Cardiovascular responses to exercise and muscle metaboreflex activation during the recovery from pacing-induced heart failure

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Augustyniak, Robert A., Eric J. Ansorge, Jong-Kyung Kim, Javier A. Sala-Mercado, Robert L. Hammond, Noreen F. Rossi, and Donal S. O’Leary. Cardiovascular responses to exercise and muscle metaboreflex activation during the recovery from pacing-induced heart failure. J Appl Physiol 101: 14–22, 2006. Rapid recovery of resting hemodynamics from tachycardia- or arrhythmia-induced heart failure (HF) has been demonstrated in both humans and animals. However, little is known about cardiovascular responses to exercise in animals or about reflex control of the cardiovascular system during exercise while recovering from HF. Inasmuch as the reduced cardiac output (CO) during exercise in HF has been shown to lead to underperfusion of active skeletal muscle and tonic activation of the muscle metaboreflex, an improved CO during exercise in subjects recovering from HF may lead to higher skeletal muscle blood flows and to relief of this metabolic stimulus. We investigated cardiovascular responses to graded treadmill exercise and metaboreflex activation [evoked by imposed graded reductions in hindlimb blood flow (HLBF) during mild and moderate exercise] in chronically instrumented dogs during control, mild to moderate HF (induced by rapid ventricular pacing), and recovery from HF. Most hemodynamic responses to graded exercise returned to control within 24 h of disconnecting the pacemaker. After 2 wk of recovery, CO and HLBF at each workload were significantly higher than control. In addition, whereas the increase in CO that normally occurs with metaboreflex activation was markedly attenuated in HF, it completely returned in the recovery experiments. We conclude that cardiovascular responses to graded exercise during the recovery from pacing-induced HF return rapidly to near or above control and that the increased CO and HLBF in recovery likely relieved the metabolic stimulus and tonic metaboreflex activation that may have occurred during moderate exercise in HF.

skeletal muscle ischemia; muscle chemoreflex; muscle afferents; central venous pressure; heart rate; vascular conductance; sympathetic nerve activity; graded exercise

Fatigue during even mild exercise is a common problem associated with subjects suffering from heart failure (HF). Our laboratory has recently described the altered hemodynamic and neurohormonal responses to exercise in dogs with moderate HF (1, 11, 12, 15, 28). During exercise in HF, cardiac output (CO) is reduced and blood pressure control relies more on peripheral vascular responses resulting from increases in sympathetic nervous system activity and the secretion of vasoactive hormones (12). The source of the increased sympathetic outflow is largely unknown. However, during exercise in subjects with HF, blood flow to active skeletal muscle is reduced, which can lead to relative ischemia (12). Our laboratory has recently shown that some of the increase in sympathetic outflow that occurs during moderate exercise while in HF results from tonic muscle metaboreflex activation (1, 11). The muscle metaboreflex is a reflex that protects the perfusion to active skeletal muscle, such that when oxygen delivery to active muscle does not meet the demand, metabolic by-products accumulate within the muscle and stimulate skeletal muscle afferents which elicits the reflex responses. In healthy dogs, this leads to marked increases in mean arterial pressure (MAP), heart rate (HR), and CO, with little if any change in total vascular conductance (therefore, no net vasoconstriction or vasodilation). However, in HF, skeletal muscle blood flow is below the threshold for metaboreflex activation, thus likely tonically engaging this reflex. With further imposed reductions in skeletal muscle blood flow, the ability of the reflex to increase CO is impaired, and the pressor response results from peripheral vasoconstriction (1, 11). Thus the often marked vasoconstriction seen in the renal and splanchnic vascular beds during strenuous exercise in HF, as well as that within the active skeletal muscle itself, may be sympathetically mediated and stem from tonic activation of the muscle metaboreflex (11, 12, 24, 46).

Many studies in animals and humans have focused on changes that occur in resting subjects during the recovery from HF. In animals, with removal of the pacing stimulus after 2–4 wk of rapid cardiac pacing, there is resumption of normal sinus rhythm. Many hemodynamic and hormone levels (including CO, MAP, stroke volume, norepinephrine, renin) return to control values within 48 h, and most variables return to control within 2 wk (6, 8, 33, 37, 48). In addition, baroreflex control of HR is markedly improved after 48 h and completely restored within 2–4 wk from the termination of pacing (10). In humans, there is a subpopulation of patients that suffer from high or abnormal heart rhythms, which can be either pharmacologically or surgically corrected. Once corrected, parameters such as ejection fraction, fractional shortening, cardiac filling pressures, systolic or diastolic atrial and ventricular volumes, and heart chamber sizes have been shown to recover and often approach normal levels. However, the time course of recovery is quite variable (days to months) (13, 21, 29, 30, 32).

To our knowledge, cardiovascular responses to exercise during the recovery from HF have never been investigated in animals; however, there are studies that have examined exercise responses in humans recovering from cardiomyopathy or

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HF (5, 22, 29, 32). Within 1 mo of the restoration of sinus rhythm, ejection fraction and maximal oxygen consumption during moderate to severe exercise approach that attained in control groups (22, 32). In addition, patients could sustain exercise for longer periods (5). The recovery of normal atrial and ventricular systolic function during exercise is controversial (22, 36, 45). However, there is a great deal of variability in the time course that parameters recover, which may result from the problems often associated with performing research in humans (variability in medications, severity and duration of HF, age, etc.). Although cardiovascular control in animals at rest during the recovery from pacing induced HF has been well described, with most parameters returning to control within 2–4 wk of the cessation of pacing (7, 8, 14, 39), several studies have documented hypertrophy and persistent ventricular dysfunction (6, 8, 13, 18, 42, 43, 48), which may affect cardiovascular control mechanisms during exercise. Therefore, the first aim of the present study was to investigate the time course of recovery of normal hemodynamic responses to mild through moderate dynamic exercise in dogs after HF induced via rapid ventricular pacing. If CO in the recovery animals normalizes during recovery responses during exercise, while limiting the possibility of a training effect.

**Metaboreflex protocol**. Metaboreflex experiments were performed during mild (3.2 km/h, 0% grade) and moderate (6.4 km/h, 10% grade) workloads. Hemodynamic measurements were taken during free-flow exercise (i.e., no occlusions) and during metaboreflex activation induced via partial graded reductions in HLBF through inflation of the vascular occluder. Free-flow exercise and each level of vascular occlusion were maintained until all parameters had reached steady state (typically 3–5 min). After the control experiments were completed, HF was induced via rapid left ventricular pacing at 225 beats/min for ~30 days, and all experiments were repeated. The pacemaker was disconnected during each experiment. After HF experiments were completed, the pacemaker was disconnected permanently and recovery experiments were performed. Graded exercise recovery responses were performed on recovery days 1, 2–4, 5–7, 8–12, 13–18, and 19–43. Besides recovery day 1, all recovery periods consisted of 3–6 days during which one to three experiments were performed. These time periods were chosen, as opposed to daily experiments, so that we could observe recovery responses during dynamic exercise, while limiting the possibility of a training effect.

**Data Analysis**

One-minute averages of all hemodynamic parameters were taken during rest, during steady-state exercise for the graded exercise experiments, and at each level of partial vascular occlusion for the metaboreflex experiments. Renal blood flow was multiplied by two to account for blood directed toward both kidneys. Renal vascular conductance (RVC) was calculated as [RBF/(MAP – CVP)]. Total vascular conductance (TVC) was calculated as [CO/(MAP – CVP)]. Hindlimb vascular conductance (HLVC) was calculated as [HLBF/ (MAP – CVP)]. Nonischemic vascular conductance (NIV; conductance directed everywhere besides the hindlimbs) was calculated as [(CO – HLBF)/(MAP – CVP)]. Metaboreflex responses were analyzed as first described by Wyss et al. (49). Initial reductions in HLBF
during mild exercise do not evoke metaboreflex responses. However, once HLBF is reduced below an apparent threshold level, there are large increases in MAP, CO, and HR. Thus the relationship between HLBF and the efferent mechanisms of this reflex during mild exercise is “dogleg” in shape. Therefore, the threshold for this reflex was approximated as the intersection of two linear regression lines: an initial response line that includes free-flow exercise and each level of partial vascular occlusion that did not evoke metaboreflex responses, and a pressor response line wherein further reductions in HLBF evoked substantial increases in the efferent responses. During moderate exercise, there is often no threshold for metaboreflex responses (i.e., the relationship between HLBF and the efferent responses is often linear). When this occurred, free-flow exercise was taken as the threshold and the data were fitted to a single linear regression. Also, mechanically reducing HLBF reduces HLVC and causes MAP to rise passively (3, 4, 34, 49). As reported previously (4), we calculated the rise in blood pressure that resulted from the mechanical reduction in HLBF and subtracted that value from the measured blood pressure. Thus we report only the active rise in arterial pressure that resulted from changes in CO and NIVC mediated via the muscle metaboreflex.

Statistical Analysis

Data are presented as means ± SE. For technical reasons, not all parameters could be measured in all animals in all settings (see figures for n values). Therefore, for data collected at rest and during exercise, multiple linear regression analysis was performed, as described previously (16, 40). The data were encoded using dummy variables for each animal and each condition (HF and each recovery period), and an interaction term was included (HF × recovery period). Data from each workload were analyzed separately. This is analogous to a two-way ANOVA for repeated measures but allows the use of all data across all conditions for all observations (40). The output of the multiple linear regression analysis also includes t statistics, which are identical to Bonferonni t values or Dunnett’s test q’ values for comparison to the respective control levels, as described by Slinker and Glantz (40). If the interaction term was statistically significant, then these individual comparisons were accepted. For the metaboreflex experiments, at each workload, the value of each variable during free-flow exercise was compared with that observed with maximal metaboreflex activation via paired t-test. An alpha level of P < 0.05 was used to determine statistical significance.

RESULTS

Comparing Standing Rest Data During Control, HF, and Recovery From HF

Figures 1 and 2 show the average data observed at standing rest during control, HF, and recovery from HF. In HF, the animals displayed a resting tachycardia and elevated CVP, whereas CO, MAP, RBF, RVC were reduced and TVC was unchanged. After ~2 wk of recovery from HF, HR, MAP, RBF, and RVC all returned to control levels, whereas CO, SV, and HLBF actually increased above control levels. CVP returned to control during the last recovery period examined.

Graded Exercise Responses: Control vs. HF

As shown in Fig. 1, during each workload while in HF, SV and CO were significantly decreased compared with control, whereas HR was significantly elevated. TVC during HF was not different from control at any workload. MAP during HF was significantly reduced compared with control during the
first two工作loads; however, it was not different from control during the highest workload achieved.

As shown in Fig. 2, HLBF was significantly decreased at rest and during all workloads except for the highest exercise intensity where it was on the cusp of significance (P \( \neq \) 0.054). HLVC during HF was not different from control, whereas RBF and RVC during HF were significantly reduced. CVP at each workload was significantly elevated compared with control.

**Graded Exercise Responses During Recovery From HF**

Figures 1 and 2 show that, within 24 h of disconnecting the pacemaker, SV and CO had either returned to or nearly returned to control levels at each workload. From that point forward, there were progressive increases in SV and CO, such that by recovery days 5–7, SV was significantly elevated above control at all workloads. The same held true for CO during the last three recovery time periods examined. In fact, for the two highest workloads, CO was significantly above baseline at recovery days 5–7. SV remained at control level from recovery days 8–12 forward. CVP returned to control level by the last recovery period examined at rest and all workloads.

**Muscle Metaboreflex Activation During control, HF, and Recovery From HF**

The mean hemodynamic values for the control, HF, and recovery from HF experiments during mild (Fig. 3) and moderate (Fig. 4) exercise. MAP, CO, HR, SV, NIVC, and CVP were plotted as a function of HLBF during free-flow exercise, metaboreflex threshold, and the peak responses attained with the largest reductions in HLBF imposed.

**Mild exercise.** Large reductions (~32%) in HLBF were required to evoke the metaboreflex during mild exercise in the control experiments. Once hindlimb perfusion was reduced below the threshold for this reflex, a large pressor response occurred, which was mediated by significant increases in CO and HR, whereas SV remained unchanged. NIVC was also unchanged, indicating no net vasoconstriction or vasodilation. In addition, there was a small but significant reduction in CVP. During HF, smaller reductions in HLBF were required to evoke the metaboreflex, although there was still a clear threshold. Metaboreflex activation led to a significant pressor response that was reduced compared with control, and there was a complete reversal in the mechanisms of the increase in arterial pressure. CO was unchanged despite a marked tachycardia because there was a small but significant reduction in SV. The significant decrease in NIVC shows that the pressor response was primarily mediated via peripheral vasoconstric-
tion. CVP increased significantly with metaboreflex activation. During free-flow exercise in the recovery animals, CO, SV, and HLBF were significantly higher than in control. Once HLBF was reduced sufficiently, the mechanisms of the metaboreflex-mediated pressor response in the recovery animals reverted back to significant increases in CO and HR with no change in NIVC, as observed in control experiments. All metaboreflex response patterns in the recovery animals were identical to those in control experiments, before the induction of HF, although CO, SV, and HLBF were significantly higher than in control.

Moderate exercise. Compared with mild exercise, smaller reductions (~14%) in HLBF were required during moderate exercise to evoke the metaboreflex and cause significant increases in MAP in the control experiments. Again, the pressor response was mediated largely via increases in CO and HR, whereas there was also a small but significant increase in SV. There was also a very small but significant reduction in NIVC during maximal metaboreflex activation, whereas CVP was unchanged. Metaboreflex activation during moderate exercise in the HF period again resulted in a large pressor response; however, there was no clear threshold, and the mechanisms of the response were altered. HR increased and while SV tended to decrease, which led to a small but significant increase in CO that was greatly attenuated from control. The reduction in NIVC was significant and much more substantial than during control experiments, thus indicating that peripheral vasoconstriction was the primary contributor to the pressor response. Finally, during moderate exercise in recovery, CO, SV, and HLBF during free-flow exercise were significantly elevated compared with control. Metaboreflex activation resulted again in a large pressor response, the mechanisms of which reverted
back to and were similar to those seen in control experiments (e.g., increased CO), although NIVC was unchanged. In addition, note that there was a clear threshold for HR and CO.

**DISCUSSION**

To our knowledge, this is the first study to investigate responses to dynamic exercise and muscle metaboreflex activation during the recovery from experimental HF induced via rapid ventricular pacing. The major new finding in this study is that cardiovascular control during dynamic exercise during recovery from mild to moderate pacing induced HF returns toward normal within just 2 wk after disconnecting the pacemaker. After just 1 wk of recovery, CO, SV, and several other hemodynamic parameters at rest and during graded exercise were elevated significantly above values obtained before the induction of HF. In addition, whereas in HF the metaboreflex pressor response was mediated primarily via peripheral vasoconstriction, during recovery it was mediated almost solely via increases in CO, similar to control experiments. Furthermore, because CO increased above control levels during recovery from HF, this likely relieved tonic metaboreflex activation and thereby reduced sympathetic outflow that occurs during moderate exercise while in HF.

**Resting Responses During Recovery From HF**

Patients suffering from abnormally high heart rates or abnormal cardiac rhythms have been shown to develop left ventricular impairment, which, if left untreated, can lead to HF (9, 19, 21, 23, 29, 31). Correction of the arrhythmia (e.g., removing the pacing stimulus in animals or pharmacological
and/or surgical intervention in humans) leads to rapid hemodynamic improvement and often complete resolution of symptoms of HF (13, 30, 47). Indeed, in our present study, resting CO, HR, and SV had all returned to control levels after just 24 h of recovery. As recovery progressed, there were further increases in resting SV and CO, such that after ~2 wk of recovery, SV and CO were elevated above control. Wilson et al. (48) made similar observations in dogs where resting CO was elevated significantly above control 1–2 wk after discontinuing ventricular pacing. Damiano et al. (8) also reported increases in both SV and CO 4 wk after the removal of the pacing stimulus, and suggested that rapid pacing resulted in a type of “training.” The increase in resting SV above control levels may have occurred for several reasons. Ventricular preload, as assessed by CVP, remained above control until the last recovery period examined. The persistent left ventricular dilatation and chronic elevation of end-diastolic volume observed during recovery (6, 8, 43) would have similar effects on preload. In addition, several studies in both dogs and pigs have shown that ventricular hypertrophy exists during recovery from pacing-induced HF (6, 13, 18, 43). Ventricular hypertrophy coupled with the reduction in ventricular afterload expected from the significant increase in TVC may also result in a higher SV.

Although CO remained at control values through recovery days 5–7, TVC was significantly elevated above control. Hence, MAP remained depressed through recovery days 8–12, at which time CO and HLBF rose significantly higher than control levels. One source of the vasodilation, which caused the reduction in MAP, was the hindlimb vasculature, as indicated by the increase in HLVC above control after just 1 day of recovery. The rapid restoration of the hindlimb vascular responses during recovery from HF indicates that little if any long-term vascular changes occurred in the hindlimb with this duration and depth of HF. The renal vascular bed responded somewhat differently, because RVC returned to baseline by recovery days 2–4 but never above baseline. As MAP began to return toward baseline with each recovery period, RBF appeared to follow the same trend. This suggests that HF may have caused an intrinsic structural or functional change within the kidneys that led to the decreased RBF during HF, because RBF did return to baseline by recovery period days 8–12. One previous study found that the reductions in RBF that occur during pacing-induced HF do not fully return to pre-HF levels even after 2 mo of recovery (37). However, the magnitude of the reduction in RBF was greater in that study, likely because the animals were paced at a higher rate (240–260 beats/min) into severe HF. Those authors (37) suggested that the large reduction in RBF may have lead to irreversible damage within the renal vasculature, although this is not known. Our hemodynamic variables recovered more rapidly and the renal vascular responses recovered completely, thus suggesting a reversible component to renovascular hemodynamics after mild to moderate HF.

Dynamic Exercise Responses During Recovery From HF

The time course of recovery of hemodynamic response patterns during dynamic exercise after pacing-induced HF were remarkably similar to that which occurred during rest. Specifically, left ventricular function during exercise appeared to be improved above that which occurred in the control experiments, as evidenced by the significant elevations in SV and CO above pre-HF levels at all workloads. In fact, three dogs were studied after 31–43 days of recovery, and SV remained elevated above control level, suggesting that left ventricular function remains altered even after 6 wk of recovery. Autonomic control of HR may have normalized because by recovery period days 2–4 and for the remainder of the study, HR was not different from control at any workload. These data would indicate that little if any training effect occurred that would be expected to lower HR below control levels at rest and all workloads (34). It is known, at least in resting dogs, that power spectral analysis of HR variability returns to normal after 2 wk of recovery from left ventricular pacing-induced HF (14). Thus, because HR responses after recovery day 1 were not different from control during any of the workloads, the increases in CO that occurred after ~1 wk of recovery resulted solely from increases in ventricular performance (i.e., increased SV), for the reasons already discussed. As occurred at rest, there was marked vasodilation (i.e., increase in TVC) during all recovery periods and all workloads. During early recovery (days 1–4), TVC was elevated, CO rapidly returned to control, whereas the arteriovenous pressure gradient remained lower than in control (i.e., reduced MAP and very high CVP). During the last 3–4 recovery periods TVC was still significantly elevated compared with control, although there were further increases in CO and the arteriovenous pressure gradient also increased (i.e., MAP increased and CVP decreased). The increase in TVC during early recovery caused the animals to be relatively hypotensive during 3.2 and 6.4 km/h despite the rapid recovery of CO. MAP at these workloads did not return to control until CO increased significantly above pre-HF levels. HLVC was significantly elevated above pre-HF levels in dynamic exercise during all recovery periods. During early recovery, the decrease in MAP was proportionately less than the increase in HLVC, which thereby allowed HLBF to return to control levels. Later in recovery (after day 4), MAP returned to control, and this increase in perfusion pressure coupled with the elevated HLVC resulted in HLBFs that were significantly elevated above control levels. The renal vascular responses during exercise appeared to recover somewhat independently of changes in perfusion pressure, particularly at the two highest exercise intensities. That is, RBF nearly doubled from that observed during HF, whereas only minor increases in MAP occurred. CVP returned to control by the last recovery period at all workloads. Thus, after 2 wk of recovery, most hemodynamic variables had either returned to control or had increased above control, which included supranormal CO at all workloads. The increase in CO and HLBF may have had the effect of improving exercise capacity.

Metaboreflex Activation During Recovery From HF

After 2 wk of recovery from HF, HLBF during both mild and moderate exercise was significantly elevated above control level. In HF, the control level of HLBF during exercise was either closer to (mild exercise) or at (moderate exercise) the threshold level for the reflex. In contrast, after recovery, larger decreases in HLBF were required to elicit the reflex at both workloads. Thus, in the recovery experiments (as well as the
control experiments), HLBF needed to be decreased below an apparent threshold, after which metaboreflex responses were observed. In HF, with no clear threshold, it could mean that the reflex is tonically active, or alternatively it may mean that the observed workload approximates metaboreflex threshold, and any further reductions in HLBF will evoke the metaboreflex. During our recovery experiments, higher HLBF, and thus increased oxygen delivery to the active skeletal muscle, would be expected to relieve some of the metabolic stimulus that may have resulted in tonic activation of the metaboreflex in HF, particularly during moderate exercise. The fact that decreases in HLBF during control or recovery experiments are necessary to evoke the metaboreflex, whereas this is not the case during HF supports this hypothesis. Therefore, our recovery experiments support our laboratory’s previous study (11) and provide the most compelling evidence to date that during moderate exercise in HF dogs the metaboreflex is a tonic mediator in cardiovascular control and contributes to excess sympathetic activation.

In all experiments, once the metaboreflex threshold was reached, large increases in arterial pressure occurred. However, the mechanisms of metaboreflex-induced pressure responses seem to exhibit marked plasticity depending on the experimental setting. Our control experiments support previous observations that muscle metaboreflex activation evokes significant increases in HR, ventricular performance, CO, and MAP with little or no net change in vascular conductance to nonisomorphic vascular beds (i.e., no net vasoconstriction or vasodilation) (1, 2, 11, 16, 20, 26, 28, 35, 38, 49). However, during HF, in addition to cardiac impairment, there is evidence that functional and molecular changes occur within the metabolically sensitive afferent fibers that stimulate the metaboreflex (41), both of which may lead to altered metaboreflex function. Indeed, muscle metaboreflex activation in exercising dogs during ventricular pacing-induced HF results in an attenuated pressor response that is almost solely mediated via peripheral vasoconstriction (1, 11, 28). This is similar to what occurs with metaboreflex activation during severe exercise when a further increase in ventricular function is limited (4). However, during our recovery experiments, the mechanisms of the metaboreflex-mediated pressor response were very similar to those before the induction of HF, i.e., large pressor response mediated via increases in CO. Consequently, with metaboreflex activation during recovery from HF, there was a complete reversal in the mechanisms of the pressor response, such that the magnitude of the metaboreflex-mediated increases in CO were not different from control experiments.

The efferent mechanisms mediating the metaboreflex responses may depend, in part, on the extent of buffering of this reflex by the arterial baroreflex (25). Our laboratory recently demonstrated in normal dogs that substantial metaboreflex-induced vasoconstriction can occur when the buffering effects of the arterial baroreflex are removed via sinoaortic denervation (17). In HF dogs, the effect of sinoaortic denervation on the patterns of the metaboreflex was much less apparent, likely reflecting the impaired baroreflex functioning in HF (16). The normalization of arterial (10) and perhaps cardiopulmonary baroreflex (50) function during recovery from pacing-induced HF may contribute to the normalization of the efferent mechanisms of the muscle metaboreflex as well as the cardiovascular responses to graded dynamic exercise.

In conclusion, we found that most cardiovascular responses to dynamic exercise during the recovery from mild to moderate HF return to control levels rapidly and virtually completely. CO, SV, and HLBF, and HLVC increased above control level by recovery days 2–4 and remained so throughout the duration of the study at all workloads. The large increases in CO observed during control experiments during metaboreflex activation were markedly attenuated during HF; however, they completely returned during recovery. To what extent these increases in SV and CO seen during 2–3 wk of recovery are sustained over the succeeding months or years is unknown. Finally, whereas it appeared as though the metaboreflex was tonically active in HF during moderate exercise, the significant increase in HLBF that occurred during recovery may have relieved the metabolic stimulus for metaboreflex activation.

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