Exaggerated Renal Vasoconstriction During Exercise in Heart Failure Patients

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Background—During static exercise in normal healthy humans, reflex renal cortical vasoconstriction occurs. Muscle metaboreceptors contribute importantly to this reflex renal vasoconstriction. In patients with heart failure, in whom renal vascular tone is already increased at rest, it is unknown whether there is further reflex renal vasoconstriction during exercise.

Methods and Results—Thirty-nine heart failure patients (NYHA functional class III and IV) and 38 age-matched control subjects (controls) were studied. Renal blood flow was measured by dynamic positron emission tomography. Graded handgrip exercise and posthandgrip ischemic arrest were used to clarify the reflex mechanisms involved. During sustained handgrip (30% maximum voluntary contraction), peak renal vasoconstriction was significantly increased in heart failure patients compared with controls (70 ± 13 versus 42 ± 1 U, P = 0.02). Renal vasoconstriction returned to baseline in normal humans by 2 to 5 minutes but remained significantly increased in heart failure patients at 2 to 5 minutes and had returned to baseline at 20 minutes. In contrast, during posthandgrip circulatory arrest, which isolates muscle metaboreceptors, peak renal vasoconstriction was not greater in heart failure patients than in normal controls. In fact, the increase in renal vasoconstriction was blunted in heart failure patients compared with controls (20 ± 5 versus 30 ± 2 U, P = 0.05).

Conclusions—During sustained handgrip exercise in heart failure, both the magnitude and duration of reflex renal vasoconstriction are exaggerated in heart failure patients compared with normal healthy humans. The contribution of the muscle metaboreceptors to reflex renal vasoconstriction is blunted in heart failure patients compared with normal controls. (Circulation. 2000;101:784-789.)

Key Words: exercise ▪ heart failure ▪ vasoconstriction ▪ kidney

During exercise in normal, healthy humans, renal cortical blood flow (RCBF) decreases and renal cortical vascular resistance (RCVR) increases.1 This renal vasoconstriction is mediated reflexively, in part by “muscle metaboreceptors.” Muscle metaboreceptors are finely myelinated type IV nerve fibers located in skeletal muscle that are activated by ischemic metabolites, such as lactic acid, diprotonated phosphates, and adenosine, generated during exercise.2-4 In animal models, chemical activation of these fibers causes a reflex increase in efferent renal sympathetic nerve activity. Similarly, in humans during static handgrip exercise, reflex renal vasoconstriction occurs.1 This reflex renal vasoconstriction helps direct blood flow from nonexercising tissues, such as the kidneys, to tissues with increased metabolic demands, such as exercising muscle. Furthermore, reflex renal vasoconstriction helps to maintain blood pressure by offsetting the vasodilatation in exercising muscle beds.5

The hallmark of congestive heart failure is fluid retention and decreased exercise tolerance. Whereas reflex renal vasoconstriction during exercise may be beneficial in healthy humans in whom renal blood flow far exceeds metabolic needs, in heart failure patients, resting blood flow is markedly diminished,6 and further renal vasoconstriction during exercise may have harmful sequelae. Further reflex increases in renal vascular resistance during exercise may lead to increased afterload and augmented sodium and water retention in patients with heart failure. The purpose of this study was to determine whether reflex renal vasoconstriction occurs during exercise in heart failure, and if so, whether it is mediated by muscle metaboreceptors, as in normal humans.

Methods

Study Population
After written informed consent had been obtained, 39 patients with advanced heart failure (left ventricular ejection fraction 21 ± 3%, NYHA class III to IV, mean age 53 ± 12 years) referred for evaluation of heart transplantation and 38 age-matched normal control subjects (controls; mean age 50 ± 15 years, P = NS) partici-
pared in these studies. Under medical supervision in the UCLA General Clinical Research Center, heart failure patients discontinued cardiac medications, including vasodilators and diuretics, for 24 to 36 hours before the research protocol. No patients were taking β-adrenergic receptor blockers. All patients tolerated the medication withdrawal without complication. The study protocols were approved by the UCLA Human Subject Protection Committee. Normal volunteers were healthy, as confirmed by normal medical history and physical examinations, complete blood count, blood urea nitrogen, and serum creatinine, and were not taking medications. Heart failure patients and controls abstained from caffeine for 18 hours before the study but otherwise were on an uncontrolled diet. The studies were performed with the subjects in the postabsorptive state.

Quantification of RCBF Based on Dynamic PET and the $[^{15}\text{O}]\text{H}_{2}\text{O}$ Technique

RCBF was quantified on the basis of dynamic PET imaging by use of the blood flow agent $[^{15}\text{O}]\text{H}_{2}\text{O}$, which has a short physical half-life, allowing repetitive measurements of RCBF within a 15-minute period. Estimates of RCBF by the $[^{15}\text{O}]\text{H}_{2}\text{O}$ dynamic PET approach have been found to correlate linearly with those obtained invasively in dogs by the microsphere and arterial reference technique. The theory for the measurement of renal blood flow by use of $[^{15}\text{O}]\text{H}_{2}\text{O}$ and dynamic PET has been described in detail by Nitzschke and colleagues. Changes of RCBF obtained by the invasive $^{133}\text{Xe}$ washout method are similar to those obtained with the noninvasive $[^{15}\text{O}]\text{H}_{2}\text{O}$ technique in both normal humans and humans with heart failure. The general principles of blood tissue exchange and its application to the measurement of blood flow were proposed by Kety. $[^{15}\text{O}]\text{H}_{2}\text{O}$ is metabolically inert and diffuses freely across the capillary and cellular membranes and thus rapidly equilibrates between the vascular and extravascular spaces. Achieve-ment of such equilibration is referred to (by definition) as the first-pass extraction fraction, which in case of $[^{15}\text{O}]\text{H}_{2}\text{O}$ approaches unity and is independent of blood flow. Thus, the net extraction as the product of first-pass extraction fraction and renal blood flow correlates linearly with renal blood flow.

The time-activity curves of the renal cortex were generated by region-of-interest analysis and corrected for dead time of the scanner and partial volume effects. RCBF was then estimated by fitting the PET-measured time-activity curves to a validated 1-compartment model for $[^{15}\text{O}]\text{H}_{2}\text{O}$. The RCBF value (mL·min $^{-1}$·g $^{-1}$) for 1 kidney was calculated as the average value for all analyzed regions of interest per kidney. All analyses were performed by a single investigator (E.U.N.) blinded to the experimental conditions. RCBV was estimated by dividing mean arterial pressure (1 third of pulse pressure plus diastolic pressure) by RCBF.

All renal PET images were acquired on a Siemens/CTI model 921/47 tomograph. This device records 47 image planes simulta-neously. The axial field of view is 15.8 cm. A 30-minute blank scan was recorded as part of the daily routine procedures. All subjects were imaged in the supine position. After a 20-minute transmission image for photon attenuation correction was obtained, study participants were injected with 30 mCi $[^{15}\text{O}]\text{H}_{2}\text{O}$ over 30 seconds into a peripheral vein while acquisition of the serial transaxial tomographic images was started. Twelve 10-second, four 30-second, and one 60-second frame were acquired. Cross-sectional images were reconstructed with a Shepp-Logan filter with a cutoff frequency of 30% of the Nyquist frequency of the system, yielding an in-plane spatial resolution of $\approx 10.8$ mm full-width half-maximum. To minimize invasiveness, the arterial tracer input function was determined from dynamic PET measurements of the abdominal aortic activity. This technique was validated recently by comparison of PET measurements of abdominal aortic activity with well counter measurements of arterial blood samples.

Miscellaneous Measurements

Blood pressure was monitored noninvasively with an automated sphygmomomanometer (Dinamap, Critikon Corp). Heart rate was monitored continuously through lead II of the ECG.

Handgrip Exercise

At the beginning of each experimental session, maximum voluntary contraction (MVC) was determined in the nondominant arm with a handgrip dynamometer. Subjects were instructed to breathe normally during exercise and to avoid inadvertent performance of a Valsalva maneuver.

Experimental Protocols

Protocol 1: RCVR Responses to Static Handgrip at 30% MVC

The purpose of this study was to determine the magnitude and direction of change in RCBF during static handgrip exercise in heart failure patients compared with healthy humans. Ten heart failure patients and 10 normal subjects participated in this protocol. Subjects were studied in the supine position in the PET scanner. The subject rested during the 20-minute transmission scan. Baseline measurements of blood pressure and heart rate were made. Then, RCBF was determined with PET $[^{15}\text{O}]\text{H}_{2}\text{O}$ as described above. Sustained handgrip at 30% MVC was performed for 3.5 minutes. At 1.5 minutes of exercise time, $[^{15}\text{O}]\text{H}_{2}\text{O}$ was administered for measurement of RCBF. Blood pressure and heart rate were measured continuously throughout exercise.

Protocol 2: RCVR Recovery

To determine the recovery time of the renal circulation after sustained handgrip exercise, 10 heart failure patients and 9 normal subjects underwent a protocol identical to the one above, except that renal blood flow was measured from 2 to 5 minutes and at 20 minutes after release of handgrip exercise. $[^{15}\text{O}]\text{H}_{2}\text{O}$ was injected at 2 to 5 minutes and at 20 minutes of recovery to determine whether RCVR had returned to baseline.

Protocol 3: RCVR Responses to Posthandgrip Circulatory Arrest

The purpose of this study was to determine the effect of the muscle metaboreflex on the renal circulation during handgrip exercise. During posthandgrip circulatory arrest, central command and the muscle mechanoreflex remains activated. Ten heart failure patients and 10 normal subjects were studied in the supine position in the PET scanner. The subject rested during the 20-minute transmission scan. Baseline measurements of blood pressure and heart rate were made. RCBF was determined with PET $[^{15}\text{O}]\text{H}_{2}\text{O}$ as described above. Sustained handgrip at 30% MVC was performed for 3.5 minutes. Just before release of handgrip, a pneumatic cuff on the upper arm was inflated to 240 mm Hg for a total of 4 minutes. At 2 minutes of posthandgrip ischemia, $[^{15}\text{O}]\text{H}_{2}\text{O}$ was administered for measurement of RCBF. Blood pressure and heart rate were measured continuously throughout exercise and during posthandgrip circulatory arrest.

Protocol 4: RCVR Responses to Static Handgrip at 10% MVC

The purpose of this study was to determine the impact of central command and/or the mechanoreceptor activation at the onset of low-intensity static handgrip exercise in heart failure patients compared with controls. Ten heart failure patients and 9 normal controls participated in this protocol. The subject rested during the 20-minute transmission scan. Baseline measurements of blood pressure and heart rate were made. RCBF was determined with PET $[^{15}\text{O}]\text{H}_{2}\text{O}$ as described above. Sustained handgrip at 10% MVC was performed for 2.5 minutes. Coincident with the onset of handgrip exercise, $[^{15}\text{O}]\text{H}_{2}\text{O}$ was administered for measurement of RCBF. Blood pressure and heart rate were measured continuously throughout exercise.

Data Analysis

Statistical analysis was performed by 2-sample $t$ tests and paired $t$ tests. Probability values ≤0.05 were considered statistically significant. Values are presented as mean±SEM.
Results

Baseline Hemodynamics

Resting renal blood flow was significantly lower and resting RCVR was significantly higher in heart failure patients than in normal humans. Resting heart rate was higher and resting blood pressure was not different in heart failure patients compared with normal humans (Table).

Protocol 1: RCVR Responses to Static Handgrip at 30% MVC

During static handgrip exercise (30% MVC), peak renal vasoconstriction was significantly greater in heart failure patients than in normal humans (Figure 1A). Similarly, nadir renal blood flow was significantly lower in heart failure patients than in normal humans (Figure 1B). At peak exercise, peak heart rate tended to be higher (86±6 versus 75±1 bpm, P=0.06) and peak mean arterial pressure lower (93±4 versus 104±3 mm Hg, P=0.04) in heart failure patients than in normal controls.

Protocol 2: RCVR Recovery

At 2 to 5 minutes of recovery from static handgrip exercise (30% MVC), RCVR remained significantly increased compared with baseline in heart failure patients (Figure 2A). In contrast, in normal humans during 2 to 5 minutes of recovery, RCVR had returned to baseline. By 20 minutes of recovery, RCVR had returned to baseline heart failure patients. The increase in RCVR during 2 to 5 minutes of recovery was significantly greater in heart failure patients than in normal controls (Figure 2B). Mean arterial pressure had returned to basal levels in both heart failure patients (78±2 versus 79±2 mm Hg, P=NS) and normal controls (78±4 versus 80±3 mm Hg, P=NS). Heart rate had returned to basal levels in both heart failure patients (77±5 versus 73±6 bpm, P=NS) and normal controls (66±1 versus 66±3 bpm, P=NS).

Protocol 3: RCVR Responses to Posthandgrip Circulatory Arrest

In both heart failure patients and normal humans, during posthandgrip (MVC 30%) circulatory arrest, RCVR was significantly increased compared with baseline. However, the peak RCVR during posthandgrip ischemic arrest was not increased in heart failure compared with normal humans (Figure 3A). In fact, the increase in RCVR in heart failure patients compared with normal humans was significantly reduced in response to posthandgrip ischemic arrest (Figure 3B). Mean arterial pressure remained elevated compared with baseline in both heart failure patients (98±6 versus 88±4 mm Hg, P=0.03) and normal controls (104±4 versus 88±2 mm Hg, P=0.0001). Heart rate remained elevated in heart failure patients (87±6 versus 77±5 bpm, P=0.02) but not in normal controls (68±3 versus 65±2 bpm, P=NS).

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Normal controls (37±2 vs 43±2 MVC) was significantly greater in heart failure patients than in normal controls (10% MVC). A, Peak RCVR during SHG exercise (10% MVC) was significantly greater in heart failure patients than in normal controls (30±2 vs 20±5 U, P=0.05).

**Protocol 4. RCVR Responses to Static Handgrip at 10% MVC**

During low-intensity (MVC 10%) static handgrip exercise, peak renal vasoconstriction was significantly greater in heart failure patients than in normal humans (Figure 4A). The increase in RCVR during posthandgrip circulatory arrest was significantly greater in normal controls than in heart failure patients (30±2 vs 20±5 U, P=0.05).

**Figure 3. Renal circulation during posthandgrip circulatory arrest.** A, Peak RCVR during posthandgrip circulatory arrest (PHG-CA) was not different between heart failure patients and normal controls (56±7 vs 50±2 U, P=NS). B, Increase in RCVR during posthandgrip circulatory arrest was significantly greater in normal controls than in heart failure patients (30±2 vs 20±5 U, P=0.05).

(86±5 versus 86±1 mm Hg, P=NS). Peak heart rate was similar in heart failure patients and normal controls (69±5 versus 66±3 bpm, P=NS).

**Figure 4. Renal circulation during sustained handgrip (SHG) exercise (10% MVC).** A, Peak RCVR during SHG exercise (10% MVC) was significantly greater in heart failure patients than in normal controls (37±2 vs 24±1 U, P=0.0001). B, Nadir RCBF during SHG exercise (10% MVC) was significantly lower in heart failure patients than in normal controls (2.3±0.04 vs 3.5±0.4 mL·min⁻¹·g⁻¹; P<0.0001).

**Discussion**

The 2 major new findings in the present study are that (1) during sustained handgrip exercise in heart failure, both the magnitude and the duration of reflex renal vasoconstriction are exaggerated in heart failure compared with normal, healthy humans and (2) the contribution of the muscle metaboreceptors to reflex renal vasoconstriction is blunted in heart failure patients compared with normal controls. This finding is suggestive of alternative afferent and/or efferent pathways underlying the exaggerated reflex renal vasoconstriction during exercise in patients with heart failure.

In patients with heart failure, the renal vasculature is markedly vasoconstricted even at rest. In fact, the peak reflex renal vasoconstriction during exercise in normal humans remains less than the resting renal vasoconstriction in patients with heart failure. Because resting RCVR is increased in heart failure patients compared with normal humans, it is necessary to compare changes in vasomotor tone during handgrip exercise in groups with unequal baseline values. Inequality in baseline vascular tone may lead to an exaggerated response to vasodilatation in the group with greater basal vasoconstriction. Studies in animals and humans have shown that an increase in baseline vascular resistance will amplify responses to vasodilator stimuli. Importantly, however, this amplification does not occur during vasoconstrictor stimuli, such as the handgrip exercise protocols used in this study. However, the problem of unequal baseline values remains.

Comparisons of peak, nadir, and delta values, rather than percentage change values, preserve and indeed highlight the abnormal physiology of the renal circulation in heart failure. The clinical relevance of these data is more readily apparent.

Despite this markedly increased basal renal vasoconstriction, heart failure patients had further, significant reflex renal vasoconstriction during exercise. The peak reflex renal vasoconstriction in heart failure patients was significantly greater than in normal, healthy humans. Not only was the magnitude of the reflex renal vasoconstriction during handgrip exercise increased in heart failure, but the duration of heightened renal vasoconstriction was prolonged as well. In normal control subjects, reflex renal vasoconstriction returned to normal levels within 2 to 5 minutes of release of handgrip exercise. In heart failure patients, in contrast, reflex renal vasoconstriction persisted at 2 to 5 minutes of recovery and was returned to baseline levels at 20 minutes after handgrip release.

In normal, healthy humans, we have previously reported that activation of the muscle metaboreceptors during exercise contributes importantly to the reflex renal vasoconstriction. In the present study, however, we found that in heart failure patients, the contribution of the muscle metaboreceptors to renal vasoconstriction during exercise was blunted. Muscle metaboreceptors were isolated from other important reflex systems by the maneuver called “posthandgrip circulatory arrest,” in which a blood pressure cuff placed proximally on the exercising arm is inflated to suprasystolic levels at the conclusion of handgrip exercise. This occludes arm.
blood flow, thereby trapping ischemic metabolites, the stimuli for muscle metaboreceptors. Immediately after cuff inflation, the forearm is relaxed, which releases muscle tension and volitional effort, the respective stimuli to muscle mechanoreceptors and central command. During this maneuver, reflex renal vasoconstriction was present in patients with heart failure. However, peak renal vasoconstriction was not significantly greater in heart failure patients than in normal controls, despite higher resting renal vasoconstriction in heart failure. In fact, the increase in reflex renal vasoconstriction was significantly blunted in heart failure patients compared with normal controls. Therefore, we conclude that, although they may normally play a role in the reflex renal vasoconstriction during handgrip exercise, muscle metaboreceptors are not the principal mediators of the exaggerated magnitude and duration of reflex renal vasoconstriction during exercise in patients with heart failure.

These findings of reduced muscle metaboreceptor sensitivity in heart failure are consistent with previous work done in patients with heart failure during exercise. Stearns et al. reported that muscle metaboreceptor activation of muscle sympathetic nerve activity during exercise is blunted. Although the muscle sympathetic activation during exercise was preserved, sympathetic nerve activity fell during posthandgrip circulatory arrest, implicating other afferent systems in addition to the muscle metaboreceptors as important mediators of the exaggerated sympathetic reflex vasoconstriction during exercise in heart failure.

Alternative afferent mechanisms that may be important in the exaggerated reflex renal renin-angiotensin system in heart failure may include activation of afferent systems, such as muscle mechanoreceptors or central command. In animals, the mechanoreflex has been shown to modulate the renal vascular bed. For example, in chloralose-anesthetized cats, mechanical stimulation of the triceps surae muscle produces an immediate reflex increase in efferent renal sympathetic nerve activity. In normal humans, we have reported that central command and/or mechanoreceptors help mediate reflex renal vasoconstriction during static handgrip exercise. We have previously reported that at the onset of low-intensity exercise, before the generation of ischemic metabolites, there was significant renal renal vasoconstriction. McClain et al. used limb congestion in healthy humans to model human heart failure. They found that mechanoreceptor control of sympathetically activated renal sympathetic nerve activity was augmented during handgrip exercise in this human model of heart failure. Similarly, there is evidence that central command may be augmented in heart failure. Silber and colleagues reported an exaggerated perceived effort during exercise in patients with heart failure, even when exercise was normalized to an individual’s maximum exercise capacity, which is suggestive of an exaggerated role for central command in heart failure patients.

Alternatively, activation of a second effector system, in addition to the sympathetic nervous system, may underlie the exaggerated reflex renal vasoconstriction during exercise in heart failure. In the setting of chronic β-adrenergic stimulation, as is present in heart failure, the sensitivity of the renal renin-angiotensin system is increased. Increased renin, stored in vesicles, is available for release. In response to acute renal β-adrenergic stimulation, renin is released within seconds and is active immediately. We speculate that in patients with heart failure, in whom the renin-angiotensin system has enhanced activity and sensitivity, reflex increases in efferent renal sympathetic nerve activity during exercise may be amplified locally by the exquisite sensitivity of the renal renin-angiotensin system, with potentially deleterious sequelae.

In these experiments in patients with heart failure, we studied renal vascular responses to static, not dynamic, exercise. Everyday activities of daily living involve dynamic exercise as well. Identical afferent and efferent reflex systems are activated during static and dynamic exercise, although the relative importance of the various systems is shifted. In static exercise, muscle ischemia is more profound, and principally muscle metaboreceptors are activated. Conversely, during dynamic, exercise, activation of the mechanoreceptors occurs repetitively and continuously throughout exercise. We have found an exaggerated reflex renal vasoconstriction in heart failure patients compared with normal controls during static exercise that is not attributable to the muscle metaboreceptors but may be attributable to mechanoreceptors. One may anticipate an even greater reflex renal vasoconstriction during rhythmic, dynamic exercise that engages primarily the muscle mechanoreceptors. Studies of RCVR during dynamic exercise are ongoing in our laboratory.

Measurements of RCBF by the [15O]H2O dynamic PET technique have been found to correlate linearly with those obtained invasively in healthy dogs by the microsphere and arterial reference technique. However, no similar studies have been performed in models of low-flow states, as occur in congestive heart failure. The effect, if any, of congestive heart failure on the accuracy of the 15O PET technique is unknown. Our control subjects and heart failure patients were age-matched but not sex- and race-matched. The impact of sex and race on RCBF is unknown.

In summary, during exercise, reflex renal vasoconstriction is exaggerated in heart failure patients compared with normal humans. Both the peak level and the duration of reflex renal vasoconstriction are enhanced in patients with heart failure. This marked reflex renal vasoconstriction occurred during mild static handgrip exercise. This level of exercise is likely to be encountered repeatedly throughout the day, such as while carrying groceries or lifting and carrying a small child. Thus, on a daily basis, patients with heart failure may be exposed to repeated bouts of exaggerated and prolonged renal vasoconstriction, which may have significant clinical sequelae.

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References


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