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Exercise training in chronic heart failure: improving skeletal muscle O₂ transport and utilization

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Hirai DM, Musch TI, Poole DC. Exercise training in chronic heart failure: improving skeletal muscle O₂ transport and utilization. Am J Physiol Heart Circ Physiol 309: H1419–H1439, 2015. First published August 28, 2015; doi:10.1152/ajpheart.00469.2015.—Chronic heart failure (CHF) impairs critical structural and functional components of the O₂ transport pathway resulting in exercise intolerance and, consequently, reduced quality of life. In contrast, exercise training is capable of combating many of the CHF-induced impairments and enhancing the matching between skeletal muscle O₂ delivery and utilization (Q˙\textsubscript{mO₂} and V˙\textsubscript{mO₂} respectively). The Q˙\textsubscript{mO₂}/V˙\textsubscript{mO₂} ratio determines the microvascular O₂ partial pressure (PmvO₂), which represents the ultimate force driving blood-myocyte O₂ flux (see Fig. 1). Improvements in perfusive and diffusive O₂ conductances are essential to support faster rates of oxidative phosphorylation (reflected as faster V˙\textsubscript{mO₂} kinetics during transitions in metabolic demand) and reduce the reliance on anaerobic glycolysis and utilization of finite energy sources (thus lowering the magnitude of the O₂ deficit) in trained CHF muscle. These adaptations contribute to attenuated muscle metabolic perturbations (e.g., changes in [PCr], [Cr], [ADP], and pH) and improved physical capacity (i.e., elevated critical power and maximal V˙\textsubscript{mO₂}). Preservation of such plasticity in response to exercise training is crucial considering the dominant role of skeletal muscle dysfunction in the pathophysiology and increased morbidity/mortality of the CHF patient. This brief review focuses on the mechanistic bases for improved Q˙\textsubscript{mO₂}/V˙\textsubscript{mO₂} matching (and enhanced PmvO₂) with exercise training in CHF with both preserved and reduced ejection fraction (HFpEF and HFrEF, respectively). Specifically, O₂ convection within the skeletal muscle microcirculation, O₂ diffusion from the red blood cell to the mitochondria, and muscle metabolic control are particularly susceptible to exercise training adaptations in CHF. Alternatives to traditional whole body endurance exercise training programs such as small muscle mass and inspiratory muscle training, pharmacological treatment (e.g., sildenafil and pentoxifylline), and dietary nitrate supplementation are also presented in light of their therapeutic potential. Adaptations within the skeletal muscle O₂ transport and utilization system underlie improvements in physical capacity and quality of life in CHF and thus take center stage in the therapeutic management of these patients.

blood flow; capillary hemodynamics; microcirculation; myocardial infarction; oxygen uptake; rehabilitation

THE MOST COMMON CAUSES OF CHRONIC HEART FAILURE (CHF) are coronary heart disease consequent to vascular incompetence, hypertension, diabetes, and cardiomyopathy. Valvular disease, arrhythmias, and congenital heart defects also contribute significantly to the CHF population. Today there are nearly 6,000,000 adult Americans with CHF and its prevalence is rising (218).

Some 250 years ago the medical pioneer William Heberden discovered that regular exercise helped restore physiological function and improve morbidity and mortality in the CHF patient (322). As the principal predictor of hospital readmission and mortality in CHF is exercise intolerance, improving physical capacity constitutes a major goal of therapeutic interventions (151). CHF is a multisystem disease that is transduced
through the oxygen (O₂) transport pathway (see Fig. 2) and severely impacts skeletal muscle function (for a review, see Refs. 244, 245, 248). Exercise training elicits, by far, the most comprehensive spectrum of beneficial adaptations that ameliorate skeletal muscle O₂ delivery (Q_mO₂) and physical capacity deficits and thus improves the quality of life and longevity in CHF patients (see Fig. 2) (53, 248). Other treatment options that mimic key facets of the exercise training response, such as reduced reactive O₂ species (ROS) and elevated systemic or local muscle/vascular nitric oxide (NO) bioavailability, are emerging as adjunct therapeutic avenues.

This brief review presents contemporary evidence for how exercise training can benefit muscle contractile function in CHF by focusing specifically on how adaptations in the O₂ transport pathway act within skeletal muscle to improve O₂ uptake (V̇O₂) regulation and thus parameters of aerobic function; V̇O₂ kinetics, submaximal [critical power (CP)], and maximal (VO₂max) via increases in microvascular O₂ partial pressure (P_mvO₂; Fig. 1) and muscle O₂ diffusing capacity (D_mO₂). Key questions posed in the 2012 review (248) have been addressed; especially regarding the plasticity of Q_mO₂ in response to exercise training and novel therapeutic strategies. For instance, in contrast to healthy animals it is now apparent that exercise training in CHF (reduced ejection fraction) acts to raise P_mvO₂, in part, via non-NO-mediated effects (134, 136).

For instance, in contrast to healthy animals it is now apparent that exercise training in CHF (reduced ejection fraction) acts to raise P_mvO₂, in part, via non-NO-mediated effects (134, 136). Additionally, inorganic nitrate supplementation (NO source) has proven to be especially effective in raising blood flow (Q̇) and Q_mO₂ to fast-twitch muscle fibers in healthy animals (76, 77) and improving cardiac output, VO₂max, and exercise capacity in CHF patients (CHF with preserved ejection fraction; Ref. 336).

With respect to the diagnosis of CHF itself, it has become apparent that distinction must be made between CHF with reduced (HFrEF) vs. preserved (HFpEF) ejection fraction (82, 128). HFpEF patients constitute about half of new CHF cases, and they are older and predominantly female. For HFpEF there is compelling evidence that peripheral (i.e., skeletal muscle) impairments conspire with central dysfunction (244, 245, 248) to impair muscle O₂ transport; in HFpEF the peripheral component may be even more important (128, 268). In contrast to HFpEF there are, at present, very limited therapeutic options for HFpEF patients with a complete absence of pharmaceutical interventions that have improved patient survival (128). Therefore, strategies that target skeletal muscle specifically and improve P_mvO₂ and/or D_mO₂ may be particularly effective and valuable in this patient population.

**Exercising Blood-Muscle O₂ Flux in Health and CHF: Mechanisms of Exercise Intolerance**

From rest to maximal exercise in healthy individuals, red blood cell (RBC)-muscle mitochondrial O₂ flux increases rapidly over two orders of magnitude. As dictated by Fick’s law of diffusion (see Fig. 1), that flux (V̇O₂) will be driven by the O₂ pressure differential between the capillary [i.e., mean capillary or microvascular PO₂ (P_mvO₂)] and the intramyocyte milieu (P_intracellularO₂) operating against a finite O₂ diffusing capacity (D_mO₂) such that:

![Fig. 1](https://www.ajpheart.org/content/10.1152/ajpheart.00469.2015)

**A**: skeletal muscle fiber with adjacent capillaries and flowing red blood cells (RBCs). The O₂ partial pressure in the microcirculation (P_mvO₂) is determined by the O₂ delivery-to-O₂ utilization ratio (i.e., Q_mO₂/V̇O₂). According to Fick’s law of diffusion, at any instant, V̇O₂ will be the product of the transmembrane O₂ gradient [P_mvO₂ − intracellular PO₂ (P_intracellularO₂)] and the diffusing capacity for O₂ (D_mO₂). There is evidence that, during muscle contractions, P_intracellularO₂ is very low (i.e., <3 mmHg) such that P_mvO₂ represents closely the pressure driving transmembrane O₂ flux. V̇O₂ is thus the product of that P_mvO₂ and the presiding D_mO₂, which itself is determined primarily by the number of RBCs in flowing capillaries adjacent to the muscle fiber(s). As discussed herein chronic heart failure (CHF) reduces the proportion of RBC-flowing capillaries and also P_mvO₂. The latter effect results from lowering Q_mO₂ at a given V̇O₂. Both conspire to impair blood-myocyte O₂ flux. In contrast, exercise training and nitric oxide-based therapeutic strategies can, at least partially, reverse these effects. **B**: schematic illustration showing the O₂ transport pathway from the RBC to skeletal muscle mitochondria. Note that, in 3 dimensions, the mitochondrial reticulum is a catenated network and not a collection of discrete bean-shaped organelles and also that the physical distance that O₂ must diffuse from the capillary to myocyte to support oxidative phosphorylation is short; p, plasma; in, interstitium.
CHF reduces \( V_{O2\max} \) achievable during large muscle mass exercise and the maximal sustainable \( V_{O2} \) (i.e., CP) and slows \( V_{O2} \) kinetics following exercise onset (for a review, see Ref. 248). At a given metabolic rate or \( V_{O2} \) these slowed kinetics elevate the so-called \( O2 \) deficit and augment intracellular perturbations of high energy phosphates (i.e., \( \Delta[PCr], [ADP_{free}] \)) as well as increasing [inorganic phosphate], \([H^+]\), and the rate of glycolysis and glycogen depletion (225). Paradoxically while restricting muscle(s) \( O2 \) delivery, CHF may increase the \( O2 \) cost of muscular work consequent to elevated ventilation (respiratory muscles), cardiac filling pressures (left and right ventricles), and the \( V_{O2} \) slow component due to greater intramyocyte perturbations (vide supra) and fiber recruitment profiles within the contracting skeletal muscles (248).

It is well established that muscle contractile performance is fundamentally dependent not only on bulk \( O2 \) delivery (\( Q_{mO2} \)) but also on the conditions of that delivery (i.e., \( Q_m \) and \( \text{arterial } O2 \) content) and its temporal and spatial matching to \( V_{mO2} \), as they set \( P_{mO2} \) (10, 129, 142, 172). For instance, increased or decreased inspired \( O2 \) fractions drive commensurate changes in exercise tolerance (via increased or decreased \( P_{mO2} \)) even when these result in only modest changes in \( Q_{mO2} \), per se (e.g., refs. 169, 170). In addition to lowering \( P_{mO2} \), via a host of mechanisms most of which are opposed by exercise training (Fig. 2) (248), HFrEF compromises microcirculatory function (reduced proportion of capillaries supporting \( RBC \) flux, capillary hematocrit, and \( Q_{mO2}-to-V_{mO2} \) matching) such that \( D_{mO2} \) is far lower in diseased than healthy muscle (Fig. 3) (73, 163, 248, 257). That CHF impairs \( D_{mO2} \) was initially obscured by the observation that patients had greater percent \( O2 \) extractions, at a given \( V_{O2} \), than their healthy counterparts (154). However, conflating \( Q_{mO2} \) and \( D_{mO2} \) as first conceived by Wagner and colleagues (260) reveals that, irrespective of whether CHF decreases or increases fractional \( O2 \) extraction, both \( Q_{mO2} \) and \( D_{mO2} \) are markedly depressed (i.e., broken lines in Fig. 3; see discussion below) (248).

Although \( V_{O2\max} \) defines the maximum pulmonary-cardiovascular-muscle \( O2 \) flux achievable, we argue that the two aerobic parameters of at least equal relevance to the CHF population being able to perform daily locomotory activities and exercise rehabilitation are their \( V_{O2} \) kinetics and CP (Fig. 4, \( D \) and \( E \)). CHF invokes a perfect storm of dysregulation in the \( O2 \) transport pathway (244, 245, 248). Specifically, the cardiovascular system switches from its healthy condition, where cardiac output and \( Q_{mO2} \) increase rapidly and proportionally to exercise-induced elevations in \( V_{mO2} \), to preservation of arterial pressure at all costs. As the failing heart remodels and cannot elevate its output appropriately almost every system that impacts skeletal muscle \( Q_{mO2} \), is compromised. Paramount among these are immune/cytokine function, autonomic/sympathetic and baroreflex overexertation, elevated circulating vasoconstrictors (e.g., angiotensin II, endothelin, and catecholamines), increased ROS and reduced NO bioavailability. Within skeletal muscle, not only are vasodilatory mechanisms severely impaired but arterial compliance is decreased and elevated venous pressures reduce the efficacy of the muscle pumping mechanism (277). Thus not only does \( Q_{mO2} \) fall, but its ability to respond rapidly to muscle contractions is reduced crippling the capability to spatially match \( Q_{mO2} \)-to-\( V_{mO2} \) (65, 257). With improved technical abilities to spatially resolve \( Q_{mO2}-to-V_{mO2} \) matching in human skeletal muscle(s) [magnetic resonance spectroscopy (MRS), positron emission tomography (PET) scan, and high-power time-resolved near-infrared spectroscopy (TRS-NIRS); Refs. 129, 172, 315], the degree to which this relationship is compromised in CHF and contributes to the reduced \( D_{mO2} \), may soon be resolved.

**Skeletal muscle microcirculation.** Within skeletal muscle(s) CHF induces morphological alterations that include fiber atrophy; greater proportion of, and reliance on, type II fibers; and reduced mitochondrial volume density and capillary involution leading to a decreased capillary-to-fiber ratio (for a review, see Refs. 73, 74, 244, 245, 248). However, as depicted in Fig. 4B, the functional changes including the decreased proportion of capillaries supporting RBC flow as well as the RBC velocity, flux, and potentially hematomcit are more extreme and likely to have a greater impact on muscle \( Q_{mO2} \) and \( D_{mO2} \). Compelling support for this hypothesis comes from restoration of the healthy \( P_{mO2} \), profile during contractions, indicative of effective \( Q_{mO2}-to-V_{mO2} \) matching, by acute topical application of the NO donor sodium nitroprusside (SNP) (78, 79). In addition, blockade of nitric oxide synthase (NOS) by nitro-l-arginine methyl ester (l-NAME) reveals that the NOS contribution to \( Q_{mO2}-to-V_{mO2} \) matching in healthy muscle is substantially reduced in HFrEF. As the NOS enzymes are upregulated by exercise training (134, 136; for a review, see Ref. 188), this, in addition to reduced oxidative stress, decreased sympathetic and humorally mediated vasoconstriction, and improved vascularity (capillary and arteriolar; see Fig. 2), led to the hypothesis that augmented NO bioavailability could help explain the efficacy of exercise therapy for decreasing morbidity and mortality in CHF.

**Skeletal muscle mitochondrial control.** As \( P_{mO2} \) is determined by the instantaneous balance between \( Q_{mO2} \) and \( V_{mO2} \) and the contracting muscle resides downstream of the microcirculation, \( V_{mO2} \) can be impacted both by \( P_{mO2} \) via its effect on blood-muscle \( O2 \) flux and also by mitochondrial \( O2 \) metabolism. In this regard, it is pertinent that severe CHF is associated with a reduced oxidative enzyme capacity in muscles comprised of all fiber types (61, 226). Until the landmark study of Simonini et al. (281) in rats, it was considered that any impairment in mitochondrial/oxidative function resulted primarily from a reduced level of physical activity. Addressing this question in humans was complicated intractably by the spectrum of standard-of-care medications prescribed for CHF. It is now recognized that this mitochondrial impairment may be present independent of reduced activity levels (281) and is associated with a reduction in cyclooxygenase I and IV mRNA rather than mitochondrial DNA content (89). Intriguingly, in saponin-skinned muscle fibers from the vastus lateralis of CHF patients with \( V_{O2\max} \) averaging 13.4 ml·min\(^{-1}\)·kg\(^{-1}\) (i.e., ~50% that of sedentary controls) mitochondrial oxidative capacity or \( V_{max} \) may be preserved (90). While it is possible that contemporary therapeutic treatments, including angiotensin-converting enzyme (ACE) inhibitors, may help preserve mitochondrial function (90, 305, 340), it is likely that the predominant impact of CHF on \( O2 \) kinetics and other parameters of aerobic performance (i.e., CP and \( V_{O2\max} \)) arises from upstream within the \( O2 \) transport pathway (i.e., perfusive and diffusive \( O2 \) conductances).
Unlike CP (282, 310) and \[ \dot{\text{V}}_{\text{O}_2} \text{max} \] (170) in healthy individuals the speed of the \[ \dot{\text{V}}_{\text{O}_2} \] kinetics is not typically limited by \( \dot{\text{Q}}_{\text{mO}_2} \) but by mitochondrial energetics (for a review, see Ref. 249). However, in CHF the site of this kinetics limitation moves into the \( \dot{\text{O}}_2 \) transport pathway (Fig. 4). Note the extremely low \( P_{\text{mvO}_2} \) values present during muscle contractions in CHF muscle (Fig. 4C) (247). This CHF-induced muscle hypoxemia is compounded by the decreased \( D_{\text{mvO}_2} \) and becomes crucially important because 1) by reducing blood-muscle \( \dot{\text{O}}_2 \) flux the speed of the \( \dot{\text{V}}_{\text{O}_2} \) kinetics becomes constrained at that time when mitochondrial energetics need to increase most rapidly. 2) This elevates the \( \dot{\text{O}}_2 \) deficit resulting in greater intracellular perturbations of metabolic controllers and precipitates enhanced glycolysis and exercise intolerance (for a review, see Ref. 264; see also Ref. 101). 3) In addition to lowering blood-muscle \( \dot{\text{O}}_2 \) flux, the reduced \( P_{\text{mvO}_2} \) itself will...
Muscle fiber atrophy and shifts in fiber type composition. Intrinsic skeletal muscle abnormalities are prominent features of CHF and are associated with an imbalance between protein synthesis and degradation, mediated mainly by reductions in the expression of insulin-like growth factor-1 (IGF-1; Refs. 117, 231) and overactivation of the ubiquitin-proteasome system (UPS; Ref. 17) resulting in skeletal muscle atrophy (HFrEF and HFP EF; Refs. 43, 45, 275, 333). Importantly, exercise training has been shown to increase IGF-1 expression (116) and decrease UPS activation (60) and it is, therefore, potentially capable of reversing the muscle atrophy found in the HFrEF state (33, 308). HFP EF patients may also benefit from such training-induced adaptations to offset reduced leg lean mass (123) and increased intramuscular adipose content (127).

CHF also produces a shift in fiber type distribution from predominantly slow-twitch oxidative to fast-twitch glycolytic fibers in both HFrEF and HFP EF individuals (68, 168, 197, 201, 272, 273, 297, 314, cf. 43). However, these shifts are not obligatory in the HFrEF condition (47, 61, 324) and certainly cannot be attributed entirely to muscle disuse (281). ACE inhibitors have been shown to attenuate CHF-induced changes in fiber type redistribution (266, 313). Although not a universal finding (33, 108, 118, 159, 160), exercise training produces changes in muscle fiber type/myosin heavy chain composition that oppose those of CHF (i.e., from predominantly fast-twitch fibers to slow-twitch fibers after training; Refs. 112, 159, 309). These phenotypic alterations in the skeletal muscle appear to be mediated largely via peroxisome proliferator-activated receptor γ coactivator (PGC-1α) overexpression (176, 191, 335). Whether HFP EF patients can benefit similarly from training programs as those found with HFrEF remains to be determined.

Muscle blood flow ($Q_m$). As discussed previously and reviewed by Poole et al. (248), CHF induces multiple cardiovascular structural and functional alterations that culminate in blunted speed and magnitude for the microvascular hemodynamic response during transitions in metabolic demand (Fig. 4; Refs. 257, 334). Nevertheless, it is important to acknowledge that HFrEF has not produced consistent alterations in bulk (i.e., total, limb) $Q_m$ during dynamic submaximal exercise, with investigations reporting decreased (23, 66, 137, 153, 228, 299) or unaltered (15, 198, 226, 274, 278) bulk $Q_m$ responses in both human and animal models. The reasons for this discrepancy are not entirely clear but may involve differences in disease severity, variations in pharmacological treatment, distinct exercise modes/intensities, and $Q_m$ redistribution within and among muscles and/or muscle groups imposed by HFrEF (i.e., $\downarrow Q_m$ to slow-twitch oxidative and $\uparrow Q_m$ to fast-twitch glycolytic fibers) (137, 203, 228). In addition, the possibility exists that redundant and/or compensatory mechanisms associated with the regulation of skeletal muscle O$_2$ delivery (130, 149) could be contributing to prevent or minimize the reductions in submaximal $Q_m$ found in HFrEF under some, but not all, circumstances (e.g., via $\uparrow$ participation of endothelium-derived hypopolarizing factors and vasodilator prostaglandins; Refs. 152, 185, 199).

To date partitioning of the intramuscular deficits related to $Q_{mO_2}$ to $V_{mO_2}$ in HFP EF patients has not been undertaken. Thus conclusions regarding the impact of this condition on $Q_{mO_2}$ and $D_{mO_2}$ are speculative, at best. Evidence supports that

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**Fig. 3.** Facets of the exercise response in chronic heart failure (CHF). Schematic illustrating the manner in which the perfusive [curved lines, Fick principle; $V_mO_2 = Q_m \times$ (arterial-venous O$_2$ content)] and diffusive O$_2$ [straight lines from origin, Fick’s law; $V_mO_2 = D_{mO_2} \times (P_{mvO_2} - P_{intracellularO_2})$] conductances conflate to yield the $V_mO_2$max during large muscle mass exercise (e.g., cycling). Note that in CHF (dashed lines), $V_mO_2$max is reduced by both impaired perfusive and diffusive O$_2$ transport and that $P_{mvO_2}$ may either be the same or lower than found in health (solid lines) even in the presence of marked diffusional derangements. Therapeutic strategies that improve both O$_2$ transport components will thus be most effective in raising $V_mO_2$max and exercise capacity.
VO₂ kinetics become O₂ degrading blood-myocyte O₂ flux, slowing exercise peak arterial-venous O₂ differences are reduced in HFrEF (37, 63, 122, 167, cf. 1) and it has been suggested that these reductions are related to impairments in skeletal muscle oxidative metabolism (37) and/or defects in microvascular (both convective and diffusive; Ref. 63) O₂ transport. Accordingly, O₂ extraction problems may be greater in the HFpEF condition (128, 268). Improvements in peak exercise arterial-venous O₂ difference seen following exercise training in HFpEF are thought to result primarily from peripheral muscle adaptations given the concomitant lack of changes in systemic O₂ delivery (i.e., +stroke volume and cardiac output; Ref. 124; see also Ref. 213). Nonetheless, resolution of the mechanistic bases for the impact of HFpEF on muscle O₂ transport must await formal measurements of QmO₂ and DmO₂ during exercise.

Exercise training appears to have no substantial impact on submaximal exercise bulk Qm and thus conduit artery O₂ delivery in HFrEF individuals (217, 226, 227, 236, 298, cf. 265). To our knowledge, this has not been examined in the HFrEF state. Whether or not bulk Qm during submaximal exercise is altered in CHF (or exercise training) is not de facto evidence that vascular adaptations are not occurring (188, 203). Accordingly, in healthy (13) and HFrEF (227) rats bulk Qm during submaximal exercise remains unaltered following en-
durance training but a substantial redistribution of that flow occurs within the limb musculature resulting in increases in $\dot{Q}_m$ to predominantly slow-twitch oxidative muscle and decreases to their fast-twitch glycolytic counterparts (227; see also Ref. 31). This training-induced redistribution of flow has been attributed, in part, to adaptations in microvascular $\dot{Q}_m$ regulation that improve capillary RBC hemodynamics (see discussion below) leading to improvements in skeletal muscle $\dot{Q}_{mO_2}$ to-$V_{mO_2}$ matching during transitions in metabolic demand (e.g., ↓ spatial heterogeneities; Refs. 129, 171, 172).

Exercise training reduces muscle sympathetic activity and humoral-mediated vasoconstriction in HFrEF as assessed indirectly via norepinephrine levels and heart rate variability or arterial stiffness (84, 165). It is thus possible that microvascular adaptations in $\dot{Q}_m$ transport and/or utilization (37, 43) in patients with HFrEF constitute the main mechanisms driving changes in exercise capacity with training (126). In fact, it has been hypothesized that training-induced increases in $\dot{V}_{O_2\text{max}}$ and exercise capacity in HFrEF are driven primarily by improvements in $D_{mO_2}$, rather than $\dot{Q}_{mO_2}$ (see Fig. 3 in Ref. 63).

To date, the effects of exercise training on peripheral vascular adaptations in HFrEF have received little attention. Contrary to HFrEF, increases in $\dot{V}_{O_2\text{max}}$ with exercise training in HFrEF have not been associated with improvements in conduit vessel endothelial function (i.e., brachial artery FMD) or arterial stiffness (84, 165). It is thus possible that microvascular adaptations in $\dot{Q}_m$ transport and/or utilization (37, 43) in patients with HFrEF constitute the main mechanisms driving changes in exercise capacity with training (126). In fact, it has been hypothesized that training-induced increases in $\dot{V}_{O_2\text{max}}$ and exercise capacity in HFrEF are driven primarily by improvements in $D_{mO_2}$, rather than $\dot{Q}_{mO_2}$ (see Fig. 3 in Ref. 63).

Muscle oxidative metabolism. As mentioned above, the literature is equivocal regarding the effects of CHF on skeletal muscle oxidative metabolism. For instance, some studies report that HFrEF induces significant structural/functional mitochondrial impairments and/or reductions in oxidative enzyme capacity (68, 156, 197, 281, 297) that vary as function of disease severity (14, 61, 65), whereas others do not (90, 154, 210, 274, 305, 319, 340). Recently, impaired skeletal muscle oxidative metabolism has also been reported in HFrEF patients (37) and animal models (43, 333). Noteworthy, at least part of these discrepancies could relate to the various effects on skeletal muscle oxidative function by different pharmacological treatments. While ACE inhibitors might exert a protective effect (90, 305, 340), statins have been reported to impair mitochondrial function (88, 238, 331; see also Ref. 216). Accordingly, any conclusions regarding the effects of CHF on muscle oxidative metabolism...
oxidative metabolism derangements and therefore their potential amelioration with training must be made with caution.

Notwithstanding the above, a substantial body of evidence supports that exercise training is able to increase oxidative capacity in CHF muscle (both HFrEF and HfPEF; Refs. 2, 33, 43, 61, 72, 74, 97, 112, 115, 136, 156, 226, 267, 307, 309) reflecting that the key signaling pathways for mitochondrial biogenesis and function, such as PGC-1α and calcineurin activation, are preserved in the skeletal muscle of CHF patients (90). Nonetheless, there are reports to the contrary (90, 160, 274, 289, 305, 319, 340). It is noteworthy that human studies have found training-induced improvements in the oxidative metabolism of contracting muscle (via \[^{31}P\text{-MRS}\]) in the setting of unchanged bulk \(Q_m\) (217, 236, 298), which may mechanistically reflect improved muscle \(Q_{mO_2}\)-to-\(V_{mO_2}\) matching (i.e., elevated \(P_{mO_2}\)) (136) and enhanced \(D_{mO_2}\), rather than improved mitochondrial function per se. As discussed previously, HFrEF and exercise training induce a profound redistribution of \(Q_m\) among and within the limb musculature even in the face of unchanged bulk \(Q_m\) (137, 203, 228). These adaptations reflect considerable heterogeneities in vasomotor control along and across discrete vascular branches related to muscle fiber type, oxidative capacity, and arteriolar branch order (182, 186–188, 202, 262, 302, 306, 311, 332) that may be susceptible to changes with age, disease, and training (13, 26, 29, 31, 137, 220, 224, 228, 276, 284, 292, 303). Heterogeneities in vasomotor control are expected to contribute to the temporal dissociation between conduit artery and microvascular \(Q_m\) responses to submaximal exercise (120) and thus complicate extrapolation of data along the vascular tree. Thus, while the potential relevance of mitochondrial and/or oxidative enzyme adaptations with training should not be discounted entirely, microvascular determinants of \(O_2\) transport upstream of the mitochondria are likely to play a major role in improved muscle function with exercise training in CHF.

Intracellular \(O_2\) transport. Contrary to the pioneering model proposed by August Krogh (177, 178), compelling contemporary experimental and theoretical evidence has shown that intramyocyte \(O_2\) diffusion distances do not limit mitochondrial \(O_2\) delivery in healthy muscles (therefore negating the notion of intracellular anoxic loci; Refs. 131, 246, 247). Thus, given that the major resistance to skeletal muscle \(O_2\) diffusion from the RBC to the mitochondria resides at the capillary-myocyte interface (i.e., the so-called “carrier-free region”) and the very low and uniform intramyocyte \(P_o2\) values (92, 103, 256), it may be tempting to speculate that potential alterations in fiber cross-sectional area and/or mitochondrial distribution might not impact \(D_{mO_2}\) significantly in diseased or exercise-trained states. While exercise training does not increase healthy human skeletal muscle myoglobin concentration (thus precluding possible increases in myoglobin-facilitated diffusion; Ref. 300), higher mitochondrial volume density with training could enhance intracellular \(O_2\) transport directly (i.e., \(\downarrow\) flux-density due to \(\uparrow\) surface area of, and \(O_2\) consumption by, mitochondria) and reduce the so-called “functionally carrier-depleted region” (140). Therefore, albeit relatively small, the potential for improved intramyocyte \(O_2\) diffusion in CHF following exercise training exists but its relevance to \(O_2\) transport capacity, if any, awaits elucidation.

Structural determinants of extracellular \(O_2\) transport. The fact that the bulk of resistance to skeletal muscle \(O_2\) flux is located at the capillary-myocyte interface suggests that many aspects of capillary anatomy including density, capillary-to-fiber ratio, tortuosity, branching, and capillary length represent major structural determinants of \(D_{mO_2}\). Thus far, it has been found that capillarity is either reduced (68, 69, 83, 156, 197, 272, 273, 297, 319, 334) or maintained in HFrEF (73, 74, 194, 201, 274, 297, 334) and may be secondary to concomitant muscle fiber atrophy (e.g., Ref. 201). Animal models of HFrEF have revealed reductions in capillary length, volume, and surface area (see Fig. 4B) (334) whereas capillary geometry and diameter remain unchanged (162). Similar to HFrEF, decreases in capillary-to-fiber ratio might also occur in HfPEF patients (168) and animal models (333). Altogether, these data suggest that derangements in structural determinants of muscle \(D_{mO_2}\) may be characteristic of CHF (59, 65).

While some investigators have shown that exercise training increases skeletal muscle capillary density (72) and capillary-to-fiber ratio (19, 74, 270) in HFrEF (these adaptations are likely facilitated by preserved vascular endothelial growth factor signaling; Refs. 73, 74, 108), others have not (33, 159, 160). Despite these differences, experimental evidence has shown that \(D_{mO_2}\) is not affected by alterations in capillary density (131) and that training-induced increases \(J\) in capillary length result from increases in capillary-to-fiber ratio and not increases in capillary tortuosity (251); and 2) in capillary-to-fiber surface area ratios are closely aligned with the oxidative capacity of the muscle as indicated by mitochondrial volume density (250). Potentially, training-induced increases in capillarity in CHF could enhance the surface area available for oxygen and substrate exchange between microvascular blood and myocyte. These structural adaptations would only play an important role in improving \(O_2\) transport, however, if the newly formed capillaries supported robust RBC flux (vide supra).

Functional determinants of extracellular \(O_2\) transport. The effective capillary surface area (i.e., that available for \(O_2\) diffusion at any given time) is determined by capillary hemodynamics (RBC velocity and flux: \(V_{RBC}\) and \(f_{RBC}\), respectively) and RBC distribution [functional capillary density, capillary hematocrit (\(Hct_{cap}\)) and RBC spacing] (246, 247). Consequently, complex interactions between structural and functional variables determine the number of RBCs along the capillary-fiber interface at any given time which promotes blood-muscle \(O_2\) flux (75, 103). In CHF, however, the fact that relatively greater functional as distinct from structural microvascular abnormalities occur in skeletal muscle (as illustrated in Fig. 4B) suggests that impairments in capillary hemodynamics and RBC distribution play a larger role in compromising transcapillary \(O_2\) flux (162, 257, 334). It is thus reasonable to anticipate that, in CHF muscles, functional (rather than structural) \(O_2\) transport properties might be more sensitive to, and important for, transducing the effects of exercise training.

HFrEF reduces significantly the proportion of capillaries supporting continuous RBC flow (healthy: 84% vs. HFrEF: 66%) and reduces \(f_{RBC}\) (\(\downarrow\) 32%) and \(V_{RBC}\) (\(\downarrow\) 34%) at rest (162). During the rest-contraction transient in HFrEF muscle, there is no increase in the percentage of RBC flowing capillaries (i.e., no “capillary recruitment”; see also Refs. 246, 247 for discussion) and the speed of increase in capillary \(f_{RBC}\) and \(V_{RBC}\) is markedly slowed. In the capillaries that do support RBC flux during contractions in HFrEF, the increases in both
f_{RBC} (↓45%) and V_{RBC} (↓48%) are blunted (257). Remarkably, that no substantial impairments in Hct_{cap} were detected across the rest-contraction transient in HFrEF indicates that effective capillary surface area at any given time was lowered in approximate proportion to the reduction in capillaries sustaining RBC flow. Taken together, these investigations demonstrate that HFrEF is associated with pronounced impairments in skeletal muscle transcapillary O₂ flux via reductions in both diffusive (i.e., D_{mO₂}; ↓ number of RBC flowing capillaries per unit muscle width x + Hct_{cap}) and convective (i.e., Q_{mO₂}; ↓ number of RBC flowing capillaries per unit muscle width x f_{RBC}) conductances (162, 257). Data from human muscle corroborate the presence of significant diffusive and convective limitations to O₂ transport in HFrEF during both small and large muscle mass exercise (i.e., knee-extension and cycling exercise, respectively; Ref. 73).

CHF markedly impacts O₂ extraction, which is determined by the interdependent relationship between the diffusive and convective O₂ transport components (260):

$$\% O_2 \text{ extraction} = 1 - e^{-D_{mO_2}/\beta Q_m} = \frac{V_{mO_2}}{Q_{mO_2}} = P_{mvO_2}$$

where $\beta$ corresponds to the slope of the O₂ dissociation curve in the physiologically relevant range. As alluded to earlier, $D_{mO_2}$ represents a lumped parameter that includes the impediments to O₂ diffusion from RBC to the mitochondria and is determined by a complex interaction between structural and functional variables. Reductions in the proportion of RBC-flowing capillaries represent the major impairment to $D_{mO_2}$ in HFrEF (75, 103, 162, 248, 257). Considering that $\beta$ is unlikely to be affected greatly by CHF and/or exercise training, it follows that alterations in $\% O_2$ extraction and thus $P_{mvO_2}$ will depend primarily on the $D_{mO_2}/Q_m$ ratio (260). This relationship is important because it demonstrates the interdependence of $P_{mvO_2}$ on the relationship between $D_{mO_2}$ and $Q_m$ and illustrates their relative contributions to fractional O₂ extraction in diseased and trained states.

**Muscle microvascular $P_{O_2}$.** As dictated by Fick’s law of diffusion, the O₂ pressure within the skeletal muscle microvasculature (i.e., $P_{mvO_2}$) constitutes the exclusive driving force for O₂ flux into the myocyte. Temporal and spatial derangements in $P_{mvO_2}$ during transitions in metabolic demand in HFrEF muscle (30, 58, 59, 65, 78, 136, 206) are thus associated with impairments in mitochondrial energetics and contractile performance (138, 164, 294, 323).

As discussed above, the rapid and biphasic pattern in the capillary $f_{RBC}$ profile found in healthy skeletal muscle following the onset of contractions is severely disrupted in HFrEF. Thus the near-instantaneous rise in $f_{RBC}$ within the first muscle contraction cycle is essentially nonexistent in HFrEF and the subsequent robust increase in $f_{RBC}$ towards the steady state seen in healthy muscle is also crippled (257). These CHF-induced impediments are thought to result from impaired muscle pump/rapid vasodilation and metabolic/conducted vasodilation, respectively (for a review, see Ref. 248). The resultant mismatch between $Q_{mO_2}$ (i.e., mainly impaired $f_{RBC}$) and $V_{mO_2}$ during both the onset of and recovery from contractions necessitates greater fractional O₂ extraction to sustain a given metabolic rate and may, therefore, reduce $P_{mvO_2}$ even in the face of marked impairments in $Q_{mO_2}$ (59, 65) as $Q_m$ falls proportionally more than $D_{mO_2}$ (see, e.g., Fig. 4C). This behavior is also seen in the increased hemoglobin + myoglobin deoxygenation profile (i.e., ↑ deoxy-[Hb + Mb]) of HFrEF patients using near-infrared spectroscopy (NIRS) during submaximal exercise (213, 290).

As illustrated in Fig. 4 and noted above, CHF-induced functional (rather than structural) impairments in skeletal muscle capillary hemodynamics play a major role in the ensuing $Q_{mO_2}$-to-$V_{mO_2}$ mismatch and lowered $P_{mvO_2}$ across transitions in metabolic demand. Notwithstanding the complex of interrelated factors regulating muscle vascular and metabolic function, alterations in NO bioavailability appear to be key to the aberrant HFrEF response and also participate in the training-induced adaptations in $P_{mvO_2}$ (136, 248). Accordingly, acute pharmacological manipulation of NO-mediated function can simulate the microvascular oxygenation profiles associated with HFrEF. In healthy skeletal muscle, decreased NO bioavailability (i.e., NOS inhibition with L-NAME) lowers $P_{mvO_2}$ and speeds its kinetics. Conversely, increased NO bioavailability (i.e., via the NO donor SNP) elevates $P_{mvO_2}$ and slows its kinetics during metabolic transitions (79, 135). In HFrEF muscle, L-NAME has a reduced effect on $P_{mvO_2}$ kinetics while SNP improved $P_{mvO_2}$ profiles towards those found in healthy muscle (78), consistent with substantial NOS-mediated endothelial dysfunction being intrinsic to the CHF condition (e.g., refs. 64, 67, 181). Importantly, acute improvement in NO signaling (i.e., phosphodiesterase-5 inhibition with sildenafil) in HFrEF patients enhances muscle microvascular oxygenation (i.e., ↓NIRS-derived deoxy-[Hb + Mb] signal) and speeds $V_{O_2}$ kinetics (i.e., ↓ time constant) during both the onset and offset of contractions and increases exercise tolerance (see Fig. 7) (291). These data support the hypothesis that improvements in NO-mediated function with exercise training (111, 193, 312) may underlie improvements in $P_{mvO_2}$ and exercise capacity in CHF.

Endurance exercise training has been demonstrated to improve skeletal muscle $Q_{mO_2}$-to-$V_{mO_2}$ matching in healthy humans (i.e., ↓deoxy-[Hb + Mb]/Δ$V_{O_2}$) (207, 221, 222, cf. 21, 179) and animal models (i.e., slowed $P_{mvO_2}$ kinetics) (134, cf. 205) during submaximal exercise. Central to these adaptations is the substantial improvement in both $D_{mO_2}$ and $Q_m$ after exercise training (27, 42, 204, 260, 279). Importantly, skeletal muscle plasticity is preserved in CHF and thus similar improvements in $D_{mO_2}$ and $Q_m$ have been reported in HFrEF patients (74). In the rat model of HFrEF [via myocardial infarction (MI) induced by left coronary artery ligation], exercise training elevates $P_{mvO_2}$ following the onset of submaximal contractions (i.e., slowed $P_{mvO_2}$ kinetics; Fig. 6) (136). This response is indicative of a reduced $D_{mO_2}/Q_{mO_2}$ ratio after training (i.e., ↑$D_{mO_2}$/↑$Q_{mO_2}$; lowered $\% O_2$ extraction) and thus suggests that adaptations in perfusive (i.e., mainly faster $f_{RBC}$ kinetics as detailed above) rather than diffusive O₂ transport are of relatively greater importance for elevating the $Q_{mO_2}$-to-$V_{mO_2}$ ratio in trained HFrEF muscle. Intriguingly, and in marked contrast to healthy skeletal muscle, reductions in NO bioavailability with L-NAME had no effect on the overall dynamic $P_{mvO_2}$ profile in trained HFrEF (136). Therefore, although exercise training constitutes an effective nonpharmacological treatment to improve the $Q_{mO_2}$-to-$V_{mO_2}$ ratio in health and disease, different mechanisms appear to be associated with these microvascular adaptations. In HFrEF, enhanced NO-
mediated function may not be obligatory to slowing the fall of 
P_{\text{mvO}_2}\) and thus increasing the driving pressure for transcapillary O2 flux following the onset of contractions. Whether these findings can be extrapolated to HFpEF muscle remains to be determined.

**Muscle \(\dot{V}_{O_2}\) (\(\dot{V}_{mvO_2}\)).** The impact of impaired \(\bar{Q}_{mO_2}\) and \(D_{mO_2}\) on \(V_{mvO_2}\) in CHF is represented graphically in Fig. 3 (i.e., “Wagner diagram”; Refs. 248, 260, 316), which demonstrates mechanistically how perfusive [i.e., curved lines, Fick principle; \(\dot{V}_{O_2} = (\bar{Q}_m) \times \text{arterial-venous O}_2 \text{ content (Ca-vO}_2)\)] and diffusive [i.e., straight lines, Fick’s law; \(\dot{V}_{O_2} = D_{mO_2} \times (P_{\text{mvO}_2} - P_{\text{intracellularO}_2})\)] O2 transport conflate to yield muscle \(\dot{V}_{O_2}\) during contractions. As demonstrated in Fig. 3, \(\dot{V}_{O_2}\) in CHF muscle can be reduced due to impairments in both perfusive and diffusive O2 conductances (i.e., broken lines), and \(P_{\text{mvO}_2}\) may be either the same (i.e., \(D_{mO_2}/\bar{Q}_m\) ratio) or lower (i.e., \(D_{mO_2}/\bar{Q}_m\) ratio) than that found in healthy muscle despite the presence of substantial derangements.

\(\dot{V}_{mvO_2}\) kinetics in healthy young muscle are, in most instances, not limited by \(\bar{Q}_{mO_2}\), but rather by intrinsic mitochondrial dynamics (22, 28, 98, 100, 196, 234, 320). In contrast, \(\dot{V}_{mvO_2}\) kinetics control in CHF muscle shifts upstream from the mitochondria (i.e., O2 utilization) to \(\bar{Q}_{mO_2}\) (i.e., O2 delivery-dependent zone in Fig. 4D). This impedance to both \(\bar{Q}_{mO_2}\) and \(D_{mO_2}\) modulates oxidative metabolism and slows \(\dot{V}_{O_2}\) kinetics (247, 248, 264). In healthy skeletal muscle, faster \(\dot{V}_{O_2}\) kinetics after endurance exercise training results primarily from improved oxidative capacity and/or allosteric regulation of mitochondrial respiration (i.e., \(\uparrow \) “parallel activation”; Refs. 18, 35, 36, 86, 133, 207, 221, 222, 242, 338, 339) (see also Figs. 6 and 7). On the other hand, in HFpEF patients, slowed \(\dot{V}_{O_2}\) kinetics occur as a function of disease severity (i.e., %left ventricular ejection fraction; Fig. 4E) (34, 132, 173, 174, 208, 259, 271, 280, 288; see also Ref. 264) and training-induced improvements in muscle O2 delivery (perfusive and diffusive; Refs. 74, 136) are requisite for eliciting faster \(\dot{V}_{O_2}\) kinetics (158, 213, 261). Importantly, at a given \(\bar{Q}_{mO_2}\), faster \(\dot{V}_{mvO_2}\) kinetics with training attenuates the O2 deficit and thus the level of metabolic perturbations (e.g., \(\Delta[PCr], [Cr], \text{and [ADP]}\)) necessary to drive oxidative metabolism (2, 156, 217, 236, 295, 298).

![Fig. 6. Top: spinotrapezius muscle microvascular PO2 (PmvO2) profiles during electrical stimulation (initiated at time zero) in sedentary (i.e., pretraining) and endurance exercise-trained CHF rats with reduced ejection fraction (HFpEF). Notice the overall slowing of the PmvO2 fall that results in a far greater PmvO2 (see posttraining ↑ PmvO2 in middle) across the transition. Adapted from Hirai et al. (136). Bottom: as this effect occurs across that crucial interval when \(\dot{V}_{mvO_2}\) is increasing most rapidly it is hypothesized that this helps facilitate the faster \(\dot{V}_{mvO_2}\) kinetics after exercise training in healthy (134) and HFpEF (136) rats.](http://ajpheart.physiology.org/)

![Fig. 7. In HFpEF patients a single dose of sildenafil (50 mg) reduces quadriceps muscle deoxygenation (synonymous with elevated PmvO2; top) and speeds \(\dot{V}_{O_2}\) kinetics (bottom) following the onset of exercise (time 0). These effects correlated significantly with a 22% increase in severe-intensity exercise tolerance (adapted from Ref. 291). \(\tau\), time constant.](http://ajpheart.physiology.org/)
Overall, these adaptations reduce the rate of glycolysis and reliance on finite energy sources associated with exercise intolerance in CHF (139, 248, 264, 304; see also Ref. 101). Reductions in CP (212) and the lactate/gas exchange threshold (96, 157, 337) are characteristic of CHF and result in an additional VO2 cost (i.e., slow component) that occurs at lower relative metabolic rates compared with their healthy counterparts. The VO2 slow component is manifested beyond the faster primary (phase II) kinetics and either delays or prevents the attainment of a steady state (i.e., when exercising in the heavy or severe intensity domains, respectively; for a review, see Refs. 147, 249). Importantly, the metabolic burdens imposed by QmO2-to-VmO2 mismatch within the active muscles of CHF patients (i.e., \(\frac{\Delta}{\Delta}O_2\) delivery as discussed above and \(\uparrow O_2\) requirement induced by the slow component) are further compounded by increased respiratory muscle work that produces a significant redistribution of cardiac output (i.e., \(\downarrow\) locomotor and \(\uparrow\) respiratory muscle \(Q_m\)) (38, 119, 200, 223, 235, 237). Conversely, exercise training increases the absolute VO2 value at which the lactate/gas exchange threshold occurs in both HFrEF and HFpEF patients (70, 105, 115, 158, 166, 211) and has the potential to reduce or even abolish the VO2 slow component for a given work rate (36, 49, 50, 269, 329; see also Ref. 148).

In summary, microvascular O2 transport adaptations to exercise training play a central role in modulating \(P_{mvO2}\) and also \(D_mO2\) which underpin improvements in sentinel parameters of peripheral O2 transport and utilization abnormalities characteristic of advanced CHF despite successful surgical interventions. The VO2 slow component is manifested beyond the faster phase II time constant and \(\downarrow\) slow component amplitude, lactate/gas exchange threshold, CP, and VO2max. Accordingly, exercise training constitutes a powerful nonpharmacological treatment option for improving exercise capacity and quality of life in both HFrEF (33, 55, 56, 62, 74, 105, 113, 115, 158, 211, 298, 307) and HFpEF patients (70, 91, 124, 165, 166, cf. 84, 287).

Potential Alternatives to Whole Body Endurance Exercise Training

As we have seen, exercise training in CHF induces an impressive range of adaptations across multiple systems that serve to improve the functioning of the O2 transport system, exercise capacity, and life quality whilst reducing morbidity and mortality (Fig. 2). Unfortunately, patient compliance problems and the inability to deliver regular exercise rehabilitation opportunities to the CHF population make this treatment modality less effective than expected (82). Moreover, even optimally treated HFrEF patients (i.e., diuretics, digitalis, carvedilol, ACE inhibitors/AR blockers) lack the ability to effectively match \(Q_{mO2}\)-to-\(V_{mO2}\) during exercise and thus sustain decrements in muscle oxygenation, slowed VO2 kinetics, lowered VO2max, and impaired exercise tolerance (390). Heart transplant recipients also persistently display many of the peripheral O2 transport and utilization abnormalities characteristic of advanced CHF despite successful surgical interventions (for a review, see Ref. 321). These include progressive declines in skeletal muscle vascular function with time (328, cf. 180), abnormal exercising muscle metabolic responses (296), increased submaximal %O2 extraction, slowed VO2 kinetics, and reduced VO2max and exercise capacity (41, 99, 146, 150, 184, 209, 240). Given these considerations, CHF patients may benefit from alternative approaches either as a primary treatment modality or in conjunction with more traditional programs such as whole body endurance exercise training. Accordingly, alternative approaches to improving microvascular oxygenation (\(P_{mvO2}\)) and \(D_mO2\) in CHF are examined below.

Nonpharmacological. DISTINCT EXERCISE TRAINING REGIMENS.

Few studies have examined the impact of different training strategies on muscle \(P_{mvO2}\) or perfusive and diffusive conductances in CHF patients. In terms of VO2max, Smart (286; see also Refs. 244, 245) ranks the efficacy of different training paradigms as high-intensity interval exercise (\(\uparrow 45\%\)), moderate-intensity exercise (\(\uparrow 12–31\%\)); functional electrical stimulation (\(\uparrow 15\%\)); inspiratory muscle training (\(\uparrow 11\%\)); and resistance training (7\%). Unfortunately, recently established methods to ensure validity of the measured VO2max (252) were not employed and it cannot be ascertained whether VO2max was measured accurately in the majority of the studies (286). Notwithstanding this concern, reported improvements in VO2max and exercise performance after high-intensity interval training are impressive and are likely to reflect substantial increases in exercising muscle(s) \(Q_{mO2}\), and \(D_mO2\) (286, 327). That said, many CHF patients are unwilling or unable to cope with the high-intensity interval training on a regular basis, and consequently, alternative exercise strategies, possibly in combination with pharmacological and/or nutritional ergogenic aids (see below: pentoxifylline, sildenafil, and beetroot juice) may be of further benefit.

1) Knee-extension: exercise modalities employing a relatively small muscle mass may avoid the low cardiac output ceiling established by CHF and be better tolerated by the patient than so-called whole body exercise paradigms such as cycling or walking/running. Esposito and colleagues (74) demonstrated that knee extension training (recruiting \(\sim 2–3\) kg quadriceps muscle) increased muscle capillarity, mitochondrial volume density, and peak VO2 (cycling and knee extension) in the absence of training-induced changes in leg \(Q_m\). Quadriceps \(Q_{mO2}\) and \(D_mO2\) increased 40–50% for both cycling and knee extension exercise in addition to improvements in exercise tolerance; despite that training only involved the knee extensors directly.

2) Inspiratory muscle training: since the respiratory muscles compete dominantly with their locomotory counterparts for the available cardiac output (119), CHF-induced increases in diaphragmatic \(Q_m\) are associated with reductions in \(Q_m\) to the exercising locomotory muscle(s) thereby compromising exercise tolerance (38, 200, 223, 235, 237). In addition, CHF is often associated with inspiratory muscle weakness (8) and, therefore, respiratory muscle training could be effective in reducing or reversing the maldistribution of cardiac output (and \(Q_{mO2}\)-to-\(V_{mO2}\) mismatch in the contracting muscle) found in the CHF condition. Chiappa and colleagues (52; for a review, see Refs. 48, 255) reported that inspiratory muscle training in HFpEF patients with inspiratory muscle weakness produced diaphragmatic hypertrophy and benefitted forearm \(Q_m\) during exercise. Although there is evidence that respiratory muscle training alone may increase VO2max (for a review, see Ref. 286), this strategy may yield more robust results in combination with exercise training (326). However, the fact that only \(\sim 30\%\) of HFpEF patients have inspiratory muscle weakness limits the application of these findings as does the inability of subsequent studies to confirm these results (for a review, see...
Ref. 81). Finally, reductions of the hyperventilation response to exercise by β-blocking agents such as carvedilol (nonselective β + α₁-blocker) may act to decrease peripheral chemoreflex sensitivity and reduce the inspiratory muscle metaboreflex thereby allowing more cardiac output to perfuse active locomotor muscles (for a review, see Ref. 244).

**Pharmacological.** Given that HFrEF-related reductions in NO bioavailability lower \( P_{mvO₂} \) and that acute NO supplementation increases \( P_{mvO₂} \) (78, 79), treatments that reduce systemic inflammatory mediators and ROS may also increase NO bioavailability. This strategy may be particularly effective in CHF patients because their \( V_{O₂} \) kinetics lie on the \( Q_{mO₂} \)-dependent arm of the relationship depicted in Fig. 4D and the speeding of their \( V_{O₂} \) kinetics, in turn, leads to improved exercise tolerance (Fig. 4E).

**Pentoxifylline.** Pentoxifylline (PTX) is a phosphodiesterase (PDE) inhibitor that improves left ventricular ejection fraction. New York Heart Association (NYHA) functional classification and exercise capacity due, in part, to decreases in plasma [TNF-α] (283, 285). In HFrEF rats, PTX administration beginning immediately following MI also reduces [TNF-α] and left ventricular end-diastolic pressure (107). In addition, PTX administration lowers circulating levels of nor-epinephrine and epinephrine, sympathetic hyperstimulation (106) and increases exercising \( Q_{mO₂} \) in HFrEF rats irrespective of muscle fiber type (283) which is expected to elevate \( P_{mvO₂} \).

**Sildenafil.** Sildenafil inhibits muscle cGMP-specific PDE-5 thereby enhancing NO signaling. Sperandio et al. (291) demonstrated that a single dose (50 mg) of sildenafil administered orally 1 h before exercise reduced muscle hemoglobin + myoglobin deoxygenation (synonymous with increased \( P_{mvO₂} \)) and accelerated \( V_{O₂} \) kinetics; a response that correlated with the substantial (22%) improvement in severe-intensity exercise tolerance (Fig. 7).

**Dietary supplementation.** Beetroot juice (source of nitrate: NO₃⁻). In CHF muscle, NOS function is downregulated consequent largely to increased oxidative stress, which uncouples NOS and promotes superoxide scavenging of NO and formation of the pernicious radical peroxynitrite; all of which lower NO bioavailability. In contrast, raising circulating [NO₃⁻] allows oral bacteria to reduce NO₃⁻ to nitrite (NO₂⁻) thereby elevating the circulating NO₂⁻ pool in the blood (via the gastrointestinal tract), which is then further reduced to NO. The low \( P_{mvO₂} \) (and often low pH) conditions that impair NOS function in exercising muscles in health (rats; for a review, see Refs. 76, 77) and HFpEF patients (336) potentiates the reduction of NO₃⁻ to NO. Accordingly, an alternative strategy for treating CHF may be to increase NO bioavailability through either direct NO₃⁻ or NO₂⁻ supplementation or via a nutritional additive such as the ingestion of concentrated beetroot juice.

Beetroot juice ingestion has been shown to elevate \( Q_{m} \) and \( P_{mvO₂} \), preferentially in exercising fast-twitch muscles (76, 77). Moreover, a single dose of beetroot juice (12.9 mmol) lowers systemic vascular resistance and elevates the ventilatory threshold, \( V_{O₂max} \) and exercise performance of HFpEF patients (336). The lack of a decrease in NIRS-measured ([Hb + Mb]) oxygenation at \( V_{O₂max} \) in exercising humans suggests that beetroot juice supplementation elevates \( Q_{mO₂} \), but the degree to which \( D_{mO₂} \) may have been affected could not be partitioned out (336). Thus dietary-supplied inorganic NO₃⁻ has the ability to improve exercising \( Q_{mO₂} \), \( P_{mvO₂} \), and \( V_{O₂max} \), whereas other vasodilators such as hydralazine and isosorbide dinitrate do not (325).

**Conclusions and Directions for Future Research**

In CHF systemic cardiovascular, immune and neural derangements conspire to restrict \( Q_{mO₂} \) to exercising skeletal muscle(s). Enhanced skeletal muscle mechanical impedance and vasocostriction impair \( Q_{mO₂} \) -to- \( V_{mO₂} \) matching and slow \( V_{mO₂} \) kinetics. This scenario lowers \( P_{mvO₂} \) and constrains blood-myocyte \( O₂ \) flux in CHF.

Although there can be oxidative downregulation and mitochondrial pathology, the principal \( O₂ \) pathway deficits found in CHF impact \( Q_{mO₂} \) and \( D_{mO₂} \), upstream of the mitochondria. A primary feature is the lack of RBC flux in a substantial proportion of the capillary bed at rest and during exercise as well as slowed kinetics of the hemodynamic response to contractions (i.e., characterized by low RBC flux and velocity responses) in those capillaries supporting RBC flow.

Structural impediments such as capillary involution and potentially a higher proportion of fast-twitch fibers may occur in CHF. However, substantial reversal of the CHF \( P_{mvO₂} \) effects (i.e., fast fall and/or low steady state \( P_{mvO₂} \)) by endogenous NO supports that the primary pathophysiology is functional and not structural in nature (Fig. 4).

The lowered \( P_{mvO₂} \) in CHF muscles potentiates NOS dysfunction and consequently reduces NO bioavailability via this pathway. Treatment strategies aimed at increasing NO efficacy via PDE inhibition (sildenafil) or dietary supplementation (inorganic NO₃⁻; beetroot juice) have improved \( P_{mvO₂} \) in contracting muscles and also exercise tolerance. In this regard, low \( P_{mvO₂} \) and pH present in fast-twitch fibers and muscles of CHF individuals promote NO₂⁻ reduction to NO and help explain the efficacy of NO₃⁻/NO₂⁻ treatments.

Exercise training raises \( P_{mvO₂} \) during muscle contractions via NOS-dependent and -independent mechanisms. Whereas training can help restore capillary and mitochondrial volume densities in CHF, it is more likely that improved \( Q_{mO₂} \) and \( D_{mO₂} \) posttraining are driven by improved arteriolar and capillary hemodynamic function. The degree to which training may restore RBC flux to nonflowing capillaries in CHF at rest and during contractions remains to be established. Such a response would be expected to improve \( D_{mO₂} \) substantially (Fig. 5).

Because single-dose sildenafil or beetroot juice enhances muscle oxygenation, \( V_{mO₂} \) kinetics, maximal \( V_{O₂} \), and exercise tolerance in CHF, a combination of approaches incorporating NO₃⁻ or NO₂⁻ supplementation and exercise therapy should be considered. Specifically, patients engaged in high intensity training (that promotes the greatest training-induced benefits) may be better able to perform this exercise paradigm when NO bioavailability is enhanced through NO₃⁻ or NO₂⁻ supplementation. Whether these strategies restore RBC flux in nonflowing muscle capillaries thereby increasing \( D_{mO₂} \) (as well as \( Q_{mO₂} \)) in CHF muscle(s) has yet to be determined.

In regards to \( Q_{mO₂} \) -to- \( V_{mO₂} \) matching within contracting muscles, it is axiomatic that, within a given region, higher \( Q_{mO₂} \) for any given \( V_{O₂} \) will raise \( P_{mvO₂} \) and improve blood-muscle \( O₂ \) flux and metabolic control. However, if this behavior occurs at the expense of impoverishing another region such that local \( P_{mvO₂} \) in that region falls due to \( Q_{mO₂} \) -to- \( V_{mO₂} \).
mismatching, this will ultimately impair contractile function and promote the early onset of fatigue. Novel technological and methodological approaches such as TRS-NIRS, PET, and intravital microscopy methods are building on the foundation in this field provided by radiolabeled microsphere investigations in animals and extending them into the human realm (129, 172). Vasomotor control along the vascular tree within and across different muscles is complex (188). However, elucidating the mechanistic bases for muscle dysfunction in CHF is crucial for designing and implementing optimal therapeutic interventions.

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