Impaired muscle metaboreflex-induced increases in ventricular function in heart failure

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O’Leary, Donal S., Javier A. Sala-Mercado, Robert A. Augustyniak, Robert L. Hammond, Noreen F. Rossi, and Eric J. Ansorge. Impaired muscle metaboreflex-induced increases in ventricular function in heart failure. Am J Physiol Heart Circ Physiol 287: H2612–H2618, 2004.—We investigated to what extent heart failure alters the ability of the muscle metaboreflex to improve ventricular function. Dogs were chronically instrumented to monitor mean arterial pressure (MAP), cardiac output (CO), heart rate (HR), stroke volume (SV), and central venous pressure (CVP) at rest and during mild treadmill exercise (3.2 km/h) before and during reductions in hindlimb blood flow imposed to activate the muscle metaboreflex. These control experiments were repeated at constant heart rate (ventricular pacing 225 beats/min) and at constant heart rate coupled with a β-adrenergic blockade (atenolol, 2 mg/kg iv) in normal animals and in the same animals after the induction of heart failure (HF). Increases in SV, resulting in large increases in CO and MAP. At constant HR, marked increases in CO still occurred but now via substantial increases in stroke volume (24). In this setting of metaboreflex activation with constant HR, marked increases in CO still occurred but note via substantial increases in stroke volume (24). Inasmuch as no significant change in central venous pressure occurred, these increases in stroke volume were unlikely a consequence of the Frank-Starling effect but rather likely reflected increases in ventricular performance. In addition, combining β-adrenergic blockade with ventricular pacing in normal dogs abolished the reflex increase in CO (31) further indicating that the rise in stroke volume with metaboreflex activation at constant HR reflected reflex increases in ventricular performance.

Recently, we observed that the ability of the muscle metaboreflex to increase CO was reduced in animals with mild to moderate congestive heart failure (HF) (11). In this setting, activation of the muscle metaboreflex still elicited a significant increase in HR, but little change in CO occurred due to a fall in stroke volume during metaboreflex activation. HR during mild to moderate exercise is significantly increased after induction of HF, thus filling time is already reduced in this setting. Substantial metaboreflex-induced tachycardia further decreases ventricular filling time, which could lead to reductions in stroke volume (42). Furthermore, the ventricles may become more afterload sensitive, and the ability of the metaboreflex to enhance ventricular contractility may be impaired. Thus the mechanisms mediating the reduced ability of the muscle metaboreflex to increase CO in HF are unclear. The present study was designed to test the hypothesis that in subjects with HF, the ability of the muscle metaboreflex to increase ventricular function is markedly impaired.

METHODS

Experiments were performed using 10 conscious, chronically instrumented dogs of either gender selected for their willingness to run on a motor-driven treadmill. All procedures were reviewed and

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approved by the institutional animal care and use committee and
conformed to National Institutes of Health guidelines.

Surgical preparation. Detailed descriptions of the surgical prepa-
ration and postoperative care have been described in several recent
previous publications (2–4, 11). Briefly, in a series of aseptic surgical
sessions, blood flow transducers (Transonic Systems) were implanted
on the ascending aorta and terminal aorta (immediately proximal to
the iliac arteries) to monitor CO and hindlimb blood flow (HBF),
respectively. A vascular occluder (InVivo Metrics) was placed distal
to the terminal aortic flow probe to activate the muscle metaboreflex
via partial reductions in HBF. Mean arterial pressure (MAP) and
central venous pressure (CVP) were measured via catheters implanted
in the abdominal aorta and atrial-caval junction via the right jugular
vein, respectively. In addition, two stainless steel ventricular pacing
electrodes were attached to the apex of the left ventricle for subse-
quent ventricular pacing. All cables and catheters were tunneled
subcutaneously and exteriorized between the scapulae. The animals
were allowed to recover at least 1 wk between surgical procedures and
between the last procedure and the first experiment.

Experimental protocols. All experiments were performed after the
animals had completely recovered from the surgical preparation, were
active, afebrile, and had a good appetite. The animal was brought to
the laboratory and directed to the treadmill. The blood flow transduc-
ers were connected to flowmeters (Transonic systems) to monitor CO
and HBF, and the catheters were connected to pressure transducers
(Transpac IV, Abbott Laboratories) to monitor MAP and CVP. HR
was monitored via a cardiotachometer triggered by the CO signal.
Data were displayed on a physiograph (Gould 3800) and were
collected on a laboratory computer at 1,000 Hz. Beat-by-beat mean
values were saved to hard disk for subsequent analysis.

The muscle metaboreflex was activated via partial reductions in
HBF during mild exercise (3.2 km/h, 0% grade). The treadmill
was started, and after 3–5 min, HBF was partially decreased via the
inflation of the vascular occluder implanted below the blood flow
transducer on the terminal aorta. HBF was decreased to the lowest
level at which we felt that animals could maintain the workload for
sufficient time to allow the responses to achieve steady state for 60 s
(usually 3–5 min). Experiments were conducted as described above
(control) and repeated on a separate day after the ventricular pacing
ectrodes were connected to a pacemaker (set at 225 beats/min)
immediately before the experiment to examine the responses to
muscle metaboreflex activation at constant HR. This pacing rate was
above any level of HR observed in the control experiments. The
pacemaker was disconnected at the end of the experiment. An
additional separate day, the experiment with constant HR was
repeated coupled with β-adrenergic blockade via atenolol (2 mg/kg iv)
administered ~15 min before the experiment.

Induction of HF. After the above experiments were completed,
congestive HF was induced via rapid ventricular pacing. The ventric-
ular pacing electrodes were connected to a pacemaker set at 225
beats/min for ~30 days. After induction of HF, the experiments were
repeated. The pacemaker was disconnected for the initial control
experiment after the induction of HF and, on separate days, the
experiments during constant HR (225 beats/min) and constant HR
plus β-adrenergic blockade were repeated. Thus each animal served as
its own control in each setting of control experiments, constant HR,
and constant HR plus β-adrenergic blockade, before and after the
induction of congestive HF.

Data analysis. All data were averaged for 1 min during steady state
at rest, free-flow exercise, and with imposed reductions in HBF. Our
objective was that after induction of HF, we would reduce HBF to the
same levels as induced before HF within each setting of control
experiments and experiments at constant HR and constant HR plus
β-adrenergic blockade. This objective was accomplished in that
within each experimental setting there were no significant differences
in the level of HBF during metaboreflex activation.

Reductions in HBF via vascular occlusion will also increase arterial
pressure independent of the muscle metaboreflex due to the passive,
mechanical effect of decreasing vascular conductance to a bed that
receives a substantial fraction of CO (4, 22). Because we simul-
taneously measured both CO and HBF, the passive, mechanical
effect of vascular occlusion on MAP can be directly calculated as
MAP = CO/MAP − CVP, and ΔHVC equals the decrease in hindlimb vascular conductance
(HVC = HBF/MAP − CVP) imparted by inflation of the vascular
occluder. This passive, mechanical effect of vascular occlusion
was subtracted from the observed level of MAP to reveal the
metaboreflex-mediated increase in MAP caused by increases in CO
and peripheral vasoconstriction (MAPactive). The extent of periph-
eral vasoconstriction was estimated by calculating vascular con-
ductance in all vascular beds except the hindlimbs, termed nonis-
chemic vascular conductance (NIVC), which was calculated as
NIVC = (CO − HBF)/(MAP − CVP). All data are reported as
means ± SE. Statistical analysis was made via two-way ANOVA
for repeated measures, and individual means were compared via
the test for simple effects using SYSTAT software (version 8.0).
Statistical significance was concluded if $P < 0.05.$

RESULTS

Table 1 shows the effect of HF on resting hemodynamics.
Rapid ventricular pacing caused modest HF characterized by
increased resting HR, CO, depressed MAP, high CVP, and
dehcreased HBF.

Figures 1, 2, and 3 show the effects of muscle metaboreflex
activation via imposed decreases in HBF on CO, HR, SV,
MAP, CVP, and nonischemic vascular conductance in control
experiments (Fig. 1), during constant HR (Fig. 2), and during
constant HR after β-adrenergic blockade (Fig. 3) before (nor-
mal) and after the induction of HF.

In normal animals during control experiments (Fig. 1),
muscle metaboreflex activation caused a substantial increase in
CO. In the same animals after induction of modest HF, the
baseline levels of CO, SV, and HBF during exercise were
significantly decreased. HBF was decreased to a similar level
as in the normal setting (483 ± 83 vs. 572 ± 137 ml/min, $P >$
0.05). CO did rise somewhat with hindlimb ischemia after
induction of HF, but the change was less than one-third of
that observed in normal animals (±1.58 ± 0.34 vs. ±0.48 ± 0.10
l/min, $P < 0.05$). In both settings, metaboreflex activation
caused substantial tachycardia; however, in normal animals
stroke volume was maintained, whereas after HF, metaboreflex

Table 1. Effect of heart failure on hemodynamic values at rest

<table>
<thead>
<tr>
<th></th>
<th>MAP, mmHg</th>
<th>CO, l/min</th>
<th>HR, beats/min</th>
<th>SV, ml</th>
<th>CVP, mmHg</th>
<th>HBF, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>97.4±3.1</td>
<td>4.13±0.28</td>
<td>91.9±5.1</td>
<td>45.5±3.1</td>
<td>1.6±0.3</td>
<td>0.70±0.05</td>
</tr>
<tr>
<td>Heart failure</td>
<td>83.9±3.5*</td>
<td>3.32±0.29*</td>
<td>122.3±6.5*</td>
<td>27.2±1.7*</td>
<td>7.8±1.0*</td>
<td>0.56±0.05*</td>
</tr>
</tbody>
</table>

Values are means ± SE at rest in animals before and after the induction of heart failure. MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; SV, stroke volume; CVP, central venous pressure; HBF, hindlimb blood flow. * Significantly different from normal.

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Fig. 1. Levels of cardiac output (CO), heart rate (HR), stroke volume (SV), mean arterial pressure (MAP), central venous pressure (CVP), nonischemic vascular conductance (NIVC), and HBF during mild exercise during control (C) and metaboreflex activation (MR) in normal animals and in the same animals after induction of heart failure from control experiments. The level of MAP during MR reflects only MAPactive. *Significantly different from respective control levels; †control values in heart failure significantly different from control values in normal animals. Horizontal brackets with * indicate a significant effect of heart failure was detected; vertical brackets with * indicate a significant effect of metaboreflex activation was detected; in these settings no significant interaction term was detected so pairwise comparisons of individual means could not be performed.

Fig. 2. Levels of CO, HR, SV, MAP, CVP, NIVC, and HBF with HR maintained constant during mild exercise before (C) and after muscle MR in normal animals and in the same animals after induction of heart failure. Abbreviations and symbol definitions as in Fig. 1.
activation caused a significant decrease. In normal animals no change in nonischemic vascular conductance occurred with metaboreflex activation, whereas after induction of HF, a significant decrease was observed with hindlimb ischemia. ANOVA revealed significant effects of both HF and metaboreflex activation on MAP\textsubscript{active}, but no significant interaction term was detected, indicating that HF decreases MAP, but the reflex increase in MAP\textsubscript{active} was similar in both groups. In normal animals no change in CVP occurred with metaboreflex activation. After induction of HF, CVP was markedly elevated during mild exercise and increased further with metaboreflex activation.

Metaboreflex activation at constant HR in normal animals induced similar hemodynamic responses as in control experiments (Fig. 2). A substantial increase in CO was again observed; however, the mechanism of this increase was reversed from control experiments in that instead of a tachycardia with sustained stroke volume, HR was experimentally held constant, and the increase in CO occurred due to a significant increase in stroke volume. In contrast, after induction of HF, both CO and stroke volume were significantly lower than in normal animals during mild exercise, and no significant change occurred in either variable with metaboreflex activation. HBF was again lower than normal during mild exercise in HF and was decreased to a similar level as in normal animals for metaboreflex activation ($P > 0.05$). As in control experiments, in normal animals no change in nonischemic vascular conductance was observed with metaboreflex activation, whereas after induction of HF, a significant decrease occurred during metaboreflex activation. ANOVA also revealed significant effects of HF and metaboreflex activation on MAP\textsubscript{active}, but no significant interaction term was observed, similar to that observed in control experiments. Again similar to control experiments, no reflex change in CVP was observed in normal animals, and after induction of HF, CVP was markedly elevated during exercise and increased further with metaboreflex activation.

Maintaining HR constant plus pretreatment with the β-adrenergic antagonist atenolol altered the hemodynamic responses to mild exercise and metaboreflex activation in both groups (Fig. 3). CO and stroke volume were depressed from control values during mild exercise in both groups but markedly so after induction of HF. Indeed stroke volume in this setting was only ~20% of normal levels. ANOVA revealed significant effects of HF and metaboreflex activation on both CO and stroke volume, but in neither case were significant interaction terms detected. HBF was reduced by nearly 50% during mild exercise after induction of HF, but the levels of HBF with metaboreflex activation were not significantly different. In normal animals, nonischemic vascular conductance decreased from control levels during exercise by ~30% and more so after induction of HF. ANOVA revealed significant effects of both HF and metaboreflex activation, but no significant interaction term was detected, indicating that both HF and metaboreflex activation lowered nonischemic vascular conductance. ANOVA revealed significant effects of HF and metaboreflex activation as well as a significant interaction term for MAP\textsubscript{active}, indicating that the reflex increase in MAP\textsubscript{active} was significantly smaller after induction of HF. CVP was substantially higher during mild exercise after induction of HF, and in contrast to control experiments, CVP increased similarly in both groups with metaboreflex activation (e.g., significant

Fig. 3. Levels of CO, HR, SV, MAP, CVP, NIVC, and HBF with HR maintained constant plus pretreatment with the β-adrenergic receptor antagonist atenolol during mild exercise before (C) and after muscle MR in normal animals and in the same animals after induction of heart failure. Abbreviations and symbol definitions as in Fig. 1.
ANOVA HF and metaboreflex effects and no significant interaction effect).

Table 2 shows the absolute observed increases in MAP in each setting (active + passive changes). In control experiments similar increases in the observed level of MAP occurred with metaboreflex activation in normal animals and after induction of HF. However, at constant HR and at constant HR plus atenolol smaller increases were observed after induction of HF.

DISCUSSION

The muscle metaboreflex is one of the most powerful cardiovascular reflexes and is capable of eliciting large increases in arterial pressure, HR, CO, CVP, central blood volume mobilization, and vasoconstriction in peripheral vascular beds (2–4, 11, 16, 18–21, 23–26, 29–32, 41, 43). In conscious dogs during submaximal workloads, the primary mechanism of this reflex is to increase CO thereby increasing the total amount of blood flow available to the active skeletal muscle (2, 4, 25, 27, 31, 43). This increase in CO in normal animals likely stems from several mechanisms (discussed below). In conscious dogs with HF, the ability of the muscle metaboreflex to increase CO is severely impaired (11). In the present study, we demonstrated that this impairment is, in part, due to decreased ability to improve ventricular function.

Control of stroke volume. Previously, O’Leary (23) demonstrated that during mild exercise the majority of the metaboreflex-induced tachycardia occurs via activation of the sympathetic nerves to the heart, inasmuch as muscarinic blockade had little effect on the reflex rise in HR, whereas most of the tachycardia was abolished by β-adrenergic blockade (23). In addition, during β-adrenergic blockade the reflex rise in MAP was also significantly reduced leading to the conclusion that the tachycardia is an important component of the pressor response. However, the results of a subsequent study (24), which were also confirmed in the present study, indicate that increases in ventricular performance are likely more important than the tachycardia per se. When HR was maintained constant via ventricular pacing, substantial increases in CO still occurred with metaboreflex activation, but the mechanism of this increase shifted from tachycardia with sustained stroke volume to constant HR (experimentally controlled) with significantly increased stroke volume. Inasmuch as no significant change in CVP occurred, this increase in stroke volume was unlikely a consequence of the Frank-Starling effect but likely reflected increased ventricular contractility. In addition, in a separate study, we (31) subsequently showed that the combination of ventricular pacing coupled with β-adrenergic blockade abolished the increase in CO. Similar results were observed in the present study (Fig. 3). These results support the concept that metaboreflex activation causes functional increases in ventricular performance, in part, via increases in sympathetic activity. In contrast, after the induction of HF, only small if any increase in CO is observed with metaboreflex activation (see Ref. 11, Fig. 1). Although a substantial metaboreflex tachycardia is still observed, stroke volume is not maintained but decreases, which limits any rise in CO. This occurs despite an increase in CVP (mechanisms and consequences of this discussed below), which would be expected to raise stroke volume via the Frank-Starling effect. However, Komamura et al. (15) concluded that the Frank-Starling mechanism is exhausted in HF; thus increases in ventricular filling pressure will have little impact on stroke volume. The substantial effect of the muscle metaboreflex on ventricular function revealed in normal dogs by the large increase in stroke volume when the reflex was activated at constant HR was abolished in HF. In this setting no significant metaboreflex-induced increases in stroke volume or CO occurred. The addition of β-adrenergic blockade to constant HR markedly depressed stroke volume and CO during mild exercise in animals after induction of HF and small decreases in both occurred with metaboreflex activation likely due to the increase in ventricular afterload. Thus the ability of the metaboreflex to raise ventricular performance via both increases in contractility as well as the Frank-Starling mechanism are markedly impaired in HF. Several studies have demonstrated a downregulation and desensitization of β-adrenergic receptors in the ventricular myocardium after induction of HF, which likely contributes to this impairment (1, 17).

Central blood volume mobilization. During dynamic exercise when sufficient cardiac reserve exists, muscle metaboreflex activation causes substantial increases in CO (2, 4, 43). However, increasing HR or ventricular contractility will have limited sustained effect on CO due to the reciprocal relationship between CO and ventricular filling pressure (31, 33). Thus increases in CO in CO will decrease CVP thereby decreasing ventricular preload, which will lower stroke volume due to the Frank-Starling effect. Therefore, increases in CO by increasing ventricular function become self limiting. Recently, Sheriff et al. (31) demonstrated that the muscle metaboreflex is one of the most powerful reflexes in the ability to increase central blood volume mobilization. This was indirectly shown by the fact that large increases in CO occur with metaboreflex activation, but no decrease in CVP is observed (see Ref. 31 and Fig. 1). A more direct demonstration of a large reflex increase in central blood volume mobilization was the observation that when the reflex was activated with CO maintained essentially constant, large increases in CVP were observed (31). Similar results were observed in the present study in both normal animals and after the induction of HF. In normal animals the combination of ventricular pacing plus β-adrenergic blockade abolished both the chronotropic and inotropic changes, little change in CO occurred, and significant increases in CVP were observed. In the animals after induction of HF, even in the control experiments a significant increase in CVP occurred despite a small rise in CO [this rise in CO would be expected to cause less than a 1-mmHg fall in CVP due to the fundamental hydraulic relationship between CO and CVP (31, 33)]. Furthermore, when HR was held constant in the subjects with HF with or without β-adrenergic blockade, little change in CO occurred and CVP increased by ~2 mmHg. Similar increases were observed in normal dogs when the reflex was activated.
with constant HR and β-adrenergic blockade in which little (Fig. 3), if any (31), significant change in CO occurred. By comparison of this response to those from other strong cardiovascular reflexes, unloading of carotid baroreceptors in conscious dogs with CO held constant results in less than a 1-mmHg rise in CVP (5). Thus the muscle metaboreflex is one of the most powerful reflexes in the ability to raise ventricular filling pressure, and this ability is sustained even in HF, wherein baseline levels of CVP are markedly elevated. However, in HF this may have little impact on stroke volume due to a reduction in the Frank-Starling mechanism (15).

Mechanisms of metaboreflex pressor responses. In normal dogs during submaximal dynamic exercise, increases in arterial pressure with metaboreflex activation occur via the increases in CO in that little, if any, change in nonischemic vascular conductance occurs (see Refs. 2, 4, 11, 43, and Fig. 1). This mechanism is markedly changed in HF. In this setting, little increase in CO occurs, and significant decreases in nonischemic vascular conductance were observed. Indeed, we (11) previously reported that virtually complete vasoconstriction of the kidney was often observed with metaboreflex activation after induction of HF. Even in normal dogs a shift in the mechanism of metaboreflex-induced increases in arterial pressure, from increases in CO to peripheral vasoconstriction, can also occur. When exercise intensity approaches maximal levels and little if any further increase in CO is possible, imposed reductions in HBF still produce a pressor response, but this increase in arterial pressure occurs solely via peripheral vasoconstriction (4). In addition, even during mild exercise, if little or any increase in CO can occur (e.g., via ventricular pacing coupled with β-adrenergic blockade), a metaboreflex pressor response still occurs but now via peripheral vasoconstriction (see Ref. 31, Fig. 3). What causes this marked shift in the mechanisms of the muscle metaboreflex in subjects with HF or even in normal subjects with acute limitations in the ability to raise CO is unknown.

Limitations. Although HBF was decreased to similar levels within each experimental paradigm before and after the induction of HF, we do not know whether this resulted in the same level of metaboreceptor activation. Sterns et al. (39) concluded that in humans with HF, metaboreceptor sensitivity may be diminished. However, in HF, the lower level of skeletal muscle blood flow during exercise may result in increased interstitial concentration of the putative substances thought to be responsible for the reflex [e.g., H+; lactate, diprotonated phosphate, ATP (13, 34–38)]. Previously, we showed that imposed reductions in HBF in animals after induction in HF as well as high workloads without vascular occlusion often resulted in massive increases in sympathetic nerve activity as evidenced by very high arterial plasma norepinephrine levels, marked peripheral vasoconstriction, as well as exaggerated release of vasopressin and renin (11, 12).

The strength of the muscle metaboreflex is also dependent on the arterial baroreflex. Using a similar preparation, Sheriff et al. (32) showed in normal dogs that the metaboreflex pressor response increased more than twofold after arterial baroreceptor denervation. Several studies have shown that baroreflex sensitivity is reduced in HF (6–10, 14, 28, 40, 44). Whether there is reduced baroreflex ability to buffer metaboreflex responses in HF is unknown.

We used increases in stroke volume observed in normal animals with metaboreflex activation at constant HR as an indirect indicator of reflex increases in ventricular performance. We feel that this is a reasonable estimate of changes in ventricular contractility, because no change in CVP occurred and this increase in stroke volume was seen despite marked increases in ventricular afterload. Furthermore, this increase in stroke volume was abolished by β-adrenergic blockade. In animals after induction of HF, metaboreflex activation at constant HR caused no change in stroke volume despite significant increases in CVP. Although it should be noted that afterload was elevated (albeit to a significantly smaller extent in HF, Table 2) and increased afterload sensitivity in HF may have obscured any effect of increased ventricular contractility that could raise stroke volume. Further studies with more direct indexes of ventricular contractility may be warranted.

We conclude that HF markedly attenuates the ability of the muscle metaboreflex to increase ventricular performance via either the Frank-Starling mechanism or via β-adrenergic receptor mediated increases in ventricular contractility. This decrease in the ability to raise CO causes a functional shift in the mechanisms of muscle metaboreflex-induced increases in arterial pressure.

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