Short-term Vasodilator Effect of Captopril in Patients With Severe Mitral Regurgitation Is Parasympathetically Mediated

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**Background.** Few data exist regarding the effects of angiotensin converting enzyme inhibitors in patients with regurgitant valvular lesions. We postulated an immediate improvement in cardiac performance with captopril in mitral regurgitation, which, in a hemodynamically compensated group of patients, might be mediated through parasympathetic vasodilation rather than through blockade of angiotensin converting enzyme.

**Methods and Results.** Hemodynamics were examined before and 90 minutes after oral captopril (25–50 mg) in 18 patients (mean age, 31 years) with chronic, severe mitral regurgitation in New York Heart Association functional class II and III. One group of patients was given captopril alone (group 1, n=9) and a second group was given captopril plus atropine 0.04 mg/kg i.v. (group 2, n=9). Captopril alone (group 1) produced decreases in heart rate (90–81 beats/min, \( p<0.001 \)), mean arterial pressure (90–73 mm Hg, \( p<0.001 \)), systemic resistance (28–23 Wood units, \( p=0.068 \)), and pulmonary wedge pressure (19–14 mm Hg, \( p<0.001 \)). There was no improvement in either arteriovenous oxygen difference or thermodilution cardiac output; in fact, the latter slightly declined (3.45–3.35 l/min, \( p=0.002 \)). Pretreatment with atropine (group 2) diminished the effects of captopril on heart rate (107–103 beats/min, \( p=0.065 \) for atropine effect by two-way ANOVA), mean arterial pressure (88–82 mm Hg, \( p=0.01 \) for atropine effect), and systemic resistance (26–27 Wood units, \( p=0.04 \) for atropine effect).

**Conclusions.** In patients with chronic, severe mitral regurgitation, captopril reduced systemic arterial and left ventricular filling pressures but did not immediately augment cardiac output as expected. Furthermore, the modest systemic vasodilator effect of captopril was parasympathetically mediated. (Circulation 1991;84:2049–2053)

The mechanism by which angiotensin converting enzyme (ACE) inhibitors alter hemodynamics in heart failure is more complex than the name of this class of drugs indicates because a sizable minority of patients with heart failure have normal plasma renin activity even after treatment with furosemide.\(^1\)\(^2\) Although clinical proof is lacking, tissue ACE inhibition,\(^3\) prostaglandins,\(^4\) and bradykinin may contribute to the hemodynamic effects of ACE inhibitors in heart failure. Recently, a parasympathetic effect of ACE inhibitors has been demonstrated in normal volunteers,\(^5\)\(^6\) in hypertensives,\(^7\) and in patients with cardiomyopathy;\(^8\) however, the importance of parasympathetic activity in mediating the effect of ACE inhibitors is unknown.

We tested the hypothesis that in patients with stable heart failure caused by chronic severe mitral regurgitation, an ACE inhibitor would improve hemodynamics by parasympathetically mediated vasodilation. We chose this group of patients to study because there are few data regarding the effects of ACE inhibitors in patients with regurgitant valve disease despite the particular appeal of vasodilator therapy in such patients.\(^9\)

**Methods**

**Subjects**

From our population of patients with valvular heart disease, we recruited for this study those with severe (by angiography and Doppler color flow mapping) nonischemic mitral regurgitation (MR) in normal sinus rhythm who were considered candidates for valve surgery based on the presence of either symptoms or left ventricular (LV) dysfunction, were at or above the age of 15 years, and did not have any serological evidence of active rheumatic carditis. The latter is the most common etiology for MR at Baragwanath Hospital. Between August 1989 and October 1990, 18 consecutive such patients were identified.

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Received November 13, 1990; revision accepted July 2, 1991.
and gave informed consent to a protocol approved by the ethics committee of the University of Witwatersrand. Precatheterization evaluation included two-dimensional echocardiography and color Doppler recordings, by which all patients were judged to have severe MR. The etiology of MR was due to rheumatic disease (n = 12), ruptured chordae (idiopathic, n = 1; healed endocarditis, n = 1), and probable myxomatous (n = 4). The mitral valve area was greater than 2 cm² in all patients as measured by two-dimensional echo or Doppler pressure half-time.

Although the exact duration of the MR could not be determined, no patient presented with abrupt onset of symptoms (less than 4 weeks), and all had either LV or left atrial enlargement or both, suggesting that the MR was not acute. Five patients in group 1 had been on long-term ACE inhibitor therapy within the preceding month, and this was discontinued 2 days (n = 1) or 3 days (n = 4) before the study. Likewise, long-term therapy was discontinued in five previously treated group 2 patients at 2 days (n = 1), 3 days (n = 1), and 1 week (n = 3) before the study. Diuretics were continued until the evening before catheterization. Digoxin was not used. None of the patients had an elevated serum creatinine or low serum sodium.

**Patient Groups**

Patients were allocated to one of two groups: Group 1 (n = 9) was treated with oral captopril alone and group 2 (n = 9) was pretreated with intravenous atropine before captopril administration. The mean ages for group 1 and group 2 were similar (30 ± 12 years versus 32 ± 11 years, p = NS), as were the body surfaces areas (1.65 ± 0.26 m² versus 1.51 ± 0.15 m², p = NS) and echocardiographic mitral valve areas (5.4 ± 3.0 cm² versus 4.2 ± 1.1 cm², p = NS). The baseline angiographic left ventricular end-diastolic volumes (257 ± 79 ml for group 1 versus 258 ± 86 ml for group 2, p = NS) and end-systolic volumes (107 ± 56 ml for group 1 versus 121 ± 40 ml for group 2, p = NS) were also similar.

**Procedure**

Patients were premedicated with Phenergan 25 mg i.m. and pethidine (meperidine) 25 mg i.m. Right heart catheterization was performed via femoral vein with a thermodilution flotation catheter. Left heart catheterization was performed retrograde via femoral artery using an 8F micromanometer catheter with a pigtail configuration.

After the right and left heart hemodynamics were measured, atropine 0.02 mg/kg i.v. was given to group 2 patients 10 minutes before LV cine. Hexabrix 40–50 ml was injected into the LV during biplane cine (30° right anterior oblique and 60° left anterior oblique). The first contrast injection was performed after atropine administration in group 2 and before the precaptopril measurements in both groups so that there would be no contrast injections between the precaptopril and postcaptopril hemodynamic measurements, thus minimizing the possible effects of contrast on interpretation of the data. The injection was gated to diastole using the ECG to reduce the induction of ectopic beats.

After a period of 15 minutes, during which the effects of contrast injection dissipated, pulmonary artery, pulmonary wedge, aortic, and LV pressures were recorded simultaneously, with thermodilution cardiac outputs at three intervals separated by 10 minutes to establish a stable baseline. “Wedging” of the flotation catheter was confirmed either by observing the characteristic waveform showing a and v waves or by oximetry.

Captopril was then given orally at a dose of 25 mg for patients with body surface area of less than 1.7 m² (n = 15) and 50 mg for larger patients (n = 3). Hemodynamics were observed continuously. At 90 minutes, when ACE inhibition activity reaches a peak, measurements were again repeated in triplicate at 10-minute intervals. These measurements were preceded by another 0.02 mg/kg atropine (total dose, 0.04 mg/kg) in group 2. LV cine studies with simultaneous micromanometer LV pressure recordings were then performed using the same injection protocol, image intensifier, and table positions as for the baseline study.

There were no complications, and no side effects of captopril were reported by the patients.

**Analysis of Catheterization Data**

Left ventricular silhouettes for each frame of the first well-opacified beat of each LV cine not preceded by an ectopic beat were digitized using a hand-held cursor. Left ventricular wall thickness was measured at the midthird of the anterior wall in the right anterior oblique view for the end-diastolic frame. Correction factors for ventricular measurements were derived from the grids positioned at the center of the ventricle. Left ventricular volume was computed using the area–length method and a regression equation. Because the silhouette borders in the left anterior oblique view were sometimes unclear over the spine and diaphragm and because segmental dysynergy was absent, volumes were computed from the single-plane right oblique view. Mitral regurgitation was graded as 4+ (opacification of the left atrium equal to the LV within the first three beats) in each patient.

The angiographic (total) stroke volume (TSV) was computed as the difference between end-diastolic and end-systolic volumes. Forward stroke volume (FSV) was computed from the thermodilution cardiac output and the heart rate. Although mixed venous and arterial saturations were also obtained to enable calculation of Fick outputs (using an assumed O₂ consumption), the thermodilution outputs were used because no patient had evidence on combined echocardiography and Doppler with color flow mapping or on physical examination of more than mild tricuspid regurgitation. Regurgitant fraction was computed from the quotient (TSV–FSV)/TSV. In our laboratory, the relation between stroke volume
calculated with angiographic volumes and that measured from thermodilution flow in patients with cardiomyopathy or mitral stenosis who had trivial or no valvular regurgitation is

\[ SV_{\text{angiographic}} = 1.02 \times SV_{\text{thermodilution}} + 23 \text{ ml} \]

where \( n = 68 \), SEE = 20 ml, \( r = 0.65 \), and \( p < 0.001 \). Thus, although the slope of the relation is near unity, stroke volume computed from angiography systematically overestimates stroke volume by thermodilution, and the standard error is considerable.

Data are reported as mean±SD. A commercially available statistics program was used to perform two-way ANOVA for repeated measures to detect time effects (during the measurements at 10-minute intervals), captopril effects, and atropine effects. Differences between measurement intervals were isolated with Tukey’s test. Baseline hemodynamics measured in triplicate remained stable by repeated-measures ANOVA over the 20-minute baseline observation period before captopril, and the three measurements at 90, 100, and 110 minutes after captopril were therefore compared with the average of the three baseline measurements.

### Results

Before pretreatment with atropine, the heart rate (93±14 beats/min), mean arterial pressure (89±4 mm Hg), pulmonary capillary wedge pressure (18±7 mm Hg), cardiac output (3.53±1.08 l/min), and forward stroke volume (39±15 ml) in group 2 did not differ from the baseline measurements for group 1 (Table 1). Even after atropine, the only baseline hemodynamic variable that was different for group 2 compared with group 1 was the heart rate.

As expected, captopril produced a marked decline in systolic, diastolic, and mean arterial pressures (Table 1). Pulmonary wedge pressure declined modestly but significantly with a slight (\( p = 0.08 \)) decrease in the magnitude of the left atrial v wave. A modest lowering of systemic vascular resistance (\( p = 0.068 \)) after captopril was associated with only a small, nonsignificant rise in forward stroke volume. Also, heart rate significantly declined. Neither thermodilution cardiac output (Table 1) nor arteriovenous oxygen difference (7.0±1.7 to 6.9±2.2 vol% for group 1; 5.8±0.8 to 5.8±1.4 vol% for group 2) improved after captopril; in fact, there was a slight but statistically significant decline in the former.

No decrease in angiographic grade of MR after captopril was detected in any patient, and the estimated regurgitant fraction did not significantly decline (0.72±0.10 to 0.70±0.11 in group 1, \( p = \text{NS} \); 0.73±0.12 to 0.71±0.17 in group 2, \( p = \text{NS} \)).

Atropine markedly attenuated the bradycardia-vasodepressor effects of captopril (Table 1). The captopril-induced decreases in mean arterial pressure, systemic vascular resistance, and heart rate were all blunted by atropine (Figure 1), although the effect on heart rate was of borderline significance. The decreases in pulmonary wedge pressure and in cardiac output were not significantly different between the two groups, and the right atrial pressure did not change in either group (5±4 to 5±5 mm Hg in group 1 and 5±4 to 6±4 mm Hg in group 2). The hemodynamic changes produced by captopril in the two groups are compared in Figure 1 as percent deviations from the respective baseline measurements.

When subgroup analysis was repeated for the 10 patients (five in each group) who had been on long-term ACE inhibitor therapy during the month before the study, the results were qualitatively unchanged; however, the parasympathetically mediated increase in forward stroke volume and decrease in systemic resistance reached statistical significance (\( p < 0.005 \))

### Table 1. Hemodynamic Effects of Captopril Without and With Atropine Pretreatment

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (without atropine)</th>
<th>Group 2 (with atropine)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre 90 Min 100 Min 110 Min</td>
<td>Pre 90 Min 100 Min 110 Min</td>
<td></td>
</tr>
<tr>
<td>AoSP (mm Hg)</td>
<td>108±10 91±12 90±9 92±9</td>
<td>104±8 98±11 100±11 100±10</td>
<td>0.000 0.003</td>
</tr>
<tr>
<td>AoDP (mm Hg)</td>
<td>79±7 63±10 64±10 66±9</td>
<td>78±5 72±7 74±6 74±6</td>
<td>0.000 0.001</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>90±7 73±9 74±9 77±10</td>
<td>88±4 82±9 83±7 84±7</td>
<td>0.000 0.01</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>19±8 14±9 14±7 15±8</td>
<td>20±6 16±6 17±6 18±6</td>
<td>0.001 NS</td>
</tr>
<tr>
<td>ΔV wave (mm Hg)</td>
<td>14±11 10±9 8±7 8±7</td>
<td>8±5 7±5 8±6 8±6</td>
<td>0.08 NS</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>13±8 10±6 10±5 11±5</td>
<td>8±6 7±7 7±7 7±7</td>
<td>0.03 NS</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>3.45±0.97 3.35±0.72 3.29±0.85 3.23±0.90</td>
<td>3.59±0.99 3.22±0.86 3.35±0.83 3.28±0.83</td>
<td>0.002 NS</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>90±18 81±17 79±17 80±19</td>
<td>107±8 103±8 101±5 101±5</td>
<td>0.000 0.065</td>
</tr>
<tr>
<td>SVR (dyncsecmm⁻³)</td>
<td>2,237±662 1,840±537 1,917±649 2,045±648</td>
<td>2,085±490 2,130±432 2,073±443 2,141±447</td>
<td>0.068 0.04</td>
</tr>
<tr>
<td>FSV (ml)</td>
<td>40±14 44±14 44±14 42±15</td>
<td>34±11 31±9 33±9 33±9</td>
<td>NS 0.02</td>
</tr>
</tbody>
</table>

Values are mean±SD before and after captopril for group 1 (no atropine) and group 2 (postatropine) parameters.

AoSP, aortic systolic pressure; AoDP, aortic diastolic pressure; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; ΔV wave, peak v mean pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; CO, cardiac output; HR, heart rate; SVR, systemic vascular resistance; FSV, forward stroke volume.
may fail to produce the anticipated increase in stroke volume for reasons that are not yet clear.

In patients with severe heart failure, ACE inhibitors reduce systemic resistance and improve cardiac performance through blockade of the renin-angiotensin system. However, a sizable minority of patients with heart failure have normal plasma renin activity even after treatment with furosemide. The question then arises as to the mechanism of action of these agents. As summarized by Dzau and Safar, there is experimental evidence that vascular ACE activity may be increased in the absence of elevated circulating renin or angiotensin II levels. Although clinical proof is lacking, this could explain the effectiveness of ACE inhibitors in patients with normal or low plasma renin. Other postulated mechanisms for the hypotensive action of ACE inhibitors in patients with normal renin levels include the effects of these drugs on prostaglandin synthesis and bradykinin. However, clinical evidence for or against these possible mechanisms is also lacking.

Recently, a parasympathetic effect of ACE inhibitors has been demonstrated in normal volunteers and in hypertensives, and in patients with cardiomyopathy. The possibility of parasympathetically mediated vasodilation intrigued us during our initial pilot studies, in which we noted a significant slowing of heart rate after administration of captopril to patients with MR. Subsequent study showed that atropine blocked the decline in systemic resistance produced by captopril and attenuated the bradycardic effect. This indicates that, at least with short-term captopril, much of the hemodynamic effect in patients with chronic, severe MR and compensated heart failure is due to activation of the parasympathetic limb of the autonomic nervous system. The finding that vasodilation in these patients was parasympathetically mediated may in part explain why cardiac output did not increase, since a vagally induced vasodilation may be associated with a decline in cardiac output caused by slowing of heart rate and, possibly, a negative inotropic effect.

Not all of the hemodynamic effects of captopril were reversed by atropine. As illustrated in Figure 1, captopril still produced a significant decline in pulmonary wedge pressure after pretreatment with atropine in group 2. There are several possible explanations of why atropine blocked the arterial vasodilator effect of captopril but failed to block the drop in filling pressure: 1) The dose of atropine required might be different, but we have no evidence to support this possibility; 2) captopril has venodilating properties that might be mediated through a reduction in sympathetic tone rather than through an increase in parasympathetic tone; however, the lack of change in right atrial pressure with captopril in either group suggests the venodilator effect was not important here; or 3) by lowering levels of angiotensin II, captopril improves LV diastolic properties and thereby lowers filling pressures even without an improvement in systolic properties. This latter hy-
A hypothesis is supported by preliminary work showing that angiotensin II may augment systolic function while impairing diastolic performance, and conversely, that ACE inhibition may improve diastolic dysfunction without improving systolic function. This seems to be the best explanation for the decrease in filling pressures with captopril even after arterial vasodilation was blocked with atropine.

It is also interesting to note that, although atropine completely blocked the effect of captopril on systemic resistance, it blunted but did not completely abolish the hypotensive effect of the drug. We suspect that this may be due to a negative inotropic effect, the potential for which has been demonstrated by Foul and coworkers" by using intracoronary enalaprilat. A negative inotropic effect may help explain why Packer et al'3 found a lesser increase in cardiac output despite a similar degree of vasodilation with captopril compared with nitroprusside.

Limitations

This study, which was designed to examine the short-term hemodynamic effects of captopril by invasive methods, does not preclude a beneficial long-term effect of captopril in patients with MR. Packer and coworkers15 showed continued hemodynamic improvement over 12 weeks after the first dose of captopril was given to 42 patients with heart failure. The work of Drexlcer and coworkers14 and Dzau and Safar1 suggest that the delayed effects of captopril are probably due to peripheral effects (tissue ACE inhibition) that cannot be predicted by either short-term hemodynamic responses or short-term serum ACE inhibition. However, since these drugs have both short- and long-term effects, a detailed analysis of the short-term effects is also essential for understanding the mechanism of action in a given disorder.

References


Key Words • angiotensin converting enzyme inhibitors • captopril • mitral regurgitation • vasodilators • atropine
Short-term vasodilator effect of captopril in patients with severe mitral regurgitation is parasympathetically mediated.
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Circulation. 1991;84:2049-2053
doi: 10.1161/01.CIR.84.5.2049

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/84/5/2049