Spontaneous baroreflex control of heart rate during exercise and muscle metaboreflex activation in heart failure

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DURING DYNAMIC EXERCISE, a mismatch between oxygen supply and oxygen demand of exercising muscles causes the accumulation of metabolic by-products within the active muscles, which evokes a reflex response known as the muscle metaboreflex (MMR). In normal individuals muscle metaboreflex activation (MRA) elicits an increase in sympathovagal reflex activity and release of vasoactive hormones, which cause increases in heart rate (HR), stroke volume (SV), cardiac output (CO), ventricular contractility, central blood volume mobilization, and vasoconstriction in inactive vascular beds, which, in turn, raise systemic arterial pressure (23–26, 30, 37, 41, 49) in order to raise perfusion pressure to help restore blood flow and reduce the O2 deficit in the active skeletal muscles. This pressor response is restrained by the arterial baroreflex, which acts to oppose the metaboreflex-induced peripheral vasoconstriction (17).

An accentuated MRA during dynamic exercise has been reported in subjects with heart failure (HF) (10, 11, 35, 38, 41). In this pathological condition, skeletal muscle blood flow is lower during exercise due to the failure of CO to raise and increase blood flow and O2 delivery in proportion to the metabolic needs of the exercising muscles. Hypoperfusion of exercising muscles would result in a tonic activation of the MMR already at moderate exercise intensity (11, 38). Hence, after induction of HF, MRA during exercise still evokes a significant pressor response. However, the efferent mechanisms of this pressor response are different in HF compared with those observed in normal subjects, with a shift from an increase in CO with little peripheral vasoconstriction in normal subjects to little increase in CO with marked peripheral vasoconstriction in HF (1, 11, 31, 38). In this setting, although a significant tachycardia still occurs, SV falls, and thus CO remains essentially unchanged (11, 31). The main mechanism by which the MMR enhances peripheral vasoconstriction to raise blood pressure in HF is a reduced buffering effect from the arterial baroreflex, although a contribution from enhanced carotid chemoreflex activation has been recently advanced (45). Kim et al. (15) demonstrated that a reduced baroreflex buffering of peripheral vasoconstriction persists across a broad range of exercise workloads in dogs with pacing-induced HF. In the same experimental model (16), sinoaortic denervation in animals with HF did not markedly alter the pressor and vasoconstrictor response to MRA, further confirming that the extent of baroreflex buffering of sympathetically-induced peripheral vasoconstriction by the MMR is reduced in HF.

In addition to an increased sympathetic activity at rest and during exercise, HF is characterized by other abnormalities in neural cardiovascular regulation, which include a defective parasympathetic cardiac control, which is manifest mainly by a depressed baroreflex control of the sinoatrial node. A depressed baroreceptor cardiac reflex sensitivity at rest is a hallmark of HF in both animals and humans (6, 8, 20, 47), with a progressive decrease in baroreflex control of the heart as HF worsens (21). However, despite cardiovascular responses to exercise and some underlying mechanisms that have been well characterized in subjects with HF, little is known about baroreflex control of HR during exercise in this pathological condi-
tion. Is it well-accepted that, in addition to central command and the MMR, the arterial baroreflex plays a primary role in modulating the autonomic and cardiovascular responses to exercise (13, 28), and both central command and the MMR have been shown to interact with the arterial baroreflex in the control of BP and HR during exercise (13). In this context, Sala-Mercado et al. (40) have recently shown that the spontaneous baroreflex sensitivity (SBRs) in the control of HR is depressed during mild and moderate dynamic exercise in normal dogs and that MRA is capable of further depressing SBRs. Since it is known that the increase in CO occurs via an increase in HR and a maintained or slightly increased SV, the above finding has been interpreted as indicating that the MRA affects baroreflex control of HR by lessening baroreflex opposition to HR increases in order to better control cardiac performance (40). Inhibition of the vagal-cardiac baroreflex could thus contribute to the greater tachycardic response that occurs during exercise with MRA.

In dogs with HF, a significant increase in HR, even greater than in the control state (11), still occurs during MRA. This could implicate, in addition to an enhanced cardiac sympathetic activation, a reduced buffering effect of the cardiac vagal component of the arterial baroreflex in an attempt to compensate for the fall in SV.

The objective of the present study was to investigate baroreflex control of HR during exercise in HF. We hypothesized that the cardiac component of the arterial baroreflex is attenuated during exercise in HF and that MRA further depresses SBRs. We used chronically instrumented dogs and evaluated SBRs during mild and moderate workloads before and during imposed MRA in dogs before and after induction of HF.

MATERIALS AND METHODS

Experiments were performed on seven healthy, adult mongrel dogs (weight ~20–25 kg) of either gender 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, previously described in detail (39). Briefly, under sterile conditions, the animals were instrumented in two surgical procedures with at least 10–14 days between surgical sessions. In the first surgical procedure, a mid-line sternotomy was performed. Two hydraulic vascular occluders (In Vivo Metrics) were placed on the superior and inferior vena cavae, respectively, for studies unrelated to the present investigation. The pericardium was then opened, and two pairs of sonomicrometry crystals (Sonometrics) were implanted in the left ventricular endocardium, also for unrelated studies. 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. A 20- or 24-mm blood flow transducer (Transonic Systems) was placed around the ascending aorta to measure CO. Three stainless steel ventricular pacing electrodes (O-Flexon, Ethicon) were sutured to the right ventricular free wall for subsequent ventricular pacing. The pericardium was reaproximated loosely, and the chest was closed in layers. After a recovery period (10–14 days) 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 (DocXS Biomedical Products) 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 mean arterial pressure (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 every experiment, each animal was transported to the laboratory and allowed to roam freely for 15–30 min and then was lead to the treadmill. The blood flow transducers were connected to the flow meters (Transonic Systems). HR was computed by a cardiometer triggered by the CO signal. The arterial catheter was connected to a pressure transducer (Transpac IV, Abbott Laboratories). The left ventricular implant was turned on and the quality of the signal verified. All data were recorded on analog-to-digital recording systems for subsequent offline analyses. For a given experimental session data were collected at rest and then at a randomly selected workload (mild exercise: 3.2 km/h, 10% grade elevation; or moderate exercise, 6.4 km/h, 10% grade elevation). Steady-state data were recorded at rest while the animal was standing on the treadmill, during exercise with unrestricted blood flow to the hindlimbs, and after MRA elicited by reductions in HLBF, achieved by partial inflation of the terminal aortic occluder, as previously described (31). Each dog completed several experiments at both workloads. After completion of the control experiments, HF was induced via rapid ventricular pacing, a technique widely accepted to create a chronic model of left ventricular failure (38). Briefly, the right ventricular pacing electrodes were connected to a pacemaker set at 240–250 beats/min for ~30 days and the experiments were repeated. The pacemaker was disconnected for ~15–20 min prior to the experiment and reconnected at the end of each experiment. When in the HF condition, only six of the seven dogs were willing to exercise at the moderate workload.

Data analysis. During the experiments beat-to-beat MAP, HR, LVP, CO, and HLBF were collected continuously. Data were collected for 3 to 5 min, so the recording period spanned multiple respiratory cycles. The data were averaged at each setting (at rest, during mild or moderate exercise with unrestricted blood flow to the hindlimbs, and after MRA) across all experiments for every animal. These mean values were then averaged across animals under each condition (normal and HF) to obtain the mean values for the population studied. Thus, each animal contributed only once to the overall averages for each condition.

As shown in Fig. 1, SBRs was dynamically assessed by the sequence analysis technique previously described in detail (2, 40). Since left ventricular systolic pressure (LVSP) is nearly identical to systolic pressure in the aortic arch, we used LVSP as the input to the arterial baroreflex. The beat-to-beat time series of LVSP and HR were searched for three or more consecutive beats in which the LVSP and HR of the following beat changed in the opposite directions. A linear regression was applied to each individual baroreflex sequence with only those sequences in which $r^2 > 0.85$ accepted, and a slope was calculated. The mean slope of the LVSP-HR relationship, obtained by averaging all slopes computed within a given test period, was calculated and taken as a measure of SBRs for that period. The mean values were then averaged across all experiments performed on the time series of LVSP and R-R interval (RRI).

Statistical analysis. Utilizing the averaged responses for each animal, statistical analyses were performed on the data with Systat software (Systat 11.0). An a-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 MRA at mild and moderate workloads under normal and HF conditions. If a significant interaction term was found, a Test for Simple Effects post
observed a significant increase in CO, HLBF, SV, and a position to free-flow mild exercise in normal animals, we also significantly decreased in HF (mmHg/s, normal vs. HF, 

to normal. HR and CO significantly increased during exercise, while SV was substantially unchanged; however, the increase in CO was significantly depressed with respect to normal. LVSP was depressed compared with normal during both rest and exercise and did not change with the transition to low workload. On the elicitation of the MMR, there was a significant increase in LVSP, although to a lesser extent than in the normal state, which was accompanied by a tachycardia that was significantly greater than in the normal state. Meanwhile, SV slightly fell, and no significant increase in CO occurred.

As shown in Table 2, moderate exercise generated a significant rise in HLBF, CO, SV, HR, and LVSP, which were higher than at low workload. With MRA, CO, SV, LVSP, and HR increased even further. In the HF state, exercise induced a significant increase in HLBF, CO, SV, HR, and LVSP, although to a lesser extent than in the normal state. During exercise with MRA, LVSP and CO still increased but were significantly depressed with respect to normal exercise; on the contrary, HR did not differ significantly between HF and normal conditions.

**Responses to exercise.** Table 1 shows the average values of HLBF, LVSP, CO, SV, HR, and a normalized number of SBRS (the “SBRS incidence”) at rest and at mild workload before and during MRA, elicited via partial reduction in HLBF in normal and HF states. Rapid ventricular pacing induced modest HF as evidenced upon physical examination by decreased activity, ascites, and decreased appetite. In addition, baseline cardiovascular parameters were also consistent with modest HF including tachycardia, decreased SV, CO, and MAP. Maximal and minimal left ventricular dP/dt at rest were also significantly decreased in HF in both the normal and HF states. Figure 1 shows an upward and leftward shift in the baroreflex stimulus-response relationship, in addition to a decrease in mean slope in HF compared with the normal state. Figure 2 shows RRI-SBRS and HR-SBRS at each setting (rest, mild exercise, MRA during mild exercise, moderate exercise and MRA during moderate exercise) in the normal and HF state. Figures 3 and 4 show the prevailing HR or RRI and LVSP during each particular setting, with its corresponding SBRS mean slope in both of the experimental states. As illustrated in Figs. 2 and 3, in the normal state in going from rest to mild exercise, HR-LVSP relationship shifted upwards with a significant decrease in SBRS (mean slope became flatter). MRA caused an upward and also a rightward shift of HR-LVSP relationship and further de-

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**RESULTS**

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**Table 1. Hemodynamic values at rest, during mild exercise and mild exercise plus muscle metaboreflex activation in normal animals and in the same animals after induction of heart failure**

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<thead>
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<th>Condition/Setting</th>
<th>HLBF, l/min</th>
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<td>0.89±0.05</td>
<td>135.7±5</td>
<td>4.86±0.21</td>
<td>46.2±2</td>
<td>106±5</td>
<td>9.4±1.6</td>
</tr>
<tr>
<td>N, mild free-flow exercise</td>
<td>1.27±0.08†</td>
<td>134.1±6.2</td>
<td>4.62±0.29†</td>
<td>49.7±2.3†</td>
<td>130±3†</td>
<td>5.8±0.9†</td>
</tr>
<tr>
<td>N, mild exercise + MRA</td>
<td>0.67±0.03†</td>
<td>175.9±5.7†</td>
<td>7.77±0.32‡</td>
<td>51.6±2.9</td>
<td>152±5†</td>
<td>5.7±0.9</td>
</tr>
<tr>
<td>HF, rest</td>
<td>0.53±0.06*</td>
<td>104.4±5.7*</td>
<td>3.66±0.27*</td>
<td>28.3±2*</td>
<td>130±7*</td>
<td>6.2±0.6*</td>
</tr>
<tr>
<td>HF, mild free-flow exercise</td>
<td>0.80±0.07†</td>
<td>111.1±4.5*</td>
<td>4.52±0.27†</td>
<td>29.5±2.2*</td>
<td>155±6*†</td>
<td>3.2±0.6†</td>
</tr>
<tr>
<td>HF, mild exercise + MRA</td>
<td>0.64±0.08‡</td>
<td>142.1±6.5*</td>
<td>4.83±0.40*</td>
<td>26.6±1.9‡</td>
<td>180±5*‡</td>
<td>2.7±0.7*</td>
</tr>
</tbody>
</table>

Values are means± SE. MRA, muscle metaboreflex activation; N, normal animals; HF, heart failure; HLBF, hindlimb blood flow; LVSP, left ventricular systolic pressure; CO, cardiac output; SV, stroke volume; HR-SBRS, number of spontaneous baroreflex sequences. For HF n = 6; for all other values, n = 7. *P < 0.05 HF vs. N; †P < 0.05 free-flow exercise vs. rest; ‡P < 0.05 free-flow exercise plus MRA vs. free-flow exercise.

**Figure 1. Example of spontaneous baroreflex relationships from one subject at rest in the normal condition (N) and after induction of heart failure (HF).** In the normal condition, the heavy line represents mean slope of heart rate (HR) vs. left ventricular systolic pressure (LVSP) relationships (spontaneous baroreflex sensitivity) obtained from each individual sequence of three or more consecutive beats in which HR and LVSP changed in opposite directions, either +HR/−LVSP or −HR/+LVSP (thin lines).

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creased SBRS. Similar results were observed during moderate exercise. In the HF state, at mild exercise intensity, an upward shift in HR-LVSP with a significant decrease in SBRS was also observed, with SBRS being significantly less than in the normal exercise. Like in the experiments performed prior to induction of HF, MRA caused a rightward shift in HR-LVSP relationship with a further decrease in SBRS (P = 0.06 vs. free-flow exercise). Moderate exercise intensity caused, in addition to an upward shift, a rightward shift in HR-LVSP even in the free-flow conditions, accompanied by a significant decrease in SBRS. MRA further shifted upward and rightward the HR-LVSP relationship, although to a lesser extent than in the transition from rest to free-flow exercise. SBRS decreased slightly, albeit not significantly (in terms of beats/min/mmHg, see Fig. 2). As expected, when compared to HR-LVSP, the RRI-LVSP relationship (Fig. 4) showed an exactly reciprocal pattern (that is, a downward and rightward shift) with a progressive decrease in SBRS in each exercise setting and condition, the only difference with respect to HR-LVSP relationship being the statistical significance of the SBRS decrease during MRA in comparison to free-flow condition at moderate workload in the HF state (Fig. 2). The occurrence of spontaneous baroreflex sequences was significantly less in HF than in the normal state, both at rest and during each exercise setting, whereas no significant differences were detected between exercise intensities under free-flow conditions and/or MRA (Tables 1 and 2).

As can be seen in Fig. 5, the relationships between HR and HR-SBRS and RRI and RRI-SBRS were nonlinear, in both normal and HF states. This shows that, although the SBRS decreases with progressive increases in HR, the reduction in baroreflex gain is greater when HR rises in situations where baseline HR is lower (i.e., rest or mild exercise). It is important to note that our conclusions were unaffected regarding the changes in SBRS by using either HR or RRI in the analysis.

**DISCUSSION**

To our knowledge, this is the first study to address the issue of spontaneous baroreflex control of HR during exercise and MRA in heart failure. The relevant and new finding in this study is that in dogs with moderate HF, SBRS is depressed during dynamic exercise, with a progressive resetting of the arterial baroreflex stimulus-response relationship, in proportion to exercise intensity and magnitude of MRA similar to the normal state.

It is well known that HF is characterized by altered neural cardiovascular regulation. This includes resting sympathetic overactivity to the heart and vasculature and depressed vagal outflow to the heart, which manifests mainly with a resting tachycardia and an attenuated baroreflex control of HR, that is, a depressed SBRS (6, 20, 47). This sympathetic overactivity to the cardiovascular system is even enhanced during exercise, possibly playing a role in the pathophysiology of this syndrome (4, 35). In this context, an enhanced MMR-induced sympathetic activation has been proposed as a key factor in the evolution and worsening of HF (4, 35). Surprisingly, despite that a reduced SBRS is a hallmark of HF and that baroreflex control of HR plays a primary role in modulating cardiovascular responses to exercise, no previous study has focused on spontaneous baroreflex control of HR during exercise in HF.

**Effect of HF on the hemodynamic responses to MRA**. The hemodynamic responses to MRA in the control and HF states were confirmatory of those of several previous studies from O’Leary and co-workers (1, 11, 15, 16, 31, 38), indicating that after the induction of HF, the inability of MMR to increase CO limits the increase in systemic pressure and therefore the ability of the reflex to partially restore blood flow to the ischemic active skeletal muscle (27). Interestingly, HR during exercise with MRA was similar in the control and HF states, confirming the results of previous studies (11, 38), indicating that after the induction of HF, although the heart became relatively inotropically insensitive, the sinoatrial node still remains chronotropically competent.

**Effect of HF on SBRS response to exercise and MRA**. In keeping with a recent (40) and previous studies (3, 14, 19, 33), in control conditions mild dynamic exercise caused an upward resetting and decrease in SBRS, and moderate exercise induced an upward and rightward resetting and further reduction in SBRS.

As expected, at rest in HF subjects, SBRS was significantly depressed with a leftward and upward shift in LVSP-HR relationship toward the lower BP and the higher HR of the HF state (Figs. 1 and 3). The impairment in arterial baroreflex control of HR is further supported by the significantly smaller HR-SBRS incidence, which would imply a lesser engagement of the arterial baroreflex by spontaneous BP fluctuations (18, 34), although the exact mechanism of the baroreceptor dysfunction in HF is still uncertain (5, 8, 43, 44). Clearly, the increase in sympathetic activity may interfere with the ability to increase vagal activity (8, 9, 12, 32); as a consequence, a depressed SBRS is likely to be secondary to either a decrease in parasympathetic activity or an increase in sympathetic activity. In HF, the mechanism of arterial baroreflex dysfunction

**Table 2. Hemodynamic values at rest, during moderate exercise, and moderate exercise plus MRA in N and in the same animals after induction of HF**

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</tr>
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<td>N, moderate free-flow exercise</td>
<td>2.70±0.06†</td>
<td>150.6±7.5</td>
<td>9.02±0.24†</td>
<td>49.6±2.5†</td>
<td>184±9†</td>
<td>5.8±1.1</td>
</tr>
<tr>
<td>N, moderate exercise + MRA</td>
<td>1.98±0.10‡</td>
<td>189.0±8.3‡</td>
<td>10.38±0.37‡</td>
<td>53.7±2.9‡</td>
<td>196±9‡</td>
<td>4.8±0.9</td>
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</tr>
<tr>
<td>HF, moderate free-flow exercise</td>
<td>2.06±0.16‡</td>
<td>134.6±8.3‡</td>
<td>7.14±0.57‡</td>
<td>37.1±2.9‡</td>
<td>192±4‡</td>
<td>1.8±0.3‡</td>
</tr>
<tr>
<td>HF, moderate exercise + MRA</td>
<td>1.66±0.18‡</td>
<td>166.6±10.4‡</td>
<td>7.61±0.62‡</td>
<td>36.4±2.7‡</td>
<td>208±4‡</td>
<td>2.4±0.3‡</td>
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Values are means ± SE. For HLBF n = 6; for all other values, n = 7. *P < 0.05 vs. N; †P < 0.05 free-flow exercise vs. rest; ‡P < 0.05 free-flow exercise plus MRA vs. free-flow exercise.
is probably multifactorial and may be located in all components of the reflex arc (8, 5, 22, 36, 47).

Although already depressed at rest, in HF subjects, SBRS underwent a progressive decrease with the increase in exercise intensity and MRA, in a manner closely similar to the control state, and in each exercise setting, it was significantly less than in control. Again, as in control, LVSP-HR stimulus-response relationship showed an intensity- and MMR-dependent rightward and upward shift.

Overall, it appears that despite that HF induces an impairment in baroreflex control of HR, a reduction in SBRS with exercise and further reduction with MRA, as well as resetting of the baroreflex to a higher pressure and HR still occurs in HF with a pattern similar to that observed in control experiments. This finding indicates that vagal activity is less in HF than in control but that even in HF, there is still vagal activity to withdraw during exercise as in normal dogs (29).

It is difficult to provide a definitive explanation of the mechanism(s) responsible for the decrease in SBRS by MRA during dynamic exercise. This issue has been addressed recently by Sala-Mercado et al. (40). The possibility of a direct action of MMR on parasympathetic pathways seems unlikely because the MMR appears to operate mainly via increases in sympathetic nerve activity with little control over parasympathetic activity (28). The most likely explanation is that the decrease in SBRS depends on the increased sympathetic activation that occurs with the increase in exercise intensity and magnitude of MRA, as reflected by the marked increase in plasma norepinephrine and renin, induced by MRA at the workloads employed in the present investigation in normal and, even more, in the HF state (11). Indeed, it has been repeatedly reported that SBRS undergoes a reduction in both physiological and pathological conditions characterized by higher sympathetic activation. This explanation would fit well with the depressed SBRS with increased HR observed at rest in the present study and with the increase in resting plasma
norepinephrine and renin reported by Hammond et al. (11) in the HF state.

In HF, the ability of the MMR to improve ventricular function is virtually abolished (11, 31), and the pressor response occurs via peripheral vasoconstriction. It has been suggested that this shift in efferent mechanisms may be due in part to a lesser ability of the arterial baroreflex to buffer MMR-induced peripheral vasoconstriction (17). In the same manner, the reduced buffering capacity of arterial baroreflex in modulating HR might have favored the MMR-induced increase in HR during exercise in HF. The similarity of HR in control and HF state during moderate exercise observed in the present investigation would support this suggestion and would confirm the hypothesis formulated recently for normal exercising dogs (40) that MRA may influence the baroreflex control over HR, in order to better control cardiac performance by modulating baroreceptor resetting and concomitantly lessening baroreflex opposition to HR increases. The possibility that the higher levels of plasma renin present at rest, and even more during exercise with MRA in HF at the workloads of the present study (11), could have contributed to the observed decrease in SBRS, though an increase in circulating angiotensin II, cannot be excluded (46). Activation of the renin-angiotensin system by increasing plasma levels of angiotensin II may indeed act on baroreflex control of HR both directly in the cardiac centers in the brain and in the peripheral nerve terminals, facilitating norepinephrine release and inhibiting acetylcholine release (46). Interestingly, in the present as in previous studies (14, 40), we reached the same qualitative conclusions by either using HR or RRI in all experimental conditions.

**Limitations of the study.** Spontaneous baroreflex sequence technique has some inherent limitations. By the use of only spontaneous BP and HR changes, the analysis could be inadequate to evaluate the full stimulus-response curve of the norepinephrine and renin reported by Hammond et al. (11) in the HF state.

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arterial baroreflex (i.e., threshold, saturation, and linear operational range of the reflex). Therefore, as described previously (40), the possibility that the decrease in SBRS observed during dynamic exercise and after MRA in control and HF may have resulted from a shift to a nonlinear region of the baroreflex stimulus-response relationship cannot be discounted. Another limitation is that the spontaneous baroreflex sequence technique examines HR responses to rapid, transient changes in arterial blood pressure that are mainly parasympathetically mediated, whereas it does not enable us to investigate the slower sympathetic component of the baroreflex. Therefore, our observations of the effect of dynamic exercise and MRA on cardiac baroreflex in HF are most likely confined to the parasympathetic component of baroreflex, and it is unknown whether and how HF affects the sympathetic component of the arterial baroreflex control of HR, an aspect that could be relevant particularly at the higher exercise intensities (25).

However, the spontaneous baroreflex sequence technique carries many advantages. It enables a qualitative and quantitative estimate of the integrated baroreceptor-cardiac response relationships during the spontaneous blood pressure fluctuations that characterize both the resting and exercise conditions. This is possible to do without the necessity of any pharmacological or mechanical interventions. This aspect is particularly relevant in the HF conditions, in which, for example, sympathostimulatory reflexes, by stretch of cardiac chambers after the phenylephrine-induced increase of afterload or a direct β-adrenergic stimulation at sinus node level by high doses of the drug superimposed to the already heightened BP of exercise, may affect SBRS determination.

In conclusion, we studied baroreflex control of HR during dynamic exercise in dogs before and after induction of HF. Although impaired at rest and during exercise and exercise with MRA, changes in arterial baroreflex control of HR occurred with a pattern, as in control experiments, with a progressive resetting of the arterial baroreflex stimulus-response relationship and a decrease in SBRS in proportion to exercise intensity and magnitude of MRA, indicating the persistence of some vagal activity to be modulated by the exercise stimulus.

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