Muscle oxygen transport and utilization in heart failure: implications for exercise (in)tolerance

David C. Poole, Daniel M. Hirai, Steven W. Copp, and Timothy I. Musch

Departments of Anatomy and Physiology, and Kinesiology, Kansas State University, Manhattan, Kansas

Submitted 22 September 2011; accepted in final form 17 November 2011

Poole DC, Hirai DM, Copp SW, Musch TI. Muscle oxygen transport and utilization in heart failure: implications for exercise (in)tolerance. Am J Physiol Heart Circ Physiol 302: H1050–H1063, 2012. First published November 18, 2011; doi:10.1152/ajpheart.00943.2011.—The defining characteristic of chronic heart failure (CHF) is an exercise intolerance that is inextricably linked to structural and functional aberrations in the O₂ transport pathway. CHF reduces muscle O₂ supply while simultaneously increasing O₂ demands. CHF severity varies from moderate to severe and is assessed commonly in terms of the maximum O₂ uptake, which relates closely to patient morbidity and mortality in CHF and forms the basis for Weber and colleagues’ (167) classifications of heart failure, speed of the O₂ uptake kinetics following exercise onset and during recovery, and the capacity to perform submaximal exercise. As the heart fails, cardiovascular regulation shifts from controlling cardiac output as a means for supplying the oxidative energetic needs of exercising skeletal muscle and other organs to preventing catastrophic swings in blood pressure. This shift is mediated by a complex array of events that include altered reflex and humoral control of the circulation, required to prevent the skeletal muscle “sleeping giant” from outstripping the pathologically limited cardiac output and secondarily impacts lung (and respiratory muscle), vascular, and locomotory muscle function. Recently, interest has also focused on the dysregulation of inflammatory mediators including tumor necrosis factor-α and interleukin-1β as well as reactive oxygen species as mediators of systemic and muscle dysfunction. This brief review focuses on skeletal muscle to address the mechanistic bases for the reduced maximum O₂ uptake, slowed O₂ uptake kinetics, and exercise intolerance in CHF. Experimental evidence in humans and animal models of CHF unveils the microvascular cause(s) and consequences of the O₂ supply (decreased)/O₂ demand (increased) imbalance emblematic of CHF. Therapeutic strategies to improve muscle microvascular and oxidative function (e.g., exercise training and anti-inflammatory, antioxidant strategies, in particular) and hence patient exercise tolerance and quality of life are presented within their appropriate context of the O₂ transport pathway.

congestive heart failure; oxygen uptake kinetics; maximal oxygen uptake; exercise training; muscle microcirculation

THIS ARTICLE is part of a collection on Cardiovascular Response to Exercise. Other articles appearing in this collection, as well as a full archive of all collections, can be found online at http://ajpheart.physiology.org/.

Chronic Heart Failure: A “Perfect Storm” of Multiple Organ System Dysfunction

As the heart fails, following a myocardial infarction or other etiology, cardiac output (Q̇TOT) at rest, and particularly during muscular exercise, is reduced consequent to a diminished ejection fraction, stroke volume, and a heart rate response that is insufficient to compensate for the reduced stroke volume. This is the initiating condition for a cascade of events that affects multiple organ systems (Fig. 1; and Rev. 129, 130).

There is a global sympathetically mediated vasoconstriction that initially serves to maintain Q̇TOT at prepathology levels and that subsequently impairs the ability to distribute and redistribute Q̇TOT to and within skeletal muscle(s) (Qm; 120, 124, 160, 173). Enhanced humoral mediators including altered circulating angiotensin, norepinephrine, endothelin-1 (154), and vasopressin levels also contribute to the systemic vasoconstriction in chronic heart failure (CHF), and intravascular sodium and water retention act to further impair vasodilation (177), as do a plethora of events within the peripheral vasculature (vide infra; 25, 44, 45; Rev. 129, 130). In addition, group III (mechanosensitive) and IV (metabosensitive) afferents within the contracting muscles increase global sympathoexcitation (9, 35, Rev. 164). In support of the “muscle hypothesis” of Coats et al. (31) for CHF, Wang et al. (164) have demonstrated that CHF sensitizes group III afferents, which likely contributes to the exaggerated exercise pressor response (EPR). Despite the same studies demonstrating that group IV...
afferents are desensitized in CHF, it is pertinent that the far slower O$_2$ uptake (V˙O$_2$) kinetics, lower V˙O$_2$, and microvascular Po$_2$ (PmV$_{O2}$) (Figs. 2–6) will all exacerbate the production and accumulation of metabolites that ultimately stimulate these afferents. Thus, despite their relative desensitization, the role of the group IV afferents in the EPR is likely substantial in CHF. This eventuality would certainly help explain how exercise training-induced speeding of the V˙O$_2$ kinetics (131, 139) reduces or even prevents a greater EPR in CHF (165).

At the proximal end of the O$_2$ transport pathway in the lung, patients with CHF develop pulmonary dysfunction including ventilation-perfusion (V˙A/V˙Q) mismatch accompanied by reduced O$_2$ diffusion capacity (5, 83–85, 170, Rev. 126) and diminished respiratory endurance (112). Whereas the V˙A/V˙Q mismatch and diffusional impairments are often so mild that they do not cause arterial hypoxemia, they are accompanied by a chronic hyperventilation resulting from sensitization of the peripheral chemoreceptors (carotid bodies; 151) that, in concert with restrictive and obstructive pulmonary abnormalities, increases the work of breathing (Rev. 126). During severe intensity exercise in health, the diaphragm and other respiratory muscles can “steal” Q from the locomotory muscles (79).
In CHF this effect is accentuated (122, 126), redistributing more $Q_{TOT}$ toward the respiratory muscles and, by heightening sympathetic vasoconstriction of locomotory muscles, further impoverishing their $Q_m$ and $O_2$ supply and compromising exercise tolerance. This condition may be exacerbated further if CHF is accompanied by anemia secondary to dysfunctional iron metabolism and heightened inflammatory stress (103). Furthermore, within skeletal muscles in CHF, the capacity to use $O_2$ is impaired with reductions in mitochondrial oxidative enzyme activity and volume density as well as mitochondrial dysfunction (e.g., 41, 58, 65, 78, 153). It is pertinent that although skeletal muscle capillarity may (e.g., 171) or may not (58) be reduced significantly, across control and CHF populations, the number of capillaries per fiber correlates highly with mitochondrial volume density (58). In addition, CHF increases the proportion of capillaries that do not support red blood cell (RBC) flux at rest and during contractions (137).

**Impact on Exercise Responses**

Four key parameters of aerobic function are the maximum $V_{O_2}$ ($V_{O_2,\text{max}}$), $V_{O_2}$ kinetics, $V_{O_2}$ gain (e.g., ml $O_2$-watt$^{-1}$-$\text{min}^{-1}$ for cycling, an approximate measure of efficiency), and the lactate threshold (Tlac) or gas exchange threshold (131, 133–135, 139, 168, 169). These parameters define the gas exchange (i.e., $V_{O_2}$) response to exercise in the transient (i.e., following exercise onset, non-steady state) and steady-state conditions and, as such, link tightly with exercise tolerance or impediment thereof.

Maximum $V_{O_2}$. $V_{O_2,\text{max}}$ has been historically considered the sentinel parameter of integrated cardiovascular function and has been widely used to judge the severity of CHF (52, 71, 98, 109, 111, 167, 168). Specifically, class A, $V_{O_2,\text{max}}> 20$ ml$\cdot$kg$^{-1}\cdot$-$\text{min}^{-1}$; class B, 16–20; class C, 10–15; and class D, <10, which broadly correspond to the New York Heart Association classifications I, II, III, and IV, respectively (167). Accordingly, it is instructive to consider the determinants of $V_{O_2,\text{max}}$ and what insights these can provide into the mechanisms by which CHF compromises systemic and muscle $O_2$ transport. Wagner and colleagues (138, 162, 163) have championed the notion that although perfusive cardiovascular $O_2$ delivery may be the strongest determinant of $V_{O_2,\text{max}}$ in young healthy individuals exercising at sea level [evidenced by inspired hyperoxia (94), pericardectomy (152), blood doping (70), and small muscle mass exercise (137), all increasing $V_{O_2,\text{max}}$ or muscle specific $V_{O_2,\text{max}}$], pulmonary and muscle diffusive $O_2$ capacities also contribute importantly to $V_{O_2,\text{max}}$. Moreover, at altitude, after exercise training, and in extremely fit individuals (high $V_{O_2,\text{max}}$), the relative importance among $O_2$ perfusive and diffusive capacities with respect to determining $V_{O_2,\text{max}}$ may shift. In CHF, it was traditionally thought that $V_{O_2,\text{max}}$ was reduced solely consequent to the lowered $Q_{TOT}$ and resultant $Q_m$ (perfusion $O_2$ transport), which was supported by the low venous $O_2$ contents measured either centrally (pulmonary artery) (167) or in the exercising muscles (s) effluent venous blood (88). Specifically, the ability to reduce venous $O_2$ content and increase fractional $O_2$ extraction (arterial-venous $O_2$ difference) to a similar (or better) extent as seen in healthy subjects led to the presumption that the effective muscle $O_2$ diffusing capacity ($D_{O_2,m}$) was unimpaired. However, as can be seen from Fig. 2, the Fick principle,

$$V_{O_2} = Q_m \times (\text{arterial-venous } O_2 \text{ content}),$$

and Fick’s law of diffusion,

$$V_{O_2} = D_{O_2,m} \times (P_{mv \text{O}_2} - \text{intramyocyte } P_{O_2}),$$

conflate to yield $V_{O_2,\text{max}}$, where the curved lines represent perfusive $O_2$ transport ($Q_{O_2,m} = Q_m \times \text{vascular } O_2 \text{ content}$) and the straight lines from the origin represent $D_{O_2,m}$. Therefore, venous $O_2$ content (or $P_{mv \text{O}_2}$, as shown) in CHF can either be normal or lowered at $V_{O_2,\text{max}}$, even in the presence of a substantially decreased $D_{O_2,m}$. This effect is seen for large muscle mass exercise (e.g., conventional cycling) and small muscle mass exercise (i.e., knee extension) (58). The precise microvascular mechanisms for the reduced $D_{O_2,m}$ in CHF involve impaired capillary hemodynamics at rest and during contractions and are considered in detail below (see Skeletal Muscle Blood Flow, Capillary Hemodynamics, and $P_{mv \text{O}_2}$). What should be appreciated from Fig. 2 is that, with respect to fractional $O_2$ extraction and thus $P_{mv \text{O}_2}$, and venous $P_{O_2}$, there is an interdependence between the muscle perfusive ($Q_{O_2,m}$) and diffusive ($D_{O_2,m}$) relationships that may be expressed as follows (138):

$$O_2 \text{ extraction} = \dot{V}_{O_2}/Q_{O_2,m} = \dot{Q}_{O_2,m} (1 - e^{-D_{O_2,m}^{Q_{O_2,m}}/\beta}),$$

where $Q_{O_2,m}$ is muscle perfusive $O_2$ delivery, $D_{O_2,m}$ is muscle $O_2$ diffusing capacity, $\beta$ is the slope of the $O_2$ dissociation curve in the physiologically relevant range, and $Q_m$ is muscle blood flow. Thus, because there is a substantial reduction in $Q_m$ with CHF, $D_{O_2,m}$ may be compromised and $O_2$ extraction either normal (ratio of $D_{O_2,m}$ to $\beta Q_m$) or, as shown in Fig. 2, increased (ratio of $D_{O_2,m}$ to $\beta Q_m$). The importance of the reduced $D_{O_2,m}$ in CHF is evident when vasodilator treatment
Exercise intolerance is multifactorial and among its mechanisms is the slowing of O2 kinetics. In CHF patients, the time to reach 63% of the maximum (t, time to reach 63%) of the response, in young healthy individuals, is 20–30 s, whereas it is slowed to 120 s or 2 min in patients with CHF (Fig. 3; 81, 118, 147, 148). Importantly, the speed of the O2 kinetics has been considered to have even better prognostic value in CHF than the O2 max (on-kinetics, 142; off-kinetics, 125). Both the close-to-instantaneous phase I (driven predominantly by increased pulmonary blood flow, omitted from Fig. 3 for clarity) and the subsequent primary (phase II) response, thought to reflect the muscle O2 kinetics (72), are impacted by CHF (148), reflecting a failure to both increase Q˙O2m and muscle V˙O2. The importance of this slowed V˙O2 kinetics is that the steady-state O2 requirement for a given task will almost certainly be no lower (and may even be higher, see below) in CHF, and so, for any given metabolic transition, the patient with CHF will incur a greater O2 deficit and therefore more extreme intracellular perturbation of high-energy phosphagens and acid-base (Fig. 3). Importantly, the greater substrate-level phosphorylation associated with slower V˙O2 kinetics accelerates glycogenolysis and contributes to fatigue and the ensuing exercise intolerance (123, 131, 139). For a given metabolic transition (ΔV˙O2), the O2 deficit incurred may be estimated as rΔV˙O2. Thus, for the same metabolic transition of, for example, 1 liter O2/min, the healthy individual with fast kinetics (τ = 30 s or 0.5 min) will incur an O2 deficit of 0.5 liter O2 (0.5 × 1.0), whereas for the patient with CHF with slowed kinetics (τ = 120 s or 2 min), their deficit will be 2 liter O2 (2.0 × 1.0), and consequently a muscle biopsy of the patients’ working muscles would reveal lower phosphocreatine concentration ([PCr]) and a greater free adenosine diphosphate concentration ([ADPfree]), thus resulting in a higher rate of glycogenolysis and [H+].

For locomotory muscles exercise such as cycling, walking, or running in young relatively fit healthy individuals, a compelling weight of evidence supports that V˙O2 kinetics are not limited by muscle O2 delivery but rather subject to mitochondrial control (O2 supply-independent zone of Fig. 3; Refs. 131, 139). In contrast in CHF, the pathognomonically lowered O2 delivery-dependent zone of V˙O2 kinetics, creating an O2 supply dependency (O2 delivery-dependent zone, Fig. 3). The direct consequences of this slowed V˙O2 kinetics in CHF and other diseases/conditions are a greater psychological perception of effort, greater intracellular perturbation of phosphagens, acid-base and glycogen, and a related decrease in exercise tolerance (see Fig. 13 of Ref. 139).

V˙O2 gain and the slow component of V˙O2 kinetics. For exercise above the Tlac (> Tlac, i.e., in the heavy or severe intensity domains), an additional V˙O2 cost (or slow component) becomes evident beyond the faster primary (phase II) kinetics as V˙O2 rises considerably above the ~10 ml O2/watt−1 min−1 gain characteristic of moderate (< Tlac) exercise (Fig. 4, Refs. 80, 86, 134, 135, 169). This extra V˙O2 arises predominantly from within the exercising muscles and is attributed to a combination of fatigue-related processes necessitating additional fiber recruitment and also metabolic processes occurring within already recruited fibers (133, 159). In healthy individuals this slow component may exceed 1 liter O2/min, reduce exercise efficiency, and for severe exercise (i.e., above the critical power, the asymptote of the hyperbolic relationship between power output and time to exhaustion for high-intensity exercise), drive V˙O2 to V˙O2 max, heralding imminent fatigue (135, Rev. 86). For the patient with CHF, whose Tlac (69, 89, 178) and critical power (131, 139) often reside at perilously low absolute V˙O2 values, the slow component represents a metabolic extravagancy that they can ill afford. Indeed, the presence of Tlac and critical power in patients with CHF at metabolic rates (V˙O2 values) far lower than seen in healthy individuals means that patients in whom muscle O2 delivery is most compromised may actually have the highest O2 requirement for muscular exercise (including a higher O2 cost incurred by the respiratory muscles, 126) even at very low work rates. As initially documented by Zelis and colleagues (173), the actual V˙O2 achieved by the patient with CHF during exercise may be lower than that for their healthy counterpart. Given the above, this should not be taken as evidence that the patient with CHF is working more efficiently. Indeed, the opposite may be the case and the lower achieved V˙O2 means that the patient is accumulating a greater (and continuous) O2 deficit leading to premature exhaustion.
Lowered lactate threshold reduces the work rate and \( \dot{V}O_2 \) at which the \( \dot{V}O_2 \) slow component emerges elevating the \( O_2 \) demand for submaximal exercise at very low work rates

Fig. 4. Facets of the exercise response in CHF: lactate threshold (Tlac). These curves are constructed from the end-exercise \( \dot{V}O_2 \) obtained in a series of independent constant-work rate exercise tests performed in a healthy individual (top) and a patient with CHF (bottom). Note the far lower work rate for the Tlac in CHF and that the \( \dot{V}O_2 \) slow component (gray areas) becomes evident only above Tlac. One consequence of this behavior is that the patient with CHF experiences an additional \( O_2 \) demand at very low work rates that may drive \( \dot{V}O_2 \) to \( \dot{V}O_2_{max} \) and herald imminent exhaustion. Mechanisms responsible for the lowered Tlac and presence of \( \dot{V}O_2 \) slow component at very low work rates include decreased bulk blood flow and \( O_2 \) delivery, reduced capillarity, impaired capillary hemodynamics, lowered PmvO2, and mitochondrial dysfunction, particularly in slow twitch highly oxidative (type I) fibers. See text for additional details.

To understand the mechanisms underlying the exercise intolerance of CHF, the bases for the decreased \( \dot{V}O_2_{max} \), slowed \( \dot{V}O_2 \) kinetics, lowered Tlac and critical power, and increased \( \dot{V}O_2 \) gain must be explored. As will be seen, these bases are strongly from compromised Qm and an inability to temporally and spatially match QO2m to requirements (VO2).

Skeletal Muscle Blood Flow, Capillary Hemodynamics, and PmvO2

Healthy. In healthy individuals with normal arterial \( O_2 \) content (~20 ml \( O_2/100 \) ml), \( Q_{TOT} \) and Qm increase between 5 and 6 liters per liter \( \dot{V}O_2 \) (Rev. 60). Following the onset of muscular exercise the \( Q_{TOT} \) increase is extremely rapid owing to an essentially instant vagal withdrawal accelerating heart rate (phase I) with a subsequent increase in stroke volume and further elevation of heart rate (phase II), driving \( Q_{TOT} \) and Qm kinetics that are appreciably faster than their \( VO_2 \) counterparts (40, 95, 133, 157, 172). This profile supports the \( O_2 \) delivery independence of \( VO_2 \) kinetics in healthy young individuals (Fig. 3; Refs. 133, 139). Thus Qm may increase sufficiently fast for moderate (72) as well as heavy and severe exercise (13, 96), such that increased \( QO_2m \) exceeds muscle \( \dot{V}O_2 \) and consequently effluent venous \( O_2 \) content increases transiently as fractional \( O_2 \) extraction is decreased. There is evidence that both rapid arteriolar vasodilation (19, Rev. 28) and muscle pumping action (Rev. 157) contribute to this almost instantaneous (within 1 s) increase in muscle (95, 157) and capillary (92) \( Q \).

Across muscles of different fiber type composition, the proportionality of the increase in Qm to \( \dot{V}O_2 \) is similar, but fast twitch muscles have a lower Qm at rest such that PmvO2 is lower (and fractional \( O_2 \) extraction higher) at rest and low metabolic rates than for slow twitch muscles (23, 60, 117). These fast twitch muscles may have a slower rate of Qm increase following the onset of contractions and may be forced to rely more heavily on \( O_2 \) extraction than slow twitch muscles (23, 117). Importantly, as most skeletal muscle capillaries may support RBC flux at rest, the increased Qm with contractions represents augmented RBC flux (and velocity) within already flowing capillaries (92, 132). Thus, following the onset of contractions, increased blood-muscle \( O_2 \) flux (diffusional \( O_2 \) capacity, \( D_{O2m} \)) occurs via a combination of the following (132): 1) increased RBC flux and velocity in individual capillaries, 2) recruitment of additional capillary exchange surface by elevating capillary hematocrit and the length of capillary over which \( O_2 \) flux occurs (i.e., “longitudinal recruitment”), 3) reduction of intramyocyte \( P_{O2} \) to establish a sufficient capillary-mitochondrial \( O_2 \) gradient, and 4) myoglobin deoxygenation to enhance intramyocyte \( O_2 \) movement.

Chronic heart failure. CHF may attenuate or even abolish the initial rapid increase in \( Q_{TOT} \) (and thus Qm; 146) following exercise onset (i.e., phase I; 148) and result in an extremely slow and often an inadequate subsequent elevation of Qm (phase II; 108, 174–177). For a share of this reduced QO2m, exercising skeletal muscle must overcome exaggerated sympathetic, humoral, and reflex-mediated vasoconstriction to compete with elevated energetic (and Qm) demands of the respiratory muscles (122, 126) and an altered distribution of available \( Q_{TOT} \) among active locomotory muscles based on, in part, their fiber-type composition (i.e., greater Qm to low oxidative type II and lower Qm to type I/oxidative type II muscles and muscle fibers in CHF vs. healthy animals; 51, 124). At \( \dot{V}O_2_{max} \) the reduced \( Q_{TOT} \) (and any decreased arterial \([O_2]\)) lowers \( QO_2m \), whereas subsequent redistribution of that lowered \( Q_{TOT} \) away from the major locomotory muscles provides an additional constraint on \( QO_2m \) (122, 126, Fig. 2). Compounding these \( Q_{TOT} \) distributional problems, arterioles within the active muscles themselves have an inherently greater vasoconstrictor tone (44, 45).

At the muscle capillary level, CHF promotes capillary invasion (171) and reduces the percentage of capillaries that support RBC flux at rest and during contractions (136). Crucially, those capillaries that do not flow at rest remain stagnant during contractions, and this helps place a low limit on \( D_{O2m} \) (see Fig. 2) as it lowers the number of oxygenated RBCs in the capillary bed at a given moment and therefore available to contribute to the instantaneous blood-myocyte \( O_2 \) flux. Figure 5, top, demonstrates that even in those capillaries that do support RBC flux at rest, the response to contractions is extremely sluggish. Consequently, even though mitochondrial \( VO_2 \) kinetics may be impaired in CHF (and especially severe CHF, 41), \( QO_2m \) kinetics are more affected and the \( QO_2m \)-to-\( \dot{V}O_2 \) ratio falls much lower driving \( PmvO2 \), either transiently (moderate CHF in young animals, Fig. 5, bottom; 46) or during the steady-state (severe CHF, old animals; 21, cf. 18, 22) to extremely low values. Importantly, muscles predominantly comprised of slow
twitch fibers are impacted most drastically (20). Thus, when compared with healthy muscles, in CHF the PmvO2 (driving blood-myocyte O2 flux) is lowered at that time when muscle V˙O2 is, or should be, increasing most rapidly with the result that V˙O2 kinetics become O2 delivery (i.e., Q˙O2m) limited and very slow (Fig. 3). This response is akin to the “overshoot” of the muscle hemoglobin /myoglobin deoxygenation profile measured by near-infrared spectroscopy by Sperandio and colleagues (150) in patients with CHF. In an attempt to preserve the blood-myocyte PO2 gradient in the face of falling PmvO2, intramyocyte PO2 is likely to decrease and exacerbate intracellular perturbations of high-energy phosphates ([PCr], [ADPfree]), glycolysis, and acid-base (8).

Not only is this situation sowing the seeds for premature fatigue in CHF, but it presages an extremely slow recovery as seen for PmvO2 in Fig. 6. The inability to increase the Q˙O2m delivery-to-V˙O2 ratio earlier or faster following cessation of muscle contractions in CHF keeps PmvO2 low, reduces intramyocyte Po2, and retards V02 and PCr recovery kinetics (89, 90). It is pertinent that recovery V02 kinetics can often be determined with greater fidelity and reproducibility than its counterpart at the beginning of exercise (89, 90). Moreover, because of the increased respiratory muscle V02 (126) as well as any sympathetic stimulation of metabolic rate and/or cachexia, the range of achievable sub-Tlac work rates may be disappearingly small. Hence, daily

response. However, the most pronounced difference in the kinetics of the PmvO2 response is evident in the off-transient (i.e., recovery) where the control muscle recovers to baseline well before its CHF counterpart has reached 50% recovery. It is pertinent that Copp et al. (33) demonstrated a strong correlation (Fig. 6, bottom; r = 0.76, P < 0.01, n = 16, control, moderate CHF, severe CHF) between the slowed PmvO2 off-kinetics and elevated left ventricular end-diastolic pressure (LVEDP), albeit driven principally by the severe CHF animals. This observation is relevant because patients with CHF often complain of prolonged fatigue that resolves very slowly following exercise or rehabilitation therapy. Ameliorating these symptoms may help improve exercise rehabilitation retention and thus efficacy in the community of patients with CHF.

Tlac (expressed as the V02 at which blood lactate begins increasing above values at rest, used here synonymously with the gas exchange threshold) is exquisitely sensitive to arterial O2 content, Q˙O2m, PmvO2, and muscle oxidative capacity (Rev. 166). As detailed above, each of these variables is impaired in CHF, and compounded by slowed V02 kinetics, it is inevitable that Tlac occurs at extremely low V02 values in patients with CHF (69, 89, 178). Moreover, because of the increased respiratory muscle V02 (126) as well as any sympathetic stimulation of metabolic rate and/or cachexia, the range of achievable sub-Tlac work rates may be disappearingly small. Hence, daily

---

**Fig. 5.** *Top:* CHF (moderate severity, LVEDP ~10 mmHg) abolishes the rapid increase in spinotrapezius capillary RBC flux found in the healthy control muscle following onset of 1-Hz contractions (time 0 s, Ref. 136). *Bottom:* PmvO2 profile in the same spinotrapezius preparation. Note that in CHF PmvO2 is lower than for the healthy muscle, and there is a transient dip below the steady state (both indicative of a QO2m-to-V02 mismatch). From the data of Copp et al. (33), with kind permission.

**Fig. 6.** *Top:* PmvO2 profiles for 180 s of 1-Hz contractions and 180 s of recovery for spinotrapezius muscles of healthy control and CHF rats. Note that in CHF PmvO2 is lower than for the healthy muscle, and there is a transient dip below the steady state (both indicative of a QO2m-to-V02 mismatch). *Bottom:* spinotrapezius PmvO2 recovery kinetics [mean response time (MRT), time delay] was progressively slowed in CHF rats with higher LVEDPs. From Copp et al. (33), with kind permission.
Mechanisms Limiting Increases of Muscle Blood Flow in CHF

Almost every aspect of muscle blood flow (Qm) control is disturbed in CHF as seen in Fig. 7. Vasoconstriction is enhanced by sympathetic nervous system-mediated α-adrenergic tone (consequent to enhanced peripheral chemoreceptor sensitivity and heightened metaboreflexes) and increased circulating catecholamines, angiotensin II, arginine vasopressin, and endothelin-1 (25, 154, Rev. 129, 130). The efficacy of the muscle pump is impeded by elevated postcapillary resistance (115, 146, 174, 175) and increased vascular stiffness. Endothelial function is compromised by endothelial cell damage and impaired reparability, in part because of low circulating endothelial progenitor cells (CPCs; 54). Nitric oxide (NO) bioavailability is compromised, which presumably constrains sympatholysis (the ability to oppose α-adrenergic vasoconstriction; 155) and shear stress-mediated vasodilation. In turn, inadequate Qm and QO2m will promote hypoxic vasodilation and increase vasodilatory metabolite efflux from the contracting muscle(s) (lactate, H+, adenosine, inorganic phosphate, potassium). The eventual outcome (i.e., reduced Qm and particularly PmVO2) in CHF indicates that the net balance favors reduced vascular perfusion and impaired QO2m.

Within muscle and other tissues, CHF increases TNF-α and IL-1β levels and the anti-inflammatory interleukin 10 (IL-10) may decrease (14, 54) irrespective of whether circulating concentrations are altered. There is also an aggravated antioxidant-antioxidant imbalance. All of these changes can impact NO bioavailability and, given the importance of decreased NO bioavailability in muscle and exercise dysfunction in CHF (see Role of NO in Regulating Contracting Muscle QO2/VO2 Matching), have been the subject of significant attention.

Role of NO in Regulating Contracting Muscle QO2/VO2 Matching

NO bioavailability can exert a commanding role in the matching of QO2m to VO2 in contracting rat muscle. For example, Hirai and colleagues (82) have determined in rats that NO-mediated vasodilation helps regulate the distribution of QO2m among active muscle fibers based on their oxidative capacity. In CHF, the capacity for N3-nitro-L-arginine methyl ester blockade of NO synthase (NOS, nonspecific isoform blockade) to reduce Qm, particularly to more highly oxidative muscle fibers, is substantially lessened (82). With the use of the superfused contracting spinotrapezius preparation, NOS blockade transforms the healthy rat PmVO2 profile into one resembling CHF (Figs. 5 and 6; and Refs. 59, 61). Moreover, in CHF muscles, the NOS blockade effect is greatly reduced and the application of sodium nitroprusside (an NO source) restores the PmVO2 profile from that present in moderate CHF back to that seen in the healthy animals (59). However, it must be acknowledged that elevating intracellular [NO] has the potential to decrease mitochondrial VO2 (10, 11, 100) and hence restore the healthy QO2m-to-VO2 ratio by decreasing the denominator as well as increasing the numerator. Notwithstanding this concern, it is evident that increased NO bioavailability has the potential to enhance blood-myocyte O2 flux in CHF by restor-

---

**KEY FACTORS MODULATING THE MUSCLE BLOOD FLOW RESPONSE TO EXERCISE IN CHF**

- **Neural:** 
  - SNS: α-adrenergic + β-adrenergic
- **Myogenic:** 
  - Autoregulation: -
- **Mechanical:** 
  - Muscle pump: +
  - Perfusion: +
  - Post-capillary resistance: -
  - Vascular stiffness: -
- **Lumen:** 
  - Vascular conductance: x
  - ΔPressure: =
  - Blood flow: down
- **Humoral:** 
  - Catecholamines: +
  - Angiotensin II: -
  - Endothelin-1: -
  - Nitric oxide: +
- **Metabolites + Hypoxia:** 
  - Lactate: +
  - H+: +
  - Adenosine: +
  - Inorganic phosphate: +
  - Potassium: +
- **Inflammatory / Cytokine:** 
  - TNFα: -
  - IL-1β: -
  - ROS: -
  - Peroxynitrite: -

---

AJP-Heart Circ Physiol • doi:10.1152/ajpheart.00943.2011 • www.ajpheart.org
Inflammatory Mediators Reduce NO Bioavailability in CHF

CHF-induced muscle vascular dysfunction and the associated decreased NO bioavailability is mediated, in part, by a combination of the reduction in endothelial cell tetrahydrobipterin (BH4, an essential cofactor for NOS), superoxide dismutase (SOD), catalase, and glutathione peroxidase protein expression and activity, as well as increased NADPH oxidase protein expression and activity, each of which serves to elevate superoxide radicals (O$_2^-$) and decrease NO (Fig. 7, inset, bottom right). Inflammatory mediators TNF-α and IL-1β promote oxidative stress and have been heavily implicated in this process (1, 2, 24, 34, 53, 65, 67, 105, 156, 158). Reducing BH4 uncouples endothelial NOS, lowering NO production (110, 149) and generating O$_2^-$, which itself enhances NO degradation and produces the peroxynitrite reactive oxygen species (Fig. 7, inset, bottom right), 149). Moreover, by the action of SOD, enhanced O$_2^-$ will elevate hydrogen peroxide, which, although a vasodilator in its own right, can be converted to iron (Fe$^{2+}$) and produce the potent vasoconstrictor hydroxyl radical via the Fenton reaction. In addition, elevated cytokines (TNF-α, IL-1β) promote inducible NOS induction such that intracellular [NO] rises and inhibits key oxidative enzymes and mitochondrial creatine kinase (4, 65, 76) as well as promoting apoptosis (3).

In aged rats, increased BH4, induced via acute exogenous bolus sepiapterin (substrate for BH4 synthesis) treatment or exercise training, improves NO signaling in skeletal muscle arterioles and restores flow-induced vasodilation (149). Whether this is also the case in CHF is an important question given the commonality between the conditions of aging and CHF with respect to these inflammatory mediators (i.e., TNF-α and IL-1β). It is pertinent that pentoxifylline, a phosphodiesterase inhibitor that also blocks cytokine expression reducing circulating and tissue TNF-α and IL-1β, improves capillary hemodynamics in ischemic conditions (in this respect analogous to CHF; 38, 50, 145) and has demonstrated clinical efficacy in patients with CHF (12, 145). Pentoxifylline may also help restore more normal skeletal muscle hemodynamics in CHF by reducing the CHF-enhanced sympathoexcitation via central effects within the paraventricular nucleus and elsewhere (75). However, this remains to be empirically determined.

Specific Effects of CHF and Exercise Training on Mediators of NO Bioavailability

In contrast to CHF, NO bioavailability and endothelial function in skeletal muscle and heart are upregulated by exercise training (73, 101, 114, 144) particularly against a background of CHF (Fig. 8; 34, 161). The effect of exercise training and its ability to combat the predations of CHF has been attributed, in part, to increased BH4 (16, 106), as well as decreased oxidative stress (increased SOD, catalase, and glutathione peroxidase; 62, 68, 102, 106, 140), reduced TNF-α and IL-1β (1, 32, 66, 104), and reduced inducible NOS that decreases intramyocyte [NO] and presumably lessens its pernicious intracellular consequences (65). Moreover, exercise training may increase muscle capillarity [facilitated by preservation of the vascular endothelial growth factor signaling pathway in patients with CHF, 57] and oxidative function in patients with CHF (56) as it does in healthy individuals (26, 141), as well as restore levels of the anti-inflammatory mediator IL-10 (14). In addition, exercise training may improve vascular endothelial function via a c-Src-dependent increase of endothelial NOS expression and NO bioavailability as well as help restore endothelial repair and function by elevating CPCs (37, 54, 56, 62, 97, 101, 114).

Conclusions

CHF compromises almost every facet of the O$_2$ transport pathway, which can explain much of the exercise intolerance and premature fatigue in this condition. V˙O$_2$ max is decreased by impaired perfusive O$_2$ transport to and within the active muscles and also compromised diffusional O$_2$ transport that may result from failure to sustain RBC flux within a substantial proportion of the capillary bed, creating a marked temporal and spatial imbalance between O$_2$ delivery (Q˙O$_2$m) and requirements (V˙O$_2$). V˙O$_2$ kinetics become Q˙O$_2$m limited and grossly retarded at very low metabolic rates, thereby incurring a large O$_2$ deficit, accentuated intracellular metabolic perturbation, and enhanced glycogenolysis. In CHF, the Tlac occurs at lower V˙O$_2$ values, necessitating the metabolic extravagation of the V˙O$_2$ slow component and raising the V˙O$_2$ gain (or at least energetic requirement) for tasks or activities that constitute moderate exercise (<Tlac, no V˙O$_2$ slow component) for healthy individuals. The plethora of structural and functional (neurohumoral, inflammatory, reflex) consequences of CHF coalesce at the muscle microcirculation and abolish the rapid increase of capillary RBC flux and velocity and RBC distribution necessary to regulate PmvO$_2$ and support fast V˙O$_2$ kinetics. Whereas a simple solution to this complex pathology may be overly optimistic, recent empirical evidence supports an important role for NO bioavailability in matching Q˙O$_2$m to V˙O$_2$. As such, strategies that enhance NO bioavailability while decreasing the predations of inflammatory cytokines (TNF-α, IL-1β) and possibly increasing anti-inflammatory cytokines (IL-10) and CPCs, for example, exercise training (66), pentoxifylline, statins (e.g., rosuvastatin, 54), and antioxidant strategies (but not acute vitamin C; 55), offer hope. In addition, if dietary nitrate supplementation can improve exercise efficiency (reduced V˙O$_2$ gain) in patients with CHF as it does in healthy individuals (10, 11, 99, 100), Q˙O$_2$m-to-V˙O$_2$ matching will be enhanced and exercise tolerance might be improved without the necessity for increased Qm, fractional O$_2$ extraction, or altered Qm distribution. Finally, the demonstration that vascular signaling mechanisms are retained in patients with CHF (e.g., vascular endothelial growth factor; 57) coupled with the ability for ventilatory assist devices to redistribute Q˙TOT to the locomotory muscles (126) and specific respiratory muscle training to enhance limb Qm and exercise tolerance in patients with CHF (27, 36, 113) suggests innovative strategies for improving cardiac rehabilitation program retention and outcomes.
The challenge for physiologists, exercise specialists, and clinician scientists is to resolve the specific mechanisms underlying CHF-induced dysfunction at each step in the O$_2$ transport pathway. This is crucial to increase exercise tolerance most effectively in the patient with CHF; in this regard, it is clear that even very aggressive contemporary pharmaceutical treatment is not reversing the Q˙O$_2$m-to-V˙O$_2$ mismatching aberrations in skeletal muscle (150). In turn, those improvements in exercise tolerance need to be quantified appropriately (168) and related to the parameters of aerobic function. As proposed by Coats and colleagues (31), skeletal muscle plays center stage in the dysfunction and prognosis of the patient with CHF and recent evidence is emerging for contracting skeletal muscles producing “myokines” that actively oppose the inflammatory condition of CHF (and other diseases/conditions) (127, 128). This is exciting and particularly relevant to CHF because small initial improvements in the O$_2$ transport pathway, insofar as these increase V˙O$_2$ max and Tlac, and speed V˙O$_2$ kinetics, thereby improving exercise tolerance, may initiate a positive feedback that eventually reverses many of the predations of CHF.

The challenge for physiologists, exercise specialists, and clinician scientists is to resolve the specific mechanisms underlying CHF-induced dysfunction at each step in the O$_2$ transport pathway. This is crucial to increase exercise tolerance most effectively in the patient with CHF; in this regard, it is clear that even very aggressive contemporary pharmaceutical treatment is not reversing the Q˙O$_2$m-to-V˙O$_2$ mismatching aberrations in skeletal muscle (150). In turn, those improvements in exercise tolerance need to be quantified appropriately (168) and related to the parameters of aerobic function. As proposed by Coats and colleagues (31), skeletal muscle plays center stage in the dysfunction and prognosis of the patient with CHF and recent evidence is emerging for contracting skeletal muscles producing “myokines” that actively oppose the inflammatory condition of CHF (and other diseases/conditions) (127, 128). This is exciting and particularly relevant to CHF because small initial improvements in the O$_2$ transport pathway, insofar as these increase V˙O$_2$ max and Tlac, and speed V˙O$_2$ kinetics, thereby improving exercise tolerance, may initiate a positive feedback that eventually reverses many of the predations of CHF.
swimming (4 × 200 m freestyle relay) at the 2000 Olympic Games in Sydney, provides evidence that, beyond the failing heart, the O₂ transport predations of CHF are potentially reversible.

GRANTS
This work was supported, in part, by National Institutes of Health Grants HL-50306, AG-19228, and HL-108328; American Heart Association grants-in-aid (to D. C. Poole and T. I. Musch); and Capes-Brazil Fulbright Fellowship program (to D. M. Hirai).

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

AUTHOR CONTRIBUTIONS
D.C.P., D.M.H., S.W.C., and T.I.M. prepared figures; D.C.P. drafted manuscript; D.C.P., D.M.H., S.W.C., and T.I.M. edited and revised manuscript; D.C.P., D.M.H., S.W.C., and T.I.M. approved final version of manuscript.

REFERENCES


AJP-Heart Physiol. • doi:10.1152/ajpheart.00943.2011 • www.ajpheart.org

Copyright © American Physiological Society. All rights reserved.


