Captopril Restores Hemodynamic Responsiveness to Atrial Natriuretic Peptide in Rats With Heart Failure

Thomas E. Raya, MD, Richard W. Lee, MD, Teresa Westhoff, BS, and Steven Goldman, MD

Atrial natriuretic peptide levels are elevated in heart failure. However, the hemodynamic responses to exogenous atrial natriuretic peptide infusion in heart failure are blunted. To determine if captopril can restore hemodynamic responsiveness to atrial natriuretic peptide infusion in rats with heart failure, studies were performed in a rat model of heart failure after coronary artery ligation. Rats with heart failure received either captopril (2 g/l drinking water) or placebo for 4 weeks and then were treated with an infusion of atrial natriuretic peptide (0.3 μg/kg/min). Captopril treatment alone improved hemodynamics. Left ventricular end-diastolic pressure, mean aortic pressure, and mean circulatory filling pressure decreased from 22±2 to 14±1, from 106±4 to 76±3, and from 10.5±0.6 to 8.8±0.4 mm Hg, respectively. Heart rate, right atrial pressure, and hematocrit were unchanged. Total blood volume decreased from 66.0±1.0 to 60.0±1.0 ml/kg; venous compliance increased from 2.1±0.1 to 2.7±0.1 ml/kg/mm Hg. Atrial natriuretic peptide alone had minimal hemodynamic effects on rats with heart failure. There was no change in right atrial pressure, mean aortic pressure, left ventricular end-diastolic pressure, mean circulatory filling pressure, and total blood volume. However, atrial natriuretic peptide infusion increased venous compliance from 2.1±0.1 to 2.4±0.1 ml/kg/mm Hg. Heart rate and hematocrit increased from 323±5 to 359±8 beats/min and from 48±1% to 51±1%, respectively. In rats with heart failure that were pretreated with captopril, infusion of atrial natriuretic peptide produced significant hemodynamic effects. Left ventricular end-diastolic pressure, mean aortic pressure, and mean circulatory filling pressure decreased from 14±2 to 10±2 mm Hg, from 84±5 to 73±5 mm Hg, and from 8.0±1.4 to 7.0±1.2 mm Hg, respectively. Captopril and atrial natriuretic peptide increased heart rate; right atrial pressure was unchanged. Captopril and atrial natriuretic peptide normalized total blood volume from 60.5±1.1 to 54.3±1.0 ml/kg. In summary, captopril restored the responsiveness to atrial natriuretic peptide in rats with heart failure. In particular, left ventricular end-diastolic pressure decreased toward normal, and total blood volume was normalized. (Circulation 1989;80:1886–1892)

Heart failure produces peripheral circulatory changes that alter both central and peripheral hemodynamics. The result is an increase in left ventricular (LV) preload and afterload. The enthusiasm to use vasodilators to alter loading conditions in patients with heart failure emphasizes the importance of these peripheral circulatory changes. It has been postulated that the changes in the peripheral circulation may be secondary to the neurohumoral alterations in heart failure. Two neurohumoral systems that are activated and that have opposing effects in heart failure are the renin-angiotensin and atrial natriuretic peptide (ANP) systems. Although both systems are activated in heart failure, the stimulus and physiologic effect for each is different. The decrease in forward flow presumably stimulates activation of the renin-angiotensin system; atrial distension causes a release of ANP. The peripheral circulatory effects of angiotensin II include vasoconstriction and sodium retention; ANP release results in natriuresis and diuresis.
The importance of activation of the renin-angiotensin system in heart failure is reflected by the fact that treatment with various inhibitors of angiotensin converting enzyme produces beneficial effects in heart failure. For example, enalapril improved survival in patients with severe LV dysfunction due to various causes, and captopril improved function and survival in rats with moderate-sized myocardial infarcts. Recent work from our laboratory suggests that the effects of inhibition of angiotensin converting enzyme are to decrease blood volume and reverse venoconstriction. Although these hemodynamic effects of converting enzyme inhibition are an important aspect of the mechanism of action, parameters such as LV end-diastolic pressure and blood volume are not completely normalized by therapy.

Although the renin-angiotensin and ANP systems are responsible for normal control of sodium and water balance, their potential counter-regulatory interactions have received little attention. In non-pathologic states, ANP has been shown to antagonize the physiologic effects of angiotensin II. For example, we have shown that, although ANP has minimal hemodynamic effect alone, it can reverse angiotensin-induced venoconstriction. Other investigators have shown in in vitro studies that ANP can produce arteriolar dilatation in the presence of angiotensin II. In pathologic states, the effects of interactions between the renin-angiotensin and ANP systems are less clear, but in patients with heart failure the hemodynamic and renal responses to exogeneous ANP infusions are blunted. Proposed mechanisms for this blunted hemodynamic response include downregulation of ANP receptors in the kidneys and a direct antagonism of ANP by angiotensin II.

The purpose of this study was to determine the efficacy of combined captopril and ANP in the treatment of heart failure. Specifically, we sought to determine whether ANP had additional effects on blood volume, end-diastolic pressure, and venoconstriction in heart failure rats pretreated with captopril. We used a rat myocardial infarction model of heart failure and studied changes in hemodynamics, blood volume, and the peripheral circulation.

**Methods**

**Coronary Artery Ligation Heart Failure Model**

Myocardial infarction was produced in male Sprague-Dawley rats (175-275 g) by techniques described previously. In brief, the rats were anesthetized with methoxyflurane, and a left thoracotomy was performed. The heart was expressed from the thorax, and a ligature was placed around the proximal left coronary artery. The heart was returned to the chest, and the thorax was closed. The rats were maintained on standard rat chow with water ad libitum.

After 3 weeks, rats were anesthetized, and a nine-lead electrocardiogram with six limb leads and three chest leads was performed as previously described. Rats with evidence of large (>40% of left ventricle) myocardial infarctions were selected for study. Rats with large myocardial infarctions have been shown by us and others to have heart failure with elevated LV end-diastolic pressure (>18 mm Hg) and electrocardiographic findings that include the presence of Q (>1 mV) waves in the limb leads (I or aVL) and the sum of the R waves in the precordial leads (<10 mV). We have previously shown that rats selected in this fashion have large myocardial infarctions averaging 48±2% of the left ventricle.

**Treatment Protocols**

Chronic angiotensin converting enzyme inhibition was accomplished by adding captopril (2 g/l) to the drinking water of rats screened for large myocardial infarctions. Control rats similarly screened were treated with placebo. After 4 weeks of treatment, the rats were anesthetized with Inactin (30 mg/kg i.p.). Polyethylene tubing (0.58 mm i.d.), telescoped into wider polyethylene tubing (0.86 mm i.d.), was inserted into the right carotid artery. The catheter was advanced into the aorta and then into the left ventricle for pressure recordings (model 2400, Gould Instrument, Cleveland, Ohio).

ANP (8-33 AA, Peninsula, Belmont, CA) was administered as an infusion (0.3 µg/kg/min) through a right femoral vein catheter to both captopril- and placebo-treated rats. All physiologic measurements were obtained in rats with stable hemodynamics, beginning 30 minutes after the start of the infusion. LV pressure, right atrial pressure, mean aortic pressure, and mean circulatory filling pressure (MCFP) were measured before and after infusion of ANP.

**Measurement of Venous Compliance**

By use of techniques previously described, MCFP and venous compliance were measured. A tracheostomy was performed, and the rats were ventilated with a volume-cycled respirator (Harvard Apparatus, South Natick, Massachusetts). The right carotid artery was cannulated with polyethylene tubing. A femoral vein was also cannulated with polyethylene tubing (0.635 mm i.d.) that was advanced to the region of the thoracic vena cava. Both fluid-filled catheters were connected to a solid-state pressure transducer (Millar Instruments, Houston, Texas). A balloon-tipped catheter, prepared by connecting a latex balloon to the polyethylene tubing (0.58 mm i.d.), was inserted into the right atrium from the right internal jugular vein.

Heart rate and mean arterial and venous pressures were recorded. Plasma volume was measured by the Evans blue technique. Briefly, a 0.5% (wt/vol) solution of Evans blue dye in a volume of 0.10–0.15 ml was injected by means of the venous catheter. Ten minutes later, a 0.35-ml arterial blood
sample was obtained, and after centrifugation the Evans blue dye concentration in the plasma was spectrophotometrically determined. Total blood volume was calculated by the equation: total blood volume = plasma volume/(1 − hematocrit/100×0.8), where 0.8 is the Fcells factor.14

After the measurement of plasma volume, two or three determinations of the baseline MCFP were made. To measure MCFP the balloon was inflated (6–8 seconds) and transiently arrested the circulation while arterial and venous pressures were recorded. The venous and arterial plateau pressures (VPP and APP) were used to calculate MCFP with the following equation: MCFP = VPP + 1/75 (APP − VPP). The arterial-to-venous compliance ratio of 1/75 is based on previous determinations in normal and hypertensive rats.14–16

To determine the MCFP–blood volume relation, MCFP was measured immediately after an increase or decrease in blood volume of 10% (6.2 ml/kg). Blood volume was immediately returned to baseline by reinfusion or withdrawal of blood after the determination of MCFP. Blood volume changes were accomplished by rapid transfusion of fresh donor blood from another rat or bleeding through the arterial catheter and were completed so that MCFP was determined within 10 seconds of the initiation of the blood volume change. The order of blood volume changes was random, and two measurements of MCFP were made at each blood volume. The average value of MCFP at each blood volume was used for construction of the MCFP–blood volume curve for each rat. Effective vascular or venous compliance was defined as the change in blood volume divided by the change in MCFP and, therefore, is equal to the reciprocal of the slope of this curve. Unstressed vascular volume was obtained by linear extrapolation of the MCFP–blood volume curve to zero pressure. Between each determination of MCFP, at least 7 minutes was allowed for pressures and heart rate to return to baseline.

Infarct Size Determination

Myocardial infarct size was measured in all animals by use of previously described techniques.5,14 The hearts were fixed in formalin and cut from apex to base in four transverse slices, which were processed in a routine manner for histological study. Sections were stained and projected. The entire length of the endocardial circumference and the segment of the endocardial circumference made by the infarcted segment of each of the four slices of the left ventricle were measured. The entire length of the epicardial circumference and the segment of the epicardial circumference made by the infarcted segment of each of the four slices of the left ventricle were measured. These were then averaged for each of the four slices. The fraction of the ventricle that was infarcted was calculated as the average of the four slices expressed as a percent of the length of circumference.

<table>
<thead>
<tr>
<th>Table 1. Body Weights and Heart Weights in Sham-Operated Control Rats, Heart Failure Rats, and Heart Failure Rats Treated With Captopril</th>
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<tr>
<td>Group 1</td>
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<tr>
<td>(n=9)</td>
</tr>
<tr>
<td>Body weight (g)</td>
</tr>
<tr>
<td>LV weight (mg)</td>
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<tr>
<td>RV weight (mg)</td>
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<tr>
<td>LV wt/body wt</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Group 1, sham-operated control rats; group 2, heart failure rats; group 3, heart failure rats treated with captopril; LV, left ventricular; RV, right ventricular.

†p<0.01 compared with group 1.

‡p<0.01 compared with group 2.

Protocol

Experimental studies were performed in five groups of rats in random fashion.

Group 1: Sham-operated rats. These rats had thoracotomies but, subsequently, were found not to have had myocardial infarctions. These rats served as controls and received placebo throughout the study (n=9).

Group 2: Heart failure rats. This group consisted of rats with heart failure that did not receive captopril or ANP (n=8).

Group 3: Heart failure plus captopril rats. This group consisted of rats with heart failure that received chronic captopril only (n=7).

Group 4: Heart failure plus ANP rats. This group consisted of rats with heart failure that received infusions of ANP (n=7).

Group 5: Heart failure plus captopril plus ANP. This group consisted of rats with heart failure that received both chronic captopril therapy and an acute infusion of ANP (n=8).

Statistical Analysis

All results are presented as mean±SEM. To compare sham-operated to heart failure rats, with and without captopril treatment, the Bonferroni modification for three preplanned comparisons was used (Tables 1 and 2). To evaluate whether there is an interaction between ANP and captopril, a two-factor analysis of variance for unbalanced data was used (SAS, PROC GLM) (Table 3). The analysis tested the main effects (captopril: yes/no; ANP: yes/no) and an interaction between captopril and ANP. If an interaction was significant, we analyzed the simple effects of ANP separately for captopril. If there was no significant interaction, the interaction term was dropped, and only the main effects were analyzed. A paired t test, for selected hemodynamic parameters, was used to compare pre- and post-ANP effects in heart failure rats without (Table 4) or with (Table 5) captopril treatment. In these same animals an unpaired t test was also used to compare differences between baseline values as well as to compare the absolute change after ANP infusion.
TABLE 2. Hemodynamics and Blood Volumes in Sham-Operated Control Rats, Heart Failure Rats, and Heart Failure Rats Treated
With Captopril

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=9)</th>
<th>Group 2 (n=8)</th>
<th>Group 3 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>353±12</td>
<td>335±6</td>
<td>338±5</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>119±5</td>
<td>106±4*</td>
<td>76±3*†</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>1.4±0.3</td>
<td>2.0±0.4</td>
<td>1.5±0.3</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>4±1</td>
<td>22±1*</td>
<td>14±1*†</td>
</tr>
<tr>
<td>MCFP (mm Hg)</td>
<td>6.8±0.9</td>
<td>10.5±0.6*</td>
<td>8.8±0.4*†</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>47±0.4</td>
<td>48±0.4</td>
<td>46±0.5</td>
</tr>
<tr>
<td>Blood volume (ml/kg)</td>
<td>55±0.5</td>
<td>66±1.0*</td>
<td>60±1.1*</td>
</tr>
<tr>
<td>Venous compliance (ml/kg/mm Hg)</td>
<td>3.2±0.1</td>
<td>2.1±0.1*</td>
<td>2.7±0.1*†</td>
</tr>
<tr>
<td>Unstressed vascular volume (ml/kg)</td>
<td>34±0.7</td>
<td>41±0.9*</td>
<td>34±0.9*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Group 1, sham-operated control rats; group 2, heart failure rats; group 3, heart failure rats treated with
captopril; LV, left ventricular; MCFP, mean circulatory filling pressure.

*p<0.01 compared with group 1. †p<0.01 compared with group 2.

Venous compliance values were determined by regression analysis by the method of least squares.

Results

A total of 39 rats were studied. There were no significant differences in age, body weight, LV weight, or hematocrit between the normal sham-operated rats and infarct rats with heart failure (Tables 1 and 2). Infarct size was similar among all groups of heart failure rats and averaged 46±2%.

In the rats with heart failure, mean aortic blood pressure decreased while LV end-diastolic pressure and total blood volume increased. There was venoconstriction with an increase in MCFP and a decrease in venous compliance. Total blood volume and unstressed vascular volume increased. Right ventricular weight increased and LV weight/body weight decreased in rats with heart failure. These changes are similar to previous data obtained from our laboratory.14

Treatment of heart failure rats with captopril decreased LV end-diastolic pressure, mean aortic pressure, total blood volume, and unstressed vascular volume. Venous compliance was increased (Table 2). These results showed an improvement but did not normalize the hemodynamics in rats with heart failure after chronic captopril treatment. Captopril decreased right ventricular weight compared with untreated heart failure rats. LV weight/body weight was decreased compared with sham-operated rats. The changes with heart failure and after captopril therapy are similar to changes that we7 and others5,6 have shown previously.

Tables 3–5 show the effects of treatment with ANP. ANP in untreated heart failure rats did not change mean aortic blood pressure, LV end-diastolic pressure, right atrial pressure, or MCFP compared with control heart failure values. Interestingly, after infusion of ANP, heart rate was significantly increased from 322±5 to 359±7 beats/

TABLE 3. Blood Volume and Peripheral Circulatory Changes in Heart Failure Rats, Heart Failure Rats Treated With
Captopril, Heart Failure Rats Treated With Atrial Natriuretic Peptide, and Heart Failure Rats Treated With Captopril
And Atrial Natriuretic Peptide

<table>
<thead>
<tr>
<th></th>
<th>Group 2 (n=8)</th>
<th>Group 3 (n=7)</th>
<th>Group 4 (n=7)</th>
<th>Group 5 (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>48±0.4</td>
<td>46±0.5</td>
<td>51±0.5*</td>
<td>50±0.7</td>
</tr>
<tr>
<td>Blood volume (ml/kg)</td>
<td>66±1.0</td>
<td>60±1.1†</td>
<td>65±2.0†</td>
<td>54±1.0‡</td>
</tr>
<tr>
<td>Venous compliance (ml/kg/mm Hg)</td>
<td>2.1±0.1</td>
<td>2.7±0.1†</td>
<td>2.4±0.1§</td>
<td>3.1±0.1</td>
</tr>
<tr>
<td>Unstressed vascular volume (ml/kg)</td>
<td>41±0.9</td>
<td>34±0.9†</td>
<td>40±1.1</td>
<td>35±1.6</td>
</tr>
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</table>

Values are mean±SEM. Group 2, heart failure rats; group 3, heart failure rats treated with captopril; group 4, heart failure rats treated with atrial natriuretic peptide (ANP); group 5, heart failure rats treated with captopril and ANP.

*p<0.01 compared with group 2. †p<0.001 compared with group 2. §p<0.05 compared with group 4 and indicating a significant interaction between captopril and ANP. ‡p<0.005 compared with group 2.
TABLE 5. Comparison of Hemodynamic Changes in Captopril-Treated Heart Failure Rats Before and 30 Minutes After Atrial Natriuretic Peptide Infusion

<table>
<thead>
<tr>
<th></th>
<th>Group 5 (n=8)</th>
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<tr>
<td></td>
<td>Pre-ANP</td>
<td>Post-ANP</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>335±9</td>
<td>390±6*</td>
</tr>
<tr>
<td>Mean aortic pressure</td>
<td>84±5</td>
<td>73±5*</td>
</tr>
<tr>
<td>(mm Hg)</td>
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<tr>
<td>Right atrial pressure</td>
<td>1.8±0.3</td>
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<tr>
<td>(mm Hg)</td>
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<tr>
<td>LV end-diastolic pressure</td>
<td>14±2</td>
<td>10±2*</td>
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<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
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<tr>
<td>MCFP (mm Hg)</td>
<td>8.0±1.4</td>
<td>7.0±1.2*</td>
</tr>
</tbody>
</table>

Values are means±SEM. Group 5, captopril-treated heart failure rats; ANP, atrial natriuretic peptide; LV, left ventricular; MCFP, mean circulatory filling pressure. ANP infusion was 0.3 µg/kg/min.

*p<0.001 compared with pre-ANP value.

4 and group 5, respectively, but there were no differences in the absolute responses. The relative changes in end-diastolic pressure were, however, significantly different. ANP induced only an 8% change in group 4; however, it induced a 30% change in this parameter in group 5 (p<0.01). There were no significant differences in pre-ANP right atrial pressure between group 4 and group 5. Neither the absolute nor relative changes in right atrial pressure were significantly different for the two groups.

Discussion

The present study is the first to evaluate the hemodynamic effects of ANP after chronic inhibition of angiotensin II conversion in heart failure. Although ANP alone increased venous compliance, it produced no other significant hemodynamic effects in heart failure. In the presence of chronic captopril treatment, ANP decreased mean aortic pressure, LV end-diastolic pressure, further increased venous compliance, and normalized total blood volume. The increase in venous compliance and decrease in total blood volume was in addition to the initial improvement in hemodynamics seen with captopril alone. Thus, in rats with heart failure, captopril restored the responsiveness of the circulatory system to ANP.

The important data from this study are the results that pretreatment with captopril restores hemodynamic responsiveness to exogenous ANP in heart failure. Our observations showing minimal effects of ANP alone in rats with heart failure are consistent with the clinical study of Cody et al. These investigators reported a blunted hemodynamic response to ANP infusion. There was no change in mean arterial pressure; however, cardiac index and hematocrit increased with a small decrease in pulmonary artery wedge pressure. In the present study, we also found no change in mean arterial pressure and an increase in hematocrit. However, LV end-diastolic pressure did not change. This difference may be attributed to the severity of heart failure in the study groups. In dogs with heart failure induced by chronic rapid ventricular pacing, ANP infusion alone produced no significant changes in hemodynamics or an increase in urine flow. Our data show no change in total blood volume, although an effect on urine flow cannot be excluded.

The explanation for this so-called "blunted response" is not known. It has been proposed that, because of the chronically elevated ANP levels in heart failure, there is a downregulation of ANP receptors analogous to the β-adrenoceptor system in heart failure. A study of kidney ANP receptors in this same experimental model of heart failure has shown such a decrease. An alternative explanation may be that exogenous ANP is unable to counteract the excess activation of the vasoconstricting and sodium-retaining effects of the renin-angiotensin system.
Another interesting finding in this study is the increase in heart rate with ANP infusion observed in both groups of heart failure rats with and without captopril treatment. It has been reported that angiotensin II attenuates the baroreflex responses in normal animals; thus, it is possible that ANP antagonism of angiotensin II at least partially restores this response. Another potential mechanism may be antagonism of the negative chronotropic effect of angiotensin II that has been demonstrated in rats. In captopril-treated rats, the heart rate response was more pronounced, perhaps because the decrease in blood volume and LV filling pressure also produced a decrease in blood pressure and, thus, a more potent stimulus to the baroreflex. A direct chronotropic effect of ANP is unlikely.

The use of angiotensin converting enzyme inhibitors in heart failure is now established therapy. In the clinical setting, angiotensin converting enzyme inhibitors have been shown to improve survival and symptoms. The mechanism for this benefit has not been completely established, but in experimental heart failure we have shown that captopril reverses the venoconstriction and alters the diastolic volume-pressure relation of the heart. Other investigators have also observed that captopril decreases the LV dilatation seen in untreated heart failure but does not normalize LV end-diastolic volume. We have shown that total blood volume is increased in heart failure and that this contributes in part to the increased LV end-diastolic volume. The combined effects of captopril and ANP in this study resulted in the normalization of venous compliance and total blood volume. The decrease in total blood volume with an associated increase in hematocrit is likely due to an increase in urinary output. The reversal of venoconstriction and decrease in total blood volume resulted in lower cardiac filling pressures. The ability of combined captopril and ANP therapy to normalize hemodynamics and volume changes is important because this can potentially normalize the LV dilatation in heart failure. LV dilatation in turn has been shown to have an adverse effect on survival in patients with myocardial infarction.

The mechanism by which this interaction occurs was not explored in this study. Michel et al. have recently shown that treatment with an angiotensin converting enzyme inhibitor in this model of heart failure resulted in normalization of plasma ANP levels. Potentially, the decrease in left heart filling pressures (therefore, decreased atrial distension) with chronic captopril therapy could have decreased circulating ANP levels resulting in an upregulation of functional receptors in the kidneys. An interaction of ANP and angiotensin with respect to blood volume adjustments was statistically demonstrated in the present study although the nature of this interaction remains unknown.

Certain concepts and limitations of the techniques used to evaluate the response of the venous circulation deserve comment. Because right atrial pressure is determined by heart rate, chamber compliance, afterload, and contractility, it alone cannot be used to reflect the status of the venous capacitance system. We, therefore, measured MCFP and venous compliance to quantify changes in venous tone. MCFP was measured within 10 seconds of circulatory arrest, which is before the activation of baroreflexes. However, stressed relaxation and reversed stress relaxation cannot be totally avoided. The total vascular pressure-volume relation is reported to be nonlinear. However, in this study, wherein a narrow range of volume changes was used, the relation is linear. Finally, unstressed vascular volume remains an extrapolated number from the pressure-volume plot because it cannot be measured directly in an intact animal.

In summary, we have shown that in an experimental model of heart failure, chronic captopril therapy improved the hemodynamic responses to ANP. There was normalization of total blood volume and venous compliance. LV end-diastolic pressure was restored toward normal. A potential interaction between ANP and the renin-angiotensin system merits further clinical study. It is possible that the combination of angiotensin converting enzyme inhibition and ANP could be used as a therapeutic strategy to treat patients with heart failure.

Acknowledgments

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References


KEY WORDS • vasodilation • captopril • atrial natriuretic peptide
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