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

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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

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

As the heart fails, following a myocardial infarction or other etiology, cardiac output (QTOT) 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 QTOT at prepathology levels and that subsequently impairs the ability to distribute and redistribute QTOT 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 O2 uptake (V̇O2) kinetics, lower V̇O2, and microvascular PO2 (PmvO2) (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 V̇O2 kinetics (131, 139) reduces or even prevents a greater EPR in CHF (165).

At the proximal end of the O2 transport pathway in the lung, patients with CHF develop pulmonary dysfunction affecting all steps in the O2 transport pathway. CHF-induced lung dysfunction redistributes blood flow (Q̇) to the respiratory muscles via locomotory muscle vasoconstriction; there may be systemic anemia, systemic vasoconstriction, and elevated left ventricular (LV) end-diastolic pressures (LVEDPs) as well as a plethora of structural and functional adaptations (increased vasoconstriction, impaired vasodilation, and muscle pump) that compromise skeletal muscle perfusional and diffusional O2 transport. VA, alveolar ventilation; VE, expired ventilation; SNS, sympathetic nervous system; QO2, whole body oxygen delivery (cardiac output × arterial O2 content); VO2, oxygen uptake; NO, nitric oxide; iNOS, inducible NO synthase; ROS, reactive oxygen species; SOD, superoxide dismutase; GPX, glutathione peroxidase. See text for more details.
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 $V_{O_2}$ ($V_{O_2,max}$), $V_{O_2}$ kinetics, $V_{O_2}$ gain (e.g., ml $O_2$-watt$^{-1}$-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 $V_{O_2}$. $V_{O_2,max}$ 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, $V_{O_2,max} > 20$ ml$\cdot$kg$^{-1}$·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 $V_{O_2,max}$ 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 $V_{O_2,max}$ 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 $V_{O_2,max}$ or muscle specific $V_{O_2,max}$], pulmonary and muscle diffusive $O_2$ capacities also contribute importantly to $V_{O_2,max}$. Moreover, at altitude, after exercise training, and in extremely fit individuals (high $V_{O_2,max}$), the relative importance among $O_2$ perfusive and diffusive capacities with respect to determining $V_{O_2,max}$ may shift. In CHF, it was traditionally thought that $V_{O_2,max}$ was reduced solely consequent to the lowered $Q_{TOT}$ and resultant $Q_m$ (perfusive $O_2$ transport), which was supported by the low venous $O_2$ contents measured either centrally (pulmonary artery) (167) or in the exercising muscle(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,

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

and Fick’s law of diffusion,

$$V_{O_2} = D_{O_2,m} \times (P_{mvO_2} - \text{intramyocyte } O_2 \text{ content}) + \text{ straight lines from the origin represent } D_{O_2,m}$$

therefore, venous $O_2$ content (or $P_{mvO_2}$, as shown) in CHF can either be normal or lowered at $V_{O_2,max}$, 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 $P_{mvO_2}$*).

What should be appreciated from Fig. 2 is that, with respect to fractional $O_2$ extraction and thus $P_{mvO_2}$, and venous $O_2$ content, 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):

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

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

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**Fig. 2. Facets of the exercise response in CHF: maximum $V_{O_2}$ ($V_{O_2,max}$).** Schematic illustrating how the perfusive (curved lines, Fick principle, $V_{O_2}$ (microvascular $O_2$ diffusing capacity ($D_{O_2,m}$) × (microvascular $P_{O_2}$ (P$_{mvO_2}$) – intracellular $P_{O_2}$) transport) and that $P_{mvO_2}$ may either be the same or lower (arrows on abscissa) than found in health even in the presence of marked diffusional derangements. Mechanisms responsible for these perfusive and diffusive $O_2$ transport derangements include reduced bulk blood flow and $O_2$ delivery, impaired blood flow distribution, reduced capillarity and percentage of capillaries supporting red blood cell (RBC) flux, lowered functional capillary hematocrit (no. of RBCs adjacent to contracting myocytes in flowing capillaries), and impaired mitochondrial function. See text for additional details.
increases $\dot{Q}_{O2m}$ but not $\dot{V}O_2_{max}$ (47, 48). To maximize their beneficial effect on $\dot{V}O_2_{max}$, therapeutic interventions should effectively increase both perfusive ($\dot{Q}_{O2m}$) and diffusive ($D_{O2m}$) $O_2$ transport.

**VO$_2$ kinetics.** Healthy individuals, let alone patients with CHF, rarely exercise at VO$_2$ max, yet daily activities require myriad glycogen depletion and sow the seeds for exercise intolerance. Mechanisms responsible for slowed VO$_2$ kinetics in CHF include slowed/absent arterioles vasodilation, impaired muscle pump (venous congestion), slowed capillary hemodynamics, lowered $P_{mvO2}$, impaired mitochondrial function, and greater intracellular perturbation (as detailed in bottom). PCR, phosphocreatine; ADP$_{free}$, free adenosine diphosphate. See text for additional details.

Fig. 3. Facets of the exercise response in CHF: VO$_2$ kinetics. CHF slows VO$_2$ kinetics (increased time constant, $\tau$) in response to moderate (as shown), heavy, and severe intensity exercise, in part, by lowering muscle perfusive and diffusive $O_2$ transport such that $O_2$ delivery becomes limiting (top, see gray $O_2$ delivery-dependent zone). Note that these slowed VO$_2$ kinetics will mandate a greater $O_2$ deficit leading to greater intracellular perturbations that accelerate glycogen depletion and sow the seeds for exercise intolerance. Mechanisms responsible for slowed VO$_2$ kinetics in CHF include slowed/absent arterioles vasodilation, impaired muscle pump (venous congestion), slowed capillary hemodynamics, lowered $P_{mvO2}$, impaired mitochondrial function, and greater intracellular perturbation (as detailed in bottom). PCR, phosphocreatine; ADP$_{free}$, free adenosine diphosphate. See text for additional details.
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

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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 \( \dot{V}O_2_{\text{max}} \) 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 \( PmvO_2 \), 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 \( \dot{V}O_2_{\text{max}} \), 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 emerge strongly from compromised Qm and an inability to temporally and spatially match \( QO_2m \) to requirements (\( VO_2 \)).

**Skeletal Muscle Blood Flow, Capillary Hemodynamics, and \( PmvO_2 \)**

**Healthy.** In healthy individuals with normal arterial \( O_2 \) content (~20 ml \( O_2/100 \) ml), \( Q_{\text{TOT}} \) and Qm increase between 5 and 6 liters per liter \( VO_2 \) (Rev. 60). Following the onset of muscular exercise the \( Q_{\text{TOT}} \) 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 \( Q_{\text{TOT}} \) 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 \( VO_2 \) 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 \( PmvO_2 \) 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 \( \dot{V}O_2 \) flux (diffusional \( O_2 \) capacity, \( D_{\text{O2m}} \)) 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 \( Q_{\text{TOT}} \) (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 \( QO_2m \), 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 \( Q_{\text{TOT}} \) 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 \( VO_2_{\text{max}} \) the reduced \( Q_{\text{TOT}} \) (and any decreased arterial [\( O_2 \)]) lowers \( QO_2m \), whereas subsequent redistribution of that lowered \( Q_{\text{TOT}} \) away from the major locomotory muscles provides an additional constraint on \( QO_2m \) (122, 126, Fig. 2). Compounding these \( Q_{\text{TOT}} \) distributional problems, arterioles within the active muscles themselves have an inherently greater vasoconstrictor tone (44, 45).

At the muscle capillary level, CHF promotes capillary involution (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 \( QO_2m \) (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 \( QO_2m-\dot{V}O_2 \) ratio falls much lower driving \( PmvO_2 \), 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 VO2 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-VO2 ratio earlier or faster following cessation of muscle contractions in CHF keeps PmvO2 low, reduces intramyocyte PO2, and retards VO2 and PCr recovery kinetics (89, 90). It is pertinent that recovery VO2 kinetics can often be determined with greater fidelity and reproducibility than its counterpart at the beginning of exercise (89, 90). Thus altered off-transient VO2 kinetics, sometimes in the presence of indiscernibly different on-kineti cs, may identify O2 transport/utilization derangements in patients with CHF (147) and therefore correspond more closely with the extent of functional compromise (39, 90, 125). This effect has also been demonstrated for the dynamics of muscle PmvO2 as seen in Fig. 6, top, for severe CHF (33). Notice that the lowered PmvO2 at rest and during contractions in CHF and the PmvO2 “undershoot” present in the 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 recoveres 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 VO2 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 VO2 kinetics, it is inevitable that Tlac occurs at extremely low VO2 values in patients with CHF (69, 89, 178). Moreover, because of the increased respiratory muscle VO2 (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

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**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-VO2 mismatch). From the data of Copp et al. (33), with kind permission.

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**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 the speed of the on-transient fall (τ) may not be substantially different but that the PmvO2 is lower at rest and throughout contractions and recovery in CHF. There is also a pronounced transient dip below the subsequent steady-state value (i.e., undershoot) for the CHF muscle. It is also striking that the recovery kinetics of the CHF muscle are markedly slowed by comparison to the on response and that of the healthy control muscle. Bottom: spinotrapezius PmvO2 recovery kinetics [mean response time (MRT), time delay + τ] was progressively slowed in CHF rats with higher LVEDPs. From Copp et al. (33), with kind permission.
tasks or activities that are sub-Tlac for healthy individuals invoke a systemic lactic acidosis and will therefore incur an extra V\text{O}_2 cost associated with the V\text{O}_2 slow component in patients with CHF (86, 131, 133). With their low V\text{O}_2\text{max} (and thus modest Tlac-V\text{O}_2\text{max} range), it is doubtful whether the slow component effect would be as large as seen in healthy/fit individuals. However, in and of itself, this would be expected to accelerate exhaustion especially if it increases the gap between muscle ATP requirements and that generated by oxidative metabolism, thereby more rapidly depleting finite nonoxidative muscle energy stores (86, 131, 135).

**Mechanisms Limiting Increases of Muscle Blood Flow in CHF**

Almost every aspect of muscle blood flow (Q\text{m}) control is disturbed in CHF as seen in Fig. 7. Vasoconstriction is enhanced by sympathetic nervous system-mediated \(\alpha\)-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 repairability, in part because of low circulating endothelial progenitor cells (CPCs; 54). Nitric oxide (NO) bioavailability is compromised, which presumably constrains sympathotolysis (the ability to oppose \(\alpha\)-adrenergic vasoconstriction; 155) and shear stress-mediated vasodilation. In turn, inadequate Q\text{m} and Q\text{O}_2\text{m} will promote hypoxic vasodilation and increase vasodilatory metabolite efflux from the contracting muscle(s) (lactate, H\text{+}, adenosine, inorganic phosphate, potassium). The eventual outcome (i.e., reduced Q\text{m} and particularly PmV\text{O}_2) in CHF indicates that the net balance favors reduced vascular perfusion and impaired Q\text{O}_2\text{m}.

Within muscle and other tissues, CHF increases TNF-\(\alpha\) and IL-1\(\beta\) 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 oxidant-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 Q\text{O}_2/V\text{O}_2 Matching"), have been the subject of significant attention.

**Role of NO in Regulating Contracting Muscle Q\text{O}_2/V\text{O}_2 Matching**

NO bioavailability can exert a commanding role in the matching of Q\text{O}_2\text{m} to V\text{O}_2 in contracting rat muscle. For example, Hirai and colleagues (82) have determined in rats that NO-mediated vasodilation helps regulate the distribution of Q\text{O}_2\text{m} among active muscle fibers based on their oxidative capacity. In CHF, the capacity for \(N^\circ\)-nitro-L-arginine methyl ester blockade of NO synthase (NOS, nonspecific isoform blockade) to reduce Q\text{m}, 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 PmV\text{O}_2 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 PmV\text{O}_2 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 V\text{O}_2 (10, 11, 100) and hence restore the healthy Q\text{O}_2\text{m}-to-V\text{O}_2 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 O\text{2} flux in CHF by restor-

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

- **Neural**
  - SNS (\(\alpha\)-adrenergic, \(\beta\)-adrenergic)
  - Myogenic autoregulation
  - Muscle pump
  - Mechanical
    - Perfusion pressure
    - Post-capillary resistance
    - Vascular stiffness

- **Endothelium**
  - CPCs

- **Lumen**
  - Vascular conductance

- **Humoral**
  - Catecholamines
  - Angiotensin II - Arg. vasopressin - Endothelin-1
  - Nitric oxide
  - Metabolites + Hypoxia
    - Lactate + H\text{+} + Adenosine + Inorganic phosphate + Potassium

- **Inflammatory/Cytokine**
  - TNF-\(\alpha\) - IL-1\(\beta\) - ROS - Peroxynitrite
  - NO
  - ONOO\text{–}
  - H\text{2}O\text{2}
  - OH\text{·}
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 tetrahydrobioppterin (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, 67, 97, 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, in the presence of Fe$^{2+}$ yields 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. $V_{\text{O2 max}}$ 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 ($Q_\text{O2m}$) and requirements ($V_{\text{O2}}$). $V_{\text{O2}}$ kinetics become $Q_\text{O2m}$ 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 $V_{\text{O2}}$ values, necessitating the metabolic extravagance of the $V_{\text{O2}}$ slow component and raising the $V_{\text{O2}}$ gain (or at least energetic requirement) for tasks or activities that constitute moderate exercise ($<Tlac$, no $V_{\text{O2}}$ 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 $P_{\text{mvO2}}$ and support fast $V_{\text{O2}}$ 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 $Q_{\text{O2m}}$ to $V_{\text{O2}}$. 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 $V_{\text{O2}}$ gain) in patients with CHF as it does in healthy individuals (10, 11, 99, 100), $Q_{\text{O2m}}$-to-$V_{\text{O2}}$ 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 $Q_{\text{TOT}}$ 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. Joyner’s (87) example of a young man, Chad Carvin, who recovered from heart failure to win a silver medal in...
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.

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DISCLOSURES

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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.

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