for heightened metabolic afferent signaling from skeletal muscle in both conditions.

The relationship between increased muscle metabolic afferent signaling and central cardiac response can be demonstrated with exercise training. In an elegant study, Saltin and colleagues (25) studied healthy young men before and after 5 wk of aerobic training. The 31-phosphate magnetic resonance spectroscopy analysis showed a decreased AVO₂ difference in the training group, indicating a reduced anaerobic contribution to energy production in trained HFpEF muscle. The decrease in AVO₂ difference was associated with increased capillary density and increased type 1 fiber content in the trained muscle biopsies, suggesting that training may increase oxidative capacity in HFpEF muscle. The reduced anaerobic contribution and increased oxidative capacity in the trained muscle biopsies is consistent with the observed improved cardiovascular fitness and reduced exercise intolerance in the trained group.

Fig. 2. Schema for impaired peripheral VO₂ kinetics in heart failure with preserved ejection fraction (HFpEF). Skeletal muscle from HFpEF patients have fewer type 1 oxidative fibers, lower type 1 to type 2 fiber ratio, and decreased capillary density around myofibrils compared with healthy muscle. At steady-state workloads, decreased early oxygen uptake may lead to increased oxygen deficit in HFpEF patients (solid line) compared with healthy controls (dashed line). Cap, capillary; I, type 1 fiber; II, type 2 fiber; MRT, mean response time.
of single leg exercise training while the opposite leg was kept untrained and cast immobilized. After 5 wk, engaging the trained muscle bed under similar workloads resulted in lower heart rate and ventilation, larger stroke volume, and lower arterial and central venous pressures compared with the deconditioned leg. In addition, circulating norepinephrine and lactate levels were lower, while blood pH was higher after exercise with the trained leg. The differential central circulatory response to diametrically trained muscle beds within the same individual suggests an important association between metabolic signaling and sympathetic activation. In HFrEF patients the consequences of whole body deconditioning, likely related to burden of chronic disease, may lead to increased myocardial work relative to aerobic power generated because of inefficient muscle metabolism. Impairments in early oxygen uptake can be a harbinger of underlying skeletal muscle oxidative impairment, and the measurement of VO2 kinetics could thus serve as a “biomarker” to identify patients at high risk for further clinical deterioration or those who could benefit from targeted exercise intervention.

Exercise as a Targeted Intervention on Muscle Oxygen Kinetics

Therapies that improve VO2 kinetics have the potential to improve functional capacity and reduce HF morbidity. Interventions that reduce MRT likely produce changes in the exercising skeletal muscle capillary bed that can generally be subdivided into two categories: therapies that either 1) improve skeletal myocyte oxidative capacity or 2) enhance muscle tissue oxygen delivery. Pharmacologically, the regulation of oxygen delivery to actively contracting muscle beds can be manipulated by compounds that enhance nitric oxide (NO) bioavailability. Increasing NO bioavailability improves vasodilatation under hypoxic conditions and can preferentially distribute blood flow to areas of the muscle bed in proportion to its oxidative capacity (19). Skeletal muscle oxidative capacity and efficiency can also be improved by exercise training, which increases capillary and mitochondrial density, changes muscle fiber subtypes distribution, and increases red blood cell capillary transit time through the skeletal muscle vasculature.

To date, no HFpEF training studies have utilized VO2 kinetics as a clinical end point to assess effectiveness of exercise intervention. Prior training studies have focused on whole body exercise to improve aerobic performance and peak VO2, gains primarily achieved through increased AV02 extraction. Targeting improvements in whole body peak VO2 while important, may not necessarily equate to practical gains in quality of life. VO2 kinetics may instead provide information regarding vascular-myofibrillar remodeling that occur with training, important mediators in normalizing abnormalities in muscle tissue oxygen utilization, impaired phosphocreatine metabolism, and anaerobic glycolysis rates in HFrEF patients that are manifest even at submaximal work. MRT may serve as a surrogate outcome variable for quantifying improvements in tissue oxygen utilization after interventions and may allow for the development of novel training regimens that do not depend on improving peak VO2 performance for establishing efficacy.

Whole body training programs focused on increasing peak VO2 may also be difficult for many patients, as the metabolic and hemodynamic demands of whole body exercise may overwhelm the ability of the cardiovascular system to respond. A focused approach to skeletal muscle training may provide more robust improvement in muscle oxidative capacity and limit patient intolerance. A study of small muscle mass training in HFpEF showed improvement in peripheral oxygen transport and oxygen utilization after 8 wk of lower body exercise with an increase in peak VO2 of nearly 40% (12). A similar approach, by targeting peripheral oxygen delivery and utilization in HFpEF patients, could yield significant improvements in VO2. Quantifying early VO2 kinetics could identify practical training programs that 1) lessen the burden of whole body exercise regimens, 2) improve muscle oxidative capacity, and 3) ultimately moderate the hyperdynamic circulatory response driven by metabolic inefficiency.

Conclusion

As the prevalence of HFpEF grows, new strategies will be necessary to combat the burgeoning epidemic of a disease that has no known therapies for reducing morbidity and mortality. Exercise training has been shown to be beneficial; however, the benefits of training derive primarily from improving peripheral oxygen utilization, an adaptation that is not necessarily represented in its entirety by solely measuring peak VO2. VO2 kinetics quantifies the oxidative efficiency of exercising muscle and provides insight into the integrative health of the cardiorespiratory-muscular system even at submaximal exercise. By designing interventions that improve early oxygen kinetics and skeletal muscle oxidative efficiency, the sleeping giant can be soothed, reducing the reactionary response of the central cardiovascular system.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

S.S. prepared figures; S.S. drafted manuscript; S.S. and B.D.L. edited and revised manuscript; S.S. and B.D.L. approved final version of manuscript.

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