Integrative research: the key to unlocking the mysteries of chronic heart failure and skeletal muscle dysfunction

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REDUCTIONS IN EXERCISE CAPACITY in patients with chronic heart failure (CHF) were originally linked solely to central limitations associated with a malfunctioning cardiac pump. However, over the last 20 years, peripheral factors related to skeletal muscle and the vascular/skeletal muscle interface have been implicated in this phenomenon. Specifically, muscle atrophy, fiber-type alterations, reduced mitochondrial enzymes, decreased mitochondrial volume density, and decreased capillarity (3, 4, 9, 12–14, 22) have gained attention since these changes have been associated with CHF. Most certainly, the central and peripheral alterations are intimately linked, requiring an integrative approach to understanding the limitations and mechanisms responsible for the diminished work capacity in this patient population.

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Copp et al. (1) employed an integrative approach to examine peripheral dysfunction in CHF as measured by the off-transient or recovery kinetics of microvascular O2 pressure (PmvO2) and coupled this peripheral measure with central hemodynamic and morphological indexes of heart failure. The most novel and important findings of this study were that 1) progressive CHF increasingly slowed the recovery of PmvO2 in a mixed fiber-type muscle, 2) mean response time of the off-transient (MRToff) and the MRToff-on differences (a measure of the asymmetry between on- and off-transients) correlated with central hemodynamic and morphological indexes of heart failure, and 3) off-transient differences may be present despite a lack of on-transient alterations. A recognized limitation of this study is the finding that the correlations of off-transient and central indexes of cardiac failure were likely driven by the inclusion of four animals with the most severe heart failure; this group could be increased in number to solidify these conclusions. Despite this concern regarding the relatively small cohort of severe CHF in the study of Copp et al. (1), these findings have potential importance in terms of functional capacity and may provide insight into why work and exercise tolerance as well as the ability to perform activities of daily living are reduced in patients with CHF.

The technique of phosphorescence quenching (20), as used by Copp et al. (1), allowed the direct determination of PmvO2 during the transition from exercise to rest in the muscle of mixed fiber type (spinotrapezius). The spinotrapezius was chosen since the muscle fiber-type composition and oxidative capacity are similar to the human quadriceps (21), thereby making this model a relevant and potentially translational animal model. PmvO2 is determined by the relationship of delivery and uptake of O2 (QO2 to VO2), which in turn facilitates blood-to-tissue O2 flux and has an impact on the regulation of cellular metabolism (6, 15, 17). Previously, in healthy muscle, McDonough et al. (16) determined that PmvO2 increased during recovery, supporting the idea that QO2 is balanced relative to VO2, such that PmvO2 and the driving pressure for O2 diffusion from the capillary are not compromised. Based on Fick’s law of diffusion, this constant driving pressure for O2 diffusion from capillary to muscle is likely important for the recovery of high-energy phosphate stores following muscular contractions (15). The reduction or slowed recovery of PmvO2, as reported by Copp et al. (1), in the muscle of rats with CHF likely interferes with the ability to recover from muscular contractions, thereby accelerating fatigue during subsequent activities, and helps to explain the observed exercise intolerance in these patients.

Given that PmvO2 represents the global balance of QO2 to VO2 at the microvascular level and the driving pressure of O2 from blood to cell at a specific location (i.e., only at a small area of muscle tissue under the phosphorimeter), the independent contribution of QO2 and VO2 may also be examined to determine the balance of dysfunction (i.e., central vs. peripheral) in CHF and other pathologies marked by a reduction in exercise capacity. Such investigations require the ability to follow the dynamics of VO2 and QO2 in separatum, the latter of which has proven more challenging. However, inferences regarding QO2 at the level of the microvasculature have been performed using near infrared spectroscopy in conjunction with pulmonary measures of VO2 to approximate muscle VO2 during the transition from rest to steady-state exercise and during ramp exercise protocols (7, 8). Although each of these approaches have their own set of caveats, such techniques may prove useful in providing further insight to the centrally mediated peripheral dysfunction in CHF and other diseases.

In keeping with the integrative study of the central and peripheral factors underlying exercise intolerance in patients with CHF, Esposito et al. (5) implemented both large (cycle ergometry) and small (single leg-knee extension) muscle mass exercise modalities and created a situation in which patients with CHF exhibited a cardiac reserve despite a failing heart. Altering QO2 by breathing 100% O2 during cycle exercise further revealed a metabolic reserve in patients with CHF; however, this was not apparent during knee-extension exercise since the O2 delivery per unit of muscle mass was already elevated in this modality compared with cycle ergometry. Interestingly, during both large and small muscle mass exercise modalities, patients with CHF displayed a significantly attenuated convective (bulk delivery of O2) and diffusive (movement of O2 from hemoglobin to mitochondria) O2 transport.
The reduction in convective $O_2$ delivery can be explained by the reduction in cardiac output due to cardiac limitation, and as skeletal muscle blood flow is reduced in CHF during maximal exercise, a longer capillary transit time allows for greater $O_2$ extraction and maintenance of arterial-venous $O_2$ differences. However, despite this maintained arterial-venous $O_2$ differences, diffusive $O_2$ transport, expressed per unit time, is attenuated, revealing a reduced ability to move $O_2$ from blood to cell, which also likely contributes to the reduction in exercise capacity in CHF.

A future examination the off-transient responses as well as diffusive $O_2$ transport limitations via pharmacological and nonpharmacological (e.g., exercise) interventions may provide a better understanding of the impact of CHF on the central and peripheral limited work capacity. Recovery kinetics can be of great clinical utility by predicting functional capacity in patients with CHF (18) and are more reliable than onset kinetics (11), making such analyses attractive for future investigation. Previous pharmacological interventions have focused on transitions from rest to exercise and on nitric oxide (NO) availability, since this molecule appears to play an important role in endothelial function/dysfunction in CHF (6, 10). Reducing NO bioavailability via $N^G$-nitro-$L$-arginine methyl ester resulted in an abrupt undershoot of $P_{mvO_2}$ and a slower rate of increase in $Q_{O_2}$ relative to $V_{O_2}$ indicative of vascular dysfunction. This undershoot was prevented by increasing NO availability by infusing sodium nitroprusside (6). Interestingly, NO blockade in healthy muscle also resulted in a off-transient change in $P_{mvO_2}$ in a similar fashion to that observed in severe CHF, which implicates a reduction in NO bioavailability as a culprit in the peripheral maladaptations observed in CHF (10). Future interventions such as hyperoxia or antioxidant supplementation that have been demonstrated to increase $O_2$ supply and reduce free radical associated oxidative stress (2, 5, 19), respectively, may be useful in improving the transport of $O_2$ from blood to cell and restoring the exercise capacity in patients with CHF.

In summary, an examination of the balance between $O_2$ delivery and $O_2$ utilization revealed that peripheral skeletal muscle function, as evidenced by slowed recovery kinetics of $P_{mvO_2}$, was reduced in animals with CHF and that this peripheral maladaptation was associated with the central indexes of heart failure (1). CHF, by definition, is characterized by a malfunctioning or failing cardiac pump. However, the consequences of this failing heart manifest in skeletal muscle and peripheral vasculature. Based on current knowledge, this peripheral dysfunction pertaining to the $Q_{O_2}$-to-$V_{O_2}$ relationship is driven by a reduction in the diffusive ability of $O_2$ to move from the blood to the myocyte (5). Further investigation of the independent contribution of $Q_{O_2}$ and $V_{O_2}$ will likely reveal the mechanisms responsible for the reduced exercise tolerance in CHF and may prove insightful regarding the potential therapeutically targets of pharmacological and nonpharmacological treatments of this disease.

DISCLOSURES

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

REFERENCES


