Prostaglandin production contributes to exercise-induced vasodilation in heart failure

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Lang, Chim C., Don B. Chomsky, Javed Butler, Shiv Kapoor, and John R. Wilson. Prostaglandin production contributes to exercise-induced vasodilation in heart failure. J. Appl. Physiol. 83(6): 1933–1940, 1997.—Endothelial release of prostaglandins may contribute to exercise-induced skeletal muscle arteriolar vasodilation in patients with heart failure. To test this hypothesis, we examined the effect of indomethacin on leg circulation and metabolism in eight chronic heart failure patients, aged 55 ± 4 yr. Central hemodynamics and leg blood flow, determined by thermodilution, and leg metabolic parameters were measured during maximum treadmill exercise before and 2 h after oral administration of indomethacin (75 mg). Leg release of 6-ketoprostaglandin F1α was also measured. During control exercise, leg blood flow increased from 0.34 ± 0.03 to 1.99 ± 0.19 l/min (P < 0.001), leg O2 consumption from 13.6 ± 1.8 to 164.5 ± 16.2 ml/min (P < 0.001), and leg prostaglandin release from 54.1 ± 8.5 to 267.4 ± 35.8 pg/min (P < 0.001). Indomethacin suppressed release of prostaglandin F1α (P < 0.001) throughout exercise and decreased leg blood flow during exercise (P < 0.05). This was associated with a corresponding decrease in leg O2 consumption (P < 0.05) and a higher level of femoral venous lactate at peak exercise (P < 0.01). These data suggest that release of vasodilatory prostaglandins contributes to skeletal muscle arteriolar vasodilation in patients with heart failure.

BLOOD FLOW to working skeletal muscle is frequently reduced during exertion in patients with heart failure (35, 40). This reduced perfusion of muscle is thought to be responsible, at least in part, for one of the major clinical symptoms experienced by such patients: exercise-induced fatigue (35, 36). The mechanism responsible for the reduction in skeletal muscle blood flow in heart failure remains unclear, and a number of factors have been postulated. The role played by various neurohormones, particularly the vasoconstrictive neurohormones such as catecholamines and angiotensin II, have received the most attention (8, 37, 38). However, a host of local factors and mechanisms of “autoregulation” may also be important in adjustment of skeletal muscle vascular resistance and blood flow. Some of these factors include thromboxane, prostacyclin, various prostaglandins, endothelin, endothelin-derived relaxation factor, tissue and vascular renin-angiotensin, intrinsic myocyte tone and myogenic responses, and metabolic factors; the role, relevance, and relative importance of each remain to be determined in heart failure (8, 10, 22, 43).

The vascular endothelium is the most prominent source of prostaglandin formation in the circulation (3, 7), and several lines of evidence suggest that local synthesis and release of vasodilatory prostaglandins may contribute to vasodilation in skeletal muscle during exercise. In animal experimental models, an increase in blood flow velocity and shear stress has been shown to release prostaglandins from the skeletal muscle microcirculation (20) and from cultured endothelial cells (13, 15). Young and Sparks (41) observed that exercise of the dog skeletal muscle increased release of prostaglandin (PG) E2. We and others (19, 39) have shown that physical exercise increases circulating levels of vasodilatory prostaglandins in normal subjects and that administration of cyclooxygenase inhibitors, which inhibit the production of these prostaglandins, reduces blood flow to working muscle during exercise (39) and attenuates the active hyperemia that occurs after ischemia and exercise (5, 19, 42). The role of vasodilatory prostaglandin release during exercise in heart failure has never been defined. Vasodilatory prostaglandins may be important in maintaining blood flow under such conditions of severe flow impairment. Alternatively, impaired release of vasodilatory prostaglandins may contribute to the flow abnormality in heart failure.

The purpose of this study was to clarify whether vasodilatory prostaglandins contribute to exercise-induced arteriolar vasodilation in patients with heart failure. Accordingly, the effects of prostaglandin synthesis inhibition with indomethacin on leg blood flow responses to exercise were examined in patients with heart failure.

METHODS

Patient population. Eight patients, aged 55 ± 4 (SE) yr, with chronic left ventricular dysfunction (left ventricular ejection fraction: 21 ± 2%) were studied. All had peak exercise O2 consumption (V˙O2) levels below the normal range for their ages; the average (range) peak exercise V˙O2 was 11.5 ± 1.1 ml·min⁻¹·kg⁻¹ (range: 5.5–16.5 ml·min⁻¹·kg⁻¹). All patients had exertional breathlessness or fatigue, or both, despite therapy with angiotensin-converting enzyme inhibitors, digoxin, and diuretic drugs, and all were classified in New York Heart Association functional class II–III. None had peripheral edema, ascites, anemia or proncrosis, intermittent dactiulation, or reduced pulses in his or her legs at the time of the study. Before enrollment in the study, all patients were optimally diuresed, with no evidence of fluid retention. Left ventricular dysfunction was attributable to coronary artery disease in six patients and to idiopathic dilated cardiomyopathy in two patients. No patient was on a nonsteroidal anti-inflammatory drug or aspirin, and none had received any vasodilator therapy for at least 48 h. The protocol was approved by the Institutional Review Board of Vanderbilt University. Written informed consent was obtained from all subjects.

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Protocol. The protocol consisted of having each patient perform maximal treadmill exercise before and 2 h after oral administration of indomethacin (75 mg).

On the day of the study, patients, having fasted overnight, arrived in the morning at Vanderbilt University Heart Failure and Heart Transplantation Program’s special procedure room. A 7-F Swan-Ganz thermodilution catheter was inserted percutaneously through an internal jugular vein and positioned in the pulmonary artery. A 5-F thermodilution catheter was inserted percutaneously into the left femoral vein and advanced to 15–16 cm anterograde into the iliac vein.

Thirty minutes after instrumentation, supine central hemodynamic measurements were obtained, which included pulmonary arterial pressure, right atrial pressure, and pulmonary capillary wedge pressure. Blood pressure was measured by a sphygmomanometer. Supine cardiac output was determined by thermodilution, in triplicate. Blood samples were drawn from the pulmonary artery for measurement of plasma hemoglobin O2 saturation and lactate concentration. Supine femoral vein flow was also determined by thermodilution, and femoral vein blood samples were obtained for measurement of mixed venous hemoglobin O2 saturation, plasma lactate concentration, and plasma 6-ketoprostaglandin F1α (6-ketoprostaglandin F1α, a stable metabolite of prostacyclin, the predominant vasodilatory prostaglandin released from the endothelium).

Patients then stood up on the treadmill, and, after a 5-min equilibration period, standing measurements of central and leg hemodynamics were recorded. Gas-exchange analysis was performed with the patient breathing into a disposable pneumotach, with his or her nose clamped, by using a Medgraphics Cardio O2 combined VO2/electrocardiographic exercise system (Medical Graphics, St. Paul, MN). The patient’s left index finger was also attached to a pulse oximeter to continuously monitor arterial hemoglobin O2 saturation.

The patient then commenced exercise on the treadmill by using a Naughton protocol. The patient was asked to rate the level of dyspnea and leg fatigue by using the Borg Scale (1). This scale rates the level of perceived symptoms by using a scale of 6 (none) to 20 (severe). All patients continued exercising until symptoms of dyspnea or fatigue, or both, forced them to stop. Respiratory gas and hemodynamic measurements were made continuously. During each 3-min exercise stage, leg blood flow was measured starting at 45 s, with a total of at least three measurements. The average of these measurements was then taken as the mean flow for the exercise stage. Central hemodynamic measurements were recorded simultaneously. Blood sampling from both pulmonary artery and femoral vein was performed during the last 45 s of the stage. Immediately after exercise was terminated, 75 mg indomethacin were administered orally; indomethacin is rapidly absorbed, reaching peak concentrations within 1–2 h after oral administration (16). After subjects rested semirecumbent for 2 h, the exercise protocol was repeated.

Central hemodynamic measurements were reproducible: exercise duration: 13.8 ± 1.2 vs. 14.2 ± 1.4 min, first vs. second exercise; systemic maximum VO2 (13.8 ± 1.0 vs. 13.3 ± 0.9 ml·min−1·kg−1); mean arterial pressure (93 ± 2 vs. 95 ± 1 mmHg); cardiac output (6.8 ± 0.7 vs. 7.3 ± 0.7 l/min); leg blood flow (2.24 ± 0.44 vs. 2.14 ± 0.31 l/min); femoral venous lactate (35.7 ± 8.8 vs. 32.7 ± 12.0 mg/dl); and leg VO2 (376 ± 62 vs. 366 ± 27 ml/min).

Blood samples for measurement of blood 6-keto-PGF1α were collected in prechilled polypropylene test tubes containing 4.5 mM EDTA and a prostaglandin synthase inhibitor, meprobamate. The plasma fraction was separated from whole blood and immediately stored at −70°C until assayed. Measurements of blood 6-keto-PGF1α were made by using commercially available radioimmunoassay kits (New England Nuclear, Boston, MA) as previously described (39). In brief, the prostaglandins were first extracted from the plasma fraction by acidifying to a pH of 3.0 with 2 M citric acid. A known amount of radiolabeled standard was added to each sample to assay recovery. Extraction, concentration, and partial purification of prostaglandins were carried out by using Bond Elut C18 columns (Analyt Chem International, Harbor City, CA). Further purification was carried out by using Bond Elut S-1 columns (Analyt Chem International). Elution with a solvent mixture (benzene-ethyl acetate-methanol) of increasing polarity was used to separate prostaglandins from other more or less polar substances. The extract was dried under nitrogen gas and reconstituted to the desired volume with an assay buffer. Recoveries ranged from 75 to 95%. If the recovery was ≤65%, samples were extracted. Results were corrected for recovery and were expressed in picograms per milliliter. The coefficient of variation for PGF1α was <5%. The sensitivity of the system was ~2.5 pg/assay tube for PGF1α.

Statistical analysis. Values are presented as means ± SE. During exercise, variables were compared at the highest identical peak exercise time achieved by both tests. Submaxi-
normal exercise variables were also determined and were defined as variables at 50% of the peak exercise. Statistical analysis was performed by using analysis of variance and the paired t-test (SPSS for Windows, version 6, SPSS, Chicago, IL). A P < 0.05 was considered as statistically significant.

RESULTS

Normal subjects. The five normal subjects studied had peak exercise VO2 levels of 24.9 ± 4.2 ml·min⁻¹·kg⁻¹. The effect of indomethacin on leg blood flow, VO2, and prostaglandin release is summarized in Table 1. There was no significant effect of indomethacin on peak exercise VO2 or any leg hemodynamic or metabolic parameter.

Patients with heart failure. Resting measurements. The effects of indomethacin on resting parameters are summarized in Table 2. At rest before the administration of indomethacin, patients with heart failure had significantly higher femoral venous PGF1a concentration than did the normal subjects (134 ± 11 vs. 70 ± 7 pg/ml) (P < 0.001), although leg PGF1a release was similar.

Indomethacin significantly decreased femoral venous PGF1a concentration and leg PGF1a release, although femoral venous PGF1a concentration was still significantly higher than in normal subjects. Resting supine cardiac output, mean arterial pressure, and systemic vascular resistance were not altered by indomethacin. However, pulmonary arterial pressure and pulmonary capillary wedge pressure were significantly higher after indomethacin. Supine leg blood flow, leg VO2, and femoral venous lactate were not altered by indomethacin.

Patients with heart failure. Exercise measurements. During control exercise, patients exercised for 10.9 ± 1.8 min and were limited by progressive dyspnea and fatigue, at reduced maximum VO2 levels of 11.5 ± 1.1 ml·min⁻¹·kg⁻¹, the normal maximum VO2 being 20–25 ml·min⁻¹·kg⁻¹. Exercise was associated with an impaired cardiac output response to exercise and markedly elevated intracardiac pressures (Figs. 1 and 2).

### Table 1. Effect of indomethacin on leg blood flow and prostaglandin release in normal subjects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Supine</th>
<th>Upright</th>
<th>Load 1</th>
<th>Load 3</th>
<th>Load 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg blood flow, l/min</td>
<td>0.6 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>1.5 ± 0.3</td>
<td>3.5 ± 0.5</td>
<td>4.7 ± 0.7</td>
</tr>
<tr>
<td>Control</td>
<td>0.5 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>1.8 ± 0.3</td>
<td>3.0 ± 0.3</td>
<td>5.0 ± 1.0</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>70 ± 7*</td>
<td>71 ± 9*</td>
<td>67 ± 6*</td>
<td>67 ± 5*</td>
<td>62 ± 13*</td>
</tr>
</tbody>
</table>

### Table 2. Effects of indomethacin on resting supine systemic and peripheral hemodynamics and metabolic variables in patients with heart failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>77.3 ± 1.2</td>
<td>80.3 ± 2.1</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>3.6 ± 0.3</td>
<td>3.5 ± 0.2</td>
</tr>
<tr>
<td>Systemic vascular resistance, Wood units</td>
<td>19.8 ± 1.4</td>
<td>20.1 ± 1.4</td>
</tr>
<tr>
<td>Right atrial pressure, mmHg</td>
<td>8 ± 2</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>Pulmonary arterial pressure, mmHg</td>
<td>27 ± 3</td>
<td>34 ± 4†</td>
</tr>
<tr>
<td>Pulmonary wedge pressure, mmHg</td>
<td>18 ± 3</td>
<td>25 ± 4†</td>
</tr>
<tr>
<td>(a-v)O2, mg/dl</td>
<td>7.0 ± 0.6</td>
<td>8.3 ± 0.6</td>
</tr>
</tbody>
</table>

Regional hemodynamics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral venous PGF1a, pg/ml</td>
<td>134.0 ± 11.3</td>
<td>100.5 ± 5.5*</td>
</tr>
<tr>
<td>Leg PGF1a, release, pg/min</td>
<td>47.2 ± 8.0</td>
<td>32.5 ± 5.2</td>
</tr>
<tr>
<td>Leg blood flow, l/min</td>
<td>0.34 ± 0.03</td>
<td>0.31 ± 0.05</td>
</tr>
<tr>
<td>Leg vascular resistance, units</td>
<td>192.9 ± 22.7</td>
<td>229.7 ± 33.0</td>
</tr>
<tr>
<td>Leg O2 extraction, %</td>
<td>40.9 ± 3.4</td>
<td>38.4 ± 3.3</td>
</tr>
<tr>
<td>Leg VO2, ml/min</td>
<td>13.6 ± 1.8</td>
<td>11.4 ± 1.6</td>
</tr>
<tr>
<td>Femoral venous lactate, mg/dl</td>
<td>8.4 ± 0.7</td>
<td>12.3 ± 2.4</td>
</tr>
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</table>

Values are means ± SE; n = 8 patients. (a-v)O2, arteriovenous O2 difference. *P < 0.05; †P < 0.01, vs. control group.

In all patients, treadmill exercise increased leg blood flow (Fig. 3). Leg vascular resistance decreased from 192.9 ± 22.7 to 14.5 ± 2.8 U (P < 0.001). There was also a graded increase in leg release of PGF1a (Fig. 4). At peak exercise, leg VO2 was 165 ± 16 ml/min, similar to levels noted at load 1 in the normal subjects (189 ± 44 ml/min, P = not significant vs. patients with heart failure). When the normal subjects and patients with heart failure were compared at these similar work levels, patients with heart failure exhibited significantly higher femoral venous PGF1a concentration (142 ± 12 vs. 67 ± 6 pg/ml) and significantly higher leg PGF1a release (267 ± 36 vs. 97 ± 14 pg/min) (both P < 0.01).

In the patients with heart failure, treatment with indomethacin markedly suppressed leg PGF1a throughout the entire period of exercise (Fig. 4). In seven of eight patients, indomethacin blunted the increase in leg blood flow with exercise (Fig. 3, P < 0.05). The exercise-induced decrease in leg vascular resistance was blunted to 24.3 ± 4.6 U (P < 0.01). This was accompanied by a decrease in leg VO2 (P < 0.05) (Fig. 3). The increase in femoral venous lactate during exercise was also higher after indomethacin (P < 0.01) (Fig. 3).

Indomethacin had no effect on the cardiac output response to exercise (Fig. 1). Mean arterial pressure and systemic vascular resistance tended to be higher after indomethacin, although this effect did not reach statistical significance. The increase in right atrial and pulmonary pressures during exercise was also not altered by indomethacin treatment (Fig. 2). Total exercise duration was unchanged (10.9 ± 1.8 vs. 10.9 ± 1.9 min, control vs. Indomethacin) as was the symptomatology, according to the Borg Scale (results not shown). In this acute study, indomethacin administration did not
alter either the maximal systemic \( \dot{V}O_2 \) (from 11.6 ± 3.3 to 11.7 ± 1.6 ml·min\(^{-1}\)·kg\(^{-1}\), control vs. indomethacin) or the systemic arteriovenous \( O_2 \) difference at peak exercise (from 14.6 ± 0.9 to 15.1 ± 0.7 mg/dl, control vs. indomethacin).

**DISCUSSION**

The vascular endothelium is the most prominent source of prostaglandin formation in the circulation (3, 7), and it has been suggested that vasodilatory prostaglandins, such as PGE\(_2\) and PGI\(_2\), collectively may play an important role in circulatory homeostasis (10). Experimental studies have demonstrated that these...
vasodilatory prostaglandins are released by the kidney and the coronary circulation during hypoperfusion of these vascular beds (14, 27). The stimuli for the local production of these prostaglandins include tissue ischemia as well as the direct influence of vasoactive substances such as angiotensin II, norepinephrine, and vasopressin (25, 30, 45). In addition to its vasodilatory effects, PGE₂ also increases sodium excretion and attenuates the activation of vasopressin on renal tubular permeability to water (23, 44). PGE₂ and PGI₂ also influence renal renin release (6). 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 (11).

Previous studies on prostaglandins in patients with heart failure. There have only been a few studies that have investigated the role of prostaglandins in patients with heart failure. Two general approaches have been employed. First, plasma levels of prostaglandins and their metabolites have been measured. Dzau and co-workers (12) have reported that plasma levels of PGE₁α and of PGM, an immunoreactive metabolite of PGE₂, were 3–10 times higher in patients with heart failure than in normal subjects. The stimuli for the increased prostaglandin synthesis and release in patients with heart failure are not known, but the relationship observed between circulating levels of prostaglandin metabolites and the vasoconstrictive hormones in these studies suggests a stimulatory effect of these vasoactive substances on prostaglandin synthesis.

The second approach used to study prostaglandins in heart failure has been the administration of cyclooxygenase inhibitors, agents that inhibit the synthesis of prostaglandins. Because the kidneys are known to release PGE₂ in a low-cardiac-output state (26), most early studies have focused on the renal effects of cyclooxygenase inhibitor. These studies demonstrated deterioration in renal hemodynamics, with reported cases of acute renal insufficiency (34). The more systemic effects of nonsteroidal anti-inflammatory drugs in heart failure were studied by Dzau and colleagues (12), who found that when indomethacin was administered to hyponatremic patients with elevated vasodilatory and vasoconstrictive hormones, there was a significant increase in pulmonary wedge pressure, mean arterial pressure, and systemic vascular resistance. In contrast, in normonatremic patients with normal concentrations of catecholamines, plasma renin activity,
and prostaglandin metabolites showed no significant hemodynamic changes after administration of indomethacin. The authors concluded that both vasoconstrictors and vasodilatory prostaglandins are operative to an increased extent in patients with heart failure complicated by hyponatremia and that nonsteroidal anti-inflammatory drugs may induce hemodynamic deterioration in this setting.

Effect of indomethacin at rest. In the present study, all of the patients were optimally diuresed, and none of the patients had evidence of fluid retention or serum sodium levels <135 mmol/l. Nevertheless, femoral venous levels of PGF$_{1\alpha}$ were about twice the levels found in the normal subjects. Cardiac outputs were significantly decreased, whereas pulmonary wedge pressures increased.

In patients with heart failure at rest, indomethacin reduced femoral venous PGF$_{1\alpha}$ levels by ~25%, although PGF$_{1\alpha}$ concentrations still remained higher than in the normal subjects. No significant change in resting mean arterial pressure or systemic vascular resistance was noted. However, pulmonary wedge pressure pressures increased substantially, indicating that indomethacin can adversely affect central hemodynamic parameters even in patients with normal sodium levels.

Prostaglandins and peripheral arteriolar vasodilatation during exercise. Over the last two decades, observations both in humans and in experimental animals suggest that exercise induces the release of prostaglandins from skeletal muscle, which may contribute to the vasodilation of skeletal vascular bed during exercise (17, 19, 37, 39). To date, all the observations made in humans have been in normal subjects. The role played by the release of these vasodilatory prostaglandins in patients with heart failure is not known. To the best of our knowledge, this is the first study to examine the role of vasodilatory prostaglandins during exercise in patients with heart failure.

To investigate the contribution of prostaglandin release to vascular regulation, leg resistance and blood flow were used as indexes of skeletal muscle resistance and flow, respectively; flow to nonmuscular tissue makes up only a small portion of leg blood flow during exercise (29). Systemic and leg VO$_2$ and femoral venous lactate were used as indexes of the adequacy of O$_2$ delivery to working muscle (2, 33). To evaluate changes during exercise, variables were compared at identical work times. Exercise level influences muscle blood flow and metabolism. Therefore, comparison of data at different work times would leave uncertain whether any change observed is due to indomethacin or differences in workload.

During control exercise, femoral venous PGF$_{1\alpha}$ concentrations and leg PGF$_{1\alpha}$ were significantly higher in the patients with heart failure than in the normal control subjects, suggesting increased prostaglandin release from skeletal muscle. In addition, all patients developed metabolic changes, suggesting impaired blood flow to working muscle. Specifically, patients were limited by fatigue at reduced maximum VO$_2$. The leg VO$_2$ and femoral venous lactate accumulated at maximum exercise were markedly increased above levels observed in normal subjects at comparable workloads (28). The limb vascular resistance noted at maximal exercise was also higher than levels observed by us in patients with normal exercise capacity, suggesting reduced limb vasodilation (35).

Indomethacin markedly attenuated leg PGF$_{1\alpha}$ release in the patients with heart failure. This effect was associated with a decrease in leg blood flow and leg VO$_2$ and an increase in femoral venous lactate concentrations at peak exercise, suggesting decreased skeletal muscle O$_2$ delivery and increased muscle glycolysis.

Interestingly, peak VO$_2$ and exercise duration remained unchanged despite the reduction in peak leg VO$_2$. It is conceivable that the VO$_2$ of other tissues increased. For example, respiratory muscle VO$_2$ could have increased. Alternatively, the reduction in peak leg VO$_2$ may have been spurious because of the imprecision of leg flow measurements or the fact that leg O$_2$ extraction was not directly measured.

It should be emphasized that the failure of peak VO$_2$ to decrease acutely does not predict the chronic effects of prostaglandin blockade. It is a widely recognized phenomenon that the acute changes observed in blood flow studies of this nature do not necessarily translate immediately to changes in exercise duration. One example of this phenomenon is with angiotensin-converting enzyme inhibitors. Such agents do not have an acute effect on exercise duration but, when administered chronically, are associated with improved exercise capacity (9). Clearly, further studies are required to examine the more chronic effects of indomethacin on exercise hemodynamics in heart failure.

Indomethacin had no significant effect on leg blood flow or VO$_2$ in the normal subjects. In a previous study, we noted that administration of indomethacin into the brachial artery of normal subjects decreased forearm blood flow at rest and during exercise (39). Therefore, the dose of indomethacin utilized in the present study may have been insufficient to block prostaglandin production. Alternatively, the degree of skeletal muscle prostaglandin activation during control exercise may have been so small that indomethacin had little measurable effect. The conclusion supported by the low femoral venous levels of PGF$_{1\alpha}$ noted throughout exercise in the normal subjects. In any event, the greater impact of indomethacin in the patients with heart failure further suggests increased vascular modulation by prostaglandins in heart failure.

Study limitations. This study has a number of limitations. First, the use of skeletal muscle glycolysis as a marker of blood flow to working muscle is supported by prior observations that reducing muscle blood flow augments glycolysis (2, 33). However, glycolysis also occurs normally in well-oxygenated working muscle and is affected by pH and substrate availability (4). We cannot totally exclude the possibility that changes in these other variables may have affected our results. Second, leg blood flow was determined by using volumetric flow measurements via an indwelling thermodilution catheter. This technique does not provide direct
Clinicians should avoid such agents in patients with heart failure. Conversely, administration of agents that impair prostaglandin release to patients with heart failure may have adverse affects on exercise performance. Nonsteroidal agents have already been shown to adversely affect reactive and functional hyperemia.

Conclusions. The present study suggests that prostaglandin release plays an important role in modulating exercise-induced vasodilation in patients with heart failure. Interventions that enhance prostaglandin release therefore may be beneficial in patients with heart failure. Conversely, administration of agents that impair prostaglandin release to patients with heart failure may have adverse affects on exercise performance. Nonsteroidal agents have already been shown to adversely affect reactive and functional hyperemia.

Clinicians should avoid such agents in patients with heart failure whenever possible.

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REFERENCES


