Maintained exercise pressor response in heart failure

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Shoemaker, J. Kevin, Allen R. Kunselman, David H. Silber, and Lawrence I. Sinoway. Maintained exercise pressor response in heart failure. J. Appl. Physiol. 85(5): 1793–1799, 1998.—The impact of forearm blood flow limitation on muscle reflex (metaboreflex) activation during exercise was examined in 10 heart failure (HF) (NYHA class III and IV) and 9 control (Ctl) subjects. Rhythmic handgrip contractions (25% maximal voluntary contraction, 30 contractions/min) were performed over 5 min under conditions of ambient pressure or with +50 mmHg positive pressure about the exercising forearm. Mean arterial blood pressure (MAP) and venous effluent hemoglobin (Hb) O2 saturation, lactate and H+ concentrations ([La] and [H+], respectively) were measured at baseline and during exercise. For ambient contractions, the increase (∆) in MAP by end exercise (MAP; i.e., the exercise pressor response) was the same in both groups (7.1 ± 1.2 vs. 7.3 ± 1.3 mmHg, HF vs. Ctl, respectively) despite larger ∆[La] and ∆[H+] for the HF group (P < 0.05). With ischemic exercise, the ∆MAP for HF (21.7 ± 2.7 mmHg) exceeded that of Ctl subjects (12.2 ± 2.8 mmHg) (P < 0.0001). Also, for HF, ∆[La] (2.94 ± 0.4 mmol) and ∆[H+] (24.8 ± 2.7 nmol) in the ischemic trial were greater than in Ctl (1.63 ± 0.4 mmol and 15.3 ± 2.8 nmol; [La] and [H+], respectively) (P < 0.02). Hb O2 saturation was reduced in Ctl from ~43% in the ambient trial to ~27% with ischemia (P < 0.0001). O2 extraction was maximized under ambient exercise conditions for HF but not for Ctl. Despite progressive increases in blood perfusion pressure over the course of ischemic exercise, no improvement in Hb O2 saturation or muscle metabolism was observed in either group. These data suggest that muscle reflex activation of the pressor response is intact in HF subjects but the resulting improvement in perfusion pressure does not appear to enhance muscle oxidative metabolism or muscle blood flow, possibly because of associated increases in sympathetic vasoconstriction of active skeletal muscle.

Recent debate on the exercise limitations in HF has focused on whether the relative muscle hyperperfusion is due to reduced vasodilation (37, 44) or to reductions in perfusion pressure (8, 14, 19, 20, 42). The low levels of muscle blood flow seen during large-muscle-mass exercise in HF may be due to diminished maximal cardiac output leading to reduced perfusion pressure (19), but it is unlikely that this mechanism is important for small muscle mass exercise.

Elevations of perfusion pressure during exercise are also due to metaboreflex-induced sympathoeexcitation, an effect that is isolated from changes in cardiac output by utilizing handgrip contractions. In healthy individuals, sympathetic discharge and blood pressure increase during fatiguing exercise. This pressor response is due, in part, to activation of chemosensitive afferent neurons originating in skeletal muscle that respond to a buildup of metabolites associated with glycolytic metabolism (1, 25). Thus this reflex is termed the "metaboreflex."

The effect of HF on metaboreflex activation is unclear. During rhythmic handgrip contractions, metaboreflex contributions to muscular sympathetic nerve activity (32) and blood pressure (29, 32) were greater in HF patients, as was intramuscular acidosis. It is speculated that the greater metaboreflex engagement in HF subjects under these conditions was due to greater accumulation of metabolic stimuli to activate muscle sympathetic afferents rather than to changes in the gain of the reflex. These conclusions are in contrast to observations of an attenuated metaboreflex in HF patients when performing static handgrip contractions despite similar levels of acidosis (34). These latter data suggest a desensitization of the reflex in HF patients during static, but not rhythmic, handgrip exercise.

The ability to elevate blood pressure may be an important component of exercise tolerance, as the pressor response is thought to improve perfusion of the active skeletal muscle (28, 30). Therefore, the ability to elevate limb perfusion pressure and muscle flow during exercise could be particularly important in HF, where alterations in muscle hyperemic (44) and metabolic responses (6, 21, 23, 36, 41) predispose subjects to premature fatigue. However, it is unclear whether the metaboreflex raises flow to the exercising muscle or actually vasoconstricts the muscle, thereby preserving blood pressure. In instrumented dogs, exercise cardiac output is increased with partial occlusion of the terminal aorta, indicating that a primary response to ischemia in these animals is an increase in total blood flow to improve limb perfusion (28, 30). In humans, however, activation of the metaboreflex results in elevated sympathetic nerve activity directed to muscle (40), possibly

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pressor response has the ability to enhance perfusion of the active muscle. Thus a critical but controversial issue is whether the pressor response has the ability to enhance perfusion of ischemic muscle.

In this study, we addressed three questions: 1) Is the muscle reflex activation of the pressor response intact in HF? 2) Can the pressor response be enhanced with flow limitation that augments muscle metabolite accumulation and the metaboreflex? 3) Can the enhanced activation of the pressor response during flow-limited exercise improve muscle metabolism in the active ischemic muscle and how is this affected by severe HF? To address these questions, we measured blood pressure and venous metabolite concentrations obtained from the exercising muscle during an ambient pressure trial and when flow to the arm was reduced by using a positive-pressure device first described for legs (7) and modified for forearm experiments (12). Flow limitation is a potent stimulus of the metaboreflex system (38). Elevated atmospheric pressure about the arm is transmitted to the deep tissue (18) so that pressure is applied equally to all vessels in the limb. However, the major hemodynamic effect must be on the veins where >50 mmHg is likely to collapse most veins and restrict the filling of postcapillary venules after a contraction. Thus limb blood flow is reduced largely because of the mechanical elevation of venous pressure and, thus, a reduction in pressure gradient for flow across the working muscle (2). Altered vascular transmural pressure with forearm positive pressure may also lead to vascular constriction (7). Therefore, improvements in limb perfusion should occur after metaboreflex-induced elevations in perfusion pressure, unless concurrent sympathetic vasoconstriction is occurring in the active limb to offset the improvements in flow. With these measures, we hoped to gain information regarding the impact of this reflex on hemodynamics and metabolism within the ischemic exercising muscle. We hypothesized that the degree of metaboreflex activation with flow limitation would be greater in the HF group vs. controls (Ctl) because of greater glycolytic metabolism. The results indicate that under ambient conditions the pressor response to rhythmic handgrip contractions was normal in this group of HF patients, despite indications of greater glycolytic metabolism suggesting a desensitized metaboreflex. Ischemic exercise evoked a greater increase in glycolytic metabolism and a larger pressor response in HF patients compared with similarly aged Ctl subjects, suggesting a normal "gain" of the reflex with ischemia with this condition. However, the augmented blood pressure did not appear to improve muscle metabolism, an index of limb perfusion.

METHODS

Subject population. Two groups of subjects were examined. The first consisted of 10 chronic HF patients. These subjects were recruited from the HF service of the Hershey Medical Center. These were compared with a group of healthy and similarly aged Ctl subjects (n = 9). The mean age of the HF (mean = 58.6 yr, ranging from 29 to 81 yr; 1 subject was 29 yr old, whereas all others were >49 yr old) and Ctl subjects (mean = 65.1 yr, ranging from 50 to 75 yr) was not statistically different (P = 0.44). Nine HF subjects were New York Heart Association functional class III and one was class IV. All HF subjects had reduced ejection fractions (range 15-40%), and medications used included diuretics (8/10), angiotensin-converting enzyme inhibitors (8/10), angiotensin receptor blockers (6/10), calcium-channel blockers (3/10), and nitrates (5/10). Five subjects had an idiopathic myopathy, four had an ischemic myopathy, and one had valvular disease. Therapy for the HF patients was not withheld during this study. All subjects gave signed consent to the experimental procedures that had been approved by the Institutional Review Board at The Milton S. Hershey Medical Center.

Experimental design and data acquisition. On arriving at the laboratory, the subjects assumed the supine position and were given a routine physical examination. The maximal voluntary isometric contraction (MVC) for the left arm was determined for each subject. Subjects were then instrumented for continuous heart rate (HR; electrocardiogram) and blood pressure (Finapres, model 2300, Ohmeda, CO) recordings. An 18-gauge, 1.25-in., catheter (Angiocath) was inserted in a retrograde fashion into an antecubital fossa vein that drained the active muscle of the exercising forearm (4). Deep venous blood was drawn from this catheter into heparinized syringes and analyzed for hemoglobin (Hb) concentration, Hb saturation, pH, and bicarbonate levels (model 510 radiometer, ABL, Copenhagen, Denmark). Deep venous lactate concentrations ([La]) were assessed as well (model 23L lactate analyzer; Yellow-Springs Instruments, Yellow-Springs, OH). Venous hydrogen ion concentration ([H+]v) was calculated from the measured pH. The exercising forearm was sealed at the elbow inside a chamber in which the air pressure could be manipulated.

Each subject performed two exercise trials. Each trial included a 5-min period of baseline measurements followed by 5 min of rhythmic handgrip exercise. During exercise, the subjects performed 30 isometric contractions per minute at 25% MVC, with each contraction lasting 1 s. Measurements of HR and mean arterial pressure (MAP) were made at each minute of the baseline period and averaged to provide a mean value for the rest period. During the final minute of baseline, a blood sample was drawn. HR, MAP, and blood samples were obtained at minutes 1, 3, and 5 of exercise. In one trial, the exercise was performed under ambient conditions. In the second trial, the exercise was performed with ischemia evoked by increasing the pressure in the arm tank device to >50 mmHg. The order of trials was varied across subjects, with four Ctl and three HF subjects performing the +50 mmHg ischemia trial first. Approximately 30 min of recovery were allowed between trials. For the ischemic trial, positive pressure was initiated after baseline values had been obtained and 20–30 s before the onset of contractions. Due to fatigue, one HF subject completed only 3 min of exercise under ambient pressure conditions and only 1 min of exercise with forearm ischemia. Therefore, only the baseline and minute 1 values for the ambient and ischemic trials were used for this subject.

Statistics. The statistical analysis of significant differences between exercise and baseline measurements of HF and Ctl subjects within a given trial and between trials in this repeated-measures design was performed with a mixed-effects linear model. An unstructured covariance structure was imposed on the model to account for within-subject correlation (16). A step-down Bonferroni adjustment was...
made to \( P \) values for the contrasts of interest to adjust for multiple comparisons, such that the overall probability of a type I error was 0.05 (10). A Wilcoxon rank-sum test was used to determine whether there was an age difference between the HF and Ctl subjects. All analyses were performed by using the SAS statistical software (SAS Institute, Cary, NC). All values are means ± SE.

RESULTS

Rest. At rest, no differences were observed between the HF and Ctl groups in deep venous blood values for [La], \([H^+]\), Hb oxygen saturation, or HR (Table 1). However, baseline MAP was lower in the HF patients compared with Ctl (Table 1). Maximal isometric contraction force for the HF group (34.5 ± 3.0 kg) was not different from the Ctl group (36.8 ± 2.5 kg).

Ambient-pressure exercise. Compared with baseline values, ambient-pressure exercise resulted in a progressive increase in MAP and \([H^+]\) for both groups \((P < 0.05)\) (Table 1). HR and venous [La] were also increased above baseline in the HF group \((P < 0.05)\) (Table 1). Hb oxygen saturation was reduced with ambient exercise for both groups (main effect; \( P < 0.0001 \)) but more so in the HF group compared with Ctl \((P < 0.05)\) (Table 1).

Ischemic exercise. For the HF and Ctl subjects, \([H^+]\) and [La] rose during the 5 min of ischemic exercise (Table 1). In both groups, MAP, [La], and \([H^+]\) were greater in the ischemic compared with the ambient trial (main effect; \( P < 0.0001 \)) (Table 1). The increase in HR was the same for both groups under both exercise conditions. The application of positive pressure caused a further reduction in exercise Hb saturation for the Ctl group (main effect; \( P < 0.0001 \)). For the HF group, the reduction in Hb oxygen saturation during exercise with positive pressure was not different from that observed during the ambient trial.

Table 1. Effects of ambient and ischemic conditions on the hemodynamic and venous blood parameters during rhythmic handgrip contractions: group × exercise time analysis

<table>
<thead>
<tr>
<th></th>
<th>Ambient Condition</th>
<th>+50 mmHg Positive Pressure</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 1 3 5</td>
<td>Baseline 1 3 5</td>
</tr>
<tr>
<td><strong>Mean arterial pressure, mmHg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ctl</td>
<td>99.7 ± 4.6</td>
<td>101 ± 4</td>
</tr>
<tr>
<td>HF</td>
<td>80.1 ± 3.8</td>
<td>81.6 ± 4.5$§$</td>
</tr>
<tr>
<td><strong>Heart rate, beats/min</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ctl</td>
<td>63 ± 3</td>
<td>63 ± 3</td>
</tr>
<tr>
<td>HF</td>
<td>69 ± 4</td>
<td>70 ± 5</td>
</tr>
<tr>
<td><strong>Lactate, mmol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ctl</td>
<td>0.66 ± 0.04</td>
<td>0.64 ± 0.06</td>
</tr>
<tr>
<td>HF</td>
<td>0.65 ± 0.05</td>
<td>0.65 ± 0.1$§$</td>
</tr>
<tr>
<td>([H^+]), nM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ctl</td>
<td>43.0 ± 0.6</td>
<td>42.9 ± 0.8</td>
</tr>
<tr>
<td>HF</td>
<td>43.6 ± 1.1</td>
<td>40.7 ± 1.0$†$</td>
</tr>
<tr>
<td><strong>S\textsubscript{02}, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ctl</td>
<td>59.1 ± 1.8</td>
<td>65.6 ± 3.2</td>
</tr>
<tr>
<td>HF</td>
<td>55.3 ± 3.3</td>
<td>72.7 ± 2.9$§$</td>
</tr>
</tbody>
</table>

Values are means ± SE. Ctl, age-matched control subjects; HF, heart failure subjects; \([H^+]\), \([\mathrm{H}^+]\) concentration; S\textsubscript{02}, hemoglobin O\textsubscript{2} saturation. *Significantly different from baseline \((P < 0.05)\); † significantly different from baseline and 1 min \((P < 0.05)\); § significantly different from baseline, 1 and 2 min \((P < 0.05)\); $§$ significantly different from Ctl \((P < 0.05)\). Data for HF group are based on \( n = 10 \) subjects for baseline and 1 min and on \( n = 9 \) subjects for 3 and 5 min.

DISCUSSION

In this study, we investigated the effect of flow limitation on muscle reflex engagement in HF patients. Blood pressure and venous effluent metabolites from the exercising limb were examined to obtain information regarding the impact of this reflex on hemodynamics and metabolism within the exercising muscle. There were two primary findings. First, the pressor reflex during rhythmic handgrip exercise was not attenuated in this group of HF patients. Second, the progressive...
increase in MAP over the course of ischemic exercise was not associated with "improvements" in venous [La], [H\(^+\)], or Hb saturation. Therefore, it does not appear that activation of the muscle pressor reflex in the HF subjects improved limb metabolism. These data suggest that engagement of the pressor reflex did not effectively improve muscle perfusion.

The conclusion of a normal (ambient trial) or augmented (ischemic trial) pressor response in HF patients is not in agreement with several reports, indicating that the ability to elevate blood pressure during exercise is impaired in these patients (8, 14, 42). However, these latter studies used exercise models that required maximal activation of a large muscle mass. Under these conditions, the increase in blood pressure during exercise may be severely limited by a diminished cardiac output in HF. We attempted to circumvent the problems associated with cardiac pumping capacity by using a small muscle mass. Accordingly, the conclusions of the present study are consistent with previous data where fatiguing forearm exercise resulted in a greater metaboreflex contribution to the exercise blood-pressure response in HF patients than in Ctl subjects (29). This finding is also consistent with prior observations that during submaximal forearm (17, 44) or leg (37, 39) exercise, HF patients demonstrate evidence for reduced blood flow (44) and altered muscle metabolic processes (6, 23, 36, 41). Thus it is possible that, during the ambient trial, changes in limb perfusion and metabolism combined to evoke an early shift to heightened levels of glycolysis in the HF subjects (44). This led to the greater release of metabolites eliciting a pressor response of similar magnitude to that observed in the normal individuals. The findings in the ambient trial of similar pressor responses in the two groups despite the greater production of ischemic metabolites in HF are consistent with the concept that, for a given level of metabolite production, the reflex is engaged less effectively in HF patients (34). It is noted that an attenuated metaboreflex response has also been observed during
handgrip exercise performed by weight lifters vs. normally active individuals (33). Thus it is possible that chronic stimulation of the muscle sympathetic afferents due to repeated bouts of heavy exercise, in the case of weight lifters, or to muscle ischemia and/or altered muscle biochemistry, in the case of HF patients, leads to a desensitization of the nerve fibers to metabolic stimulation.

In the present study, oxygen extraction was greater in the HF than in the Ctl group during ambient exercise. The application of forearm positive pressure significantly increased oxygen extraction at all exercise times for the Ctl group, but in the HF group oxygen extraction was statistically similar in the ambient and ischemic trials. However, unlike the ambient condition, six of nine HF patients who completed the ischemic exercise protocol showed a progressive reduction in Hb oxygen saturation as the contractions continued from 1 to 5 min. Markedly elevated [H+] was also observed at this time. This progressive reduction in saturation was observed in only one Ctl subject. The mechanism(s) for the progressive reduction in Hb saturation in the HF group may include progressive muscle hypoperfusion due to sympathetic constriction (13), augmented diffusion gradient for oxygen after reduction in intracellular PO2 with the relatively greater work rate (11), or elevated oxygen off-loading due to H+ accumulation (i.e., the Bohr effect). Our calculations suggest that the delayed increase in oxygen extraction in HF can be entirely accounted for by the Bohr effect. Regardless, these findings suggest that oxygen extraction under ambient conditions was maximal in the HF patients during a level of forearm exercise that was easily sustainable in the control subjects. During ischemic exercise with reductions in oxygen transport, glycolytic metabolism was accelerated, leading to greater muscle acidosis. The findings of maximal oxygen extraction and elevated acidosis in HF patients in the present study expand on earlier conclusions of flow limitations in HF (44) by suggesting that, in severe HF, skeletal muscle is situated much closer to the threshold for metaboreflex activation than in healthy control subjects.

Despite the progressive increases in blood pressure during the 5 min of forearm exercise, venous oxygen saturation did not rise, and venous metabolite concentrations did not fall in either group. This raises the question as to whether the metaboreflex, once engaged effectively, reverses the effects of flow limitation. In this study, direct measurements of blood flow were not obtained, and, therefore, our conclusions regarding the effects of this reflex on limb flow must be viewed with caution. For example, metaboreflex engagement is reported to restore up to 50% of the flow decrement induced by aortic occlusion in instrumented dogs (28). Nonetheless, the present data are consistent with previous reports of functional sympathetic vasoconstriction in active skeletal muscle of dogs (3, 27) and humans (13, 31, 35) and with the finding that, in humans, this constriction offsets the ability of an elevated perfusion pressure to improve flow to ischemic muscle (12). Thus, in the present study, it is possible that activation of the metaboreflex by a buildup of metabolites led to vasoconstriction in the active muscle, thereby leading to a further increase in metabolite accumulation.

Methodological concerns. The HF patients were not taken off of pharmaceutical therapy for this study, and many of these drugs may alter cardiovascular responses to exercise. However, many of these drugs are vasodilatory and should have attenuated the blood pressure response so that, if anything, the differences between the HF and Ctl groups may have been underestimated.

The observed differences between the HF and Ctl groups may be due to altered muscle mass and strength. This effect is unlikely in the present study, because we used the same relative workload for each subject (25% of MVC). Importantly, the mean MVC for each group was similar so that the absolute and relative workloads were also similar. Because muscle strength is related to muscle cross-sectional area, the similar MVC values suggest that differences in muscle mass between groups were minimal.

Summary. In this study, the effect of HF on activation of the exercise pressor response was assessed. Positive pressure (+50 mmHg) about the exercising forearm was used to reduce muscle blood flow and, thereby, evoke the pressor response. Ischemic exercise was associated with a greater increase in glycolytic metabolism and a larger pressor response in the HF patients compared with the similarly aged Ctl group. Therefore, metaboreflex engagement was intact in these HF patients. Unlike in the Ctl subjects, oxygen extraction was high during ambient exercise in the HF group and was not increased by ischemia. These data suggest that a blood flow limitation was, at least in part, responsible for the elevated glycolysis and pressor response observed during exercise in these patients. However, the augmented blood pressure did not improve muscle metabolism in this group of HF patients. Therefore, it is speculated that the pressor response did not effectively improve blood flow in these subjects.

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