Hemodynamic and Radionuclide Effects of Acute Captopril Therapy for Heart Failure: Changes in Left and Right Ventricular Volumes and Function at Rest and During Exercise

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SUMMARY Although the resting hemodynamic effects of captopril in congestive heart failure are known, little information is available about the hemodynamic response to captopril during exercise or about changes in noninvasive measurements of the size and function of both ventricles. In this study, 14 stable New York Heart Association class III patients were given 25 mg of oral captopril. Rest and exercise hemodynamic measurements and blood pool scintigrams were performed simultaneously before and 90 minutes after captopril. The radionuclide studies were analyzed for left and right ventricular end-diastolic volumes, end-systolic volumes, ejection fractions and pulmonary blood volume.

The primary beneficial responses at rest were decreases in left and right ventricular end-diastolic volumes from 388 ± 81 to 350 ± 77 ml (p < 0.01) and from 52 ± 26 to 43 ± 20 volume units (p < 0.01), respectively, and in their corresponding filling pressures, from 24 ± 10 to 17 ± 9 mm Hg and 10 ± 5 to 6 ± 5 mm Hg (both p < 0.001). Although stroke volume did not increase significantly, both left and right ventricular ejection fractions increased slightly, from 19 ± 6% to 22 ± 5% and from 25 ± 9% to 29 ± 11%, respectively (both p < 0.01). During exercise, similar changes were noted in both hemodynamic and radionuclide indexes.

Thus, in patients with moderate symptomatic limitation from chronic heart failure, captopril predominantly reduces ventricular volume and filling pressure, with a less significant effect on cardiac output. These effects persist during exercise, when systemic vascular resistance is already very low. Radionuclide techniques are valuable in assessing the drug effect in these subjects, particularly when ventricular volumes are also measured.

CAPTOPRIL, a competitive antagonist of angiotensin-converting enzyme, produces hemodynamic improvement at rest in patients with chronic congestive heart failure.1-7 Most studies indicate that captopril both decreases left ventricular filling pressure and increases cardiac output, and thus functions as both a preload and afterload reducer in heart failure patients. No information is available about the hemodynamic response to captopril during exercise, and only limited data are available about its effect on noninvasive measurements of rest and exercise left ventricular volume and function. The response of the right ventricle to captopril therapy has not been evaluated. The present study was designed to examine these aspects of the acute response to captopril therapy and to determine whether this response can be assessed noninvasively by radionuclide techniques.

Methods

Patient Population

Fourteen male patients, ages 48 to 72 years (mean 60 years), with New York Heart Association functional class III congestive heart failure, were studied. Heart failure resulted from coronary heart disease alone in nine patients, coronary disease with a history of hypertension in two, primary cardiomyopathy in two, and rheumatic heart disease after mitral valve replacement in one patient. Nine patients had findings of mitral regurgitation on physical examination, but these were felt to be secondary to left ventricular dysfunction in every case. Clinical heart failure had been present for 3 months to 8 years (mean 3.1 years). All patients were clinically stable, ambulatory and able to perform treadmill exercise, with their exercise tolerance ranging from 6.5-12 minutes on a Naughton protocol.8 Four had previously been treated with hydralazine, nitrates or prazosin. To ensure clinical stability, all vasodilators were discontinued at least 2 weeks before hospitalization and the patients were followed as outpatients on a stable regimen of digoxin and diuretics.

Study Protocol

All patients were hospitalized for 24-48 hours before catheterization to further ensure medication and dietary compliance. A practice exercise session was used to familiarize patients with the procedure and to determine their maximal work load. Each subject performed supine bicycle exercise to exhaustion using an inertial ergometer, beginning at a work load of 200 kpm/min and increasing by 100 kpm/min every 3 minutes. After recovery, right-heart catheterization was performed with a balloon-tipped thermodilution catheter, and a polyethylene cannula was inserted into a radial artery. Hemodynamics were monitored for 12 hours before the study. All diuretics
Baseline measurements were made with the patients at rest in the supine position. Patients next performed supine bicycle exercise using the previously described protocol. Heart rate, right atrial, pulmonary arterial and systemic arterial pressures were monitored continuously. Pulmonary capillary wedge pressure was monitored every minute. The pulmonary capillary wedge pressure at end-expiration was used as an index of left ventricular filling pressure, except in four subjects in whom it could not be consistently obtained and in whom pulmonary arterial diastolic pressure was used instead. Cardiac output was measured in triplicate in the final 2 minutes of the highest exercise stage achieved during the practice run.

Patients were allowed to recover for at least 1 hour or until their hemodynamic measurements returned to baseline. Captopril, 25 mg, was then administered orally. Resting hemodynamic measurements were recorded every 30 minutes. After 90 minutes, bicycle exercise was repeated using the same protocol. Ninety minutes was chosen as the time for repeat exercise measurements because previous studies have indicated that this is the approximate time of the peak captopril effect in most subjects. Complete hemodynamic and scintigraphic data were collected at the pre-captopril maximum work load to compare measurements before and after captopril at the same exercise work load. Although patients were permitted to continue exercising, no patient completed a higher exercise work load acutely after a single dose of captopril. Radionuclide analyses were not possible in two patients during exercise because of heart rate irregularity. Exercise hemodynamic measurement was unsuccessful in one patient because of catheter malfunction.

Radionuclide Techniques

Equilibrium blood pool scintigraphy was performed at the time of the baseline and 90 minutes after captopril hemodynamic measurements, both at rest and during exercise, using standard techniques. A single-crystal, 37 photomultiplier tube gamma camera equipped with a medium-sensitivity, parallel-hole collimator, interfaced to a dedicated minicomputer system, was used. The blood pool was labeled with 20 mCi of technetium-99m pertechnetate using the in vivo red cell technique. Scintigraphy was performed in the left anterior oblique projection providing the best separation of the right and left ventricles (usually 40–50°), with an additional 10° of caudal angulation. Care was taken to use the same camera and patient positioning for the pre- and postcaptopril studies. Resting scintigrams were obtained for 10 minutes, and the exercise images were acquired for the final 2 minutes of the highest completed stage.

Our methods of scintigraphic analysis and left ventricular volume determination have been published. Briefly, 11 64 × 64-pixel frames were obtained over the first half of the cardiac cycle, thus providing the equivalent of 20–22 frames/cycle temporal resolution. Cycles with lengths 100 msec longer or shorter than the average of the 10 cycles immediately before acquisition were rejected. The number of acquired cycles and frame duration were noted. Four-milliliter blood samples were drawn midway through the rest scintigrams and immediately after the exercise scintigrams. These were subsequently counted for 2 minutes at a distance of 18 inches from the collimator, and the time difference between blood drawing and counting was noted to permit back-calculation of blood activity at the time of scintigraphy, using the decay rate of technetium.

Analysis was performed by a single observer. Left ventricular, right ventricular and right lung regions of interest were manually defined. A region postero-lateral to the left ventricle was used to estimate both left and right ventricular background. The background-corrected left and right ventricular activity at end-diastole and end-systole were then determined, permitting calculation of both ventricular ejection fractions. The uncorrected mean lung activity per 100-pixel region was also determined as an index of pulmonary blood volume. Each of these activities was normalized for the duration of the acquisition, taking into account the number of accepted cycles and the time per frame, and for blood activity by a previously published modification of the counts-based volume methods developed by Slutsky et al. and Dehmer et al.

The left ventricular end-diastolic and end-systolic activity-to-blood activity ratios were converted to end-diastolic and end-systolic volumes (in milliliters) using a regression equation from a scintigraphic-angiographic correlation study. The standard error of the estimate in relation to angiography was 18 ml. Because a similar validation for right ventricular or pulmonary blood volumes has not been performed in our laboratory, these measurements are expressed as dimensionless units to permit comparison between the pre- and postcaptopril findings.

Data Analysis

The significance of changes before and after captopril were determined by Student t tests for paired samples. Hemodynamic measurements were not available in one patient because of catheter malfunction, and exercise scintigraphy was unsatisfactory in two patients because of irregularity in heart rate.

Results

Hemodynamic Effect of Captopril at Rest

The hemodynamic effects of a single 25-mg oral dose of captopril at rest are shown in table 1. Although resting measurements were recorded every 30 minutes for the first 2 hours and then hourly for 6 more hours, only measurements obtained 60–90 minutes after captopril are reported here, because this was the time of postcaptopril scintigraphy and immediately preceded the repeat exercise measurements. These measurements represented peak captopril hemodynamic effect in eight of the 13 subjects,
and the peak effect was observed within 30 minutes of that time in three others. Two subjects appeared to have a delayed peak drug effect, at 4 and 6 hours.

Mean arterial pressure fell from 86 ± 10 to 73 ± 13 mm Hg (p < 0.001) for the group, and this decrease exceeded 20 mg Hg in four subjects. Heart rate declined modestly but significantly. The primary beneficial hemodynamic effect of captopril was a drop in the filling pressures of both ventricles. Left ventricular filling pressure fell from 24 ± 10 to 17 ± 9 mm Hg (p < 0.001) and right atrial pressure decreased from 10 ± 5 to 6 ± 5 mm Hg (p < 0.001). The increase in cardiac index and stroke volume index at 90 minutes did not achieve statistical significance because of decreases in two subjects. Figure 1 shows the relatively greater effect of captopril on filling pressure than on stroke volume at rest.

Effect of Captopril on Radionuclide Measurements at Rest

Both left and right ventricular ejection fractions increased modestly but significantly, from 19% to 22% and from 25% to 29%, respectively (p < 0.01) (table 2, figs. 2 and 3). These changes resulted almost entirely from reductions in end-diastolic volume, from a mean of 388 ± 81 ml to 350 ± 77 ml (p < 0.01) for the left ventricle, and from 52 ± 26 to 43 ± 20 dimensionless units (p < 0.01) for the right ventricle, since no significant change occurred in calculated stroke volume. End-systolic volumes decreased by a similar amount.

The radionuclide measurements correspond to the hemodynamic findings in demonstrating that the predominant effect of captopril is a reduction in ventricular filling pressure and volume rather than an increase in stroke volume (fig. 4). The radionuclide index of pulmonary blood volume also fell significantly, from 14.5 ± 3.4 to 12.2 ± 3.0 U (p < 0.01).

Hemodynamic Effects of Captopril During Exercise

The hemodynamic responses to captopril at the same exercise work load are shown in table 1 and figure 1. Again, arterial pressure and heart rate were significantly lower after captopril. The decrease in left ventricular filling pressure was smaller than that at rest, but remained highly significant. In contrast, the increase in stroke volume after captopril, although still modest, was significant. Thus, during exercise, captopril produced more comparable improvement in both left ventricular filling pressure and stroke volume

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**Figure 1.** The changes in stroke volume index and left ventricular filling pressure at rest and during exercise. The lines originating with open circles indicate the means for the group. At rest, left ventricular filling pressure fell from 24 ± 10 to 17 ± 9 mm Hg (p < 0.001), but the stroke volume increase was not significant. During exercise, the filling pressure reduction was less dramatic, but the improvement in stroke volume was statistically significant.
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Figure 2. After captopril administration, left ventricular ejection fraction (LVEF) at rest increased, predominantly because of the decrease in LV end-diastolic volume (EDV); stroke volume (SV) did not change significantly. End-systolic volume (ESV) fell significantly.

Effect of Captopril on Radionuclide Measurements During Exercise

The radionuclide findings during exercise (table 2, figs. 5 and 6) were similar to those at rest. Again, both ventricular ejection fractions rose, predominantly as a result of reduction in end-diastolic volumes without changes in total stroke volume. End-systolic volumes also dropped significantly, but changes in pulmonary blood volume were not significant.

The changes in left ventricular filling pressure and volume were directionally similar (fig. 4). However, in this higher range, the reduction in pressure was less for a similar decrease in volume when compared to the findings at rest.

Discussion

Although the acute resting hemodynamic effects of captopril in patients with severe heart failure have been reported,7 the present study is the first to examine the response to captopril during exercise and the first to use radionuclide measurements of both left and right ventricular volumes and function.

Hemodynamic Findings

Our resting hemodynamic findings generally confirm those of previous investigations, although they differ in the magnitude of change in cardiac output and stroke volume. Similar to previous studies, we noted a significant reduction in arterial pressure and a modest drop in heart rate. While these changes were generally well tolerated, they emphasize the need for starting captopril under close observation. Captopril therapy must be undertaken in the hospital in most patients with severe heart failure. The most dramatic beneficial effect of the drug was a marked decrease in elevated left ventricular filling pressures; in our patients, this averaged 30% (from 24 to 17 mm Hg), in agreement with previous series in which the reduction ranged from 28% to 46%.5,7 Other investigators have also noted increases in cardiac and stroke volume indexes, ranging from 19% to 38%.1,3 These changes have consistently been less impressive than the reduction in left ventricular filling pressures, but they have always been statistically significant. In our patients, only an 8% increase in these measurements 90 minutes after captopril was noted, and the changes were not significant.

Several factors might explain our divergent results. Although the pretreatment hemodynamic characteristics of our subjects (mean cardiac index 2.1 liters/min, pulmonary capillary wedge pressure 24 mm Hg) were similar to previous series, our patients were generally less ill. Each of our subjects could exercise for at least 6.5 minutes on a Naughton treadmill protocol and all were in New York Heart Association class III, unlike the subjects in prior reports. Our patients were also studied electively in that they had been followed as outpatients on a consistent medical regimen for at least 2 weeks and hemodynamic measurements were delayed more than 12 hours after catheterization. These differences in patient population probably explain the lower systemic vascular resistance, which averaged 1620 dyn-sec-cm⁻⁴ in our group, compared with 1800–2200 dyn-sec-cm⁻⁴ in previous studies. In fact, Ader et al.9 reported that the hemodynamic response to captopril is inversely proportional to the pretreatment vascular resistance. Also, our protocol was designed to collect simultaneous invasive and noninvasive measurements at a single point in all patients, anticipating that the peak hemodynamic effect.
would occur at approximately 90 minutes after the dose. Had we reported the peak captopril effect, the changes would have been somewhat greater.

The hemodynamic values during exercise were similar to those at rest. The decrease in left ventricular filling pressure after captopril was less dramatic, while the increase in stroke volume was more consistent and was statistically significant. This beneficial hemodynamic response to captopril during exercise is important because systemic resistance drops during exercise as a result of peripheral vasodilation and the additive effect of a converting-enzyme inhibitor could not be taken for granted. Our inability to find any acute increase in exercise capacity is in keeping with previous studies that failed to show such a change after very short term therapy. The reasons for this inconsistency between improvement in exercise hemodynamics and lack of acute change in exercise capacity have been discussed. The Radionuclide Findings

The most interesting finding of the present study is the change in ventricular volumes. We measured consistent decreases in both left and right ventricular volumes, both at end-diastole and end-systole. No change in radionuclide stroke volume was noted; thus, the modest increase in ejection fraction from 19% to 22% was entirely the result of a decrease in ventricular size. In two studies, radionuclide ejection fraction was measured and showed contrasting results: One showed an increase and the other did not. Again, captopril produced beneficial effects during exercise when the pretreatment systemic vascular resistance was already quite low and also at rest when systemic resistance was much higher.

The agreement between the radionuclide and the hemodynamic findings is striking. By both techniques, the predominant effect of captopril was a decrease in left ventricular preload. Acute increases in cardiac output or stroke volume, and hence, ejection fraction in moderately ill patients, are modest and may be difficult to detect. Nonetheless, because of the agreement with simultaneous invasive measurements, our findings certainly raise the possibility of monitoring the effects of captopril noninvasively in laboratories that determine ventricular volume as well as ejection.

**Table 2. Radionuclide Indexes of Captopril Response**

|        | Rest
|--------|--------|--------|--------|
|        | Precap | Cap    | p
| LVEF (%) | 19 ± 6 | 22 ± 5 | <0.01 |
| LVEDV (ml) | 388 ± 81 | 350 ± 77 | <0.01 |
| LVESV (ml) | 319 ± 75 | 271 ± 75 | <0.01 |
| RVEF (%) | 25 ± 9 | 29 ± 11 | <0.01 |
| RVEDV (U) | 52 ± 26 | 43 ± 20 | <0.01 |
| RVESV (U) | 40 ± 22 | 32 ± 17 | <0.01 |
| PBV (U) | 14.5 ± 3.4 | 12.2 ± 3.0 | <0.01 |

|        | Exercise
|--------|--------|--------|--------|
|        | Precap | Cap    | p
| LVEF (%) | 15 ± 5 | 22 ± 5 | <0.001 |
| LVEDV (ml) | 431 ± 87 | 357 ± 79 | <0.001 |
| LVESV (ml) | 330 ± 88 | 279 ± 78 | <0.001 |
| RVEF (%) | 25 ± 8 | 29 ± 10 | <0.01 |
| RVEDV (U) | 54 ± 26 | 47 ± 19 | <0.05 |
| RVESV (U) | 41 ± 21 | 34 ± 15 | <0.05 |
| PBV (U) | 12.5 ± 4.0 | 11.2 ± 3.1 | <0.10 |

Values are mean ± SD.

Abbreviations: LV = left ventricular; RV = right ventricular; EF = ejection fraction; EDV = end-diastolic volume; ESV = end-systolic volume; PBV = pulmonary blood volume; Cap = captopril; Precap = before captopril.
fraction. In this group of patients, hemodynamic measurements offered little more to the assessment of captopril than the radionuclide measurements together with frequent blood pressure determinations.

Mechanism of Captopril Effect

Vasodilators are often classified as preload or afterload reducers by whether their predominant effect is on the venous or arteriolar beds and by whether they

Figure 4. The changes in pulmonary capillary wedge (PCW) pressure after captopril vs the change in end-diastolic volume. In general, there was agreement between the hemodynamic and radionuclide indexes of left ventricular preload, both at rest and during exercise. There is a greater fall in PCW pressure for a similar decrease in volume at rest than with exercise.

Figure 5. The left ventricular (LV) radionuclide findings during exercise were similar to those at rest: Ejection fraction (EF) increased due to a decrease in end-diastolic volume (EDV). ESV = end-systolic volume; SV = stroke volume.
produce a greater beneficial response in left ventricular filling pressure or cardiac output.18-20 While such an approach has some clinical value, it is a simplification because of the complex interaction between these variables. Captopril, as a competitive antagonist of angiotensin-converting enzyme, would be expected to have its major effect on the arteriolar resistance bed.21 This is supported by the inverse relationship between pretreatment arteriolar resistance and the captopril effect.3 Yet, captopril has had a greater effect on ventricular filling pressure than cardiac output in previously published studies1,4 and in our patients.

This preload-reducing effect may have several mechanisms. Increased venous capacitance is likely;6 but the mechanism for such a venous effect remains unclear. Angiotensin II, itself, has little vasoconstricting effect.22,23 However, converting enzyme is also active in the metabolism of bradykinins, and a build-up of these potent venulectomists could play an important role in the acute response to captopril.24 26 Angiotensin II is also a potent stimulant to catecholamine release.26 27 The drop in ventricular filling pressures and the surprising decrease in heart rate could reflect catecholamine withdrawal.28 A reflex decrease in sympathetic tone from improved peripheral perfusion due to an increased cardiac output has been suggested,28 but our findings do not support this hypothesis.

Our results indicate that the major beneficial effect of captopril is a reduction in ventricular volume and in filling pressures; they also corroborate that this agent functions as an afterload reducer. Systemic vascular resistance falls modestly, both at rest and during exercise. More important, the decrease in both left ventricular volumes and arterial pressure could be expected to decrease systolic wall tension. The actual degree to which the preload- and afterload-reducing effects of captopril become manifest is probably determined by the pretreatment hemodynamic status of the patient and by the level of activity of the renin-angiotensin-aldosterone system.29

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