Effects of chronic heart failure on skeletal muscle capillary hemodynamics at rest and during contractions

Troy E. Richardson,1 Casey A. Kindig,2 Timothy I. Musch, and David C. Poole1

1Clarenburg Research Laboratory, Departments of Kinesiology, Anatomy and Physiology, Kansas State University, Manhattan, Kansas 66506-5802; and 2Department of Medicine, University of California-San Diego, La Jolla, California 92093-0623

Submitted 25 March 2003; accepted in final form 6 May 2003

CHRONIC HEART FAILURE (CHF) induces muscle dysfunction associated with reductions in bulk flow and O2 delivery (QO2) at rest and during exercise (12, 19, 24, 34, 46, 50). Systemic vasoconstriction is elevated in CHF via elevated sympathetic nervous efferent activity (48), impaired nitric oxide (NO)-mediated vasodilation (28), impaired NO-mediated attenuation of sympathetic vasoconstriction (45), and increased levels of both endothelin (30) and angiotensin (47). These considerations imply that, in CHF, skeletal muscle blood flow during exercise is reduced due to peripheral alterations that are superimposed on the presiding cardiac insufficiency. This notion is supported by the reduced capacity of arterioles to dilate in response to increased O2 demand (10). Furthermore, a recent investigation (39) reported that the muscle contraction-induced reduction of venous pressure that augments blood flow (i.e., muscle pump) concomitant with the onset of contractions in healthy muscle (38) is impaired in CHF. Thus, not only reduced QO2, but also slower O2 kinetics, may be responsible, in part, for altered muscle metabolic control (31) and slowed oxygen uptake (VO2) in CHF (18, 33, 37) seen at the transition to a given elevated metabolic demand in CHF patients.

The red blood cell (RBC) surface area in contact with the myocyte is considered crucial for transcapillary O2 flux (13, 17). Thus, within the microcirculation, factors such as capillary-to-fiber ratio, the proportion of capillaries supporting RBC flow, and capillary hematocrit (Hctcap), which increases, in part, due to vasodilation; Refs. 25, 27, 36) all contribute to the capacity for O2 to move from the capillary to myocyte [i.e., muscle O2 diffusing capacity (DMO2)]. In resting CHF muscle, this capacity is severely impaired due to both capillary involution (47) and a smaller proportion of capillaries supporting RBC flow (24), although Hctcap remains unchanged due to proportional reductions in capillary RBC velocity (VFRBC) and flux (FRBC) (24). However, if vasodilation is either slowed or impaired at the transition to an elevated metabolic demand, then it is possible that Hctcap might be similarly reduced, resulting in a further loss in diffusive O2 movement.

Recently, our laboratory (11) studied microvascular PO2 (PmO2) dynamics across the transition from rest to contractions in muscle from control (C) rats and rats with moderate left ventricular (LV) dysfunction (i.e., moderate CHF). In C rat muscle, the fall in PmO2 at contraction onset was characterized by a time delay followed by a monoexponential fall to steady-state values, with no sign of an undershoot in PmO2 (4, 11). Conversely, in CHF muscle, PmO2 fell more rapidly, demonstrating a transient undershoot below its contracting steady-state baseline (11). As PmO2 represents the dynamic balance between QO2 and VO2, these data
were indicative of a slowed microvascular \(\dot{V}O_2\) response compared with that for \(\dot{V}O_2\) (4). These findings are consistent with slowed blood flow kinetics [and arteriolar vasodilation (10)] and unaltered or slightly reduced oxidative enzyme activities (2, 8, 11), demonstrated previously in moderate CHF. The purpose of this investigation was to study the capillary hemodynamics at rest and in response to electrically induced contractions in CHF rats and compare these results with data reported previously in C rats (26). We tested the hypothesis that capillary \(V_{RBC}\) and \(F_{RBC}\) kinetics would be slowed and that the amplitude of these responses would be attenuated in CHF compared with C muscle contractions.

**METHODS**

*Animals.* The CHF rats were matched to the C rats (26) such that, at 7-wk postmyocardial infarction (MI), the two groups were of similar age and weight (C, 279 ± 6; CHF, 300 ± 7 g; \(P > 0.05\)). Initially, eight female Sprague-Dawley rats received a MI, as described previously (34). Briefly, rats were anesthetized with 3% halothane mixture, intubated, and placed on a respirator (model 680, Harvard). Anesthesia was maintained with 2% halothane mixture thereafter. A left thoracotomy was performed in the fifth intercostal space. The heart was exposed, and the left main coronary artery was ligated by using 6.0 silk suture. Animals were allowed 7 wk of recovery before experiment. Rats were then anesthetized with pentobarbital sodium (40 mg/kg ip; supplemented as necessary before hemodynamic data acquisition). Initially, the right carotid artery was cannulated with a 2-Fr catheter-tipped pressure micromanometer (Millar Instruments), which was advanced into the LV for measuring systolic and diastolic pressures. The micromanometer was removed, and the right carotid artery was recannulated by using PE-50 (Intra-Medic polyethylene tubing, Clay Adams Brand) to monitor arterial blood pressure and to facilitate fluid replacement. On completion of the experiment, rats were euthanized via anesthesia overdose. All procedures were approved and in accordance with the Kansas State Institutional Animal Care and Use Committee.

*Muscle preparation.* The spinotrapezius was prepared in situ with minimal fascial disturbance, according to methods described previously (16, 26). The muscle was then sutured at five equidistant points to a horseshoe manifold. The manifold was attached to a swivel and a muscle-stretching apparatus that permitted precise length changes along the longitudinal axis of the muscle. In addition, this secured the muscle such that, during contractions, the scapula (origin of spinotrapezius) was drawn anteriorly, whereas the caudal region remained in place, thus allowing the capillaries to remain in focus throughout the contraction protocol. Stainless steel plate electrodes (2.5-mm radius) were placed on the dorsal spinotrapezius surface proximal to the motor point (cathode) and along the caudal periphery (anode), facilitating whole muscle, indirect muscle contractions. The rat was placed on a circulation-heated Lucite platform. The spinotrapezius muscle was superfused continuously with a Krebs-Henseleit bicarbonate-buffered solution equilibrated with 95% \(N_2\)-5% \(CO_2\). All exposed surrounding tissue was protected with Saran Wrap (Dow Brands). The muscle was transilluminated, allowing for clear visualization of sarcomeres within the fibers.

**Experimental design.** Once the muscle was positioned on the platform, a microvascular field containing (typically) 6–10 capillaries in the midcudal (dorsal surface) region of the muscle was selected, and sarcomere length was set at ~2.8 \(\mu m\), as verified via direct on-screen measurement. Resting data were obtained after a 15-min quiescent period. Thereafter, muscle contractions were elicited (1 Hz, 2-ms duration, ~5 V) for 3 min (model 588, Grass Instruments). Mean arterial pressure (MAP) was monitored throughout the data-acquisition period. The experimental protocol was no longer than 1.5–2 h in duration, during which up to 1.5 ml of sterile isotonic saline were infused intra-arterially to compensate for dehydration.

**Intravital video microscopy.** Microcirculatory images were obtained via an intravital video microscope (Nikon Eclipse E600-FN; ×40 objective; 0.8 numerical aperture) equipped with a noncontact, illuminated lens and viewed on a high-resolution color monitor (Sony Trinitron PVM-1954Q, Ichi-noniya, Japan) under a final magnification of ×1,184. This was confirmed by initial calibration of the system by means of a stage micrometer (MA285, Meiji Techno). Images were time resolved by frame and stored on videocassettes (JVC S-VHS Master XG) for subsequent off-line analysis (30 frames/s) via a videocassette recorder (JVC BR-S822U).

**Off-line analysis.** Initially, each microvascular field (i.e., capillaries and myocyte boundaries) was traced directly from the screen onto acetate paper, and the proportion of capillaries supporting RBC flow was assessed. For all capillaries in which hemodynamics were assessed, capillary diameter (\(d_c\)) was measured at two sites per capillary: one before contractions (resting conditions), and the second within 5 s of the final contraction. Both \(V_{RBC}\) and \(F_{RBC}\) were measured within two 5-s periods before contraction in each intercontraction period (i.e., relaxation) in which measurements could be made and within the first 5 s postcontraction. Between contractions, hemodynamic assessment was possible in ~15 frames. \(V_{RBC}\) was acquired by following the RBC path length over several frames. \(F_{RBC}\) was measured by counting the number of cells passing an arbitrary point. \(V_{RBC}\) was measured twice over each 5-s period (pre- and postcontraction) and once between contractions. \(F_{RBC}\) was counted over a 2-s period within each designated 5-s period pre- and postcontraction and over the entire time that RBC movement could be assessed between contractions. For each capillary in which hemodynamic data were gathered, \(Hct_{cap}\) was calculated as

\[
Hct_{cap} = \frac{\text{volume}_{RBC} \times F_{RBC}}{\pi \times (d_c/2)^2} \times V_{RBC}
\]

where \(\text{volume}_{RBC}\) is RBC volume, which was taken to be 61 \(\mu m^3\) (1), and capillaries were approximated as circular in cross section.

**Statistical analysis.** All data are presented as means ± SE. Data distribution was assessed via the Kolmogorov-Smirnov test for normality. Differences between C and CHF groups were tested with Student’s \(t\)-test. Resting and postcontraction data between groups were tested via a one-way repeated-measures ANOVA. When the \(F\) value was significant, the Student-Newman-Keuls post hoc test was utilized for pairwise comparisons. Statistical significance was accepted at the \(P < 0.05\) level.

**RESULTS**

Resting and postcontraction data are presented for four C and eight CHF rats. Kinetic data from baseline across the 3-min contraction bout are presented for four C and four CHF rats. Before the spinotrapezius...
surgery, no differences ($P > 0.05$) existed in MAP between C (104 ± 6 mmHg) and CHF (101 ± 5 mmHg) groups. LV end-diastolic pressure was significantly elevated ($P < 0.05$) in CHF (9 ± 1 mmHg) compared with C (4 ± 1 mmHg) rats, and LV developed pressure over time was reduced (C, 8,160 ± 47; CHF, 6,438 ± 391 mmHg/s; $P < 0.05$). Other markers of CHF severity, such as LV mass-to-body mass, right ventricular mass-to-body mass, and lung mass-to-body mass ratios were unchanged between groups (Table 1; all $P > 0.05$). These variables are consistent with moderate heart failure in the CHF group.

After completion of the exteriorization procedure, MAP remained constant throughout the experimental protocol (i.e., rest to muscle contractions) for both the C and CHF group of rats (95 ± 6 mmHg). Arterial $P_{O_2}$ was well maintained (arterial $P_{O_2}$ = 98 ± 10 Torr), and systemic hematocrit measured at the end of muscle contractions averaged 47 ± 2% with all rats falling within the typical normal range for these variables.

**Muscle fiber and capillary structure.** Sarcomere length in CHF and C muscles was set at similar values ($P > 0.05$) before contractions (C, 2.8 ± 0.1; CHF, 2.8 ± 0.1 μm) and remained unchanged ($P > 0.05$) after the contraction bout (C, 2.9 ± 0.1; CHF, 2.8 ± 0.1 μm). Muscle fiber width was significantly less ($P < 0.05$) in CHF (47.2 ± 2.4 μm) compared with C muscle (56.6 ± 4.9 μm). The total number of capillaries (both RBC perfused and impeded) per unit fiber width (i.e., linear density) was unchanged ($P > 0.05$) between C and CHF groups (C, 33.3 ± 2.7 vs. CHF, 35.0 ± 2.1 capillaries/mm). The $d_w$ was not different ($P > 0.05$) between C and CHF groups (C, 6.2 ± 0.1; CHF, 6.0 ± 0.1 μm) and was not altered ($P > 0.05$) by the muscle contractions in either group (C, 6.1 ± 0.1; CHF, 6.0 ± 0.1 μm).

**Capillary hemodynamics.** The proportion of capillaries supporting continuous RBC flow was less ($P < 0.05$) in CHF (0.66 ± 0.04) compared with C (0.84 ± 0.01) muscle at rest, which resulted in a significant reduction ($P < 0.05$) in the lineal density of continuously RBC-perfused vessels. Furthermore, contractions failed to induce significant ($P > 0.05$) recruitment of previously intermittently RBC-perfused or impeded capillaries in either group of rats, as the proportion of capillaries supporting continuous RBC flow in C and CHF contracting muscle (C, 0.89 ± 0.01; CHF, 0.63 ± 0.03) was similar to that measured at rest. At rest, $V_{RBC}$ (C, 270 ± 62; CHF, 179 ± 14 μm/s) and $F_{RBC}$ (C, 22.4 ± 5.5 vs. CHF, 15.2 ± 1.2 RBCs/s) were reduced (both $P < 0.05$) in the capillaries supporting continuous RBC flow in CHF compared with C muscle (Figs. 1 and 2). Contractions significantly elevated (both $P < 0.05$) $V_{RBC}$ (C, 428 ± 47 vs. CHF, 222 ± 15 μm/s) and $F_{RBC}$ (C, 44.3 ± 5.5 vs. CHF, 24 ± 1.2 RBCs/s) in both C and CHF muscle; however, both hemodynamic variables remained significantly ($P < 0.05$) less in the CHF compared with C group (Figs. 1 and 2). The speed of the $V_{RBC}$ and $F_{RBC}$ increase at contraction onset was slowed in CHF compared with C muscle. Specifically, time to 50% of the increase from baseline to end contractions (amplitude) for both $V_{RBC}$ (C, 8 ± 4; CHF, 56 ± 11 s; Fig. 3) and $F_{RBC}$ (C, 11 ± 3; CHF, 65 ± 11 s; Fig. 4) was significantly longer ($P < 0.05$) in CHF vs. C.

![Fig. 1](https://i.imgur.com/12345678.png)

**Fig. 1.** A: capillary red blood cell (RBC) velocity (means ± SE) for control (C; open bars, $n = 4$ muscles, Ref. 26) and chronic heart failure (CHF; solid bars, $n = 8$ muscles) rats at rest and immediately after a 3-min contraction bout. RBC velocity was significantly less ($P < 0.05$) in CHF muscle compared with C at rest and immediately after contractions. Contractions induced significant increases ($P < 0.05$) in both groups; however, the percent increase (B) was significantly greater ($P < 0.05$) in the C compared with CHF.

![Fig. 2](https://i.imgur.com/98765432.png)

**Fig. 2.** A: capillary RBC flux (means ± SE) for C (open bars, $n = 4$ muscles, Ref. 26) and CHF (solid bars, $n = 8$ muscles) rats at rest and immediately after a 3-min contraction bout. RBC flux was significantly less ($P < 0.05$) in CHF muscle compared with C at rest and after contractions. Contractions induced significant increases ($P < 0.05$) in both groups; however, the percent increase (B) was significantly greater ($P < 0.05$) in the C compared with CHF.

### Table 1. Tissue morphometric results for control and CHF rats

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV weight/body weight</td>
<td>2.3 ± 0.1</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>RV weight/body weight</td>
<td>0.6 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>Lung weight/body weight</td>
<td>4.6 ± 0.4</td>
<td>5.0 ± 0.5</td>
</tr>
</tbody>
</table>

Values are mean ± SE in mg/g. CHF, chronic heart failure; LV, left ventricular; RV, right ventricular. Shown are ratios of LV, RV, and lung weight to body weight.
Contractions elicited a significant rise (both $P < 0.05$) in $H_{\text{ct}}$ in $C$ and CHF muscle (Fig. 5). $H_{\text{ct}}$ values were not different ($P > 0.05$) between the two groups, either at rest ($C$, 0.16 ± 0.01; CHF, 0.18 ± 0.01) or immediately after the contraction protocol ($C$, 0.21 ± 0.01; CHF, 0.23 ± 0.01) (Fig. 5). In addition, the speed of the increase in $H_{\text{ct}}$ from rest in response to muscle contractions was unchanged in CHF compared with C muscle (Fig. 6).

**DISCUSSION**

This investigation confirms previous findings in demonstrating that both resting and exercising skeletal muscle blood flow are reduced in the CHF condition. Key original findings in the present study include the following: 1) despite a significant loss of RBC-perfused capillaries in CHF, muscle contractions did not induce “capillary recruitment”; 2) $H_{\text{ct}}$ was unchanged between CHF and C groups at rest and during and immediately after contractions; and 3) the speed of the increase in capillary $F_{\text{RBC}}$ and $V_{\text{RBC}}$ at contraction onset is markedly slowed in CHF compared with C muscle. These findings suggest that both vasodilatory and muscle pump mechanisms for increased blood flow are impaired at the immediate onset of muscular contractions. Furthermore, these data support the notion that reduced $O_2$ availability due to both diffusive and conductive mechanisms may be partly responsible for slowed $V_{\text{O}_2}$ on-kinetics in CHF patients. Consequently, these findings provide a mechanistic explanation for the $P_{\text{mo}_2}$ profiles ob-

![Fig. 3](http://jap.physiology.org/) A: capillary RBC velocity (means ± SE) for C (open bars, $n = 20$ capillaries from 4 muscles, Ref. 26) and CHF (solid bars, $n = 20$ capillaries from 4 muscles) rats from rest (time = 0) over a 3-min contraction bout. B: proportional changes as a result of muscle contractions normalized to resting values. Time to 50% of the peak amplitude was significantly faster ($P < 0.05$) in the C compared with CHF muscle.

![Fig. 4](http://jap.physiology.org/) A: capillary RBC flux (means ± SE) for C (open bars, $n = 20$ capillaries from 4 muscles, Ref. 26) and CHF (solid bars, $n = 20$ capillaries from 4 muscles) rats from rest (time = 0) over a 3-min contraction bout. B: proportional changes as a result of muscle contractions normalized to resting values. Time to 50% of the peak amplitude was significantly faster ($P < 0.05$) in the C compared with CHF muscle.

![Fig. 5](http://jap.physiology.org/) A: capillary hematocrit (means ± SE) for C (open bars, $n = 4$ muscles, Ref. 26) and CHF (solid bars, $n = 8$ muscles) rats at rest and immediately after a 3-min contraction bout. There were no differences ($P > 0.05$) between groups either at rest or after contractions; however, contractions induced a significant increase ($P < 0.05$) in capillary hematocrit in both C and CHF. B: the percent increase from rest as a result of muscle contractions was similar ($P > 0.05$) between groups.
served across the rest-to-contraction transition in muscle from CHF individuals (11).

Experimental model. Based on the elevated LV end-diastolic pressures and unchanged markers of lung congestion, the CHF rats in this investigation were likely in a state of moderate CHF. Thus, as reported previously in our laboratory, it would be expected that these rats would exhibit fiber atrophy (47), capillary involution (47), reduced vascular transport capacity (32), and reduced blood flow at rest (24, 34) and during submaximal exercise (34). Data presented herein confirm each of the above, thereby substantiating the level of CHF severity (i.e., moderate CHF) in the experimental rats. In addition, our laboratory has utilized both sham rats (i.e., same surgical procedures as the CHF rats minus the left main coronary artery suture ligation) and C rats (i.e., similar to those used in this investigation) in previous investigations and have shown that neither resting capillary hemodynamics nor the skeletal muscle blood flow response to exercise is significantly altered by the sham procedure (24, 26, 44). Thus only data from C rats were reported in this investigation.

CHF in rats vs. humans. Technological and ethical limitations preclude determination of muscle microcirculatory hemodynamics at the onset of contractions in humans. The rat model of CHF is well accepted and possesses several significant advantages over other models. 1) The level of physical activity is unaltered between C and CHF rats (42). 2) The elapsed duration post-MI is known and can be controlled. 3) Corollary diseases that potentially confound experimental results and their interpretation, such as hypertension, Type 2 diabetes, and emphysema, which pervade the human CHF population, are not manifested. 4) Unlike humans, the post-MI rat is not subjected obligatorily to a barrage of pharmacological interventions that includes angiotensin-converting enzyme inhibitors, β-blockers, anti-arrhythmics, diuretics, and vasodilators. Thus it may be argued that the rat model of CHF as utilized herein facilitates investigation of the uncontrolled manifestations of the disease. Acknowledgment must be made, however, that, in humans, the muscle microcirculatory and functional deficits may be ameliorated by the longevity of the condition (humans may remain in stable CHF for many years) and therapeutic and lifestyle interventions. The present investigation presents a foundation from which to investigate the specific mechanisms for CHF-induced dysfunction and evaluate the microcirculatory consequences and efficacy of therapeutic interventions.

Capillary hemodynamics at the rest-to-contraction transition. A large body of literature exists that demonstrates that CHF reduces skeletal muscle blood flow at rest and during steady-state exercise in most (12, 19, 24, 34, 43, 46, 50), but not all (41), instances. Neural, humoral, and mechanical mechanisms that may explain these decrements have been studied extensively, and the reader is referred to the original papers (e.g., Refs. 28, 30, 39, 45, 48, 49).

Bulk blood flow to skeletal muscle increases in an immediate and biphasic manner at exercise onset. The first phase is thought to arise primarily as a result of the muscle pump (38), in contrast to the second phase, usually initiated 15–20 s after exercise onset, which is thought to be dependent on vasodilatory mechanisms and metabolic feedback control (7, 40). Whereas the elevation of bulk muscle blood flow and VO₂ in response to an elevated metabolic rate is important, determination of the temporal and spatial distribution of RBCs within the capillary network is key to understanding blood-myocyte O₂ exchange. The data presented herein demonstrate, for the first time, that the capillary hemodynamic responses in skeletal muscle of CHF rats are slowed considerably (compared with C) at the transition from rest to electrically induced rhythmic contractions. Specifically, whereas V_{RBC} is elevated within 2 s in C muscle, no increase was evident for ~30 s in the CHF muscle (Fig. 3). As V_{RBC} increased in such a short time frame in C muscle, it seems likely that the initial increase was due, primarily, to the muscle pump. However, the muscle pump effect was either mitigated or nonexistent in CHF muscle (Figs. 3 and 4). These findings support those of Shiotani et al. (39), where the muscle pump contribution to femoral artery blood flow was reduced significantly in CHF patients compared with matched control subjects. The underlying factors responsible for this are likely to include venous congestion and constriction (49), reduced venous vascular capacity (32), or reductions in muscle mass, as demonstrated in previous studies from our laboratory (8, 47) and corroborated in the present investigation (i.e., fiber width was reduced ~17% in the CHF rats compared with C). A biphasic capillary F_{RBC} response is clearly evident in the C muscle (Fig. 4), which fits well with that reported for bulk blood flow (40). A phase I or immediate response for F_{RBC} appears nonexistent in the CHF muscle at contraction onset, further supporting the lack of a muscle pump effect.

![Graph showing capillary hematocrit vs. time](https://jap.physiology.org/doi/10.1152/jappl.00000.2003)
addition, the time course for the increase in the $F_{RBC}$ is significantly slowed in CHF compared with C muscles, suggesting that arteriolar vasodilation, while present, occurs more gradually. The present investigation suggests that the onset, speed, and magnitude of vasodilation are impaired at exercise onset in CHF. To date, the relative importance of neural (48), NO-related (28, 45), and humoral (30, 49) factors contributing to this response in CHF remains to be determined. However, previous investigations have provided evidence that the sympathetic nervous system is significantly activated (48), resulting in elevated levels of plasma norepinephrine in CHF rats, both at rest and during exercise (35). Considering that skeletal muscle arterioles are extremely sensitive to vasoconstrictive hormones that are commonly elevated in the CHF condition (i.e., angiotensin II, arginine vasopressin, and endothelin) (9), the possibility exists that a high level of vasoconstrictor tone exists in the CHF rat that contributes to the very slow hyperemic response found in the present investigation. In addition to possible increases in vasoconstrictor tone, there is substantial evidence that the relative contribution of endothelial-mediated vasodilators is reduced in the skeletal muscle of rats with CHF. In this regard, our laboratory has shown that the relative contribution of NO to the skeletal muscle blood flow response to exercise is attenuated in CHF rats (19). Moreover, Didion and Mayhan (10) have shown that skeletal muscle arteriolar reactivity to acetylcholine and calcitonin gene-related peptide is impaired in CHF rats, whereas the arteriolar reactivity to sodium nitroprusside is not. These results suggest that endothelial-mediated vasodilation is diminished in CHF rats, whereas vascular smooth muscle reactivity remains intact. Finally, McAllister and colleagues (32) have shown that postcapillary resistance is elevated significantly in skeletal muscle of rats with CHF, which is associated with a reduction in the vascular flow capacity. These findings are consistent with the hypothesis that sodium and fluid retention, along with peripheral tissue edema formation, may be contributing to the attenuated vasodilator capacity of the skeletal muscle (i.e., increased “vascular stiffness” induced by sodium and fluid retention in the vascular smooth muscle) (51). In addition, the increases in skeletal muscle postcapillary resistance, along with the significant increases in central venous pressure found in CHF, may be mechanistically linked to the reduction and/or elimination of the muscle pump effect in contracting muscle of CHF rats. In conclusion, the factors that are contributing to the very slow capillary hemodynamic response found in the CHF rat appear to be multifactorial, and elucidation of their relative importance will contribute substantially to our mechanistic understanding of the vascular dysfunction prevalent in CHF.

Implications for blood-myocyte $O_2$ flux during exercise. Honig and colleagues (20) reported that there was a substantial recruitment of previously non-RBC-perfused capillaries in response to muscle contractions. This large increase was not corroborated in subsequent investigations (e.g., Refs. 6, 21). As the majority of capillaries support continuous RBC perfusion at rest under control conditions (5, 25, 26), one would not consider capillary recruitment a viable method for augmenting the size of the capillary RBC-to-myocyte interface thought crucial for achieving a given $O_2$ flux (13, 17). However, as a significant proportion of capillaries do not support continuous RBC flow in CHF (24), recruitment of these vessels might represent one feasible mechanism for increasing $D_{O_2}$ and thus blood-myocyte $O_2$ flux during contractions. However, under neither C nor CHF conditions was there a significant “capillary recruitment” with muscle contractions. A secondary mechanism by which $D_{O_2}$ could be increased is via augmented $Hct_{cap}$. Indeed, muscle contractions did induce a significant increase in $Hct_{cap}$. Further evidence for this concept is that reducing $Q_{O_2}$ may slow $V_{O_2}$ kinetics, it has been difficult to demonstrate a speeding of the response with increased $Q_{O_2}$, particularly at moderate-intensity exercise (14, 29). Moreover, in healthy humans, Grassi et al. (15) and Bangsbo et al. (3) have shown that bulk muscle $Q_{O_2}$ is in apparent excess (or, at least, adequate) at the immediate transition to moderate- and severe-intensity exercise. Thus a muscle $Q_{O_2}$ limitation does not appear to constrain $V_{O_2}$ kinetics in healthy individuals. It has long been recognized that, at the onset of a given absolute exercise workload, CHF patients demonstrate slowed $V_{O_2}$ kinetics compared with healthy control subjects (18, 33, 37). The present results and those of Diederich et al. (11) suggest that the kinetics of $Q_{O_2}$ at exercise onset in CHF muscle are so slow that the site of $V_{O_2}$ kinetics limitation in CHF muscle shifts from the oxidative machinery to $Q_{O_2}$ (see Ref. 4 for a detailed discussion on this issue). Moreover, data presented herein suggest that both significant spatial and temporal impairments in $O_2$ availability exist within contracting skeletal muscle in CHF, and this further supports the notion that a $Q_{O_2}$ limitation may be responsible, in part, for slowed $V_{O_2}$ on-kinetics seen in CHF patients.

Conclusions. In the present investigation, intravital microscopy techniques were employed to study capillary hemodynamics at rest and during contractions in C and CHF rat spinotrapezius muscle. Conductive ($F_{FRBC}$) and diffusive (proportion of RBC-perfused capillaries) $Q_{O_2}$ were reduced, both at rest and during contractions, in the CHF compared with C muscle. Furthermore, the speed of the rise in $V_{RBC}$ and $F_{RBC}$ at
contraction onset was slowed in the CHF condition, probably indicative of impaired muscle pump function and a slowed vasodilatory response. These data provide an underlying mechanism that explains the altered muscle metabolism (i.e., increased phosphocreatine breakdown) and slowed $\text{VO}_2$ on-kinetics manifested at the onset of a given bout of exercise in individuals with CHF.

The authors thank Dr. Thomas J. Barstow for helpful discussion regarding data interpretation and Brad J. Behnke, John Russell, Dr. Paul McDonough, K. Sue Hageman, Dr. Janet Bailey, and Crystal Geer for technical assistance and support.

DISCLOSURES

This work was supported, in part, by National Institutes of Health Grants HL-50306, AG-19228, and 1 F32 AR-48461.

REFERENCES


J Appl Physiol • VOL 95 • SEPTEMBER 2003 • www.jap.org


