Influence of Chronic Captopril Therapy on the Infarcted Left Ventricle of the Rat

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SUMMARY. To determine whether the relationship between infarct size and ventricular performance, volume, and compliance could be altered favorably, captopril was administered to rats for 3 months following coronary artery ligation. Baseline left and right ventricular and systemic arterial pressures and aortic blood flow, and maximal stroke volume and cardiac indices attained during a volume loading, were measured. Passive pressure-volume relations of the left ventricle were determined, and the slopes of segments of this relation were analyzed to characterize ventricular chamber stiffness. In untreated rats, left ventricular end-diastolic pressure progressively rose (from 5-28 mm Hg) as a function of infarct size, whereas, in captopril-treated rats, filling pressure remained within normal limits (5 ± 1 mm Hg) in all but those with extensive infarcts. Chronic captopril therapy reduced baseline mean arterial pressure and total peripheral resistance, yet maintained cardiac and stroke outputs in rats both with and without infarcts. In untreated rats, maximal pumping ability progressively declined with increasing infarct size, whereas, in captopril-treated rats, peak stroke volume index remained within normal limits in all but those with extensive infarcts. The in vitro left ventricular volumes of captopril-treated rats were significantly less than those of untreated rats. The maintenance of forward output from a lesser dilated left ventricle yielded an index of ejection fraction for treated rats with moderate and large infarcts that was significantly elevated compared with that of untreated rats with infarcts of comparable size. Left ventricular chamber stiffness, which fell as infarct size increased in untreated rats, was normalized by chronic captopril therapy. Thus, captopril attenuated the left ventricular remodeling (dilation) and deterioration in performance that were observed in rats with chronic myocardial infarction. (Circ Res 57: 84-95, 1985)

THE power failure consequent to the loss of contracting myocardium as a result of myocardial infarction evokes a constellation of compensatory mechanisms which act to maintain systemic perfusion. These mechanisms include enhancement of sympathetic tone, alterations in regional vascular resistance, activation of the renin-angiotensin-aldosterone system, sodium retention, and ventricular dilation. Despite these compensatory efforts, cardiac pumping function may be ineffective and heart failure supervenes, with morbidity and sometimes fatal consequences. There is general agreement that the prognosis of patients with heart failure following myocardial infarction is poor (Braunwald, 1984).

In the rat model of myocardial infarction produced by coronary artery ligation, we have observed, 3 weeks after operation, a wide spectrum of left ventricular impairment, ranging from minimal dysfunction to overt heart failure, depending on infarct size and ventricular volume (Pfeffer et al., 1979; Fletcher et al., 1981). On the assumption that progressive ventricular dilation may exert an adverse effect on ventricular performance in heart failure, and the finding that captopril, a converting enzyme inhibitor, reduces both preload and afterload (Awan et al., 1981), the present study was undertaken to determine whether this agent could alter favorably and chronically the relationship between infarct size and ventricular performance, volume, and compliance.

Methods

Experimental Infarction

Myocardial infarctions were produced in 4- to 5-month-old female normotensive Wistar rats (West Jersey Biological Supply) by a previously described method (Pfeffer et al., 1979; Fletcher et al., 1981). In brief, the rats were anesthetized with ether, intubated, and ventilated by a positive pressure respirator. After a left-sided thoracotomy, the heart was gently exteriorized, and the left atrium was retracted to facilitate ligation of the left coronary artery between the pulmonary outflow tract and left atrium. The heart was replaced in the thorax, the lungs inflated by increasing positive end-expiratory pressure, and the wound rapidly closed by a previously placed purse-string suture. There is a 40–60% mortality rate within the first 48 hours following this procedure. The administration of captopril [2 g/liter of drinking water (Pfeffer et al., 1982a)] was initiated either 2 or 21 days after production of the myocardial infarction and was continued for 3 months; control rats received tap water. All rats were housed under identical conditions in a 12-
hemodynamic and maximum flow-generating capacity were assessed (Pfeffer et al., 1979). After induction of anesthesia with ether, a tracheostomy was performed, and ventilation and anesthesia were maintained by a positive pressure respirator connected in series with an ether-drip apparatus. The right carotid artery and jugular vein were cannulated and their saline-filled catheters (PE 50), which were connected via a stopcock to a Millar micromanometer and Statham (P50) transducer, respectively, were advanced into the respective left and right (whenever possible) ventricles. The respirator connection was detached and, under light ether anesthesia and spontaneous respiration, measurements were made of ventricular systolic and end-diastolic pressures and \( \frac{dP}{dt} \) and, subsequently, to the withdrawal of the cannulas into their vessels, of phasic and mean systemic arterial and right atrial pressures and heart rate. Although the fluid-filled catheter system overestimates \( \frac{dP}{dt} \), the values of \( \frac{dP}{dt} \) thus obtained were used solely to provide a relative comparison between therapy groups and not as an absolute measure of \( \frac{dP}{dt} \).

The animal was again attached to the respirator and a mid-sternal thoracotomy was performed by heat cautery to expose the ascending aorta for placement of an electromagnetic flow probe (2.0 or 2.5 mm i.d.; C+C Instruments) which permitted the continuous measurement of phasic and mean (cardiac output less coronary blood flow) aortic blood flows. Stroke volume was calculated as the quotient of cardiac output and heart rate, and total peripheral resistance was calculated as the quotient of the difference between mean systemic and right atrial pressures and cardiac output. All variables derived from blood flow were corrected for body weight. Phasic and mean pressures and flow were recorded every 2 minutes over a stable 10-minute period, then were averaged to provide baseline hemodynamic values.

To assess the maximum flow-generating capacity of the heart, warmed (39°C) Tyrode's solution was infused rapidly (40 ml/min per kg for 45 seconds) into a femoral vein to produce a rise in cardiac output to a plateau level, at which point cardiac output failed to increase further, despite continued elevations of right atrial pressure. After the return of all hemodynamic variables to baseline levels, the flow probe was removed and the arterial catheter was advanced into the left ventricle for continuous monitoring of pressure. The volume-loading procedure was repeated and the end-diastolic pressure at which maximum stroke volume occurred was determined; from these data and the subsequently determined pressure-volume curves (see below), the end-diastolic volume at which maximal stroke volume occurred was determined. An index of ejection fraction was obtained as the maximum stroke volume attained during the in vivo volume loading and the in vitro ventricular volume obtained from the passive pressure-volume relationship (Pfeffer et al., 1979). Since ejection fraction was calculated from two variables measured at different points in time, the term ejection fraction index is used as an estimate of ejection fraction. Although volumes obtained in the postmortem left ventricle could be different from those obtained in vivo, Bersohn and Scheuer (1977) have demonstrated a high correlation (\( r = 0.91 \)) between volumes obtained by the indicator dilution technique in the beating rat heart and those obtained by direct measurement in the same heart following fixation at the in vivo end-diastolic pressure of each animal. The range of ventricular volumes (0.3-0.6 ml) determined by these investigators was similar to that of the noninfarcted rats in the present study.

### Hemodynamic Studies

At the end of the therapy period, baseline hemodynamics and maximum flow-generating capacity were assessed (Pfeffer et al., 1979). After induction of anesthesia with ether, a tracheostomy was performed, and ventilation and anesthesia were maintained by a positive pressure respirator connected in series with an ether-drip apparatus. The right carotid artery and jugular vein were cannulated and their saline-filled catheters (PE 50), which were connected via a stopcock to a Millar micromanometer and Statham (P50) transducer, respectively, were advanced into the respective left and right (whenever possible) ventricles. The respirator connection was detached and, under light ether anesthesia and spontaneous respiration, measurements were made of ventricular systolic and end-diastolic pressures and \( \frac{dP}{dt} \) and, subsequently, to the withdrawal of the cannulas into their vessels, of phasic and mean systemic arterial and right atrial pressures and heart rate. Although the fluid-filled catheter system overestimates \( \frac{dP}{dt} \), the values of \( \frac{dP}{dt} \) thus obtained were used solely to provide a relative comparison between therapy groups and not as an absolute measure of \( \frac{dP}{dt} \).

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### Pressure-Volume Relation

To assess the passive pressure-volume characteristics of the left ventricle, the heart was arrested in diastole and a double-lumen catheter was inserted into the aorta, then advanced into the left ventricle for the simultaneous infusion of saline and recording of pressure (Fletcher et al., 1981). The left ventricle was isolated by ligation of the atrioventricular groove and the right ventricle was incised to eliminate any possible compressive effect. Reproducible pressure-volume curves were generated over a pressure range of 0-30 mm Hg within 10 minutes of cardiac arrest and before the onset of rigor mortis. Ventricular volumes were determined at every unit mm Hg of pressure on the pressure-volume curve.

To analyze the various segments of the pressure-volume curve, we determined chamber stiffness constants over several pressure ranges. From 0-3 mm Hg the pressure-volume relation was linear, and the slope of this relation was designated as \( k_1 \). Above 3 mm Hg, the pressure-volume data were fitted to the exponential function, \( P = b e^{k_2} \), to derive the stiffness constants: \( k_2 \) (2.5-30 mm Hg), the overall chamber stiffness constant; \( k_3 \) (3-10 mm Hg); \( k_4 \) (10-20 mm Hg); and \( k_5 \) (20-30 mm Hg) (Fletcher et al., 1981). The expression of the curvilinear pressure-volume data in the form, \( dP/dV = kP \), permitted within-treatment and between-treatment analyses to be made by comparisons of slopes (k).

After inscription of the pressure-volume curves, a volume of formalin corresponding to 5 mm Hg on the pressure-volume axis was infused into the left ventricle and kept constant by closure of the stopcocks in the double-lumen catheter system. The heart (with catheter) was excised and fixed by immersion in formalin for 24 hours. The right and left ventricles then were separated and weighed.

#### Infarct Size Measurements

The left ventricle was embedded in paraffin and 50-\( \mu \)m sections (of which every 20th section represented 1 mm of length) were cut serially from apex to base. These representative sections were stained with Masson trichrome (from which hematoxylin was omitted) and were mounted on slides for projection to a magnification of \( \times 12 \). The lengths of scar and of noninfarcted muscle for both the endocardial and epicardial surfaces of each histological section were determined by planimetry. The lengths of scar for the endocardial and epicardial surfaces for all histological sections were numerically summed separately, as were the endocardial and epicardial circumferences. The ratio of the sums of the lengths of scar and of surface circumferences defined the infarct size for each of the myocardial surfaces. Final infarct size was expressed in percent as the average of the infarct sizes of the endocardial and epicardial surfaces times 100.

#### Statistical Analysis

Results are expressed as mean ± 1 SEM, except where indicated. For analysis, rats were classified into groups according to infarct size. By Student's \( t \)-test, it was determined that the variables (all of those presented in this
paper) of groups whose therapy was initiated at 2 or 21
days did not differ, and these data were pooled. For
within-treatment comparisons, if a one-way analysis
of variance determined the presence of differences between
the various groups, a t-test was used to compare each
group with infarcts to its respective group without infarcts
by Bonferroni's t-statistic for four preplanned comparisons
(Gill, 1978). We made between-treatment comparisons of
groups with comparable infarct sizes by Student's t-test.
Linear correlation and least squares linear regression also
were performed. To examine the effect of treatment on
the pressure-volume relation of all infarcted rats, we em-
ployed a random effects model, which accounted for the
correlated nature of the seven pressure-volume data points
per animal and for the continuous covariate, percent in-
farction (Laird and Ware, 1982).

Results

Infarct Size Distribution

Infarcts were classified as small (≤20% of left
ventricular circumference), moderate (>20 <40%),
large (≥40 ≤45%), and extensive (>45%). This dis-
tribution produced groups with comparable infarct
sizes for between-treatment comparisons (Table 1).
Rats that underwent coronary artery ligation with-
out sustaining myocardial infarction were desig-
nated as the noninfarcted group.

Baseline Hemodynamics

The mean body weight of the groups ranged from
292-342 g; significant differences occurred only be-
tween the untreated and captopril-treated rats with
small infarcts (292 ± 11 vs. 342 ± 11 g, respectively;
P < 0.005). Ventricular weights and flow-related
variables accordingly were corrected for body
weight. With infarcts ranging from 0-62%, the ratio
of left ventricular weight to body weight of the
untreated rats did not vary with infarct size (Fig. 1).
Similarly, the extent of infarction did not alter the
ratio of left ventricular weight to body weight in the
captopril-treated rats. However, at comparable in-
farct sizes, this ratio was always significantly less in
the treated than in the untreated rats.

Prethoracotomy left ventricular systolic pressure
progressively declined with increasing infarct size in
untreated rats, becoming significantly lower in
rats with moderate, large, and extensive infarcts,
compared with noninfarcted rats (Table 2). In the
captopril-treated rats, the decline in left ventricular
systolic pressure was similar to that of untreated
rats, in that rats with moderate and extensive infarcts
had lower systolic pressures than noninfarcted rats;
however, systolic pressures were lower in treated
rats, compared with untreated rats without infarcts,
and with moderate and extensive infarcts. The max-
umum rate of rise of left ventricular systolic pressure,
+dP/dt, also declined progressively with increasing
infarct size to a similar extent in captopril-treated
and untreated rats, so that this variable was signifi-
cantly decreased in rats with moderate, large, and
extensive infarcts, compared to rats without infarcts.
In untreated rats, with moderate, large, and exten-
sive infarcts, left ventricular end-diastolic pressure
rose to levels that were significantly greater than
those of noninfarcted rats (Fig. 2). In contrast, left
ventricular filling pressure remained within normal
limits as infarct size increased in captopril-treated
rats, and was significantly elevated (compared to
noninfarcted rats) only in captopril-treated rats with
extensive infarcts. Even then, the left ventricular
end-diastolic pressure of treated rats with extensive
infarcts was significantly lower than that of un-
treated rats with infarcts of comparable size (15 ± 2
vs. 28 ± 2 mm Hg, respectively, P < 0.01).

![Figure 1](http://circres.ahajournals.org/FIG/1. The ratio of left ventricular weight to body weight of untreated (H2O) and captopril-treated (CAP) rats grouped according to infarct size. **P < 0.05 ††P < 0.01, and †††P < 0.001 captopril-
treated vs. untreated rats with infarcts of comparable size.

Table 1

<table>
<thead>
<tr>
<th>Myocardial Infarct Size Distribution in Untreated and Captopril-Treated Rats</th>
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<tr>
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H2O, untreated rats; MI, myocardial infarct; CAP, captopril-treated rats; n, sample size.
TABLE 2

Prethoracotomy Left and Right Ventricular Pressures of Untreated and Captopril-Treated Rats with Myocardial Infarction

<table>
<thead>
<tr>
<th>Infarcted</th>
<th>Noninfarcted</th>
<th>Small</th>
<th>Moderate</th>
<th>Large</th>
<th>Extensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂O</td>
<td>145 ± 2</td>
<td>140 ± 5</td>
<td>129 ± 2†</td>
<td>124 ± 5‡</td>
<td>122 ± 1‡</td>
</tr>
<tr>
<td>CAP</td>
<td>123 ± 3†</td>
<td>126 ± 5</td>
<td>112 ± 4†</td>
<td>111 ± 4</td>
<td>104 ± 2‡</td>
</tr>
<tr>
<td>+dP/dt (mm Hg/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂O</td>
<td>16,396 ± 636</td>
<td>17,368 ± 964</td>
<td>11,470 ± 901</td>
<td>9,488 ± 791‡</td>
<td>8,405 ± 590‡</td>
</tr>
<tr>
<td>CAP</td>
<td>14,492 ± 797</td>
<td>15,938 ± 1165</td>
<td>11,663 ± 594</td>
<td>10,212 ± 1009</td>
<td>8,362 ± 626‡</td>
</tr>
<tr>
<td>RVSP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂O</td>
<td>33 ± 2 (9)</td>
<td>40 ± 4 (4)</td>
<td>32 ± 4 (8)</td>
<td>34 ± 5 (8)</td>
<td>56 ± 8 (4)†</td>
</tr>
<tr>
<td>CAP</td>
<td>34 ± 2 (5)</td>
<td>34 ± 2 (7)</td>
<td>34 ± 2 (16)</td>
<td>32 ± 2 (7)</td>
<td>36 ± 3 (13)§</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂O</td>
<td>1.4 ± 0.6</td>
<td>1.4 ± 0.4</td>
<td>2.6 ± 1.3</td>
<td>3.8 ± 1.3</td>
<td>5.4 ± 2.1*</td>
</tr>
<tr>
<td>CAP</td>
<td>0.8 ± 0.5</td>
<td>2.3 ± 0.3</td>
<td>2.1 ± 0.5</td>
<td>2.8 ± 0.6</td>
<td>2.7 ± 0.6</td>
</tr>
</tbody>
</table>

* P < 0.05, † P < 0.01, ‡ P < 0.001, †† P < 0.005 untreated or captopril-treated infarcted rats compared to the respective noninfarcted control; § P < 0.01, †† P < 0.001 captopril-treated compared to untreated rats with comparable infarct size. LVSP, left ventricular systolic pressure; +dP/dt, maximum rate of rise of LVSP; RVSP, right ventricular systolic pressure; RVEDP, right ventricular end-diastolic pressure; H₂O, untreated rats; CAP, captopril-treated rats. The sample size for right ventricular pressure measurements appears in parentheses in the RVSP row.

The right ventricular systolic and end-diastolic pressures of untreated rats did not increase until infarct size exceeded 45%, at which point these pressures were significantly greater than those of noninfarcted rats (Table 2). On the other hand, in captopril-treated rats, right ventricular pressures remained within normal limits for all infarct groups. The ratio of right ventricular weight to body weight reflected the level of left ventricular end-diastolic pressure of the various infarct groups of both treated and untreated rats (Fig. 3, upper panel). In untreated rats with moderate and extensive infarcts, this ratio was increased to values that were significantly greater than those in noninfarcted rats. In captopril-treated rats, this ratio remained within normal limits for all infarct groups except those with extensive infarcts, in which this ratio was significantly greater than in noninfarcted rats but was significantly (P < 0.01) less than that in untreated rats with extensive infarcts (Fig. 3, lower panel).

Alterations in post-thoracotomy baseline pressure and blood flow variables with increasing infarct size were minimal in both untreated and treated rats (Table 3). Mean arterial pressure did not change with infarct size in either untreated or treated rats, but at comparable infarct sizes, the mean arterial pressure was always significantly lower in captopril-treated rats than in untreated rats. Baseline cardiac and stroke volume indices were altered minimally by infarction; only in untreated rats with large infarcts and in treated rats with extensive infarcts were these flow indices decreased, compared with noninfarcted rats. The cardiac index of captopril-treated rats with large infarcts was increased, compared with that of untreated rats with large infarcts, and the stroke volume index of treated rats with both moderate and large infarcts was increased, compared with that of untreated rats with infarcts of comparable size. Only in untreated rats with large infarcts was total peripheral resistance increased compared with noninfarcted rats. The lower mean arterial pressure and the tendency for an increased forward output in the captopril-treated rats significantly decreased vascular resistance in all infarct groups (except for extensive infarcts), compared with untreated rats with infarcts of comparable size. Heart rate was not affected by either infarct size or treatment.

Left Ventricular Ejection Characteristics

Volume loading with Tyrode's solution revealed the difference between the treated and untreated rats in maximal pumping ability (Fig. 4, upper panel). In untreated rats, there was a progressive decline in maximum stroke volume index with increasing infarct size, such that this flow index was
significantly decreased in rats with moderate, large, and extensive infarcts compared with noninfarcted rats, whereas in captopril-treated rats the maximum stroke volume index was not reduced in any of the infarct groups except in rats with extensive infarcts in which this index was less than that of noninfarcted rats. There were no differences between the maximum stroke volume indexes in treated and untreated rats with infarcts of comparable size, except in those with small infarcts.

The ventricular volume from which maximum stroke volume was ejected also differed in treated and untreated rats. Although, in both treated and untreated rats, ventricular volume increased as a function of infarct size, the magnitude of this increase was less for treated than untreated rats, so that the end-diastolic volume index of rats with moderate and large infarcts treated with captopril was significantly less than that of untreated rats with infarcts of comparable size (Fig. 4, middle panel).

These two beneficial effects of captopril therapy, i.e., the maintenance of maximal forward output and the lesser degree of ventricular dilation, were associated with a preservation of ejection fraction. The index of ejection fraction decreased with increasing infarct size in both treated and untreated rats, but not to the same extent (Fig. 4, lower panel). Ejection fraction index in untreated and captopril-treated rats, respectively, was reduced by 48% and 36% in moderate infarcts, by 64% and 48% in large infarcts, and by 70% and 64% in extensive infarcts. The ejection fraction index was significantly higher in captopril-treated rats with moderate and large infarcts, compared with that of untreated rats with infarcts of similar size.

Pressure-Volume Curves

Although the reduction of left ventricular filling volumes of the captopril-treated rats (Fig. 4, middle panel) could have been due solely to the lower left ventricular filling pressures of the treated rats (movement downward and to the left on an unchanged pressure-volume curve), this was not the case. When the individual passive pressure-volume curves of all of the rats treated with captopril were compared with those of all of the untreated rats, using a random effects model, there was a significant overall effect of treatment on ventricular volume, i.e., for any given infarct size there was a significant leftward shift of the pressure-volume relation (a lower volume for any given pressure) in the captopril-treated rats, compared with untreated rats. These relations are presented as discrete groups according to infarct size in Figure 5, in which the pressure-volume curve of the noninfarcted rats is represented by the shaded area (the mean volumes ± 2 sd). As shown in Figure 4 (middle panel), under maximum preload conditions (volume loading) which occurred over a filling pressure range of 17–30 mm Hg, the end-diastolic volume index of the captopril-treated rats with infarcts was less than that of untreated rats with comparable infarcts (statistically less in those with moderate and large infarcts), despite the fact that the left ventricular filling pressures at maximal preload of the treated rats were similar to those of the untreated rats with infarcts of similar size (except for extensive infarcts in which the filling pressures were lower in treated rats than in untreated rats). In addition, the baseline operating volume index of the captopril-treated rats with infarcts was less than that of untreated rats matched for infarct size (see vertical arrows in Fig. 5); these differences achieved significance in rats with large and extensive infarcts.

The chamber stiffness constant (k, the slope of the log pressure versus volume per kilogram relation) was used to assess the stiffness of the left ventricular chamber (i.e., the change in cavity volume for a given change in distending pressure). The overall stiffness of the left ventricle (k over the pressure range, 2.5 to 30 mm Hg, i.e., k₀), decreased with increasing infarct size in untreated rats so that the k₀ of rats with moderate, large, and extensive

![Pressure-Volume Curves](image-url)
infarcts was significantly less than that of noninfarcted rats (Table 4). This reduction in ventricular stiffness with infarction was not consistently observed in captopril-treated rats, in that \( k_0 \) remained normal in all rats with infarcts except for those with extensive infarcts in which \( k_0 \) was significantly less than that of noninfarcted rats. The segmentation of the pressure-volume relation into more discrete pressure ranges revealed at what points on the curve the differences in \( k \) values between the treated and untreated rats with infarcts occurred (Table 4). Over the linear portion (0-3 mm Hg) of the pressure-volume curve, the chamber stiffness constant, \( k_1 \), decreased in proportion to infarct size in both treated and untreated rats. Ventricular filling in this pressure range is associated with distension of the scar from the collapsed state, and therefore probably would not differ in treated and untreated rats with infarcts of the same size (Fletcher et al., 1981). Over the low pressure range (3-10 mm Hg) of the exponential portion of the curve, infarction affected the chamber stiffness constant minimally: the \( k_2 \) of untreated rats with moderate infarcts and of treated rats with extensive infarcts was less than that of their respective noninfarcted controls. The \( k_2 \) of treated rats without infarcts and with moderate infarcts was greater than that of untreated rats with infarcts of like size. On the other hand, over the intermediate pressure range (i.e., 10-20 mm Hg, the range of ventricular filling pressures in which most untreated rats with moderate or greater infarcts operated), infarction had a marked effect on chamber stiffness in the untreated rats, so that \( k_3 \) was significantly reduced in animals with moderate, large, or extensive infarcts compared with noninfarcted controls, whereas among captopril-treated rats, \( k_3 \) was reduced only in those with extensive infarcts. Over the high-pressure range (20-30 mm Hg), the effect of infarction on the ventricular chamber stiffness constant, \( k_4 \), was similar in treated and untreated rats, in that \( k_4 \) decreased with increasing infarct size in both groups.

**Discussion**

The purpose of this investigation was 2-fold: to examine the chronic effects of infarcts on left ventricular dynamics and compliance in the rat, and to examine the chronic effects of treatment with the vasodilator, captopril, on these dynamic and static properties.

**Chronic Effects of Infarction**

The immediate consequences of a myocardial infarction are an initial reduction in the total force generated by the ventricle and a decrease in forward output as a result of the loss of contractile myocardium. To maintain systemic perfusion, the heart may utilize its systolic (increase in contractility) and/or diastolic (Frank-Starling mechanism) reserves. Using a theoretical two-component model of myocardial infarction (non-contractile scar and normal residual...
myocardium), Swan et al. (1972) hypothesized that before an alteration in ventricular volume occurred, an increase in contractility of the remaining viable myocardium could increase stroke volume by 20%, resulting in a return to a normal forward output in a small infarct (10% of the left ventricle), but not in a large (40%) infarct. Indeed, when estimated contractile element velocity ($V_{CE}$) was used by Parmley et al. (1972) as a measure of overall ventricular contractility in patients with acute myocardial infarction, contractility was found to be within the normal range in two-thirds of the patients, suggesting an increase to normal from an initially depressed contractile state, perhaps as a result of sympathetic stimulation. In dogs with an acute (4–7 days) experimental myocardial infarction, Hood (1970) observed that stroke volume was maintained as a consequence of normal or augmented fiber shortening and not by an increased ventricular volume, both in small infarcts (17 ± 2%) and in those of moderate size (28 ± 2%).

Should an increase in contractility fail to preserve stroke volume, the heart may call upon its preload reserve (increase in myocardial fiber length) to effect adequate systemic perfusion. The mechanical advantage of delivering the same stroke volume from a greater end-diastolic volume is a decrease in the extent of circumferential fiber shortening required. An increase in fiber length (end-diastolic volume) may be brought about by an increase in end-diastolic pressure, i.e., moving upward on an unchanged pressure-volume curve (ventricular distension) and/or by a rightward shift (an increase in volume for any given pressure, i.e., ventricular dilation) of the pressure-volume curve, with or without an increase in filling pressure. The former mechanism is more likely to occur during the acute phase of myocardial infarction, whereas the latter mechanism is more likely to be in force during the chronic phase as the result of ventricular remodeling.

Using an isotropic spherical model of the left ventricle as a membrane of uniform thickness composed of normal myocardium and a noncontractile region of varying stiffness, Bogen et al. (1980) postulated that cardiac reserve would be depressed in infarcts greater than 23% of the left ventricle if the Frank-Starling mechanism (ventricular distension to an end-diastolic pressure at the optimal level of 24 mm Hg) were the sole compensation available. On the other hand, ventricular dilation would permit a greater end-diastolic volume for the optimal filling pressure and, thereby, the ejection of a greater stroke volume. Indeed, Klein et al. (1967) proposed a theoretical model in which, beyond a critical infarct size (20%–25% of ventricular surface area), myocardial fiber shortening capacity would be exceeded and forward output could not be maintained unless ventricular dilation occurred. However, to determine whether ventricular distension and/or dilation is responsible for an increase in end-diastolic volume
TABLE 4
Left Ventricular Chamber Stiffness Characteristics of Captopril-Treated and Untreated Rats with Myocardial Infarction

<table>
<thead>
<tr>
<th>Infarcted</th>
<th>Noninfarcted</th>
<th>Small</th>
<th>Moderate</th>
<th>Large</th>
<th>Extensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_0$ (2.5–30 mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$H_2O$</td>
<td>2.35 ± 0.08</td>
<td>1.99 ± 0.24</td>
<td>1.76 ± 0.09</td>
<td>1.81 ± 0.13</td>
<td>1.69 ± 0.11</td>
</tr>
<tr>
<td>CAP</td>
<td>2.31 ± 0.07</td>
<td>2.36 ± 0.15</td>
<td>2.18 ± 0.10</td>
<td>2.10 ± 0.20</td>
<td>1.72 ± 0.10</td>
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<td></td>
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</tr>
<tr>
<td>$k_1$ (0–3 mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$H_2O$</td>
<td>3.10 ± 0.18</td>
<td>2.79 ± 0.47</td>
<td>1.30 ± 0.12</td>
<td>1.11 ± 0.14</td>
<td>0.97 ± 0.16</td>
</tr>
<tr>
<td>CAP</td>
<td>3.02 ± 0.17</td>
<td>2.49 ± 0.29</td>
<td>1.83 ± 0.25</td>
<td>1.24 ± 0.10</td>
<td>1.15 ± 0.10</td>
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<td></td>
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</tr>
<tr>
<td>$k_2$ (3–10 mm Hg)</td>
<td></td>
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</tr>
<tr>
<td>$H_2O$</td>
<td>1.94 ± 0.07</td>
<td>2.16 ± 0.30</td>
<td>1.48 ± 0.12</td>
<td>1.70 ± 0.14</td>
<td>1.59 ± 0.12</td>
</tr>
<tr>
<td>CAP</td>
<td>2.14 ± 0.09</td>
<td>2.27 ± 0.17</td>
<td>2.17 ± 0.14</td>
<td>2.05 ± 0.24</td>
<td>1.59 ± 0.11</td>
</tr>
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<td></td>
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<tr>
<td>$k_3$ (10–20 mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$H_2O$</td>
<td>2.32 ± 0.11</td>
<td>2.00 ± 0.19</td>
<td>1.93 ± 0.11</td>
<td>1.94 ± 0.11</td>
<td>1.81 ± 0.11</td>
</tr>
<tr>
<td>CAP</td>
<td>2.46 ± 0.07</td>
<td>2.41 ± 0.17</td>
<td>2.24 ± 0.09</td>
<td>2.22 ± 0.21</td>
<td>1.87 ± 0.09</td>
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<tr>
<td>$k_4$ (20–30 mm Hg)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$H_2O$</td>
<td>2.56 ± 0.20</td>
<td>2.10 ± 0.23</td>
<td>2.11 ± 0.12</td>
<td>2.04 ± 0.14</td>
<td>1.96 ± 0.14</td>
</tr>
<tr>
<td>CAP</td>
<td>2.78 ± 0.14</td>
<td>2.72 ± 0.20</td>
<td>2.29 ± 0.10</td>
<td>2.20 ± 0.14</td>
<td>2.07 ± 0.08</td>
</tr>
</tbody>
</table>

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.005$ captopril-treated and untreated rats with infarcts compared to their respective noninfarcted controls. ** $P < 0.05$, ‡‡ $P < 0.01$ captopril-treated compared to untreated rats with infarcts of comparable size. $k$, ventricular chamber stiffness; $H_2O$, untreated rats; CAP, captopril-treated rats.

requires the analysis of an extensive segment of the diastolic pressure-volume relation, which is difficult, in humans.

The failure of most studies of experimental myocardial infarction in dogs to show an impairment of cardiac performance may be related to the relatively small size of infarcts in surviving animals. We have developed a model of myocardial infarction in the rat which displays a broad spectrum of cardiac dysfunction, from minimal impairment to overt heart failure, in relation to infarct size (Pfeffer et al., 1979; Fletcher et al., 1981). In these previous studies, baseline hemodynamics measured 3 weeks post-infarction were minimally altered, whereas a significant negative correlation existed between maximal pumping (peak stroke volume, cardiac, and ejection fraction indices) and pressure-generating (peak developed pressure during aortic occlusion) capacities and infarct size. Left ventricular volumes at any given left ventricular pressure determined from passive diastolic pressure-volume curves increased as a function of infarct size.

In the present study in which measurements were made 3–4 months post-infarction, a time when most post-infarction adjustments had been completed, a hemodynamic profile similar to that observed in dogs with large infarcts 3–4 months post-infarction, was observed (Fletcher et al., 1981). However, there were two notable differences: (1) ventricular volumes were increased further at any given distending pressure at 3 months post-infarction (for example, by 30% (from 2.2–2.9 ml/kg) at 20 mm Hg in rats with infarcts >40%), and (2) the chamber stiffness constant ($k$), an index of ventricular stiffness, tended to decline as infarct size increased (Table 4). Thus, by 3 months post-infarction, in the present study, even further ventricular dilation was associated with a reduction in chamber stiffness in relation to infarct size.

We have also observed a reduction of chamber stiffness in rats with chronic (12 weeks) arteriovenous fistulas that was similar to that observed in rats with large infarcts 3–4 months post-infarction. In these volume-loaded rats, a 57% (1.27 ± 0.02 to 1.99 ± 0.18 ml/kg, $P < 0.01$) increase in left ventricular volume at 20 mm Hg distending pressure was associated with a reduction in chamber stiffness constant, from a $k$ of 2.34 ± 0.08 in controls to a $k$ of 1.63 ± 0.17 in rats with arteriovenous fistulas (unpublished observations). This reduction in chamber stiffness was remarkably similar to that observed in the present study for rats with extensive infarcts (1.69 ± 0.11 vs. 2.35 ± 0.08 for controls). The reduction in ventricular chamber stiffness with an increase in cavitary volume and infarct size may be explained on the basis of an expression for chamber stiffness derived by Mirsky et al. (1983): $\Delta P/\Delta V \sim (4/9)(E_{INC}/V)/(1 + V/VW)$, where chamber stiffness ($\Delta P/\Delta V$) is directly proportional to myocardial stiffness ($E_{INC}$) and inversely proportional to cavitary volume ($V$) and the cavitary volume-to-wall volume ratio ($V/VW$). In the case of the chronically dilated heart with moderate, large, and extensive infarcts, it is the increased cavitary volume component of this expression which dominated and allowed chamber...
compliance to be increased in spite of a possible increase in myocardial stiffness as a result of the extensive scar tissue present. Thus, chronic extensive myocardial infarction in the rat is characterized by a remodeling of the ventricle such that not only is its chamber size increased, but its stiffness is reduced.

The results of the present study differ from most of those reported on ventricular volumes and compliance in experimental myocardial infarction in dogs. In the very early (1-hour) phase after myocardial infarction, Forrester et al. (1972) noted a significant increase in left ventricular compliance in dogs with 25% infarcts, even though the absolute ventricular volumes were not different from controls. In dogs several (3–7) days post-infarction, Hood reported a significant decrease in postmortem ventricular volumes at elevated (10–40 mm Hg) and normal in vivo distending pressures (Hood et al., 1970; Hood, 1970). Weisse et al. (1970) also observed normal left ventricular end-diastolic volumes despite elevated filling pressures in dogs with 11% infarcts studied during the early (3–4 weeks) and late (6–8 weeks) phases of scar formation. In the present study carried out 3–4 months after myocardial infarction, when the ventricle's response to infarction had stabilized, a distinct increase in left ventricular diastolic volumes occurred (Fig. 4, middle panel). The apparent discrepancy in ventricular volumes between the above-mentioned studies and the present investigation might be explained by the relatively small size and short duration of infarction in the former studies. In small (≤20%) infarcts, we too found normal end-diastolic volumes 3–4 months post-infarction [Figs. 4 (middle panel) and 5a], and during the acute (2 days) phase, we too have observed normal ventricular volumes even in large (≥45%) infarcts (Pfeffer et al., 1982b). However, when a relatively large infarct is present for a prolonged period, the ventricle becomes both distended and dilated.

Although an increase in left ventricular chamber size permits the ejection of the same stroke volume with a lesser extent of fiber shortening, the use of this diastolic reserve may eventually become mechanically disadvantageous in the chronically failing heart. Shortly after the onset of systolic ejection in the normal heart, the magnitude of the reduction in cavitory volume begins to exceed that of the increase in pressure such that wall force begins to decline from its peak value which is reached during early systole. On the other hand, in the dilated heart there is a relatively smaller reduction in volume during ejection so that wall force may remain elevated or even increase further during systole, thereby sustaining the load on the left ventricle and further limiting the ventricle's shortening capabilities (Weber and Janicki, 1979). The systolic reserve (contractility) of these failing ventricles is often so compromised that they are usually relatively refractory to inotropic agents. Thus, therapeutic interventions have been directed primarily toward reducing the systolic wall force (unloading) of the left ventricle by reducing systolic pressure and/or volume by the use of arterial and venous dilators and diuretics.

**Effects of Chronic Treatment with Captopril**

Captopril is effective both as an afterload and a preload reducing agent. When given acutely to patients with chronic congestive heart failure, this angiotensin-converting enzyme inhibitor lowers left ventricular filling and systemic arterial pressures and decreases systemic vascular resistance, yet maintains or increases forward cardiac output (Davis et al., 1979; Ader et al., 1980; Awan et al., 1981; Massie et al., 1984a). Heart rate usually does not change. When captopril was administered chronically (3 or 19 months), these salutary hemodynamic effects were sustained (Cannon et al., 1983; Massie et al., 1984a, 1984b). In the present study, the chronic administration of captopril to rats with myocardial infarction and failure yielded hemodynamic results similar to those noted above in patients with congestive heart failure: ventricular and systemic arterial pressures and total peripheral resistance were reduced and aortic blood flow was preserved or augmented, compared with untreated rats with infarcts of comparable size, effects attributable to arteriolar vasodilators.

In rats with infarcts, captopril also demonstrated some effects not usually observed with the chronic administration of primary afterload reducing agents such as hydralazine: a reduction in right and left ventricular filling pressures and an attenuation of left ventricular dilation. Left ventricular end-diastolic pressure was maintained within normal limits by chronic captopril therapy for all rats with infarcts, except for those with extensive (>45%) infarcts. Even with infarcts of this size, the filling pressures of captopril-treated rats with extensive infarcts were considerably less than those of untreated rats with comparable infarcts. Despite this reduction in filling pressure (and thereby, ventricular volume), forward output was maintained or augmented in captopril-treated rats. Quite unlike the preload-reducing effect of diuretics which act to reduce circulating volume and often, forward output, this reduction in preload by captopril was probably the consequence of a decrease in venous return as the result of its venular dilating property (Awan et al., 1981), which, acting in concert with its afterload reducing property, lowered both ventricular pressure and volume to the extent that the decrease in systolic force and subsequent increase in circumferential fiber shortening counterbalanced the effect of a lesser ventricular volume so that stroke volume and ejection fraction index could be maintained (Weber and Janicki, 1979). This long-term elevation of pump performance may not be effected by all vasodilators, as suggested by Franciosa et al. (1982), who reported that ejection fraction remained depressed (compared to placebo) in patients with chronic heart failure.
treated with hydralazine for an average of 20 months.

Another beneficial effect of preload reduction was that observed on the right ventricle. The prevention by captopril of the increase in right ventricular weight-to-body weight ratios observed in rats with infarcts (Fig. 3, lower panel) suggests that the reduced left (end-diastolic) and right (systolic and end-diastolic) ventricular pressures of the treated rats were sustained chronically. The observation that left ventricular dysfunction is one of the most common (probably the most common) causes of pulmonary hypertension—and, thereby, of right ventricular hypertrophy—was made in the early studies utilizing cardiac catheterization in humans (Bloomfield et al., 1946). More recently, Polak et al. (1983) demonstrated that, among patients with ischemic heart disease, those with more severe left ventricular dysfunction had a greater depression of right ventricular ejection fraction. Thus, the chronic reduction of left and right ventricular systolic and diastolic pressures by captopril without a concomitant reduction in cardiac output in rats with myocardial infarction may prevent the development of the chronic pressure overload and failure of the right ventricle, which is a common consequence of severe left ventricular dysfunction.

A major finding in this study is that the reduction in ventricular volumes of captopril-treated compared to untreated rats with infarcts was the result of both a downward displacement on the pressure-volume relation (less ventricular distension) and an attenuation of the rightward shift of that relation (less ventricular dilation) which occurs with time in untreated rats with myocardial infarcts (Fletcher et al., 1981; Pfeffer et al., 1982b). This ability of captopril to reduce the "remodeling" of the infarcted left ventricle which occurs during the months following infarction is probably the result of both its preload- and afterload-reducing properties acting in concert to decrease the load resisting shortening, and thereby permit the ejection of a normal stroke volume from a less dilated ventricle. The chronicity of captopril’s two beneficial effects appeared to alter permanently the size and stiffness of the left ventricular chamber, as reflected in its passive pressure-volume relations (Fig. 5). Although a direct effect on the heart by captopril or the hormones induced by its administration could affect ventricular dilation, there was no effect on ventricular volume in

![Figure 5](https://example.com/figure5.png)

**Figure 5.** The pressure-volume (per kg) relation of untreated (o) and captopril-treated (x) rats with small (panel A), moderate (panel B), large (panel C), and extensive (panel D) infarcts. The shaded area in each panel represents the volumes ±2 so of the noninfarcted controls. The vertical arrows in each panel indicate the baseline operating volumes (per kg) of the treated and untreated rats for each infarct size group. *P < 0.05, untreated vs. treated rats at comparable infarct size for baseline operating volume index.
the captopril-treated noninfarcted rats. The smaller operating end-diastolic volumes of captopril-treated rats, compared with those of untreated rats with similar infarcts well may explain the normal chamber stiffness exhibited by the treated rats with infarcts (except for those with extensive infarcts). As mentioned previously, ventricular chamber stiffness is related directly to myocardial stiffness and inversely to ventricular volume (Mirsksy et al., 1983). In untreated rats with moderate, large, and extensive infarcts, ventricular volume was increased sufficiently that chamber stiffness became reduced. Treatment of rats with moderate and large infarcts with captopril may have prevented ventricular enlargement enough to prevent the resultant reduction in chamber stiffness, and, thereby, the latter remained normal.

In summary, in rats studied 3–4 months after myocardial infarction, we have demonstrated a depression in cardiac performance and a dilation of the left ventricle as a function of infarct size. We observed a continuum of heart failure in which there was a progressive rise in left ventricular filling pressure and a decrease in maximal forward output and ejection fraction index as infarct size increased. Associated with this chronic depression of ventricular performance was a compensatory remodeling (dilation) of the left ventricle to allow preservation of forward output at any filling pressure. The extensive chronic dilation that occurred in infarcts of moderate and large size resulted in a reduction of chamber stiffness. The chronic administration of captopril to rats with infarcts ameliorated the reduction in forward output in all but those with extensive infarcts, and attenuated the ventricular dilation, and, thereby, the change in left ventricular chamber stiffness. Thus, the preload- and afterload-reducing properties of this angiotensin-converting enzyme inhibitor worked in tandem to preserve the pumping ability of the lesser dilated, normally compliant, chronically infarcted left ventricle of the rat.

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INDEX TERMS: Myocardial infarction • Hemodynamics • Pressure-volume relation • Ventricular dilation • Preload and afterload reduction
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J M Pfeffer, M A Pfeffer and E Braunwald

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