Chemical Mediators of the Muscle Ergoreflex in Chronic Heart Failure
A Putative Role for Prostaglandins in Reflex Ventilatory Control

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Background—The overactivity of ergoreceptors (intramuscular afferents sensitive to products of skeletal muscle work) may be responsible for the abnormal responses to exercise and symptoms of exercise intolerance in chronic heart failure (CHF); however, little is known of the chemical nature of the stimuli involved. We investigated biochemical factors (H+, VCO2, VO2, HCO3, K+, phosphate, lactate, PGE2, PGF1α, and bradykinin) potentially involved in ergoreceptor activation.

Methods and Results—Sixteen stable patients with CHF (64.9±2.7 years, peak VO2 15.8±0.7 mL/kg per min) and 10 age-matched controls were studied. The ergoreceptor test involved two 5-minute handgrip exercises. On one occasion, the subjects recovered normally (control recovery), whereas on the other a posthandgrip regional circulatory occlusion was induced in the exercising arm, isolating the stimulation of the ergoreceptor after exercise. The ergoreflex was quantified as the difference in ventilation between the posthandgrip regional circulatory occlusion and the control recovery periods. During the protocol, the local muscular blood effluent concentrations of metabolic mediators were assessed. Patients had an ergoreflex effect on ventilation greater than controls (4.8±1.4 versus 0.4±0.1 L/min, P<0.01). During the ergoreflex test in patients, the following metabolites were elevated with respect to resting values in comparison with controls: PGE2 (3.7±0.7 versus 1.1±0.2 pg/mL), PGF1α (16.2±2.8 versus 7.2±1.2 pg/mL), and bradykinin (2.1±0.3 versus 1.0±0.1 pg/mL), P<0.05 for all comparisons. Only the increases in prostaglandins were predictors of the ergoreflex response (r>0.41, P<0.01).

Conclusions—Although multiple metabolites are concentrated in exercising muscle in CHF, only prostaglandins correlated with ergoreflex activity, suggesting these factors as potential triggers to the exaggerated ergoreflex, which is characteristic of CHF. This may have important implications for novel therapies to improve exercise tolerance.

Key Words: exercise muscles ventilation

Chronic heart failure (CHF) is a common cardiovascular condition with both a high mortality and a high burden of morbidity. Muscle fatigue and breathlessness are major symptoms and relate to a poor prognosis; objectively, patients show reduced exercise tolerance and an increased ventilatory response to exercise, and relate to a poor prognosis; objectively, patients show reduced morbidity. Muscle fatigue and breathlessness are major symptoms of oxidative enzymes in patients with CHF.

The ergoreflex consists of a brain-stem autonomic and ventilatory response activated by signals from the periphery, such as free nerve-ending group III and IV muscle afferents. It has been hypothesized that muscle metabolic abnormalities or circulatory insufficiency of CHF might cause local overproduction and accumulation of muscle metabolic products, which activate these afferents. This is in accordance with the observation of a decreased muscular metabolic capacity, attributable to structural and functional changes within the muscles, such as changes in fiber type and decreased activity of oxidative enzymes in patients with CHF.

The triggering factors responsible for the ergoreflex stimulation and their involvement in the abnormal exercise responses in CHF are yet to be established. In anesthetized animals, hydrogen ions (H+), phosphate and lactate, adeno-
sine and arachidonic acid, prostaglandins (iPGE_2, i6-keto-PGF_1α), potassium (K⁺), bradykinin, sodium (Na⁺), acetylcholine, histamine, serotonin, and vasodilator substances have all been proposed and investigated as putative triggers. Studies have also been performed in humans, but none have investigated whether any metabolic factor is specifically involved in the ergoreflex overactivation of patients with CHF.

We therefore set out a novel study to investigate putative trigger factors correlated with the ergoreflex activation in patients with CHF. Their identification could lead to development of treatments specific for reduction of the ergoreflex overactivation, which in turn may improve symptom control in this syndrome. Because a possible role of prostaglandins has been proposed, we have also specifically investigated the effect on the ergoreflex of chronic aspirin (acetylsalicylic acid) therapy, a powerful enzymatic inhibitor of prostaglandin production, common treatment in ischemic heart disease.

**Methods**

**Study Population**

Sixteen patients with stable CHF attributable to ischemic heart disease or idiopathic dilated cardiomyopathy were compared with 10 age-matched healthy control subjects. All patients were consecutively recruited from the outpatient Heart Failure Clinic at our institution, whereas control subjects were recruited from the 316 Club, comprised of former members of the executive of British Aerospace at Stevenage (England, UK). Baseline characteristics are shown in Table 1.

Inclusion criteria for patient population were clinical stability and no change of medications in the 3 months before the study, no involvement in any exercise-training program, and absence of significant chronic lung disease, valvular heart disease, neuromuscular disorders, exercise-induced myocardial ischemia, arrhythmias, claudication, peripheral vascular disease, myopathy, or liver, renal, or thyroid dysfunction. The patients were all symptomatic during exercise and limited by breathlessness or muscle fatigue. No subject from the control group had clinical signs or past history of heart or pulmonary diseases.

The study was approved by the local ethics committee and conformed to the Declaration of Helsinki. All subjects gave written informed consent.

**Protocol**

All experimental sessions were carried out in a temperature-controlled, air-conditioned room. The subjects were asked to avoid strenuous physical activity for 24 hours before each test and to refrain from eating and smoking or consuming caffeine for 3 hours before the study. The tests were preceded by 30 minutes in a quiet environment.

After an initial clinical screening, all subjects performed a routine cardiopulmonary exercise test to determine their exercise capacity and to familiarize themselves with the laboratory environment, using a maximal symptom-limited, modified Bruce protocol (commencing at stage 0, 1.0 mph at 5.0% gradient) on a Marquette Case 15 treadmill.

**Ergoreceptor Test**

On a separate day, each subject underwent the forearm ergoreceptor test. After a 5-minute resting period, 2 exercises were performed in a random order: (1) a 5-minute session of rhythmic handgrip achieved by squeezing the balloon of a sphygmomanometer (30 squeezes/min) at 50% of the predetermined maximal capacity; and (2) the same protocol followed by 3 minutes of arterial ischemia (posthandgrip regional circulatory occlusion [PH-RCO]) on the exercising arm by inflation of an upper-arm bicep tourniquet to 30 mm Hg above systolic pressure at the beginning of recovery. This protocol has been shown to fix the metabolic state of the muscle and to maintain activation of the ergoreceptors. Sixty minutes separated each bout of arm exercise.

**Data**

**Ventilatory Data and Heart Rate**

Ventilatory and heart rate (HR) data were recorded throughout the test. Subjects breathed through a mouthpiece and wore a nose clip. Ventilation and respiratory rate were measured continuously online using a calibrated heated pneumotachograph, whereas oxygen uptake (VO₂) and carbon dioxide production (VCO₂) were measured breath by breath using a respiratory mass spectrometer (Amis, Innovision). HR was measured by standard ECG leads.

**Blood Tests**

Blood was taken from an antecubital vein in the exercising arm during the last minute of each phase of the ergoreceptor test (resting, exercise handgrip, PH-RCO, and control recoveries) and immediately placed on ice for subsequent analysis.

**Blood Gas Analysis** was performed by a CIBA-Corning 278 Blood gas system and a CIBA-Corning 270 CO-oximeter to assess concentration of H⁺, bicarbonate (HCO₃⁻), partial pressure of venous CO₂ (VCO₂), and O₂ (VO₂). Sodium was measured using a Beckman-Corning 614 Na⁺/K⁺ analyzer. Potassium (K⁺) was assessed by an indirect ion-specific electrode, with the Beckman Synchron CX9 ALX Clinical Analyser (Beckman Instruments, Fullerton, CA).
Reference values in our laboratory range from 3.5 to 5.2 mmo/L, with a coefficient of variation (CV) of <3% at a concentration of 5 mmol/L.

Plasma phosphate was measured using its reaction with ammonium molybdate in acid solution to form a colored phosphomolybdate complex, with the Beckman Synchron CX9 ALX Clinical Analyser (Beckman Instruments Inc). Reference values in our laboratory range from 0.80 to 1.40 mmol/L (CV <6% at a concentration of 1.4 mmol/L).

Lactate was measured using lactate oxidase to catalyze the oxidation of lactate; the concentration of lactate was calculated by monitoring O2 consumption with an O2 electrode using the Analox LM3 Analyser (Analox Instruments, London, UK). The reference range in our laboratory is 0.6 to 2.5 mmol/L (CV <6% at 2.3 mmol/L).

Bradykinin was measured by enzyme immunoassay using the Bradykinin enzyme immunoassay (EIA) kit (Peninsula Laboratories Inc), with sample extraction using a C18 column. In our laboratory, the reference range is 0.2 to 7.5 pg/ml. The detection limit is 0.02 pg/ml with an interassay variation <14%.

6-Keto-Prostaglandin F1α (PGF1α) was measured by Biotrak 6-keto-prostaglandin F1α EIA system (Amersham Pharmacia Biotech UK Ltd), with sample extraction using Amprep C2 columns; the detection limit is 3 pg/ml, with an interassay variation <15%. In our laboratory, the ranges are from 19.14 to 90.48 pg/ml.

Prostaglandin E2 (PGE2) was measured by Biotrak prostaglandin E2 EIA system (Amersham Pharmacia Biotech UK Ltd). The detection limit is 0.5 pg/ml with an interassay variation <11%. In our laboratory, the published reference ranges for healthy control subjects is 4.4 to 6.8 pg/ml.

Statistical Analysis

Data are presented as mean±SEM. For the ventilatory variables, blood metabolites and HR comparison of each phase of the test (ie, the average of the 5 minutes of resting phase, the last minute of handgrip exercise, and the 3-minute PH-RCO and control recovery periods) between the 2 handgrip exercises was performed, analyzed by a repeated measures ANOVA. Dunn’s test was used for all pair-wise comparisons.

The ergoreflex contribution to ventilatory variables was computed as the difference of the changes in each variable between the mean resting values and the average of the 2nd- and 3rd-minute recoveries with and without PH-RCO.

The contribution for each metabolite during the ergoreflex test was computed as the difference between the PH-RCO sample value and the control recovery sample value versus the respective resting sample values.

Pearson’s product-moment correlation coefficient was used to quantify the relationship between changes in blood metabolites during the ergoreflex test and the ergoreflex contribution to the ventilatory response to exercise. P<0.05 was considered significant.

To explore the role of prostaglandin inhibition by aspirin on muscle ergoreflex, we compared the activity of the reflex and the contribution for prostaglandins and bradykinin in the 2 CHF populations taking and not taking aspirin therapy by Student’s t test.

Results

All subjects completed the protocol without adverse events. Two patients complained of some discomfort during the PH-RCO, but none described it as painful or asked to finish the test prematurely. The resting values of all considered variables (respiratory and blood metabolites) were not significantly different before the 2 exercises (ie, with and without PH-RCO) within either subject group. Patients showed higher ventilation and respiratory rates and increased blood concentrations of PGF1α and bradykinin but lower O2 consumption (Table 2).

Handgrip Exercise

During exercise, no difference in any variable was observed between the 2 handgrip runs (ie, before PH-RCO and control recoveries) within either subject group. Exercise increased ventilatory variables in both subject groups, whereas heart rate increased in the group with CHF only. In both groups, exercise also increased H+, VC02, K+, lactate, PGE2, PGF1α, and bradykinin with reduction in VO2. Patients versus controls showed higher blood concentrations of PGE2, PGF1α, bradykinin, and lactate during exercise (Table 2).

Recovery and Ergoreflex

An ergoreflex contribution to the ventilatory and VC02 responses was evident in CHF patients only. During recovery with PH-RCO, ventilation and VC02 remained higher when compared with the control run in patients, a feature not seen in control subjects in this study (Table 3).

During PH-RCO recovery compared with control recovery, the blood concentrations of Na+, H+, VC02, Hco3, PGE2, PGF1α, and bradykinin were significantly elevated in patients, whereas only Na+, H+, and VC02 were elevated in control subjects. VO2 was reduced in both groups of subjects.

Lactate, prostaglandins, and bradykinin also remained significantly elevated in patients versus control subjects during PH-RCO, but only PGE2, PGF1α, and bradykinin significantly contributed to the ergoreflex in patients compared with healthy controls (Table 3). Experimental result from the average of the data from patients and the healthy subjects is expressed graphically in Figure 1.

Correlation Between Blood Metabolites and Ergoreceptor Activation

Only the changes in concentration of the prostaglandins correlated with the ergoreflex contribution to the ventilatory response to exercise by linear regression analysis (PGE2, r=0.41, P<0.05, PGF1α, r=0.60, P<0.001) (Figure 2), whereas bradykinin did not (r=0.346, P=NS).

Effects of Aspirin on Ergoreceptor Activation

When we divided our study CHF population according to aspirin treatment (8 patients taking aspirin, 8 patients not taking aspirin), the 2 groups with CHF did not differ in clinical characteristics (aspirin versus no aspirin population, 65.8±3.1 versus 64.1±2.8 years; peak VO2 15.0±0.9 versus 16.6±1.1 mL/min per kg, Ve/VCO2 slope, 47.1±3.3 versus 41.3±3.2), or in concomitant therapy. However, patients taking aspirin versus those not taking aspirin presented a significantly lower ergoreflex activity in the control of the ventilatory response (2.1±0.6 versus 7.5±2.3 L/min, P<0.05), associated with reduction of blood concentration of PGF1α (10.7±2.9 versus 21.1±3.2 pg/mL, P<0.05) and nonsignificant changes in heart rate (6.04±3.3 versus 1.2±1.6 bpm, P=NS), PGE2 (3.1±0.8 versus 4.6±0.8 pg/mL, P=NS), and bradykinin (1.4±0.6 versus 2.6±0.2 pg/mL, P=NS).

Discussion

Background

When work is performed, metabolites are produced within the exercising muscle. These metabolites may stimulate nerve
TABLE 2. Values of Ventilatory Variables, Heart Rate, and Blood Metabolite Between the 2 Handgrip Exercises (With PH-RCO or Control Recovery) at Rest (Average of 5-Minute Resting Periods) and on Exercise (5th Minute of Exercise) in Heart Failure Patients and Healthy Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients PH-RCO</th>
<th>Patients Control</th>
<th>Control PH-RCO</th>
<th>Control</th>
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<th>Control</th>
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<td>Ventilation</td>
<td>12.4 (0.6)*</td>
<td>13.5 (0.7)*</td>
<td>11.5 (0.6)</td>
<td>11.8 (0.6)</td>
<td>15.7 (0.6)†</td>
<td>15.0 (0.6)†</td>
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<td>VO₂</td>
<td>0.33 (0.02)*</td>
<td>0.33 (0.02)*</td>
<td>0.39 (0.02)</td>
<td>0.39 (0.02)</td>
<td>0.38 (0.02)†</td>
<td>0.36 (0.02)*</td>
</tr>
<tr>
<td>VCO₂</td>
<td>0.28 (0.02)</td>
<td>0.30 (0.02)</td>
<td>0.32 (0.02)</td>
<td>0.33 (0.02)</td>
<td>0.36 (0.02)†</td>
<td>0.35 (0.02)†</td>
</tr>
<tr>
<td>RR</td>
<td>17.3 (0.8)*</td>
<td>18.7 (0.9)*</td>
<td>14.2 (1.0)</td>
<td>14.7 (0.09)</td>
<td>21.3 (1.2)*†</td>
<td>21.2 (1.1)*†</td>
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<td>HR</td>
<td>73.1 (4.6)</td>
<td>78.3 (3.7)</td>
<td>66.3 (7.5)</td>
<td>66.6 (7.5)</td>
<td>82.2 (3.5)*†</td>
<td>81.0 (3.6)*†</td>
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<td>Metabolite data</td>
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<td></td>
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<tr>
<td>Na⁺</td>
<td>141.6 (1.0)</td>
<td>141.8 (0.8)</td>
<td>141.5 (0.7)</td>
<td>140.9 (0.6)</td>
<td>143.0 (1.0)</td>
<td>142.9 (0.6)</td>
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<tr>
<td>H⁺</td>
<td>39.9 (0.9)</td>
<td>40.7 (0.7)</td>
<td>40.7 (0.5)</td>
<td>42.5 (0.7)</td>
<td>45.6 (1.1)†</td>
<td>44.2 (1.0)†</td>
</tr>
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<td>PaCO₂</td>
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<td>5.7 (0.1)</td>
<td>5.8 (0.1)</td>
<td>6.0 (0.1)</td>
<td>7.0 (0.2)†</td>
<td>6.8 (0.2)†</td>
</tr>
<tr>
<td>PaO₂</td>
<td>6.4 (0.5)</td>
<td>6.5 (0.3)</td>
<td>6.2 (0.4)</td>
<td>5.8 (0.4)</td>
<td>4.2 (0.2)†</td>
<td>4.1 (0.2)†</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>26.2 (1.1)</td>
<td>25.8 (1.0)</td>
<td>25.9 (0.5)</td>
<td>25.5 (0.4)</td>
<td>28.2 (1.0)</td>
<td>28.3 (1.0)</td>
</tr>
<tr>
<td>K⁺</td>
<td>4.2 (0.1)</td>
<td>4.1 (0.1)</td>
<td>4.1 (0.1)</td>
<td>3.9 (0.1)</td>
<td>4.5 (0.1)†</td>
<td>4.5 (0.1)†</td>
</tr>
<tr>
<td>Phosphate</td>
<td>1.0 (0.1)</td>
<td>1.0 (0.04)</td>
<td>0.9 (0.03)</td>
<td>0.9 (0.03)</td>
<td>1.0 (0.1)</td>
<td>1.1 (0.1)</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.6 (0.2)</td>
<td>2.1 (0.2)</td>
<td>1.3 (0.2)</td>
<td>1.4 (0.1)</td>
<td>2.3 (0.3)†</td>
<td>2.3 (0.2)*</td>
</tr>
<tr>
<td>PGE₂</td>
<td>6.3 (0.5)</td>
<td>7.1 (0.6)</td>
<td>5.5 (0.5)</td>
<td>6.3 (0.5)</td>
<td>12.4 (1.2)*†</td>
<td>12.2 (1.2)*†</td>
</tr>
<tr>
<td>PGF₁α</td>
<td>89.5 (4.5)*</td>
<td>95.4 (3.7)*</td>
<td>76.1 (2.5)</td>
<td>80.8 (2.6)</td>
<td>123.7 (6.2)*†</td>
<td>118.1 (5.5)*†</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>6.4 (0.4)*</td>
<td>7.4 (0.4)*</td>
<td>5.2 (0.3)</td>
<td>5.7 (0.3)</td>
<td>10.6 (0.5)*†</td>
<td>9.9 (0.5)*†</td>
</tr>
</tbody>
</table>

Values are mean (SEM).

*P<0.01 vs control subjects.

†P<0.01 vs respective resting values.

endings within unmyelinated and small myelinated afferents in skeletal muscle, ie, muscle ergoreceptors. These receptors have been shown to contribute to the ventilatory, hemodynamic, and autonomic responses to small muscle exercises in physiological conditions, although controversy exists on the importance of the role of the ergoreceptor activity during leg exercise in healthy subjects.

In patients with CHF, it has been observed that stimulation of these nerves leads to a reflex increase in ventilation. An essential role of muscle afferents in the excessive ventilation, sympathetic activation, and vasoconstrictive responses to exercise of CHF has been proposed, and a putative role in the genesis of symptoms of exercise intolerance has been suggested.

Patients with CHF have abnormalities in skeletal muscle metabolism, characterized by an earlier acidification and accumulation of metabolic products in the muscle compared with control subjects at matched workload. The cause of this metabolic abnormality seems to be related to a decreased activity of the mitochondrial oxidative enzymes, whereas the role of altered hemodynamic variables seems of less importance. The build up of metabolic products may stimulate the ergoreflexes, with consequently increased ventilatory, hemodynamic, and sympathetic responses to exercise. Knowledge of the specific metabolic triggers of the muscle ergoreceptors may be of benefit in understanding the pathophysiology of symptom generation in CHF. This may lead to potential treatments to improve symptoms and quality of life in patients with CHF by reducing the activation of these receptors.

Present Study

In agreement with previous reports, we found a significantly higher production of metabolic products of muscle work in patients with CHF. Lactate, PGE₂, PGF₁α, and bradykinin were all elevated, confirming the abnormalities in the hemodynamic control mechanisms in patients with CHF.

The novelty of this study is the demonstration, for the first time, that in patients with CHF a significant ergoreflex response was associated with a rise in several metabolites, such as Na⁺, H⁺, VCO₂, HCO₃⁻, PGE₂, PGF₁α, and bradykinin. However, only the rises in prostaglandins and bradykinin were characteristic of the response of CHF patients during the ergoreflex (response absent in controls); only the increases in prostaglandins predicted the ergoreflex response significantly. This finding, ie, the key role of prostaglandins and, perhaps, bradykinin in ergoreflex overactivation in CHF, should not be considered unexpected, based on the important role played by the vasodilator metabolites in the pathophysiology of this syndrome.

Prostaglandins

Prostaglandins are released from vascular endothelial cells during exercise and can be responsible for much of the
flow-induced vasodilatation observed, and, in particular, those of the E-series may contribute to the vasodilatation occurring in working skeletal muscles. The stimuli for the local production of these substances include tissue ischemia as well as the direct influence of vasoactive substances, such as angiotensin II, norepinephrine, and vasopressin. In addition to its vasodilator effects, PG E2 also increases sodium excretion and attenuates the activation of vasopressin on renal tubular permeability to water. Thus, it has been suggested that in vasoconstrictive states such as heart failure, these prostaglandins, together with atrial natriuretic factor, dopamine, and kinins, serve as counter-regulatory mechanisms to the potent vasoconstrictor sodium-retentive hormones, such as renin-angiotensin and sympathetic nervous system and vasopressin.

Inhibition of prostaglandin synthesis by indomethacin suppresses the release of PGF 1α, increases blood pressure, and reduces coronary and leg blood flow during exercise in patient with heart failure. This is associated with a corresponding decrease in leg O2 consumption and a higher level of femoral venous lactate at peak exercise.

Based on these findings, it is possible to hypothesize that the prostaglandins overproduced as compensatory responses may mediate increased ventilation on exercise throughout the stimulation of the muscle ergoreflex. This hypothesis is also supported by the study of Stebbins et al, who observed that prostaglandins contribute to cardiovascular reflexes evoked by muscular contraction.

When we divided our study CHF population according to aspirin treatment, we found that prostaglandin production inhibition significantly buffered the ergoreflex, in keeping with the putative role of these hormones in triggering this reflex. The powerful analgesic effect of the aspirin may have also subdued the pain related to the ergoreflex test itself (ie, regional ischemia in the contracting muscle) and therefore decreased the related hyperventilation during the test. The lack of a bradycardic response during the ergoreflex test in patients taking aspirin (a response that usually accompanies the analgesic effect) does not support this effect as a main component of this pharmacological treatment. However, there is no distinct difference between ergoreceptors and nociceptors (pain receptors), because they are both comprised of free nerve-ending group III and IV muscle afferents. Aspirin has a direct and indirect effect on respiration and increases O2 consumption and CO2 production (especially in skeletal muscle). These pharmacological properties could have a confounding effect on the observed findings. Specifically designed studies are required to confirm the role of prostaglandins on the muscle ergoreflex.

| TABLE 3. Values of Ventilatory Variables, Heart Rate, and Blood Metabolites at the End of the Recovery Phases of the 2 Handgrip Runs (With PH-RCO and Without) and the Differences in the Changes Induced by PH-RCO and Control Recovery Versus Respective Resting Values (Ergoreflex Δ) in Patients and Control Subjects |
|----------------------|------------------|------------------|------------------|------------------|------------------|
|                      | Patients PH-RCO | Patients Control | Patients Ergoreflex Δ | Control PH-RCO | Control Ergoreflex Δ |
| **Ventilatory and heart rate data** |
| Ve                   | 17.2 (1.5)*     | 13.4 (0.6)†      | 4.8 (1.4)*        | 12.2 (0.7)      | 11.5 (0.6)        | 0.40 (0.09) |
| V̇O2                  | 0.34 (0.02)     | 0.34 (0.02)†     | 0.03 (0.01)       | 0.37 (0.02)     | 0.36 (0.02)       | 0.005 (0.01) |
| V̇CO2                 | 0.35 (0.02)     | 0.30 (0.02)†     | 0.08 (0.02)*      | 0.34 (0.02)     | 0.32 (0.02)       | 0.01 (0.01) |
| RR                   | 21.9 (1.2)*     | 19.4 (0.9)*      | 3.6 (1.4)*        | 15.2 (1.2)      | 14.3 (0.9)        | 0.42 (0.48) |
| HR                   | 78.7 (3.8)      | 77.7 (4.0)       | 2.7 (2.1)         | 66.0 (7.5)      | 66.8 (7.5)        | -1.6 (1.3)  |
| **Metabolite data**  |
| Na+                  | 143.6 (0.8)     | 140.8 (1.0)†     | 1.7 (0.4)         | 143.6 (0.9)     | 141.2 (0.7)†      | 1.8 (0.8)   |
| H+                   | 47.3 (1.3)      | 41.8 (1.2)†      | 6.2 (1.5)         | 47.9 (1.2)      | 43.3 (0.7)†       | 6.4 (0.9)   |
| PvCO2                | 7.1 (0.2)       | 6.0 (0.2)†       | 1.1 (0.2)         | 7.1 (0.5)       | 6.2 (0.1)†        | 1.0 (0.4)   |
| PvO2                 | 3.5 (0.2)       | 6.1 (0.3)†       | -2.5 (0.6)        | 3.9 (0.4)       | 5.6 (0.4)†        | -2.2 (0.7)  |
| HCO3a                | 27.6 (0.9)      | 26.4 (0.9)†      | 0.8 (0.8)         | 26.3 (1.5)      | 26.0 (0.5)        | -0.1 (1.4)  |
| K+                   | 4.3 (0.2)       | 4.1 (0.1)        | 0.1 (0.2)         | 4.2 (0.1)       | 4.0 (0.1)         | 0.02 (0.2)  |
| Phosphate            | 1.0 (0.1)       | 1.0 (0.04)       | 0.004 (0.02)      | 0.9 (0.1)       | 0.9 (0.03)        | -0.04 (0.03)|
| Lactate              | 2.8 (0.3)*      | 2.2 (0.2)*       | 1.1 (0.3)         | 1.7 (0.1)       | 1.5 (0.1)         | 0.4 (0.1)   |
| PGE2                 | 9.4 (0.6)*      | 6.6 (0.5)†       | 3.7 (0.7)*        | 6.4 (0.4)       | 6.2 (0.6)         | 1.1 (0.2)   |
| PGF1α                | 105.2 (4.4)*    | 95.4 (4.1)†      | 16.2 (2.8)*       | 82.7 (2.9)      | 80.2 (2.6)        | 7.2 (1.2)   |
| Bradykinin           | 8.4 (0.4)*      | 7.2 (0.3)†       | 2.1 (0.3)*        | 6.0 (0.2)       | 5.5 (0.2)         | 1.0 (0.1)   |

Values are mean (SEM). *P<0.01 vs control subjects. †P<0.01 vs PH-RCO.
A significant elevation of bradykinin levels on exercise and during the ergoreflex test was observed, which, however, did not predict the ergoreflex activity. This suggests a minor role (but still evident) of this metabolite as a trigger of the ergoreflex. This finding is in keeping with the role played by bradykinin in the synthesis of prostaglandins together with its influence on the excitability of the group III and group IV nerve endings in vivo.30

Experimental studies have shown that bradykinin is released from skeletal muscle during relative high-intensity static contraction. Decreased pH and increased lactate during ischemia are correlated with bradykinin release; this suggested that a bradykinin-induced reflex on the cardiovascular system in vivo could possibly be stimulated by intense exercise and that small doses of bradykinin can stimulate skeletal muscle afferents.31

However, it has been suggested that bradykinin and prostaglandins are capable of independent contributions to the expression of the exercise reflex.31 After blocking the prostaglandin synthesis by indomethacin, the vasodilatory response to exercise was augmented with captopril, a drug that enhances the effect of bradykinin by decreasing its degradation. Thus, we can hypothesize that bradykinin may largely contribute to other nonventilatory aspects of the ergoreflex responses (such as hemodynamic or autonomic responses), although there is little evidence of chemically specific ergoreceptor responses to date.

Hydrogen Ions and Lactate

Other biochemical stimuli, such as H⁺, K⁺, and lactate, have been shown to enhance sensory nerve activity in skeletal muscle afferents. Hydrogen ions in the skeletal muscle do play an important role to the ventilatory response during exercise: accumulation of H⁺, arising from lactic acid, because of static contraction, may cause a metabolic stimulus to evoke reflex autonomic effects.32

In CHF, the limiting factor in exercise performance is the high rate of skeletal muscle lactate accumulation and high-energy phosphate depletion, which is caused by intrinsic skeletal muscle metabolic changes rather than reduced peripheral blood flow.7 Our finding confirmed that in patients with CHF both H⁺ and lactate were elevated during handgrip exercise and ergoreflex tests; only the increases in lactate were typical of the patients, whereas the increase in H⁺ was similarly present in healthy subjects who were free from any ergoreflex activation. However, the higher lactate production of CHF did not predict the ergoreflex response, suggesting the acid production may be only indirectly involved in triggering the muscle reflex.

Interestingly, a recent study that has evaluated patients with McArdle’s disease, ie, a congenital absence of muscle glycogenolysis, has questioned the role of muscle acid production alone on exercise ergoreflex activation.33

![Figure 1. Experimental results of the average of the data of all patients with heart failure and all healthy subjects graphically expressed. We compared the handgrip exercise with control recovery (△) versus exercise run with PH-RCO recovery (●) (ie, the ergoreflex effect). Note the significant ergoreflex effect (ie, elevation in ventilation during PH-RCO recovery) in patients with heart failure (top), absent in healthy subjects (bottom). *P<0.01 vs control recovery.](http://circ.ahajournals.org/)

![Figure 2. Significant correlation by linear regression analysis between the ergoreflex contribution to the ventilatory response to exercise and prostaglandin (PGE₂, □, PGE₁, ◦) concentration during the ergoreflex test.](http://circ.ahajournals.org/)
Other Metabolites
Importantly, no significant contribution of $K^+$ to the ergoreflex response was observed, in contrast with previous study demonstrating a role of this ion as a stimulus for peripheral chemoreflex during exercise.34 $K^+$ is released from the exercising muscle and causes systemic vasodilation during maximal exercise and activates group III and IV muscle afferents.11 These results have supported the idea that $K^+$ released during static muscle contraction stimulates the initiation of the reflex cardiovascular response to this type of contraction. However, although $K^+$ rises during exercise, the increment is smaller in the more severe stages of CHF.35 When higher chemoreflex and ergoreflex activity is present, it is possible that $K^+$ may still have a role in physiological states (ie, controls), but its role in pathological conditions (such as CHF) is still unknown.

A limitation of this study was the measurement of only total plasma phosphate, and so the contribution of inorganic or organic fractions remains uninvestigated.

Conclusion
A key role of prostaglandin and, to some extent, bradykinin as triggering factors in the overactivation of the ergoreflex is proposed and consequently in symptom generation in heart failure. The relationships between these hormones and physiological reflex responses are consistent with the muscle hypothesis of symptom generation in CHF. The use of inhibitors of these factors on exercise may potentially help in treating symptoms of breathlessness and fatigue and thus improving quality of life in patients with CHF. However, additional studies are required to confirm this hypothesis.

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References
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