Alterations in Left Ventricular Function and Coronary Hemodynamics with Captopril, Hydralazine and Prazosin in Chronic Ischemic Heart Failure: A Comparative Study

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SUMMARY In 14 patients with chronic heart failure, changes in coronary hemodynamics, myocardial metabolism and left ventricular function were evaluated after administration of captopril, prazosin and hydralazine. Eleven patients received captopril in incremental doses (6.25-150 mg) until the arterial pressure decreased by 10 mm Hg; 11 patients received prazosin (5 mg) and 10 patients received hydralazine (100 mg). The control hemodynamics and metabolic variables before each drug trial were similar. All three vasodilators increased cardiac index (captopril 19%, p < 0.001; prazosin 29%, p < 0.001; hydralazine 36%, p < 0.001), and decreased the pulmonary capillary wedge pressure (captopril 24 ± 6 to 17 ± 6 mm Hg, p < 0.001; prazosin 20 ± 7 to 13 ± 6 mm Hg, p < 0.001; hydralazine 19 ± 8 to 16 ± 7 mm Hg, p < 0.025), indicating improved left ventricular function with all three agents. The average rate-pressure product decreased after captopril and prazosin by 27% and 14%, respectively, but only captopril decreased the myocardial oxygen consumption significantly (19%, p < 0.025). There was myocardial lactate production, indicating ischemia, in one patient with captopril, two patients with prazosin and two patients with hydralazine.

These results suggest that only captopril consistently improves left ventricular function at a decreased metabolic cost. Despite improved hemodynamics and left ventricular function, metabolic function can deteriorate during vasodilator therapy in some patients with chronic ischemic heart failure.

VASODILATOR drugs have gained widespread acceptance in the treatment of congestive heart failure.1 Most vasodilators appear to improve left ventricular pump function and overall cardiac performance.1 However, little information is available regarding the effects of vasodilator therapy on regional circulations, such as the coronary circulation. The evaluation of changes in coronary hemodynamics in patients with chronic heart failure is particularly relevant when obstructive coronary artery disease is the underlying cause of the heart failure.2

Although most vasodilators improve left ventricular pump function by peripheral vasodilation, the mechanism of vasodilation differs. Hydralazine causes direct smooth muscle relaxation of the peripheral vascular bed, predominantly the arteriolar resistance vessels.3 Prazosin produces vasodilation by postsynaptic α-adrenergic blockade; venodilation is also consistently observed.4 Reduced formation of angiotensin II appears to be the primary mechanism by which captopril causes vasodilation.5,6 The response of the coronary vascular bed to these vasodilator agents, therefore, may not be similar.7,8 Despite the qualitative similarity, quantitative differences in the hemodynamic effects to these different vasodilator agents may influence coronary hemodynamics differently.

Therefore, we evaluated changes in coronary hemodynamics and myocardial metabolism in patients with chronic ischemic heart failure in response to captopril, prazosin and hydralazine.

Materials and Methods

Patient Population

Fourteen male patients, mean age 60 years (range 46-70 years), who had chronic congestive heart failure secondary to coronary artery disease were studied. All 14 patients had electrocardiographic evidence of anterior myocardial infarction, presumably due to left coronary artery disease; six patients also had inferior myocardial infarction. Four of the 14 patients had severe three-vessel coronary artery disease documented by selective coronary arteriography. Ten patients were in New York Heart Association class III and four were in class IV. The duration of heart failure ranged from 2 months to 8 years. All patients were taking digoxin and diuretics. In two of our patients we could not determine lactate and oxygen saturations. One patient received all three drugs and the other received only prazosin and hydralazine. In eight of 14 patients, captopril, prazosin and hydralazine were administered sequentially. Three patients received captopril only, two prazosin and hydralazine, and one patient prazosin only. Thus, the hemodynamic and metabolic effects of captopril were evaluated in 11 patients, prazosin in 11 patients, hydralazine in 10 patients, and all three agents in eight patients.

Study Protocol

Each patient gave informed, written consent. All vasodilator drugs were discontinued 4 days before the study. Digoxin and diuretics were continued and given every evening after the completion of the study.

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| Table 1. Hemodynamic, Coronary Hemodynamic and Cardiac Metabolic Effects of Captopril (n = 11) |
|----------------------------------------|-------------------------------|-------------------|---------------------------------|-------------------------------|
| HR (beats/min) | Mean BP (mm Hg) | Diastolic BP (mm Hg) | PCWP (mm Hg) | SWI (g-m/m²) | CI (l/min/m²) |
| C | 86 ± 12 | 84 ± 11 | 62 ± 11 | 24 ± 6 | 29 ± 11 | 2.1 ± 0.5 |
| Peak | 80 ± 11 | 64 ± 11 | 47 ± 9 | 17 ± 6 | 30 ± 8 | 2.5 ± 0.5 |
| p < 0.005 | p < 0.001 | p < 0.001 | p < 0.001 | NS | p < 0.001 |

Data are mean ± SD. Peak values defined as variables measured when there was a 10-mm Hg decrease in diastolic pressure.

Abbreviations: HR = heart rate; mean BP = mean arterial pressure; diastolic BP = diastolic arterial pressure; PCWP = pulmonary capillary wedge pressure; SWI = stroke index; CI = cardiac index; SVR = systemic vascular resistance; HR × BP = heart rate–blood pressure product; MVO₂ = myocardial oxygen consumption; CBF = coronary sinus flow; ART-CS DO₂ = arterial-coronary sinus oxygen extraction; LE = lactate extraction; C = control.

Right-heart catheterization was performed using a #7 Swan-Ganz thermodilution flow-directed balloon-tipped catheter inserted percutaneously into the right subclavian vein. Right atrial (RAP), pulmonary arterial (PAP) and pulmonary capillary wedge pressures (PCWP) were recorded with this catheter. Using the same catheter, cardiac output was determined in triplicate by the thermodilution technique. Arterial pressure was recorded directly by cannulating the radial artery. The hemodynamic variables were calculated as follows: SV = CO/HR, where SV = stroke volume and HR = heart rate; SWI = SVI × (MSP – PCWP) × 0.036, where SVI = stroke work index, SV = stroke volume index and MSP = mean systolic pressure; SVR = (MAP – RAP)/CO × 80, where SVR = systemic vascular resistance and MAP = mean arterial pressure.

The coronary sinus was catheterized using a #8 thermodilution coronary sinus flow catheter introduced into the left subclavian vein. To minimize coronary sinus reflux, the catheter was advanced under fluoroscopy into the great cardiac vein. Coronary sinus flow was measured by the constant infusion thermodilution technique. Coronary sinus flow was calculated as

\[
\left( \frac{\text{Tb} - \text{Ti}}{\text{Tb} - \text{Tm}} - 1 \right) \times 1.08 \times 46 \text{ ml/min}
\]

where CSF = coronary blood flow, Tb = temperature of blood, Ti = temperature of injectate, Tm = temperature of mixture of blood and the indicator, 1.08 = a constant accounting for specific heat and density of both blood and indicator and 46 ml/min is the injection rate of the indicator (DSW) through the Harvard pump. Arterial and coronary sinus blood samples were drawn simultaneously for the determination of oxygen saturation, oxygen content and lactate concentration. The lactate concentration was measured using the enzymatic fluorometric method of Loomis, and the oxygen saturations were measured using a Corning 175 automatic blood and pH analyzer. Oxygen content was calculated as oxygen content – oxygen saturation × hemoglobin × 1.34. The arterial–coronary sinus oxygen difference (myocardial oxygen extraction) was also calculated. Myocardial lactate extraction was calculated as (arterial lactate – coronary sinus lactate)/arterial lactate × 100.

Drug Administration

Once the catheters were inserted the patients were permitted to rest for 1 hour and two sets of baseline values were obtained 15 minutes apart. Captopril was given in increasing doses (2.5, 6.25, 12.5, 25, 50, 100 and 150 mg) every 2 hours until the mean and diastolic blood pressures decreased by 10 mm Hg. Systemic and coronary hemodynamic and metabolic measurements were made 2 hours after each dose.

After the response to captopril had been evaluated, hemodynamics were allowed to return to control values (usually within 24 hours). All patients then received a single 5-mg oral dose of prazosin and the hemodynamic and metabolic measurements were repeated at 1, 2, 4 and 6 hours. After the hemodynamics had returned to control, a 100-mg dose of hydralazine was administered orally and the measurements were repeated at 1, 2, 4 and 6 hours. Using fluoroscopy and injection of renograin, we ensured that the coronary sinus catheter remained in the same position throughout the study.

Statistics

For each drug, the variables at peak effect were compared with control values by paired t test. When the effect of the different drugs at control and peak values were compared, a two-way analysis of variance was done using the Student–Neuman-Keuls test.

Results

Captopril (table 1)

One patient responded after 6.25 mg of captopril, three patients after 12.5 mg, four after 25 mg, two after 50 mg and one patient after 150 mg. In these 11 patients, captopril increased cardiac index from a mean of 2.1 ± 0.5 to 2.5 ± 0.5 l/min/m² (p < 0.001) and decreased pulmonary capillary wedge pressure from 24 ± 6 to 17 ± 6 mm Hg (p < 0.001). Mean arterial pressure decreased from an average of 84 ± 11 to 64 ± 11 mm Hg (p < 0.001) and diastolic arterial pressure decreased from 47 ± 9 mm Hg (p < 0.005). In the four patients in whom standing blood pressure was also measured, there was no further decrease in blood pressure on standing. Systemic vascular resistance also decreased significantly. The changes in heart rate, peak systolic pressure and rate-pressure product in individual patients are illustrated in figure 1. Heart rate decreased in 10 patients,
TABLE 1. (continued)

<table>
<thead>
<tr>
<th>SVR (dyne/sec/cm²)</th>
<th>HR × BP (x 10⁻³)</th>
<th>MVO₂ (ml/min)</th>
<th>CSF (ml/min)</th>
<th>Art-CS DO₂ (vol%)</th>
<th>LE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1560 ± 314</td>
<td>11.1 ± 1.8</td>
<td>8.07 ± 2.96</td>
<td>62 ± 22</td>
<td>12.7 ± 2.1</td>
<td>33 ± 16</td>
</tr>
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<td>985 ± 209</td>
<td>8.1 ± 1.9</td>
<td>6.50 ± 3.24</td>
<td>54 ± 26</td>
<td>12.0 ± 2.1</td>
<td>35 ± 18</td>
</tr>
</tbody>
</table>

*p < 0.001

systolic pressure in 11 and rate-pressure product in 11. The rate-pressure product decreased by 27% (*p < 0.001). There was a slight but statistically significant decrease in myocardial oxygen extraction. This decrease in oxygen extraction was due to a higher coronary sinus oxygen content. In 10 of 11 patients, coronary sinus flow decreased (average 13%) (fig. 2), and in nine of 10 patients, myocardial oxygen consumption decreased (average 19%) (fig. 3). Lactate extraction was determined in 10 of 11 patients, and the average was unchanged. However, in one of the 10 patients, there was myocardial lactate production (fig. 4), indicating myocardial ischemia.12

**Prazosin (table 2)**

The peak hemodynamic effects of prazosin were an increase in cardiac index, from 2.1 ± 0.5 to 2.7 ± 0.3 l/min/m² (*p < 0.001), and a decrease in pulmonary capillary wedge pressure, from 20 ± 7 to 13 ± 6 mm Hg (*p < 0.001). There were marked decreases in mean arterial pressure, from 81 ± 9 to 65 ± 11 mm Hg (*p < 0.001), and in diastolic arterial pressure, from 63 ± 9 to 49 ± 9 mm Hg (*p < 0.001). There was also a 36% decrease in SVR. Changes in heart rate, peak systolic pressure and rate-pressure product in individual patients are shown in figure 1. Heart rate increased in six patients, decreased in two and was unchanged in one. Peak systolic pressure decreased in nine patients. The rate-pressure product did not increase in any patient, decreased in eight patients and did not change in one patient. For the group, the rate-pressure product decreased by an average of 14% (*p < 0.001). Changes in coronary sinus flow were determined in 10 of 11 patients, and a variable response was observed. Coronary sinus flow increased in five patients, decreased in four and was unchanged in two. For the group, there was no significant change. Myocardial oxygen extraction decreased from 11.9 ± 1.2 to 11.1 ± 1.6 vol% (*p < 0.01). Changes in myocardial oxygen consumption in individual patients paralleled changes in coronary sinus flow. In nine of 11 patients, changes in myocardial lactate extraction were determined; the average lactate extraction decreased significantly after prazosin therapy, and in two patients there was lactate production.

**Hydralazine (table 3)**

With hydralazine (10 patients), cardiac index increased from 2.2 ± 0.4 to 3.0 ± 0.6 l/min/m² (*p < 0.001) and the pulmonary capillary wedge pressure decreased from 19 ± 8 to 16 ± 7 mm Hg (*p < 0.05). There were decreases in mean arterial pressure (79 ± 9 to 73 ± 11 mm Hg, *p < 0.01) and in diastolic arterial pressure (60 ± 9 to 52 ± 9 mm Hg, *p < 0.001). Heart rate increased from 90 ± 16 to 94 ± 17 beats/min (*p < 0.05). The changes in heart rate, peak systolic pressure and rate-pressure product in individual patients are illustrated in figure 1. Heart rate increased in four patients, remained unchanged in three and decreased in one patient. Peak systolic pressure decreased in five patients and remained unchanged in three. Although the average rate-pressure product did not change, the responses varied in individual patients. In two of 10 patients, the rate-pressure product increased, in four it decreased, and in the remaining four there was no change. Changes in cor-

**FIGURE 1.** Captopril decreased the heart rate, systolic arterial pressure and rate-pressure product in all patients. With prazosin, the decrease in systolic arterial pressure was enough to overcome the increase in heart rate in seven patients, such that the rate-blood pressure product decreased in all patients. Hydralazine had no predictable effect on heart rate or systolic arterial pressure. The change in heart rate or systolic arterial pressure did not predict whether a patient would produce lactate. Solid symbols indicate patients who produced lactate. BPM = beats/min.
Cardiovascular sinus flow in individual patients tended to parallel changes in the rate-pressure product \((r = 0.6, p < 0.05)\). The average coronary sinus flow, myocardial oxygen consumption, arterial-coronary sinus oxygen difference and myocardial lactate extraction remained unchanged.

**Comparative Effects of Captopril, Prazosin and Hydralazine (table 4)**

The hemodynamic and metabolic responses to captopril, prazosin and hydralazine in the same eight patients are summarized in table 4. The control hemodynamics before captopril, prazosin and hydralazine were similar. There was a smaller increase in cardiac index after captopril than after prazosin or hydralazine. The increase in stroke volume index with all three agents was similar because of the different heart rate response. Although both prazosin and hydralazine caused a slight increase in heart rate, captopril caused a decrease. With hydralazine, the decrease in arterial pressure and pulmonary capillary wedge pressure were significantly less than those with captopril or prazosin \((p < 0.05)\). Systemic vascular resistance decreased by a similar magnitude with all three agents.

The control rate-pressure product, coronary sinus flow, myocardial oxygen consumption, arterial-coronary sinus oxygen difference and percent lactate extraction were similar before captopril, prazosin and hydralazine. With captopril, the rate-pressure product decreased in all eight patients; coronary sinus flow and myocardial oxygen consumption also decreased.

**Figure 2.** Captopril decreased the coronary blood flow in all but one patient and decreased the rate-pressure product in all 11 patients. Prazosin had no predictable effect on the coronary blood flow, but decreased the rate-pressure product in all 11 patients. Hydralazine tended to change the coronary blood flow in the same way as it changed the rate-pressure product \((r = 0.6, p < 0.05)\). With all three drugs, the patients that decreased their coronary blood flow produced the most lactate (*). Individual responses at the peak effect of each drug and the mean ± SEM are plotted for each drug.

**Figure 3.** With captopril, the decrease in myocardial oxygen consumption paralleled the decrease in rate-pressure product \((r = 0.6, p < 0.05)\). Prazosin had no predictable effect on the myocardial oxygen consumption, despite decreasing the rate-pressure product in these nine patients. Hydralazine tended to change the myocardial oxygen consumption in the same way as it changed the rate-pressure product \((r = 0.6, p < 0.1)\). With all three drugs, the patients that decreased their coronary blood flow produced the most lactate (*). Individual responses at the peak effect of each drug and the mean ± SEM are plotted for each drug.
but not significantly. Despite a significant reduction in the rate-pressure product after prazosin, coronary sinus flow and myocardial oxygen consumption remained unchanged. With hydralazine, there was no significant change in the average rate-pressure product, coronary sinus flow or myocardial oxygen consumption.

Discussion

The beneficial hemodynamic effects of captopril, prazosin and hydralazine in patients with chronic heart failure documented in previous studies were observed in the present study. With all three agents, cardiac output and stroke volume increased and pulmonary capillary wedge pressure decreased, although the magnitude of decrease in pulmonary capillary wedge pressure with hydralazine was significantly less than with captopril or prazosin. Nevertheless, left ventricular function improved with all three agents. However, the present study demonstrates that although all three agents improve left ventricular function, their effects on coronary hemodynamics and myocardial oxygen consumption are different.

With captopril, the rate-pressure product, an index of myocardial oxygen demand, decreased in all patients. Coronary blood flow decreased in 10 of 11 patients and myocardial oxygen consumption decreased in nine of 10 patients. The changes in coronary blood flow and myocardial oxygen consumption were significantly correlated to the changes in rate-pressure product. A lower left ventricular filling pressure with captopril, which is presumably associated with a decrease in left ventricular diastolic volume and myocardial oxygen demand, might also have contributed to the decrease in myocardial oxygen consumption. Angiotensin II causes a sustained vasoconstriction of the large conductance vessels, but only a transient vasoconstriction of the smaller resistance vessels. Attenuation of the effect of angiotensin with captopril and the possible decrease in angiotensin-induced coronary vasoconstriction, therefore, might be expected to preserve autoregulation. The present study suggests that changes in coronary sinus flow and myocardial oxygen consumption with captopril in patients with congestive heart failure are largely produced by the hemodynamic determinants of myocardial oxygen demand.

With hydralazine, there was also a general correlation between changes in coronary blood flow, myocardial oxygen consumption and changes in myocardial oxygen demand. Discordant changes between coronary blood flow and the rate-pressure product were seen in three of 10 patients. In two patients, coronary blood flow increased, despite no change or a slight decrease in the rate-pressure product. Both patients had documented anterior myocardial infarctions; it is unlikely, therefore, that the difference in the coronary anatomy could account for the differences in coronary blood flow. In the third patient, coronary blood flow decreased without a change in the rate-pressure product. In patients without heart failure and no obstructive coronary artery disease, hydralazine decreases coronary vascular resistance and increases coronary blood flow. A reflex increase in heart rate and contractile state with hydralazine may also contribute to the increase in coronary blood flow in normal patients. The present study indicates that the effects of hydralazine on coronary blood flow and myocardial oxygen consumption are largely mediated by changes in the determinants of myocardial oxygen demand. The changes in coronary blood flow and myocardial oxygen consumption usually parallel the changes in rate-pressure product. These results indicate a major difference in the effects of hydralazine on the coronary blood flow and myocardial oxygen consumption of patients with coronary artery disease and congestive heart failure, and normal patients or patients with coronary artery disease without failure.

With prazosin, no correlation was found between changes in coronary blood flow or myocardial oxygen consumption and changes in the determinants of myocardial oxygen demand. In all patients, the rate-pressure product decreased significantly with prazosin.
TABLE 3. Hemodynamic, Coronary Hemodynamic and Cardiac Metabolic Effects of Hydralazine (n = 10)

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>Mean BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>SWI (g-m/m²)</th>
<th>CI (l/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>90 ± 16</td>
<td>79 ± 9</td>
<td>60 ± 9</td>
<td>19 ± 8</td>
<td>28 ± 11</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>Peak</td>
<td>94 ± 17</td>
<td>73 ± 11</td>
<td>52 ± 9</td>
<td>16 ± 7</td>
<td>36 ± 13</td>
<td>3.0 ± 0.6</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.025</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
<td>&lt; 0.025</td>
<td>&lt; 0.005</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

Data are mean ± sd. Peak values defined as variables measured at the time of the lowest systemic vascular resistance. Abbreviations: See table 1.

and there was a substantial decrease in left ventricular filling pressure, which was presumably associated with a decrease in left ventricular diastolic volume. Decreased left ventricular volume should further decrease myocardial oxygen demand, yet coronary blood flow decreased in only four of 11 patients in whom changes in coronary blood flow were measured during prazosin therapy. In four of the remaining six patients, the coronary blood flow increased, and in two there was no change, despite a decreased rate-pressure product. Changes in myocardial oxygen consumption usually paralleled changes in coronary blood flow in these patients. The mechanism of this divergent response to prazosin remains unclear. Changes in contractile state were not determined in this study. In experimental studies with isolated papillary muscle preparations, prazosin does not appear to possess any direct positive inotropic effect at therapeutic concentrations. Also, when given to patients in congestive heart failure, prazosin acutely decreases the plasma epinephrine and norepinephrine concentrations. However, in our study, the large decrease in blood pressure caused by prazosin may have caused a reflex increase in plasma epinephrine and norepinephrine. Because the change in heart rate reflects the change in sympathetic tone, and because the three patients that increased their myocardial oxygen consumption increased their heart rate by more than 6 beats/min, in some patients a norepinephrine-induced increase in heart rate and contractile state might cause an increase in coronary blood flow, despite a decrease in the other determinants of myocardial oxygen demand. The arterial diastolic pressure decreased in all patients with prazosin; therefore, changes in perfusion pressure cannot be responsible for this variable response of prazosin on coronary blood flow. Prazosin is a potent postsynaptic α-blocking agent; therefore, a primary decrease in coronary vascular resistance could have caused an increase in coronary blood flow in some patients, despite a decrease in the determinants of myocardial oxygen demand.

Despite a favorable hemodynamic response, vasodilator therapy can enhance myocardial ischemia in some patients with chronic heart failure due to ischemic heart disease. With captopril in one patient and with both prazosin and hydralazine in two patients, there was myocardial lactate production. It has been suggested that lactate extraction to 5% or less indicates myocardial ischemia. Using this criterion, myocardial ischemia could have occurred during captopril, prazosin or hydralazine therapy in three additional instances. However, Gertz et al. argued that anything short of myocardial lactate production cannot be regarded as abnormal and indicative of myocardial ischemia. Whatever criterion is used during vasodilator therapy with these agents, potential apparently exists for precipitating myocardial ischemia. In most cases, myocardial ischemia occurred despite a decrease in the rate-pressure product. We do not know why myocardial ischemia was observed in some patients. It does not appear to be related to the type of vasodilator agent used, as abnormal myocardial lactate metabolism was seen with all three vasodilators. Coronary blood flow decreased in all patients who had biochemical evidence of myocardial ischemia. In these patients, coronary blood flow could have decreased in excess of that expected from the decrease in myocardial oxygen demand, thereby precipitating an imbalance between myocardial oxygen supply and demand. In all instances in this study, there was a significant decrease in arterial perfusion pressure, which

TABLE 4. Comparative Hemodynamic, Coronary Hemodynamic and Cardiac Metabolic Effects of Captopril, Prazosin and Hydralazine

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>Mean BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>SWI (g-m/m²)</th>
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<td>Captopril (n = 8)</td>
<td></td>
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<tr>
<td>C</td>
<td>90 ± 12</td>
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<tr>
<td>Peak</td>
<td>83 ± 9</td>
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<td>p</td>
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<td>Prazosin (n = 8)</td>
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<tr>
<td>p</td>
<td>&lt; 0.05</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.005</td>
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<td>Hydralazine (n = 8)</td>
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<tr>
<td>C</td>
<td>91 ± 14</td>
<td>77 ± 7</td>
<td>57 ± 4</td>
<td>21 ± 8</td>
<td>27 ± 12</td>
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<tr>
<td>Peak</td>
<td>94 ± 15</td>
<td>72 ± 11</td>
<td>50 ± 8</td>
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</tr>
<tr>
<td>p</td>
<td>&lt; 0.025</td>
<td>&lt; 0.005</td>
<td>&lt; 0.05</td>
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</table>

Data are mean ± sd. Peak values as defined in tables 1, 2 and 3. Abbreviations: See table 1.
might have compromised myocardial perfusion disproportionately.\(^{22}\)
Without knowledge of the degree of proximal coronary artery stenosis, and the state of the distal coronary vascular bed resistance, the relationship between the changes in perfusion pressure and coronary blood flow remains uncertain. A decrease in the transmomyocardial pressure gradients, which occurred in almost all patients, might have helped precipitate myocardial ischemia by decreasing subendocardial perfusion. However, the transmyocardial pressure gradient decreased in many other patients who did not have decreased lactate extraction or lactate production (fig. 5).

The other possible explanation for myocardial ischemia with the use of these vasodilators is the diversion of blood flow from relatively ischemic myocardium to nonischemic myocardium.\(^{23, 24}\) All three vasodilator agents appear to have appreciable arteriolar dilating effects. In experimental studies, the potential for the coronary steal syndrome with arteriolar dilators has been demonstrated,\(^{25}\) and cannot be excluded as the mechanism for myocardial ischemia in the patients who had abnormal lactate metabolism. It is possible that captopril does not influence autoregulatory resistance of the coronary vascular bed; thus, the coronary steal phenomenon is less likely to occur with captopril.\(^{9}\) However, the role of the coronary steal phenomenon with vasodilator therapy in patients with ischemic heart failure remains speculative. Whatever the mechanisms, in some patients with chronic heart failure associated with ischemic heart disease, vasodilator agents like captopril, prazosin or hydralazine can precipitate myocardial ischemia, which may not be clinically apparent. Changes in coronary hemodynamics were evaluated in this study after the administration of single or few doses of vasodilator agents, and different effects can be observed during chronic therapy.

In conclusion, our study suggests that in patients

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**Table 3. (continued)**

<table>
<thead>
<tr>
<th>CI (l/min/m²)</th>
<th>SVR (dyn/sec/cm²)</th>
<th>HR × BP (× 10⁻³)</th>
<th>MVO₂ (ml/min)</th>
<th>CSF (ml/min)</th>
<th>Art-CS DO₂ (vol%)</th>
<th>LE (%)</th>
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<td>2.1 ± 0.5</td>
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<td>2.7 ± 0.4</td>
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<tr>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>2.0 ± 0.5</td>
<td>1553 ± 379</td>
<td>10.4 ± 1.6</td>
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<td>11.9 ± 1.4</td>
<td>34 ± 16</td>
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<td>11.0 ± 1.6</td>
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</tr>
<tr>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.001</td>
<td>NS</td>
</tr>
<tr>
<td>2.1 ± 11</td>
<td>1445 ± 279</td>
<td>10.6 ± 1.9</td>
<td>7.15 ± 4.09</td>
<td>58 ± 34</td>
<td>12.2 ± 1.6</td>
<td>36 ± 13</td>
</tr>
<tr>
<td>2.9 ± 0.7</td>
<td>955 ± 271</td>
<td>10.5 ± 1.7</td>
<td>7.04 ± 5.36</td>
<td>58 ± 43</td>
<td>12.2 ± 1.8</td>
<td>39 ± 18</td>
</tr>
<tr>
<td>&lt; 0.001</td>
<td>&lt; 0.005</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
</tr>
</tbody>
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with chronic heart failure associated with obstructive coronary artery disease, captopril consistently decreases myocardial oxygen consumption. This decrease appears to be primarily related to a decrease in myocardial oxygen demand. Prazosin and hydralazine, however, tend to produce a variable response. The changes in myocardial oxygen consumption with hydralazine seem to be influenced by concomitant changes in the determinants of myocardial oxygen demand. With prazosin, changes in coronary blood flow or myocardial oxygen consumption correlate poorly with changes in myocardial oxygen demand. In the acute setting, despite an improvement in left ventricular function, deterioration in metabolic function can

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**Figure 5.** Although nearly all the patients decreased their transmomyocardial pressure gradient, this change did not predict which patients would produce lactate. Solid symbols indicate patients who produced lactate.
occur during vasodilator therapy in some patients with chronic heart failure due to ischemic heart disease.

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**References**

Alterations in left ventricular function and coronary hemodynamics with captopril, hydralazine and prazosin in chronic ischemic heart failure: a comparative study.

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