Tissue-Specific Activation of Cardiac Angiotensin Converting Enzyme in Experimental Heart Failure

Alan T. Hirsch, Chris E. Talsness, Heribert Schunkert, Martin Paul, and Victor J. Dzau

In addition to the circulating renin-angiotensin system, recent data demonstrate the existence of tissue renin-angiotensin systems that may be important in cardiovascular homeostasis. However, the relative activities of the circulating and tissue renin-angiotensin systems have not been examined previously in pathophysiological states, such as congestive heart failure. The present study was performed to examine the status of plasma and tissue angiotensin converting enzyme (ACE) activities in compensated experimental heart failure induced by coronary artery ligation in the rat. Three groups of male Sprague-Dawley rats were examined: 1) nonoperated rats (NO, n=5), 2) sham-operated rats (SO, n=5), and 3) heart failure rats (HF, n=11). Rats were studied an average of 85 days postoperatively. In HF animals, plasma renin concentration and serum ACE activities were not different compared with NO and SO control animals. Cardiac ACE activity was 50% greater in the right ventricle than the interventricular septum in NO and SO rats. Both right ventricular and interventricular septal ACE activity increased approximately twofold in HF animals as compared with NO and SO groups (p<0.05). In contrast, pulmonary, aortic, and renal ACE activities were not altered in HF rats compared with control animals. A positive correlation existed between the histopathological size of myocardial infarction and the level of right ventricular ACE activity (r=0.75, p≤0.05). Such a relation between infarct size and either serum or noncardiac tissue ACE activities was not observed. To confirm that increased cardiac ACE activity was due to local synthesis, right ventricular myocardium from additional SO (n=4) and HF (n=6) rats was examined to determine the relative expression of ACE mRNA in this disease state. Harvested RNA was amplified by polymerase chain reaction (25 cycles); subsequent quantitation demonstrated a twofold increase in ACE mRNA level that also correlated with infarct size (r=0.67, p<0.05). These data demonstrate that compensated experimental heart failure is associated with tissue-specific activation of cardiac ACE activity, but not plasma or other tissue ACE activities. Additionally, the local activation of this component of the cardiac renin-angiotensin system appears to be directly associated with the magnitude of left ventricular dysfunction as suggested by the infarct size. Increased cardiac ACE mRNA level, ACE activity, and local synthesis of angiotensin II in experimental heart failure may be physiologically important and pertinent to the beneficial effects of ACE inhibition. (Circulation Research 1991;69:475–482)

Angiotensin converting enzyme (ACE) inhibition has been demonstrated to attenuate cardiac dilatation and improve survival of rats with experimental heart failure induced by coronary ligation.\(^1,2\) Indeed, when administered to patients with left ventricular dysfunction within 1–2 weeks after myocardial infarction, captopril has been demonstrated to prevent cardiac dilatation and improve ventricular function.\(^3,4\) However, the mechanisms underlying these effects of ACE inhibitors have not been fully elucidated. The stable, compensated phase of heart failure in both experimental animals and humans is characterized by depressed cardiac output,

From the Cardiovascular Physiology Laboratory, Division of Vascular Medicine and Atherosclerosis, Brigham and Women’s Hospital and Harvard Medical School, Boston, Mass.

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Addresses for reprints: Alan T. Hirsch, MD, Cardiovascular Division, University of Minnesota Hospitals, Box 508-UMHC, 420 Delaware Street S.E., Minneapolis, MN 55455; and Victor J. Dzau, MD, Stanford University School of Medicine, Division of Cardiovascular Medicine, Falk Cardiovascular Research Center, 300 Pasteur Drive, Stanford, CA 94305.

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a redistribution of regional blood flow, and renal sodium avidity. In this state, the circulating renin-angiotensin system is not activated, but ACE inhibition improves cardiac function, normalizes regional blood flow, and induces natriuresis.

Recent data suggest that tissue renin-angiotensin systems may be important in the regulation of local tissue function. An increased local angiotensin II concentration may subserve regional vasoconstriction and renal sodium retention. We hypothesized that tissue angiotensin systems may be activated in early and compensated heart failure and may contribute to the pathophysiology of this disease state. In the present study, we examined the status of plasma and tissue ACE activities and cardiac ACE mRNA expression during the compensated phase of experimental heart failure induced by coronary ligation in the rat. Additionally, we examined the effect of disease severity (myocardial infarct size) on tissue and plasma ACE activities and cardiac ACE expression.

Materials and Methods

Male Sprague-Dawley rats weighing 200–250 g were used. The status of plasma and tissue ACE activities was examined in an initial experiment in three groups of rats: 1) nonoperated (NO) rats (n=5), 2) sham-operated (SO) rats (n=5), and 3) heart failure (HF) rats (n=11). Cardiac ACE mRNA expression was studied in an additional 10 rats (SO, n=4; HF, n=6) in a second protocol. These animals were studied an average of 85 days after coronary ligation or sham operation. All groups were studied concurrently and at the same age. Animals were allowed free access to a 0.4% sodium diet, and water was provided ad libitum. These studies were approved by the Harvard Standing Committee on Animals and were performed according to guidelines of the US Public Health Service and the American Association for the Accreditation of Laboratory Animal Care.

Experimental Heart Failure

The coronary-ligated rat model of heart failure was prepared for study using standard methods. This model has been well studied and displays the characteristics of human heart failure. With the animals under ether anesthesia, the left anterior thorax was dissected, the heart exteriorized briefly, and the left coronary artery ligated with 6-0 prolene suture. There is an approximate 40% surgical attrition from this procedure. One week postoperatively, surviving animals were stratified by a modified 10-lead electrocardiogram into sham or myocardial infarction (HF) study groups. Group stratification in all cases was confirmed at postmortem by quantitative left ventricular histopathology.

Tissue Preparation

Animals were killed by decapitation. Trunk blood was collected for determination of plasma renin concentration and serum ACE activity. The heart and aorta were removed en bloc, and lungs and kidneys were excised rapidly. All tissues were weighed and washed extensively with normal saline to remove all contaminating blood. The right ventricle and a 2.0-mm slice of interventricular septum were dissected rapidly and processed for the determination of cardiac ACE activities. Left ventricular ACE activity was not assessed to avert the confounding contribution of varying amounts of nonviable fibrous tissue to the biochemical measurements, which would have rendered the results difficult to interpret. Instead, the left ventricle was preserved in 10% buffered formalin for quantitative planimetric determination of infarct size as described. The thoracic aorta was stripped of its adventitia. Kidneys were removed from their capsules. Peripheral sections of pulmonary tissue were used preferentially to exclude the major pulmonary vasculature from biochemical analysis. All tissue specimens were immediately snap frozen in liquid NO, and stored at −70°C for later biochemical and molecular biological studies. Assays for each tissue ACE activity were performed simultaneously to minimize interassay variability.

Biochemical Assays

Plasma renin concentration was assayed by angiotensin I generation as described. Serum and tissue ACE activities were determined using a fluorometric assay modified from that described by Cushman and Cheung. This assay measures the generation of His-Leu from a Hip-His-Leu substrate. Each tissue was homogenized immediately and incubated for 10 minutes at 37°C, pH 7.50, in the presence of Hip-His-Leu; the reaction was stopped by the addition of NaOH, pH 8.5. His-Leu product then was tagged with 0.1% phthalaldehyde and quantitated fluorometrically (SLM 8000C, SLM Instruments Inc., Urbana, Ill.) at an excitation wavelength of 386 nm and emission wavelength of 436 nm. The sensitivity of this assay is less than or equal to 0.02 nmol/mg tissue/min; the generation of His-Leu is linear from 0.02 to 15 nmol/mg/min in each tissue.

Molecular Biological Studies

Homogenization of various tissues was carried out in 4 M guanidine thiocyanate, 0.5% sodium N-lauryl sarcosine, 25 mM sodium citrate, 0.1 M β-mercaptoethanol, and 2 M CsCl; RNA was pelleted by ultracentrifugation. The RNA was suspended in 0.2 M sodium acetate, pH 5.5, rocked at 4°C for 1 hour, and precipitated in 2 vol ethanol. The precipitated RNA was dissolved in water and the amount quantitated by absorbance at 260 nm in duplicate. Comparison of relative mRNA levels was made in reference to the same amount of total RNA applied per sample.

The sense primer used for the polymerase chain reaction (PCR) spanned oligonucleotide bases 492–512 (GCCCTCCCAAAAGACTGCCA), and the antisense primer spanned bases 860–880 (CCACATGTCTCCACGAGATG) of the human ACE cDNA. Rat heart right ventricular total RNA or
anglerfish pancreatic islet RNA (which served as a negative control) were subjected to cDNA first strand synthesis in a reaction mixture containing 0.5 mM dATP, dCTP, dGTP, and dTTP, as well as 1 µl RNase inhibitor, 100 pmol random hexamer, and 200 units reverse transcriptase in PCR buffer (50 mM KCl, 20 mM Tris-Cl, 2.5 mM MgCl₂, 100 µg/ml bovine serum albumin, pH 8.4). The total volume of the reaction was 20 µl. Samples were incubated at room temperature for 10 minutes, followed by incubation at 42°C for 45 minutes and a heat shock at 95°C for 5 minutes. Tubes were then chilled immediately on ice for PCR amplification.

Ten picomoles of each upstream and downstream primer and 1 unit of Taq polymerase in 80 µl PCR buffer were added to the reaction mix of the reverse transcriptase reaction. Twenty-five PCR amplification cycles were run in the following cycles: denaturation (30 seconds at 95°C), cooling (1 minute to 55°C), annealing (30 seconds at 55°C), heating (30 seconds to 72°C), primer extension (30 seconds at 72°C), and heating (1 minute to 95°C). After amplification, 30 µl of each reaction mixture was run on 1.5% agarose gel, cross-linked, hybridized, and exposed for 16 hours. DNA on nitrocellulose filters was cross-linked by UV light. A solution of 50% formamide, 5× Denhardt’s solution, 25 µg/ml yeast tRNA, 25 µg/ml salmon sperm DNA, 10 µg/ml poly(A) RNA, and 10 µg/ml poly(C) RNA in 0.2% sodium dodecyl sulfate was used for prehybridizing the blots for 4 hours. Blots were hybridized overnight in the same buffer, to which [32P]cDNA was added. After hybridization, the blots were washed in 0.2× SSC with 0.1% sodium dodecyl sulfate at room temperature for 10 minutes, and then three times at 60°C for 30 minutes. Blots were exposed for 16 hours to XAR x-ray film (Eastman Kodak Co., Rochester, N.Y.).

To verify relative linearity of PCR amplification procedures, four dilutions of RNA (2.5, 1.25, 0.613, and 0.317 µg) from normal right ventricles were subjected to the above methods. The results from eight experiments demonstrated a mean r value of 0.93.

Slot blot analyses were performed to quantify cardiac ACE mRNA expression. Multiple dilutions of total right ventricular RNA (0.5, 1.0, and 2.0 µg) of each sample were amplified by these PCR methods. Ten microliters of the reaction mixture was blotted onto nylon membranes (Gene Screen, New England Nuclear, Boston) using a slot blot apparatus (Schleicher & Schuell, Inc., Keene, N.H.) and was UV cross-linked, hybridized, and exposed to x-ray film as described above.

Autoradiograms generated by slot blots were scanned with an LKB microdensitometer (Paramus, N.J.) with background set to zero for each autoradiograph. Regression lines were calculated from the integral values obtained by scanning the serial concentrations of each sample. The relative signals of the specific DNA were estimated from the slope of the regression line, and only values of r ≥ 0.90 were accepted. Slopes of specific mRNA for each condition were compared as relative ratios. Sufficient material was available to study specimens with multiple sample applications. Our intrablot coefficient of variation was 15%.

All hybridization studies of ACE mRNA were performed with a human ACE cDNA probe. A plasmid vector (Bluescript KS, pB 35-19) containing 3,334 bp of human ACE cDNA was cut with EcoRI and Bgl II to yield 1.7 and 1.6 kb inserts of ACE cDNA. Both fragments were separated from the 3.0 kb vector on an agarose gel, were oligolabeled with [32P]dCTP, and were used as probes for ACE mRNA.

**Hemodynamic Studies**

Indirect systolic blood pressure was determined by the tail-cuff method and represents the mean of recordings performed at the same time of day on three consecutive days. The correlation of indirect blood pressures with direct pressure measurements in our laboratory achieves a correlation coefficient of 0.98. This correlation is comparable to that reported by Bunag.

**Morphometric Analysis of Infarct Size**

The left ventricle was sectioned transversely in at least five planes, stained with Masson’s trichrome and hematoxylin and eosin, and projected for quantitative planimetry of infarct size. The mean of the endocardial and epicardial scar circumferences was compared with total left ventricular circumference to calculate percent total infarction size. All infarctions were transmural and involved only the free wall of the left ventricle.

**Statistical Analysis**

All data are presented as mean ± SEM. Differences observed between groups at death were compared using the Student’s t test for unpaired data. The relations of serum and tissue ACE activities and mRNA expression with left ventricular myocardial infarct size were examined by univariate regression analysis. Statistical significance was accepted at the 95% confidence limit (p < 0.05).

**Results**

**Group Characteristics**

SO and HF animals were studied an average of 85 days postoperatively. In addition, a nonoperated (NO), age-matched parallel control group was included in the study. At the time of death, the age and body weights of the animals in each group were comparable (Table 1). The mean infarct size in HF rats was 37±4% of the left ventricular circumference. There was a tendency for systolic blood pressure to be lower in HF rats compared with NO.
or SO controls (114±6 mm Hg for HF versus 122±3 mm Hg and 124±3 mm Hg for NO and SO rats, respectively); however, this difference did not reach statistical significance.

**Effect of Heart Failure on Plasma and Tissue Angiotensin Converting Enzyme Activities**

Plasma renin concentrations were not different among NO, SO, and HF animals (Table 2). Additionally, serum ACE activities were not different among the three study groups.

At baseline, cardiac ACE activity was 50% greater in the right ventricle than in the septum in NO and SO rats. No significant differences in cardiac ACE activities could be demonstrated between SO and NO controls. On the other hand, cardiac ACE activities increased significantly in HF rats (Figure 1). The right ventricular ACE activity was increased approximately twofold in HF animals as compared with both NO and SO groups ($p<0.05$). Similarly, interventricular septal ACE activity also was higher in HF hearts as compared with NO and SO hearts (twofold increase, $p<0.005$ and $p<0.01$, respectively). The left ventricle was not studied, because the infarcted scar tissues may complicate the biochemical analysis. In contrast to the heart, pulmonary, aortic, and renal ACE activities remained unaltered in HF rats as compared with control rats (Table 3).

Figure 2 demonstrates a positive correlation between histopathological size of the myocardial infarction and right ventricular ACE activity ($r=0.75$, $p=0.05$). This correlation also was present between the interventricular septal ACE activity and infarct size ($r=0.95$, $p=0.005$). A single HF rat with a 14% myocardial infarction is excluded from the plotted regression; if this animal, whose infarct size was smallest and whose interventricular septal ACE value was in the normal range, is included in the regression analysis, then $r=0.69$ and $p=0.09$. No relation with infarct size was observed for serum and noncardiac tissue ACE activities (Table 4).

**Effect of Heart Failure on Cardiac Angiotensin Converting Enzyme mRNA Expression**

The relative paucity of ACE mRNA in cardiac tissue and small sample size do not permit routine performance of Northern blotting or poly(A) purification of this mRNA. Therefore, PCR procedures were used to qualitatively assess the relative expression of ACE mRNA in this tissue. A representative Southern blot is displayed in Figure 3, which demonstrates the relative increase in ACE message from the right ventricle of HF rats compared with SO control rats. Five different RNA amounts were amplified by PCR to control for relative linearity of this amplification (Figure 4). Comparison of the regression slopes for cardiac ACE expression for HF versus SO animals demonstrated a twofold increase in ACE expression in HF ventricles ($p<0.05$). This increased ACE mRNA level also directly correlated with the infarct size ($r=0.67$, $p<0.05$; Figure 5).

**Discussion**

The circulating peptide hormone angiotensin II elicits tissue-specific responses at many target organs,

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<th>Table 1. Baseline Characteristics of Study Rats at Death</th>
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<td>n</td>
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<tr>
<td>Weight (g)</td>
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<tr>
<td>Age (days)</td>
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<td>Systolic blood pressure (mm Hg)</td>
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Values are mean±SEM. NO, nonoperated rats; SO, sham-operated rats; HF, heart failure rats. Intergroup baseline characteristics were not statistically significant.

<table>
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<th>Table 2. Effect of Experimental Heart Failure on Plasma Renin Concentration and Serum Angiotensin Converting Enzyme Activity</th>
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<tr>
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<tr>
<td>PRC</td>
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<tr>
<td>Serum ACE</td>
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</table>

Values are mean±SEM. NO, nonoperated rats; SO, sham-operated rats; HF, heart failure rats; PRC, plasma renin concentration (ng angiotensin I/ml/min); ACE, angiotensin converting enzyme. Serum ACE activity expressed as nmol/ml/min. Intergroup differences were not statistically significant.

<table>
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<th>Table 3. Effect of Experimental Heart Failure on Selected Noncardiac Tissue Angiotensin Converting Enzyme Activities</th>
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<tr>
<td>Aorta</td>
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<tr>
<td>Kidney</td>
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<tr>
<td>Lung</td>
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</table>

Values are mean±SEM. NO, nonoperated rats; SO, sham-operated rats; HF, heart failure rats. Tissue angiotensin converting enzyme activities are expressed as nmol/mg/min. Intergroup differences were not statistically significant.
including the blood vessel, kidney, heart, brain, and adrenal. Recently, an endogenous renin-angiotensin system has been demonstrated in many important tissues. Reninlike enzymatic activity, renin substrate, and ACE have been demonstrated at the tissue level using biochemical, immunohistochemical, and molecular biological techniques. In addition, angiotensin II receptors have been demonstrated in the human ventricle. Although the magnitude of activation of the circulating renin-angiotensin system in both experimental models of heart failure and patients has been demonstrated to be dependent on disease acuity and severity, the status of the tissue renin-angiotensin system has not been studied previously. The present study therefore was performed to investigate whether the activities of the serum and various tissue ACE activities are altered in this disease state, in which local tissue angiotensin II production may have particular relevance.

We chose the model of heart failure induced by experimental myocardial infarction. This model is particularly pertinent to the study of the renin-angiotensin system. Although plasma renin activity is elevated acutely after myocardial infarction and during advanced, decompensated heart failure, our results demonstrate that the circulating renin-angiotensin system is not activated during the chronic compensated stage (greater than 1 month postoperatively). These characteristics are similar to those of patients with chronic compensated heart failure.

During this chronic stage of heart failure, this model also is characterized by decreased cardiac output, regional blood flow redistribution, sodium avidity, progressive ventricular dilatation, and reduced survival. Pfeffer and coworkers have demonstrated previously that the size of left ventricular infarction (percent of total left ventricular circumference) correlates well with the degree of impairment of systolic function. Larger infarct size also correlates with both the magnitude of increase in left ventricular enddiastolic pressure and the decline in cardiac output.

The most common clinical features of human congest-

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**TABLE 4. Lack of Relation of Selected Noncardiac Tissue Angiotensin Converting Enzyme Activities to Left Ventricular Infarct Size in Heart Failure Rats**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Heart failure rats</th>
<th>Total group</th>
<th>r</th>
<th>p</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aorta</td>
<td>0.37 NS</td>
<td>0.05 NS</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Kidney</td>
<td>0.27 NS</td>
<td>0.01 NS</td>
<td></td>
<td></td>
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<tr>
<td>Lung</td>
<td>-0.58 NS</td>
<td>-0.29 NS</td>
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</tbody>
</table>

*Total group refers to pooled data from all sham-operated and heart failure rats.

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**FIGURE 3. Representative Southern blot demonstrating relative increase in right ventricular angiotensin converting enzyme mRNA expression in heart failure (MI) vs. sham-operated (CONTROL) rats.**

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**FIGURE 4. Representative experiment demonstrating relative linear amplification of total right ventricular mRNA via polymerase chain reaction methods. See text for details.**
tive heart failure, namely, elevated left ventricular end-diastolic pressure, depressed cardiac output, and the inability to excrete a sodium load, are reproduced in this animal model.

The presence of ACE in the rat heart has been demonstrated previously by Cohen and Kurz and Unger et al. Recent data suggest that this cardiac ACE is located throughout cardiac tissues but may be greater in the atria, vasculature, conduction system, and cardiac valves than in ventricular myocardium. In hypertensive rats, the magnitude of serum or aortic ACE activity has not been demonstrated to correlate with the relative severity of the hypertension. It is noteworthy that in the present study, cardiac ACE activity was highest in the right ventricle and interventricular septum of rats with presumably the greatest left ventricular dysfunction, as predicted by infarct size. We did not study left ventricular ACE activity, because interpretation of this biochemical data would be confounded by a variable contribution of infarcted fibrous tissue. The present data demonstrate that the increase in right ventricular and interventricular septal ACE activities is due to the induction of ACE expression with increased local synthesis of converting enzyme. In this model of heart failure, Drexler et al. also have demonstrated induction of the expression of atrial natriuretic factor in the ventricular myocardium in proportion to the extent of myocardial infarction. Angiotensinogen expression also has been reported to increase in the atria and ventricles of rats in the early phase (within 5 days) after experimental myocardial infarction, but this expression is normalized 25 days later in the chronic heart failure state. The exact stimulus for the induction of cardiac ACE in heart failure is unclear. It is possible that an increase in ventricular dimension or wall tension may be a direct stimulus. It also is possible that an increased myocardial neurosympathetic activity may be responsible. Increased cardiac ACE activity is, in any case, a result of increased local expression; contamination or uptake of serum ACE is unlikely to contribute to the increased cardiac ACE activity, because heart ACE activity is selectively increased in HF rats. In other words, serum, aortic, pulmonary, and renal ACE activities were not increased in HF rats nor in SO and NO control rats.

The present documentation of the status of tissue ACE in the chronic, compensated state of experimental heart failure has potential clinical relevance. As in the human disease, plasma renin and serum ACE activities are not elevated during the chronic compensated phase. We hypothesize that the tissue renin-angiotensin system also may contribute to the pathophysiology of progression of heart failure by vascular, renal, and cardiac effects of local angiotensin II. Increased vascular angiotensin II levels in heart failure would contribute to decreased arterial and venous compliance, increasing cardiac preload and afterload. We recently have observed that renal angiotensinogen mRNA expression is increased in these HF rats. In that study, we also observed that the renal angiotensinogen mRNA level was influenced by the size of myocardial infarction. It is not yet known whether the renal renin-angiotensin system contributes to sodium retention and increased plasma volume in heart failure. However, despite normal plasma renin activity in these animals, treatment with ACE inhibitors has been demonstrated by others to elicit renal vasodilation and natriuresis. Thus, vascular and renal renin-angiotensin systems, via contributing to decreased vascular compliance or increased plasma volume, may promote progressive ventricular dilatation. Furthermore, cardiac dilatation is blunted, and the survival of these rats is improved by ACE inhibition. We postulate that the beneficial effect of ACE inhibitor therapy in this condition is related to the inhibition of tissue angiotensin II production. However, increased bradykinin, reduced sympathetic adrenergic nerve terminal catecholamine release, or increased vasodilator prostaglandins also may contribute to the action of ACE inhibitors.

The increase in cardiac ACE activity may have other important pathophysiological implications in heart failure. In rats with experimental left ventricular hypertrophy induced by aortic banding, cardiac ACE activity also is increased, with an associated increase in the transmyocardial conversion of angiotensin I to angiotensin II. Locally synthesized cardiac angiotensin II in failing myocardium may exert a direct inotropic effect and indirectly augment cardiac systolic function via facilitation of norepinephrine release from sympathetic nerve terminals. Cardiac angiotensin may participate in ventricular hypertrophy and remodeling via its growth-promoting effects. Thus, increased cardiac ACE activity
and increased local angiotensin II concentrations may contribute to the compensatory ventricular remodeling that is ultimately responsible for cardiac dilatation and progressive heart failure.

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