Dynamics of microvascular oxygen partial pressure in contracting skeletal muscle of rats with chronic heart failure

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Abstract

Objective: This investigation tested the hypothesis that the dynamics of muscle microvascular $O_2$ pressure ($PO_m$, which reflects the ratio of $O_2$ utilization [$VO_2$] to $O_2$ delivery [$QO_2$]) following the onset of contractions would be altered in chronic heart failure (CHF).

Methods: Female Sprague–Dawley rats were subjected to a myocardial infarction (MI) or a sham operation (Sham). Six to 10 weeks post Sham ($n=6$) or MI ($n=17$), phosphorescence quenching techniques were utilized to determine $PO_m$ dynamics at the onset of spinotrapezius muscle contractions (1 Hz). Results: MI rats were separated into groups with Moderate ($n=10$) and Severe ($n=7$) CHF based upon the degree of left ventricular (LV) dysfunction as indicated by structural abnormalities (increased right ventricle weight and lung weight normalized to body weight). LV end-diastolic pressure was elevated significantly in both CHF groups compared with Sham (Sham, 3±1; Moderate CHF, 9±2; Severe CHF, 27±4 mmHg, $P<0.05$). The $PO_m$ response was modeled using time delay and exponential components to fit the $PO_m$ response to the steady-state. Compared with Shams, the time constant ($\tau$) of the primary $PO_m$ response was significantly speeded in Moderate CHF ($\tau$, Sham, 19.0±1.5; Moderate CHF, 13.2±1.9 s, $P<0.05$) and slowed in Severe CHF ($\tau$, 28.2±3.4 s, $P<0.05$). Within the Severe CHF group, $\tau$ increased linearly with the product of right ventricular and lung weight ($r=0.83$, $P<0.05$).

Conclusions: These results suggest that CHF alters the dynamic matching of muscle $VO_2$-to-$QO_2$ across the transition from rest to contractions and that the nature of that perturbation is dependent upon the severity of cardiac dysfunction.

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1. Introduction

Chronic heart failure (CHF) is characterized by an impaired exercise tolerance. In CHF patients at exercise onset, the dynamics of pulmonary oxygen uptake ($VO_2$) are slowed substantially [1–5] resulting in an elevated oxygen ($O_2$) deficit and greater intracellular perturbations of high energy phosphates and hydrogen ions. One common presumption is that these slowed pulmonary $VO_2$ kinetics result from impaired cardiovascular dynamics which limits muscle $O_2$ delivery ($QO_2$) at the onset of exercise. Whereas there is certainly a muscle blood flow deficit during exercise in CHF patients [6], there is also clear evidence in heart transplant patients that an elevated cardiac output prior to exercise onset does not always speed pulmonary $VO_2$ kinetics [5]. Such observations suggest that skeletal muscle dysfunction per se may play an important mechanistic role in the slowed pulmonary $VO_2$ kinetics in CHF. However, to date there are no measurements of microvascular $O_2$ pressures ($PO_m$) within muscle in CHF that could help elucidate this issue.

Moderate-to-severe left ventricular (LV) dysfunction causes profound structural and functional alterations within skeletal muscle that reduce the ability to distribute and utilize $O_2$ [7–10]. For example, arteriolar vasodilation is impaired (spinotrapezius [11]) and capillary involution (plantaris [12]) occurs concomitant with a substantial increase in the number and proportion of non-flowing...
capillaries (spina-trapezius, [13]). As well as decreasing QO₂, CHF reduces muscle oxidative enzyme capacity but only in response to severe LV dysfunction [i.e., LV end-diastolic pressures (LVEDP) above 20 mmHg (hindlimb muscles [8,14])]. Thus in moderate LV dysfunction (LVEDP~10 mmHg) the ability to deliver and distribute O₂ within skeletal muscle is impaired but muscle oxidative capacity remains normal. In contrast, in severe LV dysfunction (LVD) both QO₂ and its distribution as well as oxidative capacity are dysfunctional [8,11,14,15]. Based upon these observations, it is likely that the temporal profile of the muscle VO₂-to-QO₂ relationship across the transition to contractions is altered profoundly in CHF and in a manner that is determined by the severity of LVD (i.e., Moderate vs. Severe CHF).

Phosphorescence quenching measurement of PO₂,m provides a rapid, high precision assessment of the VO₂-to-QO₂ relationship within muscle [16,17]. Moreover, it provides an index of the upstream O₂ diffusion pressure that drives blood–muscle O₂ exchange. The purpose of the present investigation was to determine the effect of CHF (Moderate and Severe) on PO₂,m within skeletal muscle of rats at rest and following the onset of contractions. Based upon the evidence presented above and the responses observed by Behnke et al. [17], the following hypotheses were tested: (1) Moderate CHF (induced by MI and indicated by moderate LVD) will accelerate the PO₂,m kinetics of the contracting spina-trapezius muscle. We also anticipate that PO₂,m may undershoot the steady-state value early in contractions consequent to slowing of QO₂ dynamics coupled with preserved muscle oxidative function. (2) Severe CHF (induced by MI and indicated by severe LVD) will produce very slow PO₂,m kinetics in the contracting spina-trapezius. We anticipate that this response is the consequence of an impairment of both VO₂ and QO₂ dynamics found in the Severe CHF condition.

2. Methods

2.1. Animals

Twenty-three female Sprague–Dawley rats (initial body weight=235–270 g) were used in this study. All procedures were approved by the Institutional Animal Care and Use Committee at Kansas State University. Rats were housed individually at 23 °C and were maintained on a 12:12 h light:dark cycle. All rats were fed rat chow and water ad libitum.

2.2. Myocardial infarction procedures

Rats were assigned randomly to undergo either sham or MI procedures, as described previously [18]. Briefly, rats were anesthetized with a 5% halothane/O₃ mixture. They were intubated and connected to a rodent respirator (Harvard Model 680) and maintained on a 2% halothane/O₂ mixture. A left thoracotomy was performed between the fifth and sixth ribs (~1.5 cm in length) to expose the heart. The pericardial sac was opened and the heart was exteriorized. In rats receiving a MI a 6-0 suture was used to encircle and ligate the left main coronary artery approximately 2–4 mm distal to its origin. Sham operations were completed by using the same surgical procedures with the exception that the coronary artery was not ligated. The lungs were hyperinflated and the ribs approximated with 3-0 gut. The muscles of the thorax were sewn together with 4-0 gut, and the skin incision closed with 3-0 silk. The opportunity for infection was reduced by the administration of antibiotics (Ampicillan, 200 mg/kg). Anesthesia was withdrawn and the rats were extubated and monitored for 8–12 h post-operation.

2.3. Experimental protocol

Six to 10 weeks after MI or sham procedures, the rats were anesthetized with pentobarbital sodium (30 mg/kg i.p., supplemented as needed). A 2-French catheter-tip pressure manometer (Millar Instruments) was used to cannulate the right carotid artery. The manometer was advanced into the left ventricle in a retrograde fashion to measure LV end-diastolic pressure (LVEDP) and the rate of pressure change within the chamber (LV dP/dt). Subsequently, the manometer was replaced with a fluid-filled catheter (PE-50) to monitor arterial blood pressure and heart rate for the duration of the experiment (Digi-Med BPA Model 200). This fluid-filled catheter was used for the administration of additional anesthesia and for the sampling of arterial blood. Rectal temperature was monitored and maintained at 37 °C with a heating pad.

The left spina-trapezius was exposed as previously described [19]. Briefly, the skin and fascia was carefully removed from the caudal portion of the dorsal region of the muscle. Vascular and neural tissues branch primarily from the scapular origin of the spina-trapezius and were left undisturbed. Stainless steel electrodes were used to stimulate the muscle. The cathode was placed in close proximity to the motor point (0.5–1.0 cm caudal to the scapula), while the anode was sutured in place at the caudal edge of the muscle, near the fourth thoracic vertebrae. Moreover, stimulation parameters (i.e., voltage and placement of electrodes) were held constant between all animals. The phosphor, palladium meso-tetra-(4-carboxyphenyl)-porphine dendrimer (R2), was infused at a dose of 15 mg/kg through the arterial cannula ~15 min prior to each experiment.

The muscle was kept moist using a Krebs–Henseleit bicarbonate-buffered solution equilibrated with 5% CO₂/95% N₂ at 37 °C during a 10-min stabilization period following surgical exposure and throughout the subsequent experiment. The muscle was stimulated to contract at 1 Hz (~5 V, 2.0 ms pulse duration, twitch contractions) for 3 min
2.4. PO$_2$m measurements

The probe of a PMOD 1000 Frequency Domain Phosphorimeter (Oxygen Enterprises Ltd, Philadelphia, PA) was positioned ~2 mm above the spinotrapezius, as described by Bailey et al. [19]. A light guide contained within the probe focuses on the medial region of the exposed muscle. The right spinotrapezius was excised, frozen in liquid N$_2$, and saved for PO$_2$ m measurements.

Upon completion of the experiment, each rat was killed with an overdose of anesthesia (pentobarbital sodium, ≥50 mg/kg, i.a.). The thorax was opened and the lungs and heart were excised. The right ventricle (RV) was separated from the LV and all tissues were weighed and normalized to the body weight of each animal. The right spinotrapezius was excised, frozen in liquid N$_2$, and saved for citrate synthase activity determination.

2.5. Citrate synthase activity

The citrate synthase activity for the right spinotrapezius was determined spectrophotometrically at 23°C as described by Srere [24].

2.6. Data analysis

Based on anatomical dissection and morphological measurements MI rats were further divided into two groups prior to analysis of PO$_2$ m profiles. The degree of LVD and the severity of CHF was based on the presence of lung congestion (lung weight to body weight ratio: LW/BW) and right ventricular hypertrophy (RV weight to body weight ratio: RV/BW). Rats with a LW/BW and RV/BW greater than 4 standard deviations (S.D.’s) above the mean for Sham were placed in the Severe CHF group, while the remaining MI rats remained in the Moderate CHF group. Rats receiving a sham operation comprised the Sham group.

KaleidaGraph software (Kaleidagograph 3.5) was used to describe the time-course of each PO$_2$ m response using an exponential function, following a time delay (TD):

$$\text{PO}_2\text{m}(t) = \text{PO}_2\text{m}_{(\text{rest})} - \Delta\text{PO}_2\text{m}(ss)(1 - e^{-\frac{\tau}{2}})$$

where $\tau$ is the time constant of the response, TD is the time delay, and $\Delta\text{PO}_2$ is the difference between rest and the steady-state or end-contraction value.

When a marked undershoot occurred in the PO$_2$ m response prior to the attainment of a steady-state, a second exponential term was included in the model in order to reduce the residual sum of squares:

$$\text{PO}_2\text{m}(t) = \text{PO}_2\text{m}_{(\text{rest})} - A_1(1 - e^{-\frac{\tau}{2}}) + A_2(1 - e^{-\frac{\tau}{2}})$$

where $A_1$ and $A_2$ are the amplitudes of the two components of the response, respectively. For control (Sham) responses, the single exponential with TD provided an excellent fit to the PO$_2$ m data at the onset of contractions as judged from: (1) coefficient of determination ($r^2$), (2) sum of the squared residuals ($\chi^2$) and (3) visual inspection of the raw data and the fit of the residual error to a linear model [17]. This was also true for the MI rats with Severe CHF but not for the MI rats with Moderate CHF in which the more complex model with two exponentials (as described above), each with independent delays was required to fit the PO$_2$ m response [25].

A one-way analysis of variance among groups was performed on PO$_2$ m, PaCO$_2$, PaO$_2$, LVEDP, LV dP/dr, LW/BW, RV/BW, and TD and Tau from the mathematical modeling results. A Student–Newman–Keuls test was used for post-hoc analysis. Spinotrapezius CS activity was also mea-
Table 1
Rat body weight, mean arterial pressure, arterial blood gases and lactate concentrations

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Moderate CHF</th>
<th>Severe CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>300±7</td>
<td>301±9</td>
<td>288±8</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>98±3</td>
<td>99±3</td>
<td>89±3</td>
</tr>
<tr>
<td>$P_{O_2}$ (mmHg)</td>
<td>90±5</td>
<td>90±3</td>
<td>87±3</td>
</tr>
<tr>
<td>$P_{CO_2}$ (mmHg)</td>
<td>44±1</td>
<td>43±3</td>
<td>42±3</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>1.7±0.2</td>
<td>2.1±0.3</td>
<td>1.8±0.3</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; $P_{O_2}$, $P_{CO_2}$ of arterial blood. Values are mean±S.E.M. Sham, $n$=6; Moderate CHF, $n$=10; Severe CHF, $n$=7.

sured and analyzed by one-way analysis of variance. Since analysis of between groups differences were planned a priori, the least significance difference (LSD) test was utilized to determine differences between mean values. Linear regressions were performed using standard least-squares techniques. In all instances a significance level of $P\leq0.05$ was accepted.

3. Results

Upon completion of the study, of the 17 animals that received the MI surgery, seven were categorized as possessing Severe CHF based upon the predetermined criteria (i.e., LW/BW and RV/BW greater than 4 S.D.’s from mean of Sham). Thus, data are presented from six Sham, 10 MI rats with Moderate CHF and seven MI rats with Severe CHF. The groupings were distinct with respect to both criteria for all rats. Tables 1 and 2 show anatomical, blood gas status, hematological and muscle citrate synthase data for the three groups.

The Moderate CHF group showed significant MI on the anterior lateral wall of the LV, but the animals showed no differences in LW/BW or RV/BW compared to the Sham group ($P>0.05$). In comparison, the Severe CHF group demonstrated a significant elevation in both indices compared to the Moderate CHF and Sham groups ($P<0.05$, Table 2). LVEDP was elevated significantly in both CHF groups (Table 2).

The $PO_2\text{m}$ response to electrical stimulation of the spinotrapezius muscle differed substantially between the three groups of rats both qualitatively (as demonstrated in Fig. 1) and quantitatively (Table 3). In all instances, the Sham $PO_2\text{m}$ response to stimulation could be fit adequately with a single component plus delay, whereas the Moderate CHF response consistently demonstrated an

Table 2
Heart morphometrics and spinotrapezius citrate synthase activity

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Moderate CHF</th>
<th>Severe CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV/BW (mg/g)</td>
<td>0.61±0.03</td>
<td>0.72±0.03</td>
<td>1.31±0.12</td>
</tr>
<tr>
<td>LV/BW (mg/g)</td>
<td>3.9±0.1</td>
<td>4.2±0.2</td>
<td>11.3±1.6</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>2.9±0.6</td>
<td>8.8±1.9*</td>
<td>26.6±4.2</td>
</tr>
<tr>
<td>LV $dP/dt$ (mmHg/s)</td>
<td>7410±580</td>
<td>5870±413*</td>
<td>4417±397</td>
</tr>
<tr>
<td>CS (μmol/min/g wet weight)</td>
<td>13.2±1.0</td>
<td>13.8±1.0</td>
<td>10.6±0.5</td>
</tr>
</tbody>
</table>

RV/BW, right ventricle wt/body wt; LV/BW, lung weight/body wt; LVEDP, left ventricular end diastolic pressure; LV $dP/dt$, left ventricular rate of pressure change; CS, citrate synthase activity. Values are mean±S.E.M.

* $P<0.05$ vs. Sham.

** $P<0.05$ vs. Moderate CHF. Sham, $n$=6; Moderate CHF, $n$=10; Severe CHF, $n$=7.
undershoot with the PO_{m} response falling transiently below the steady-state or end-contraction value (Fig. 1, Table 3). Therefore, for the Moderate CHF response the more complex two-component model was required in order to satisfactorily fit the PO_{m} profile. This was confirmed via analysis of the sum of the squared error terms. In contrast to Moderate CHF, the Severe CHF response resembled grossly (i.e., no overshoot of the steady-state PO_{m}) that of the Sham group albeit with an altered kinetic profile (Fig. 1, Table 3). The speed of the primary PO_{m} component (τ_i) was significantly faster in the Moderate CHF group than that observed in Sham rats, and was significantly slower in the Severe CHF group compared to both Moderate CHF and Sham rats (Table 3). Within the Severe CHF group, the primary τ also showed a significant correlation with the degree of CHF or cardiopulmonary pathology present (defined here as the product of RV/BW*LW/BW; Fig. 2).

### 4. Discussion

This investigation tested the hypothesis that CHF rats will exhibit altered muscle PO_{m} kinetics across the transition from rest to electrical stimulation compared with Sham animals. The results demonstrate clearly that CHF causes profound changes in PO_{m} kinetics and moreover that the direction and magnitude of the changes in the PO_{m} profile are dependent upon the severity of the MI sequelae. Specifically, in MI rats with Moderate CHF without either pulmonary congestion or extensive skeletal muscle metabolic abnormalities (CS activity presented herein [10,14]), PO_{m} dynamics were accelerated (biphasically) compared to Shams. On the other hand, MI rats suffering from Severe CHF, pulmonary congestion and metabolic abnormalities (present results; [10,14,15,26]) exhibited slowed PO_{m} kinetics compared with both Sham and MI rats with Moderate CHF. We postulate that the more rapid reduction in PO_{m} and subsequent undershoot seen in the Moderate CHF group likely reflects a reduced QO_{2} (relative to VO_{2}) and consequent reduction of capillary O_{2} driving pressure from blood to muscle. The former process will increase the transit delay from muscle-to-lung. The latter may actually reduce muscle VO_{2} according to Fick’s law. Because either a speeding or a slowing of PO_{m} kinetics may reflect a reduced net muscle and pulmonary O_{2} exchange, the altered PO_{m} dynamics attendant with both Moderate and Severe CHF are consistent with and mechanistically linked to, the slowed pulmonary VO_{2} kinetics present in CHF.

#### 4.1. Interpretation of PO_{m} kinetics

Whereas at present there are no direct measurements of VO_{2} within the spinotrapezius muscle preparation at exercise onset in health or disease, it is known that QO_{2}
increases following the first contraction with virtually no delay in healthy muscle [27–31]. Accordingly, the constancy of \( PO_{2,m} \) for 10–15 s after the onset of contractions must result from an increased \( \dot{V}O_2 \) that is proportional in magnitude to the elevation of \( \dot{Q}O_2 \) [17]. The presence of the \( \sim 10 \) s time delay in Moderate CHF indicates that the proportionality between \( \dot{Q}O_2 \) and \( \dot{V}O_2 \) responses found in muscle is preserved at least for the first few seconds of contractions. In Severe CHF, the delay is foreshortened and \( PO_{2,m} \) begins to decrease after only \( \sim 6 \) s. This is likely to be the consequence of an extreme impairment of the \( \dot{Q}O_2 \) response at the onset of contractions. The dichotomous subsequent \( PO_{2,m} \) response (following the delay) in Moderate (speeding of \( \tau PO_{2,m} \)) versus Severe (slowing of \( \tau PO_{2,m} \)) CHF is consistent with the observation that arteriolar function and muscle blood flow are impaired progressively in Moderate and Severe CHF whereas muscle oxidative capacity is reduced in Severe but not Moderate CHF (presents results; [14]). A low muscle oxidative capacity is associated mechanistically with slowed \( \dot{V}O_2 \) [32,33] and \( PO_{2,m} \) [34] kinetics.

As discussed previously, \( PO_{2,m} \) serves as an index of the relationship between \( \dot{V}O_2 \) and \( \dot{Q}O_2 \) such that:

\[
PO_{2,m} = k \left[ CaO_2 - \frac{[CaO_2]^2}{[VO_2/(QO_2)]} \right] \tag{1}
\]

where \( k \) accounts for the position and shape of the \( O_2 \) dissociation curve, and \( CaO_2 \) is arterial \( O_2 \) content. Eq. (1) describes altered \( PO_{2,m} \) under steady-state conditions of either rest or contractions. To resolve the temporal \( PO_{2,m} \) profile across the rest–contractions transition, the respective amplitudes (\( \Delta \)), delays (TD), and \( \tau \)’s of the \( \dot{V}O_2 \) and \( \dot{Q}O_2 \) responses must be considered:

\[
PO_{2,m} = CaO_2 - \left[ \frac{[VO_2] + \Delta VO_2 (1 - e^{-(r-TD)/r(\dot{V}O_2)})}{[QO_2] + \Delta QO_2 (1 - e^{-(r-TD)/r(\dot{Q}O_2)})} \right] \tag{2}
\]

Characterization of the \( PO_{2,m} \) dynamics across the rest to stimulation transition allows inferences to be made regarding the relative dynamics of \( \dot{V}O_2 \) and \( \dot{Q}O_2 \). The technology needed to simultaneously measure \( \dot{V}O_2 \) and \( \dot{Q}O_2 \) is not presently available for the type of in situ preparations used in this study. Furthermore, Laughlin and Shrage [35] have cautioned against direct muscle venous sampling on the grounds that it affects muscle vascular control and hemodynamics. However, mathematical modeling may serve as a valuable tool for evaluating the impact of the kinetic profiles of both \( \dot{V}O_2 \) and \( \dot{Q}O_2 \) on that of \( PO_{2,m} \) (Figs. 3a and b). Eq. (2) was formulated to resolve a continuous \( PO_{2,m} \) profile across the rest–contractions transition. The values for TD, \( \tau \), as well as the baseline and amplitude (\( \Delta \)) of the \( \dot{V}O_2 \) and \( \dot{Q}O_2 \) response can be manipulated independently to characterize the ensuing effects on the \( PO_{2,m} \) profile. Representative depictions of the model output that replicate most closely the measured responses of \( PO_{2,m} \) for the MI rats with Moderate and Severe CHF are given in Figs. 3a and b, respectively. The effects of the dynamic relationship between \( \dot{V}O_2 \) and \( \dot{Q}O_2 \) kinetics on \( PO_{2,m} \) are illustrated clearly in these figures. For the same rate of change of \( \dot{V}O_2 \), the \( PO_{2,m} \) at any point after the time delay is lower than the Sham response when \( \dot{Q}O_2 \) is slower (Fig. 3a). However, consistent with the finding of an unchanged steady-state contracting spinotrapezius \( \dot{Q}O_2 \) between Sham and Moderate CHF (Behnke, Poole, and Musch, unpublished observations), the end-contracting \( PO_{2,m} \) was not different between Sham and Moderate CHF values. This means that the rate of decrease of the \( PO_{2,m} \) profile will be relatively steep compared to muscles in which \( \dot{Q}O_2 \) increases rapidly (i.e., Sham) [29]. This is consistent with the notion presented above that in the muscles of rats with Moderate CHF, \( \tau \dot{V}O_2 \) may be normal but \( \tau \dot{Q}O_2 \) is slowed [36]. Fig. 3a further demonstrates that when \( \dot{V}O_2 \) increases more
rapidly relative to \( \text{QO}_2 \) across the initial transition \( \text{PO}_{2m} \) will undershoot the steady-state value. Fig. 3b illustrates that when the kinetic profile of \( \text{VO}_2 \) is slowed in concert with that of \( \text{QO}_2 \), \( \text{PO}_{2m} \) kinetics will also be slowed without exhibiting an undershoot. This profile is consistent with that found in the group of rats with Severe CHF where the progressive slowing of \( \text{PO}_{2m} \) kinetics is correlated with the degree of LVD (Fig. 2). Note that the \( \text{PO}_{2m} \) profile in the CHF groups of rats departs markedly from that observed in the Sham.

4.2. Inferences from modeling

The \( \tau \) for the \( \text{PO}_{2m} \) response to electrical stimulation was significantly faster in the group of rats with Moderate CHF than in the Sham animals. According to the previous discussion, this change suggests that the response of \( \text{QO}_2 \) is slow compared to that of \( \text{VO}_2 \). While LVD is present in MI rats categorized as Moderate CHF, it would appear that the amount of LVD present is not enough to elicit significant decrements in the metabolic properties of the spinotrapezius muscle (i.e., oxidative capacity is thought to be a primary determinant of \( r\text{VO}_2 \); Ref. [33] and Table 2).

As discussed previously, there is a dichotomous effect of CHF on muscle hemodynamic (\( \text{QO}_2 \)) versus metabolic (oxidative enzyme capacity, \( \text{VO}_2 \)) responses. Specifically, several studies suggest that metabolic abnormalities are present only in Severe CHF (e.g., class III and IV CHF patients) in contrast to \( \text{QO}_2 \) deficits, which may be found in more moderate cases [9,10,13,14]. For example, Drexler and colleagues [9] reported that only patients with severe CHF (\( \text{VO}_2 \) max < 16 ml/min/kg) had a reduction in the volume density of mitochondria. Similarly, Delp et al. [14] reported a decrease in oxidative enzymes across seven hindlimb muscles (containing type I, IIa, and IIb fibers) in MI rats with Severe CHF, while only a single muscle (being predominately type IIb) showed a significant decrease in the MI rats with Moderate CHF. Brunotte and colleagues [10] used sciatic nerve stimulation in an in situ hindlimb preparation to demonstrate that at the same work rate, there was a greater fall in \( \text{PCR}/\text{Pi} + \text{PCr} \) in muscles of rats with Severe CHF when compared with Sham and MI rats with Moderate CHF, which were not different from one another.

4.3. Model considerations

1. The spinotrapezius is a postural muscle used to stabilize the scapula in the rat. It is possible that the amount of LVD and CHF found in the MI rats used in this study may have different effects on muscles used primarily for locomotion.

2. Left main coronary artery ligation has been an effective tool for inducing CHF in rats for decades. However, it is not possible to precisely control the severity of LVD and CHF that will develop within a given rat. The young, female Sprague–Dawley rats used in this study proved to be a very robust population. Despite an apparently large portion of necrotic myocardium produced in the LV, most of the rats were able to avoid developing the signs of severe LVD and ‘congestive’ heart failure (i.e., stable pulmonary edema as indicated by congestive lungs (increases in LW/BW) and hypertrophied right ventricle (increases in RV/BW)).

3. Regarding measurement of \( \text{QO}_2 \), technical difficulties including the extended stability of the preparation have so far precluded simultaneous measurement of \( \text{PO}_{2m} \) and capillary red blood cell hemodynamics across the rest–exercise transition. However, we do have measurements of spinotrapezius bulk blood flow (via radio-labeled microspheres) in moderate CHF rats at rest and in the steady-state of contractions (Behnke, Poole, Musch, unpublished observations). These results demonstrated that during steady-state contractions, the spinotrapezius \( \text{VO}_2 \) is similar in Sham and Moderate CHF rats. These data are similar to those found for selected hindlimb muscles of rats with Moderate CHF during locomotion [15] and they are consistent with the concept that the \( \text{PO}_{2m} \) in the steady-state is not different than that found for the Sham rats (see Fig. 3a).

5. Conclusion

The present results support the hypothesis that CHF alters the dynamic matching of \( \text{VO}_2 \) to \( \text{QO}_2 \) (as determined from \( \text{PO}_{2m} \) measurements) across the rest–contractions transition in a manner that is dependent upon the severity of LVD that develops in the animal. Specifically, in muscles from MI rats with Moderate CHF, muscle oxidative enzyme activity is unchanged (Table 2) and thus muscle \( \text{VO}_2 \) kinetics are expected to be normal. However, there is substantial evidence that MI rats with Moderate LVD suffer from impaired muscle capillary blood flow [13] which will slow \( \text{QO}_2 \) kinetics. The significantly faster fall of \( \text{PO}_{2m} \) found at the onset of contractions in the muscles of rats with Moderate CHF followed by an undershoot of the steady-state \( \text{PO}_{2m} \) is characteristic of a slower \( \text{QO}_2 \) response compared with \( \text{VO}_2 \) (see modeling Fig. 3a) [36]. In contrast, substantial decrements in muscle oxidative capacity occur within muscles of MI rats with Severe CHF (Table 2) and the slow \( \text{PO}_{2m} \) kinetics found in this group may be explained by slow \( \text{VO}_2 \) kinetics in combination with slow \( \text{QO}_2 \) kinetics (Fig. 3b). The \( \text{PO}_{2m} \) profiles evident in both groups of MI rats are consistent with a reduced net blood–muscle \( \text{O}_2 \) flux across the rest–exercise transition. Thus, the behavior of \( \text{PO}_{2m} \) determined in the present investigation may provide important information regarding the mechanistic explanation for the slow pulmonary \( \text{VO}_2 \) dynamics (i.e., large \( \text{O}_2 \) deficit) found in CHF patients.
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