Exercise Oxygen Kinetics in HFpEF

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

Abbreviated Title: Exercise Oxygen Kinetics in HFpEF

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Abstract

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. non-cardiac, 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 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.

Key words: Heart failure, skeletal muscle, oxygen kinetics, exercise
Introduction

Heart failure (HF), defined as progressive dyspnea with activities in the setting of elevated intra-cardiac filling pressures, affects almost 6 million patients in the US and is growing in prevalence. (31) The majority of patients diagnosed with HF have depressed systolic function though a significant number of these patients, between 30 to 50%, have relatively preserved ejection fraction (HFpEF) at rest and suffer similar mortality and re-hospitalization rates as those with depressed EF. (6, 13, 27) Unlike HF with reduced ejection fraction (HFrEF), to date no evidence-based intervention has improved survival or quality of life in such patients. Traditional targets of the cardiovascular system, e.g. neuro-hormonal blockade, have failed to improve mortality or reduce HF symptoms and exacerbations. Other therapies targeting myocardial fibrosis and stiffening, elevated pulmonary vascular pressures and chronotropic incompetence have shown limited or no efficacy. (11, 20, 30)

The ineffectiveness of current pharmacologic therapies challenges the paradigm of a solely “cardio-centric” cause for HFpEF. A growing body of evidence suggests abnormalities in the “peripheral” determinants of oxygen uptake and utilization may be largely responsible for reduced peak VO2 and exercise tolerance. Specifically, failure to increase arterial-venous oxygen (AVO2) extraction contributes to decreased exercise performance. Studies of exercise training in HFpEF subjects seem to support this notion. (7, 16, 22) In addition, much of the significant improvement in peak VO2 seen in aerobic exercise training studies has come in spite of limited changes in cardiac parameters such as stroke volume or heart rate reserve. (14, 17) The benefit of exercise training can occur within regimens as short as 3 months, highlighting the substantive 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 VO2 as a gauge of interventional effectiveness. While peak VO2 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. VO2 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. In order 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. Breath by breath measures of pulmonary VO$_2$ are plotted in the time domain and fitted by a mono-exponential model:
Exercise Oxygen Kinetics in HFrEF

\[ \text{VO}_2 = \text{VO}_2(b) + A\left[1 - e^{-\left(t-TD\right)/\tau}\right] \]

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 minutes during light to moderate exercise. (Figure 1) The VO2 kinetic response is quantified as mean response time (MRT) or time to reach 63% of the VO2 plateau phase from rest assuming first order kinetics.

Prolonged or slowed VO2 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 phospho-creatine, until oxygen delivery and utilization equilibrates for the imposed workload. A slow MRT causes a fall in intracellular myocyte pH, rapidly depletes phospho-creatine 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 VO2 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 VO2 kinetics correlate well with functional limitations and provide a more representative assessment of work necessary for activities of daily living than peak VO2. (4) In HFrEF, VO2 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 VO2 kinetics via improved
Exercise Oxygen Kinetics in HFpEF

bulk delivery of oxygen to exercising muscles. (33) Changes in VO2 kinetics can be a helpful indicator of response to therapy and may even precede improvements in maximal VO2 and exercise time. (28, 32)

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 glycogen storage disorder condition marked by inability to catabolize glycogen 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 to the young suggesting limitations to vascular-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 non-cardiopulmonary barriers to peak exercise (e.g. arthritis, back pain, frailty), characterizing MRT may be clinically more practical and could help identify individuals with significantly impaired cardio-respiratory 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
Exercise Oxygen Kinetics 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 doubt a large degree of exertional intolerance is a result of exercise induced pulmonary edema, recent studies suggest abnormalities in peripheral oxygen uptake occur even during sub-maximal 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 versus 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 sub-type, may be the primary factor responsible for impaired functional capacity as represented by prolonged VO2 kinetics.

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 phospho-creatine compared to 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. (Figure 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 hyper-dynamic cardiac response to exercise with cardiac outputs higher than expected for a given VO2. This hyper-dynamic 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 studied healthy young men before and after five weeks of single leg exercise training while the opposite leg was kept untrained and cast immobilized. After five weeks, 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 to the de-conditioned 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 HFpEF 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 due to 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...
Exercise Oxygen Kinetics in HFpEF

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 AVO2 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 vasculo-myofibril remodeling
that occur with training, important mediators in normalizing abnormalities in muscle
tissue oxygen utilization, impaired phosphocreatine metabolism, and anaerobic glycolysis
rates in HFpEF patients that are manifest even at sub-maximal 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
HFrEF showed improvement in peripheral oxygen transport and oxygen utilization after
8 weeks 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
hyper-dynamic circulatory response driven by metabolic inefficiency.
Exercise Oxygen Kinetics in HFpEF

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 cardio-respiratory-muscular system even at sub-maximal 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

The authors have nothing to disclose.
Exercise Oxygen Kinetics in HFpEF

Figure Legend

Figure 1
VO₂ kinetics for a fixed submaximal workload. Hatched area represents the O₂ deficit, the amount of work supplied by non-aerobic metabolism. Tau, or mean response time, is time to reach ~ 63% of plateau phase of VO₂ from rest. A longer tau for a given fixed workload leads to a larger O₂ deficit and increased reliance on phosphocreatine and anaerobic metabolism to supply energy during the period of oxygen debt.

Figure 2
Schema for impaired peripheral VO₂ kinetics in 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 to healthy muscle. At steady state workloads, decreased early oxygen uptake may lead to increased oxygen deficit in HFpEF patients (solid line) compared to healthy controls (dashed line). Cap – capillary; I – type 1 fiber; II – type 2 fiber; MRT – mean response time.
Exercise Oxygen Kinetics in HFpEF

References


Exercise Oxygen Kinetics in HFpEF


Exercise Oxygen Kinetics in HFpEF


Exercise Oxygen Kinetics in HFpEF


\[
VO_2(t) = VO_2(b) + A(1-e^{-(t-TD)/\tau})
\]
“Normal” Muscle

HFpEF Muscle

\[ \text{Type 1 Fibers} \]

\[ \text{Capillary Density} \]

\[ \text{VO}_2 \]

\[ \text{Normal} \]

\[ \text{HFpEF} \]

\[ \text{MRT} \]

\[ \text{O}_2 \text{ Deficit} \]

\[ \text{Time} \]