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Heart failure attenuates muscle metaboreflex control of ventricular contractility during dynamic exercise

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Sala-Mercado JA, Hammond RL, Kim JK, McDonald PJ, Stephenson LW, O’Leary DS. Heart failure attenuates muscle metaboreflex control of ventricular contractility during dynamic exercise. Am J Physiol Heart Circ Physiol 292: H2159–H2166, 2007. First published December 22, 2006; doi:10.1152/ajpheart.01240.2006.—Underperfusion of active skeletal muscle elicits a reflex pressor response termed the muscle metaboreflex (MMR). In normal dogs during mild exercise, MMR activation causes large increases in cardiac output (CO) and mean arterial pressure (MAP); however, in heart failure (HF) although MAP increases, the rise in CO is virtually abolished, which may be due to an impaired ability to increase left ventricular contractility (LVC). The objective of the present study was to determine whether the increases in LVC seen with MMR activation during dynamic exercise in normal animals are abolished in HF. Conscious dogs were chronically instrumented to measure CO, MAP, and left ventricular (LV) pressure and volume. LVC was calculated from pressure-volume loop analysis ([LV maximal elastance (Emax) and preload-recruitable stroke work (PRSW)] at rest and during mild and moderate exercise under free-flow conditions and with MMR activation (via partial occlusion of hindlimb blood flow) before and after rapid ventricular pacing-induced HF. In control experiments, MMR activation at both exercise (3.2 km/h) and moderate exercise (6.4 km/h at 10% grade) significantly increased CO, Emax, and PRSW. In contrast, after HF was induced, CO, Emax, and PRSW were significantly lower at rest. Although CO increased significantly from rest to exercise, Emax and PRSW did not change. In addition, MMR activation caused no significant change in CO, Emax, or PRSW at either workload. We conclude that MMR causes large increases in LVC in normal animals but that this ability is abolished in HF.

When exercising skeletal muscle does not receive sufficient blood flow to meet the ongoing metabolic demands, by-products of metabolism such as lactic acid, H+, adenosine, potassium, diprotonated phosphate, and arachidonic acid products, among others, accumulate within the muscle and stimulate group III and IV afferent neurons, which evokes a reflex response known as the muscle metaboreflex (MMR). This reflex response consists of increases in effenter sympathetic nerve activity (SNA) and mean arterial pressure (MAP) (1, 3, 11, 17, 18, 24, 31–35, 39, 40, 43, 46, 47, 52, 53). In addition, MMR activation causes increases in cardiac output (CO), heart rate (HR), and plasma levels of vasoactive hormones and produces vasoconstriction in the renal and the nonischemic active skeletal muscle vasculature to partially restore arterial O2 delivery and blood flow to the hypoperfused muscles (25, 33, 36). The rise in CO likely results from increases in ventricular performance, HR, and central blood volume mobilization (32, 42, 43). By this means the MMR-induced increases in ventricular performance act to slightly increase or sustain stroke volume (SV) despite decreases in ventricular filling time due to the reflex tachycardia (32, 53).

It is very well known that patients with HF have a limited ability to tolerate exercise. O’Leary et al. (35) recently investigated the ability of the MMR to improve left ventricular (LV) function in dogs during mild dynamic exercise under normal and heart failure (HF) conditions (induced via rapid ventricular pacing). In normal animals, MMR activation caused a significant rise in HR with no change in SV, resulting in a large increase in CO and MAP. With MMR activation when HR was acutely held constant (ventricular pacing 225 beats/min), CO still increased significantly, but this time because of substantial increases in SV at the constant HR. Since central venous pressure (CVP) did not change and this rise in SV was abolished by β-adrenergic blockade, the reflex increase in SV at constant HR likely reflected increased ventricular contractility via increased sympathetic activity. After the induction of HF, much smaller increases in CO occurred with MMR activation, because although HR still increased, SV decreased. In addition, under this condition when HR was maintained constant, no increase in CO was observed with MMR activation, albeit CVP increased substantially. After β-adrenergic blockade, CO and SV decreased with MMR activation, so the investigators concluded that in HF, the ability of the muscle metaboreflex to increase ventricular function via increases in contractility as well as in filling pressure are evidently impaired.

SV, ejection fraction, and maximal rates of myocardial relaxation and contraction (dP/dtmax), among other parameters, have been utilized as indicators of reflex modulation of ventricular performance. These parameters are known to be sensitive not only to contractile state but also to loading conditions (9, 23, 41). To accurately evaluate the MMR effect on ventricular contractility during dynamic exercise under normal conditions, we recently investigated LV performance in the pressure-volume plane in conscious dogs during mild and moderate exercise (42). In agreement with previous investigations, we found a significant increase in dP/dtmax and LV maximal elastance (Emax) from rest to moderate exercise. When MMR was activated during exercise, we found a substantial increase in Emax as well as dP/dtmax. Thus the reflexes arising from skeletal muscle

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affecting contractility in normal subjects. We conducted this investigation in an effort to clarify whether the MMR modifies LV contractility in subjects with HF. We used chronically instrumented dogs and studied their ventricular function during mild and moderate dynamic exercise before and after the induction of HF. Ventricular contractility was assessed by employing the slope of the line intersecting the end-systolic pressure-volume relationships ($E_{\text{max}}$: maximal elastance index) and preload-recrutable stroke work index (PRSW) calculated from the stroke work-end-diastolic volume relationship. Both have been shown to be sensitive to changes in ventricular contractility and relatively insensitive to loading conditions, and the latter measure (PRSW) has been shown to be independent of changes in ventricular chamber size (9, 14, 15, 21, 23, 49, 50). We hypothesized that in the HF state, the muscle metaboreflex-induced increase in LV contractility during mild and moderate dynamic exercise would be impaired as shown by a smaller rise or no change in $E_{\text{max}}$ and PRSW.

**MATERIALS AND METHODS**

Experiments were performed on five healthy adult mongrel dogs (weight ~20–25 kg) of either sex, selected for their willingness to run on a motor-driven treadmill. The protocols employed in the present study were reviewed and approved by the Wayne State University Animal Investigation Committee.

**Surgical preparation.** All animals were accustomed to human handling and trained to run freely on a treadmill before the surgical procedures. The surgical procedures utilized have been described in detail previously (42). Briefly, the animals were surgically instrumented under sterile conditions in a series of two surgeries with at least 1 wk between surgical sessions and between the last surgery and the first experiment. In the first surgical session, a midline sternotomy was performed. Two hydraulic vascular occluders (In Vivo Metrics) were placed on the superior and inferior vena cavae, respectively. The pericardium was then widely opened, and a 20- or 24-mm blood flow transducer (Transonic Systems) was positioned around the ascending aorta to measure CO. Two pairs of sonomicrometry crystals (Sonometrics) were implanted in the endocardium of the left ventricle to measure the anterior-to-posterior (short axis) and base-to-apex (long axis) dimensions. Three stainless steel ventricular pacing electrodes (O-Flexon; Ethicon) were sutured to the right ventricular free wall. A fully implantable telemetered blood pressure transducer (model PAD-70; Data Sciences International) was placed subcutaneously on the left side of the chest. Its catheter was tunneled into the thoracic cavity and located inside the left ventricle for measuring left ventricular pressure (LVP). The pericardium was reaproximated loosely, and the chest was closed in layers. After 10–14 days of recovery, a second surgical session was performed through a left abdominal retroperitoneal approach. A 10-mm blood flow probe (Transonic Systems) was placed on the terminal aorta to measure blood flow to the hindlimbs (HLBF). A hydraulic vascular occluder (In Vivo Metrics) was placed on the terminal aorta just distal to the flow probe. All arteries branching from the aorta between the iliac arteries and the HLBF probe were ligated and severed, and a catheter was placed through a lumbar artery proximal to the HLBF probe and occluder to measure MAP. All cables, wires, occluder tubings, and the aortic catheter were tunneled subcutaneously and exteriorized between the scapulae.

**Experimental procedures.** All experiments were performed after the animals had fully recovered from instrumentation (i.e., active, afebrile, and of good appetite). Before the experimental sessions, each animal was transported to the laboratory, allowed to roam freely for 15–30 min, and then led to the treadmill. The blood flow transducers were connected to the flow meters (Transonic System). HR was computed by a caridiacotachometer triggered by the CO signal. The arterial catheter was connected to a pressure transducer (Transpac IV; Abbott Laboratories). The LV implant was turned on and the quality of the signal verified. All crystals were coupled to the sonomicrometer. All data were recorded on a pen-chart recorder (Gould model RS 3800) as well as computerized analog-to-digital recording systems for subsequent off-line analyses. For a given experimental session, data were collected at rest and then at a randomly selected workload (mild exercise: 3.2 km/h, 0% grade elevation; moderate exercise: 6.4 km/h, 10% grade elevation). Steady-state data and data obtained during transient vena cava occlusions (several sets of variably loaded pressure-volume loops) were recorded at rest while the animal was standing on the treadmill, during exercise with unrestricted HLBF, and after MMR activation elicited by reductions in HLBF, achieved by partial inflation of the terminal aortic occluder as described in previous studies (32–35). Each dog completed several experiments at both workloads. After completion of the control experiments, congestive heart failure was induced via rapid ventricular pacing. This technique has been widely accepted to create chronic model of LV failure and has been utilized by others and us previously (11, 12, 19, 37). Briefly, the right ventricular pacing electrodes were connected to a pacemaker set at 240 beats/min for ~30 days, and the experiments were repeated. When in the HF condition, only four of the five dogs were able to exercise at the moderate workload. Thus each animal served as its own control.

**Data analysis.** During the experiments MAP, HR, LVP, CO, HLBF, and LV short- and long-axis dimensions were collected continuously. Later, off-line data analyses yielded LV $dP/d\text{dmax}$ and $dP/d\text{dmax}$, SV, LV end-systolic pressure-volume loop relationships, and PRSW (Advanced CODAS, Data Instruments/CardioSoft 3.4.24, Sonometrics).

The data obtained before caval occlusion were averaged during steady state for 30 s so that the recording period spanned multiple respiratory cycles. The data were averaged at each condition (at rest, during exercise with unrestricted HLBF, and after MMR activation) across all experiments for each animal. These mean values were then averaged across animals to obtain the mean values for the population studied. Thus each animal contributed only once to the overall averages. Left ventricular volume (LVV) was calculated as a modified ellipsoid (6), using the equation $\text{LVV} = (\pi/6) \times D_{\text{LA}} \times D_{\text{SA}} \times D_{\text{LA}}$, where $D_{\text{LA}}$ is the anterior-to-posterior (short axis) LV diameter and $D_{\text{SA}}$ is the apex-to-base (long-axis) LV diameter. It has been previously demonstrated by Nozawa et al. (30) and other investigators (29) that this method gives a consistent measure of LVV despite changes in LV loading conditions, configurations, and HR. The pressure-volume relationship for each beat during cavae occlusion was plotted, and the end-systolic pressure and volume values were selected as the upper left corner point of each loop (as shown in Fig. 1). Any ectopic beat and the following beat were discarded. During the later stage in the occlusion, if HR rose by >10%, then the subsequent beats were excluded. For the validated beats, a linear regression analysis was performed on the selected points, to determine $E_{\text{max}}$ and PRSW.

**Statistical analysis.** Utilizing the averaged responses for each animal, we performed statistical analyses on the data with Systat software (Systat 8.0). An $\alpha$-level of $P < 0.05$ was set to determine statistical significance. Two-way analysis of variance for repeated measurements was used for comparing hemodynamic data obtained at rest and during exercise under free-flow conditions and during MMR activation at mild and moderate workloads under normal and HF conditions. If a significant interaction term was found, a test for simple effects post hoc analysis was performed to determine significant group mean differences. Data are expressed as means ± SE.
RESULTS

Table 1 shows the average levels of HLBF at rest and at each workload before and after the induction of HF. Note that for MMR activation, HLBF was reduced to similar levels in the normal and HF conditions.

Figure 1 shows two sets of LV pressure-volume loops (and the respective end-systolic pressure-volume slope, $E_{\text{max}}$) from the same animal, performed at rest in normal (control) and HF conditions. Note the clear decrease in SV and increase in end-diastolic pressure-volume point after the induction of HF. Also, in HF, $E_{\text{max}}$ was shifted downward and to the right, which correlates with a decrease in the systolic function of the left ventricle (5). In the same manner, pressure-volume loops were obtained during mild and moderate exercise under free-flow conditions and after the MMR was activated via partial reduction of the terminal aortic flow.

Figures 2 and 3 show the effects of MMR activation via imposed decreases in HLBF on HR, SV, CO, MAP, $dP/d_{\text{min}}$, $E_{\text{max}}$, and PRSW during dynamic exercise at mild and moderate workloads under normal and HF conditions. As shown in Fig. 2 and in agreement with previous investigations, under normal conditions we observed a substantial tachycardia and an increase in SV and CO during mild exercise compared with the standing (resting) position, whereas MAP remained unchanged. Therefore, the decrease in total vascular resistance that occurs during exercise due to skeletal muscle vasodilatation counteracts the increase in CO, resulting in little or no change in MAP. MMR activation during this workload significantly raised MAP compared with the free-flow condition. A large tachycardia and a further increase in CO occurred with no change in SV. As expected, at rest after the induction of heart failure MAP, SV and CO were significantly reduced compared with normal conditions, and HR was substantially higher. In this condition (HF), mild exercise produced a significant increase in HR and CO, but no changes MAP and SV occurred, which correlates with the failing condition of the heart. Furthermore, MMR activation caused a substantial rise in MAP and HR and a significant decrease in SV, and as a result, CO did not change. The pressor response was less than in the normal condition, and this can be attributed to the inability of the reflex to modify the cardiac performance or to the inability of the failing heart to respond effectively and adequately to MMR activation.

As also shown in Fig. 2, in normal animals moderate exercise generated a significant rise in HR and SV, and thus in CO and MAP. In addition, with MMR activation, MAP and HR increased substantially, and a significant increase in CO was observed. Although SV tended to rise, the increase was not statistically significant ($P = 0.082$). When in HF, the animals at rest showed substantially decreased SV, CO, and MAP values with significantly higher HR. During moderate exercise, HR and SV significantly increased, and as a result, CO also increased. MAP also increased substantially, although it remained below normal resting levels. With MMR activation, MAP and HR increased substantially, but as during mild exercise, SV and CO remained unaffected.

As shown in Fig. 3, under normal conditions, from rest to mild exercise there were no significant changes in any of the contractile or relaxation parameters ($dP/dt_{\text{max}}$, $dP/dt_{\text{min}}$, $E_{\text{max}}$, and PRSW). In addition, when the MMR was activated, all four indexes significantly changed. Compared with free-flow exercise values, $dP/dt_{\text{max}}$, $E_{\text{max}}$, and PRSW significantly increased; meanwhile, LV $dP/dt_{\text{min}}$ became more negative.

As expected, at rest in HF conditions, not only $E_{\text{max}}$ and PRSW but also LV $dP/dt_{\text{max}}$ and LV $dP/dt_{\text{min}}$ were significantly decreased. Under HF conditions, from rest to mild exercise there were small but statistically significant changes in LV $dP/dt_{\text{max}}$ and $dP/dt_{\text{min}}$; meanwhile, $E_{\text{max}}$ and PRSW did not change. Moreover, although LV $dP/dt_{\text{max}}$ and $dP/dt_{\text{min}}$ showed small yet statistically significant changes with MMR activation in this condition, $E_{\text{max}}$ and PRSW did not. It is important to mention that although both LV $dP/dt$ values increased, they were still well below the values observed in normal conditions.

Table 1. Average hindlimb blood flow collected in both normal and heart failure conditions at standing rest and during mild and moderate exercise, under free-flow exercise and with metaboreflex activation

<table>
<thead>
<tr>
<th>Condition, Setting</th>
<th>HLBF at Mild Exercise, l/min</th>
<th>HLBF at Moderate Exercise, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, rest</td>
<td>0.81 ± 0.05</td>
<td>0.82 ± 0.07</td>
</tr>
<tr>
<td>N, free-flow exercise</td>
<td>1.10 ± 0.05</td>
<td>2.49 ± 0.19</td>
</tr>
<tr>
<td>N, exercise + MRA</td>
<td>0.53 ± 0.03</td>
<td>1.63 ± 0.23</td>
</tr>
<tr>
<td>HF, Rest</td>
<td>0.59 ± 0.06</td>
<td>0.59 ± 0.07</td>
</tr>
<tr>
<td>HF, free-flow exercise</td>
<td>0.88 ± 0.07</td>
<td>2.16 ± 0.17</td>
</tr>
<tr>
<td>HF, exercise + MRA</td>
<td>0.47 ± 0.04</td>
<td>1.41 ± 0.18</td>
</tr>
</tbody>
</table>

Values are means ± SE of hindlimb blood flow (HLBF), both normal (N) and heart failure (HF) conditions, collected at rest or during mild (3.2 km/h, 0% grade) and moderate (6.4 km/h, 10% grade) exercise under free-flow conditions and with metaboreflex activation (MRA). ANOVA revealed significant condition and setting effects during mild exercise and a significant condition effect during moderate exercise with no significant interaction term at either workload.
As also shown in Fig. 3, under normal conditions, from rest to moderate exercise there was significant increase in all indexes (dP/dt_{min}, E_{max}, and PRSW). With MMR activation, all values increased even further. The ANOVA for LV dP/dt_{max} showed no significant interaction term between settings and conditions, so pairwise comparisons could not be made; however, this analysis did show significantly different workload and condition effects. Thus the changes in dP/dt_{max} showed the same pattern in both conditions. There were no significant changes in the dP/dt_{min} values from rest to moderate exercise, although substantial decreases occurred with MMR activation. As previously stated, at rest, E_{max}, PRSW, LV dP/dt_{max}, and LV dP/dt_{min} were depressed in HF. From rest to moderate exercise, LV dP/dt_{max} and LV dP/dt_{min} significantly increased (became more positive and negative, respectively) in HF. In addition, with MMR activation, LV dP/dt_{max} increased and LV dP/dt_{min} decreased somewhat further. In contrast, neither E_{max} nor PRSW changed significantly from rest to moderate exercise or with MMR activation in HF.

**DISCUSSION**

To our knowledge, this is the first study to investigate in the pressure-volume plane the effects of muscle metaboreflex activation on ventricular contractility during mild and moderate dynamic exercise in dogs before and after the induction of HF. Accurate evaluations of the contractile state of the heart are challenging. Different methods such as SV, ejection fraction, cardiothoracic ratio, circumferential shortening velocity, and dP/dt_{max}, among others, are frequently used to study ventricular contractility, despite their major limitations: they are
known to be sensitive not only to changes in contractility but also to loading conditions (9, 23, 41). Moreover, they also are influenced by changes in cardiac mass and morphology. It is widely accepted that the end-systolic pressure-volume relationship, as well as its slope, $E_{\text{max}}$, are relatively insensitive under physiological conditions to changes in preload and afterload yet sensitive to changes to the contractile state of the ventricle (7, 14, 15, 21, 22, 49). Since $E_{\text{max}}$ also is known to be susceptible to changes in chamber size (an increase in cardiac size-volume decreases $E_{\text{max}}$ regardless of contractility) (48), we also calculated PRSW [a modification of the Sarnoff’s curve that represents the slope of the relationship between stroke work (SW = pressure × volume) and end-diastolic volume (EDV)]. PRSW has been shown not only to be sensitive to changes in contractile function but also independent of chamber geometry and mass (which are markedly altered in HF conditions). Furthermore, the SW-EDV slope has been shown to be fairly comparable among normal human and animal hearts (14, 15).

Hypoperfusion of active skeletal muscle during dynamic exercise in conscious animals evokes a powerful pressor response known as the MMR. During submaximal exercise and in normal conditions, the most important mechanism employed by this reflex is the increase in flow (CO), which increases perfusion pressure to help restore the blood flow deficit in the active skeletal muscle. MMR has been shown to be capable of inducing a significant increase in SNA, MAP, HR, CO, SV, central blood volume mobilization, plasma levels of vasoactive hormones, and vasoconstriction in the peripheral vasculatures (1–3, 8, 11, 31–35, 40, 43, 44, 53).

We have recently demonstrated that in normal dogs during mild and moderate dynamic exercise, MMR improves LV
performance by increasing contractility and enhancing ventricular relaxation (42). In accordance with that study, in the present investigation when the MMR was activated at both workloads, ventricular contractility increased significantly, as shown by substantial increases in all three indexes, dP/dt, E\text{max} and PRSW. Ventricular relaxation was also enhanced as evidenced by a substantial fall in dP/dt upon metaboreflex activation at both workloads. Thus one major capacity that MMR has in normal animals during submaximal workloads is to directly regulate LV contractility. MMR in normal conditions during submaximal exercise is a flow-raising, pressure-raising reflex, since virtually all the reflex rise in MAP can be attributed to the increase in CO.

HF and MMR pressor response. Moe et al. (26) showed that in HF, LV contraction [using dP/dt, E\text{max}, and PRSW corrected for the developed LV pressure [(dP/dt)/P] and the ejection phase indexes] as well as relaxation (raised end-diastolic pressure and prolonged relaxation time constant, \( \tau \)) are impaired. No exercise was performed in that study. Previous studies from our laboratory (11, 12) have shown that in pacing-induced HF dogs, when MMR was activated during mild to moderate dynamic exercise, the increase in CO was significantly attenuated and the pressor response was more dependent on responses within the peripheral vasculature that result from increases in sympathetic outflow as well as the secretion of vasoactive hormones. In the present study after the induction of HF, we observed that SV and end-systolic pressure decreased. Furthermore, end-systolic volume as well as end-diastolic pressure-volume points significantly increased (Fig. 1). In addition, both end-systolic and end-diastolic pressure-volume points were shifted toward much larger volumes. These observations directly represent the large degree of LV chamber remodeling that is typical in failing ventricles with dilated cardiomyopathy and correlates with previous pacing-induced HF studies (13). In the HF condition, there was a marked decrease in the contractile and relaxation function of the LV. Not only dP/dt, E\text{max}, and PRSW were significantly reduced, but also dP/dt, E\text{min} showed a less negative value compared with control. This reduction in dP/dt, E\text{min} values represents a reduction in the lusitropic property of the LV. Reduced diastolic performance can be a result of different factors: myocardial (changes in calcium homeostasis) and extramyocardial mechanisms (changes in the myocardial extracellular matrix, neurohumoral and cardiac endothelial mechanisms). All affect LV relaxation (55). Previous studies have shown that reduction in the lusitropic performance is mainly related to changes in calcium homeostasis and that reduced diastolic compliance is frequently observed in pacing-induced HF and has been attributed to, among other things, an increase in interstitial collagen formation and/or its nonuniform orientation (28, 54).

In HF, not only dP/dt, E\text{max} significantly increased, but dP/dt, E\text{min} significantly decreased from rest to both mild and moderate free-flow exercise. Furthermore, both indexes changed somewhat after MMR activation in HF, although to a lower extent compared with the normal condition. If only dP/dt, E\text{max} were taken into account, one might conclude that the contractile state of the LV increased. However, there was no change in E\text{max} and PRSW values. In addition, with MMR activation at moderate exercise, these latter indexes tended to decrease compared with free-flow exercise. Thus our results are in support of previous investigations that found E\text{max} and PRSW to be better indexes for evaluating LV contractility (15, 16, 23, 49). The observed changes in dP/dt, E\text{max} and dP/dt, E\text{min} may be due to alterations in loading conditions.

What accounts for the lack of increase in LV contractility with MMR activation in HF conditions? This lack of response can be attributed to alterations in the myocardium and systemic factors. Likely, impaired MMR increases in LV contractility in HF are due to combined alterations of at least three mechanisms: the Frank-Starling mechanism, the force-frequency relationship, and the autonomic nervous system. Significant abnormalities have been described in detail for all three mechanisms in HF. Komamura et al. (20) demonstrated in dogs with pacing-induced HF that the failing ventricle is not able to increase SV in response to acute volume loads. In addition, in normal dogs, MMR activation causes substantial central blood volume mobilization (35), which maintains ventricular filling pressure that would otherwise decrease due to the rise in CO (43, 45). In HF, this central blood volume mobilization still occurs, as evidenced by large increases in central venous pressure (11), but evidently even this increase in filling pressure is ineffective in raising CO during MMR activation. Prabhu and Freeman (38) reported that alteration of length-dependent activation is a fundamental defect in the development and progression in HF. Mulieri et al. (27) investigated isometric tension generation of isolated failing human myocardium at different contraction frequencies. This group demonstrated marked reduction in the tension and force-frequency relations in failing myocardia compared with normal ones. In normal conditions, the MMR increases SNA to the heart, causing an increase in LV contractile state, HR, and CO. It is important to note that in HF, the MMR still evokes a significant tachycardia as seen in the present study (Fig. 2). However, the increases in sympathetic tone to the heart stimulate not only cardiac \( \beta \)-adrenergic receptors but also \( \alpha \)-adrenergic receptors within the coronary vasculature. Previously, we showed that even in normal dogs, the increases in cardiac sympathetic activity with MMR activation functionally restrains coronary vasodilation (2). In HF, actual coronary vasoconstriction was observed (decreases in coronary vascular conductance) (1). This may limit increases in ventricular contractility (10). Furthermore, a decreased density of \( \beta \)-receptors has been shown previously in canine pacing-induced failing hearts, which in turn can lead to subsensitivity of \( \beta \)-adrenergic pathways and reductions in \( \beta \)-agonist-stimulated muscle contractions (4, 19, 51). Thus the sympathetic pathways the MMR uses in normal conditions are altered in HF, in addition to intrinsic alteration in the myocardial cells and interstitial tissue (myocardial cell death, hypertrophy) (13). Therefore, although MMR control of the chronotropic state of the heart is preserved, its inotropic control is meanwhile impaired in HF. So, in summary, alteration of all three mechanisms may contribute to the lack of increase in LV contractile state with MMR activation in HF. Our results are in accordance with previous investigations where it was shown that the muscle metaboreflex is still capable of generating a pressor response during mild to moderate exercise in HF dogs, although the mechanisms of this response are different compared with those observed in normal conditions (11, 12). In HF conditions, the pressor response must depend on responses within the peripheral vasculature (vasoconstriction), because the increase in CO is virtually
abolished. Given that we (11) have previously shown that during moderate exercise in HF, skeletal muscle blood flow is already reduced sufficiently to tonically activate the MMR, the increased sympathoactivation observed in HF subjects during exercise may stem from exaggerated activation of the MMR.

**Limitations.** Our analysis assumed a linear end-systolic pressure-volume relationship. It has been shown previously that when tested over a wide range of pressures, the relation is actually curvilinear, yet over the range in which we obtained the data, the relationship was well approximated by a straight line (29).

There is a limitation with the technique we employed to measure LV volume, which we have previously described in detail (42). Briefly, on average, the SV calculated from the LV dimensions measured by sonomicrometry consistently underestimated by 54% the SV obtained by integration of the CO flow signal (from an ultrasonic time-transit probe placed on the ascending aorta). However, the correspondence between both techniques is extremely close, as previously shown (42). Furthermore, the SV values we obtained with the sonometric technique are highly consistent with those reported in the literature by other investigators (23, 29). A possible explanation for this discrepancy in SV could be that the location and the number of crystals can impact the measurement. We used two pairs of crystals to reduce the insult to the left ventricle, considering the large amount of instrumentation placed in the heart.

Although HLBF was decreased to similar levels within each condition before and after the induction of HF, we do not know whether this resulted in the same level of metaboreceptor activation. Our group has previously demonstrated in this model that after induction of HF, during moderate exercise any mechanical terminal aortic occlusion elicits important increases in SNA, as evidenced by increases in arterial levels of plasma norepinephrine, marked peripheral vasconstrictor, and exaggerated release of vasopressin and renin (11, 12, 34). The inability of one animal to perform moderate exercise long enough to observe MMR responses in HF limited the number of observations in this setting to only four animals; however, none of these four animals showed any noticeable change in $E_{\text{max}}$ or PRSW in this setting (similar to all 5 during mild exercise); therefore, we are confident that the statistical conclusions reached are valid within the confines of this experimental approach.

In conclusion, one mechanism the normal heart uses to increase SV during exercise and even more with MMR activation is the increase in ventricular contractile state. In HF, this mechanism is abolished in that $E_{\text{max}}$ and PRSW remained unchanged. We conclude that at mild and moderate dynamic exercise, muscle metaboreflex improves LV performance via increasing contractility and enhancing ventricular relaxation. In HF conditions, this ability to modulate LV contractility and relaxation is impaired.

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