Active renin and angiotensinogen in cardiac interstitial fluid after myocardial infarction

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Hirsch, Alan T., John A. Opsahl, Mary M. Lunzer, and Stephen A. Katz. Active renin and angiotensinogen in cardiac interstitial fluid after myocardial infarction. Am. J. Physiol. 276(Heart Circ. Physiol. 45): H1818–H1826, 1999.—The renin-angiotensin system promotes cardiac hypertrophy after myocardial infarction. The purpose of this study was to measure renin and angiotensinogen in plasma and myocardium 10 days after myocardial infarction. Infarction involving 45 ± 4% of left ventricular circumference with accompanying hypertrophy was induced in rats (n = 14). Plasma and myocardial renin were increased after infarction compared with sham controls (n = 6) (27.4 ± 3.2 vs. 7.5 ± 1.8 ng ANG I·ml plasma·h⁻¹, P < 0.0002; and 8.8 ± 1.6 vs. 2.5 ± 0.1 ng ANG I·g myocardium·h⁻¹, P < 0.008, respectively). After infarction, myocardial renin was correlated with infarct size (r = 0.62, P < 0.02) and plasma renin (r = 0.55, P < 0.04).

Plasma angiotensinogen decreased in infarct animals, but myocardial angiotensinogen was not different from shams (1.1 ± 0.08 vs. 2.03 ± 0.06 nM/ml plasma, P < 0.002; and 0.081 ± 0.008 vs. 0.070 ± 0.004 nM/g myocardium, respectively). In conclusion, myocardial renin increased after infarction in proportion to plasma renin and infarct size, and myocardial angiotensinogen was maintained after infarction despite decreased plasma angiotensinogen and increased levels of myocardial renin.

METHODS

Male Sprague-Dawley rats (Harlan, Madison, WI) weighing 265–300 g were fed a moderate low-sodium (0.04%) food
(Tekland, Madison, WI) for 3 wk with free access to food and tap water. Moderate dietary sodium depletion was used to increase plasma and myocardial renin levels so that myocardial renin assays (especially renin glycoform assays) would be above the lower limits of detection. Animals were anesthetized with ether, and a left thoracotomy was performed, the heart briefly exteriorized, and portions of the left coronary artery ligated with 6-0 prolene suture. The thorax and skin were then closed by a 2-0 purse-string suture. Sham-operated animals underwent the identical procedure without ligation of the left coronary artery. After 5–7 days, both infarct and sham animals were lightly anesthetized with ether and underwent 12-lead electrocardiography. After 5–7 days, infarct and sham-operated animals were separated to assess renin concentration in scarred and nonscarred myocardium. These animals satisfied the same criteria for the Accreditation of Laboratory Animals.

Sample Collection

Approximately 7 ml of trunk blood were collected into tubes containing 200 µl of 5% EDTA. The blood was mixed, stored on ice, and centrifuged at 2,000 g for 15 min at 4°C. Separated plasma was snap frozen in liquid N₂ and stored at −25°C for subsequent determination of plasma active renin, angiotensinogen, and active renin glycoforms. Hearts were quickly excised, followed by retrograde perfusion of the aorta with 10 ml ice-cold heparinized saline to remove all plasma from the myocardium, and then the pericardial tissue, atria, great vessels, and right ventricle were removed. In a previous report (7), hearts underwent retrograde perfusion for 1.5–2.0 min vs. 15–30 s in the present study. Both studies show similar control ratios of circulating/cardiac active renin and angiotensinogen, indicating that different perfusion times below 2 min do not greatly influence these ratios. The hearts were then examined grossly for myocardial infarction both on the endocardial and epicardial surfaces. Infarct size was also determined by quantitative planimetry of the scar from a single section of left ventricle after Masson’s trichrome staining. Both sides of the remaining left ventricular wall were then blotted, weighed, snap frozen in liquid N₂, and stored at −25°C. Total left ventricle preparation was ∼3 min. Coronary-ligated animals not exhibiting electrocardiogram evidence consistent with myocardial infarction, or animals with myocardial infarction of <18% of the left ventricle, were excluded from the study.

Myocardial and Plasma Renin Determinations

Left ventricles homogenized. Left ventricles were thawed and homogenized at 0°C in a handheld 7-ml Kontes glass homogenizer at a ratio of 1 mg tissue to 5 µl proteolytic inhibitor buffer (PIB) containing serine-, metallo-, and thiolprotease inhibitors and 1.0% BSA at pH 7.5 as previously described (7, 15). Homogenates were split into three aliquots and stored at −25°C. Each aliquot was thawed and centrifuged at 14,000 g for 4 min at 4°C to remove tissue debris, and the resulting supernatants were assayed for active renin, angiotensinogen, or active renin glycoforms.

Renin measurement. Plasma was diluted 20-fold in PIB to yield renin concentrations similar to myocardial homogenates. Both plasma and homogenates were therefore diluted in the same solvent (PIB) and assayed identically in duplicate as previously described (7, 15). Briefly, assay tubes consisting of diluted plasma, myocardial homogenate, or PIB (sample blanks) were combined with 48-h anephric unfractonated rat

plasma (angiotensinogen source) prepared from normal salt rats. Aliquots were incubated at 0 and 37°C for 18–24 h. Detectable average ANG I in the 0°C tubes (endogenous immunoreactive ANG I in sample and substrate source) was subtracted from the 37°C tube average to calculate generated ANG I, although 0°C tube ANG I concentrations were often undetectable. The corresponding difference in the sample blank tubes was also subtracted from the generated ANG I value to correct for small amounts of endogenous renin activity in the substrate source. Sample blanks ranged from 1 to 40% of the generated ANG I, and the higher range was present only in the bilateral nephrectomy reference group. During the 37°C incubation, ANG I was generated in direct proportion to the sample renin concentration. Only 4% or less of the total available angiotensinogen was converted to ANG I, and linear generation of ANG I over time was verified throughout the study (11, 25). Addition of extra renin (derived from plasma) to either a plasma or myocardial sample calculated to double the measured renin activity resulted in an average 1.93-fold increase in ANG I generation rate (range 1.85–2.05, n = 6). Renin concentration was expressed as nanounits of ANG I per milliliter of plasma or grams of myocardium per hour of incubation.

ANG I was assayed by radioimmunoassay (RIA) using a modified Du Pont Ang I RIA (Wilmington, DE). Major modifications included preparation of ANG I standards with the same solution contents as samples. RIA data were linearized with a log-logit transformation resulting in a correlation coefficient of −0.99 or better. The average labeled ANG I bound 60% to the primary antibody without competition. The average percentage of error for predicting the standard concentration from the transformed curve was <6%.

Myocardial and Plasma Angiotensinogen Determinations

Angiotensinogen concentrations from left ventricular myocardial homogenate supernatants and plasma were measured by adding a large excess of exogenous porcine renin, and thereby converting all the angiotensinogen present to ANG I (verified by ANG I generation plateau). ANG I concentrations were subsequently determined by RIA and converted to angiotensinogen concentrations based on a 1:1 molar relationship between ANG I generation and angiotensinogen depletion. Angiotensinogen assay details and assay validation have been previously described (7, 15). Briefly, plasma was diluted 70-fold in PIB to yield comparable angiotensinogen concentrations to myocardial homogenates. Both plasma and homogenates were therefore diluted in the same solvent (PIB) and assayed identically. Seven milliliters of porcine renin (Sigma, St. Louis, MO) in 325 µl PIB were added to 25 µl of diluted plasma or myocardial homogenate at 0°C, and then incubated in duplicate at 37°C for 20 min. Another set of duplicates was incubated for 40 min. An Ang I generation plateau was reached by 20 min, indicating complete conversion of angiotensinogen to ANG I. Addition of exogenous plasma to ventricular homogenates yielded predictable angiotensinogen determinations equal to the sum of the homogenate plus plasma values determined separately.

Myocardial Scar, Cardiac Membranes, and Bilateral Nephrectomy

A second group of five coronary-ligated animals was evaluated to assess renin concentration in scarred and nonscarred myocardium. These animals satisfied the same criteria for myocardial infarction as the first study cohort. Hearts were removed as described, but normal and scarred myocardium were separated by dissection before snap freezing, storage, and subsequent renin assay.
In a third group of animals, two sham and two infarcted hearts were examined for cardiac membrane-associated renin activity. Myocardial homogenates were prepared and assayed as described above and also after an additional centrifugation at 100,000 g for 1 h at 4°C to pellet all myocardial membranes. The pellets were resuspended in PIB, recentrifuged, and then assayed in the presence of 1% Triton X-100 as previously described for measurement of renin activity from cell membranes of normal hearts (15) and myocyte membranes (7). Each supernatant was also assayed for renin activity.

In a fourth group of animals, seven rats underwent bilateral nephrectomy (BNX), and after 48 h, plasma and myocardial tissue were harvested and assayed for renin as described above. Myocardial renin concentration from these animals provided a comparative reference to animals with intact kidneys.

**Shallow Gradient Isoelectric Focusing**

Rat active renin was resolved into five major glycoforms (I-V) using shallow gradient isoelectric focusing to determine if myocardial renin glycoform distribution was altered after infarction. Complete matching of plasma and myocardial renin glycoform profiles also helped verify that the measured myocardial reninlike activity was indeed due to renin. The sample treatment and methods were identical to those used previously (7).

**Renin Glycoform Measurement**

After application of treated plasma or corresponding myocardial homogenate to the focusing gels, the gels were run for 23 h at 500 V, serially sliced into 60 gel segments, and each gel segment was eluted in an individual polystyrene tube with 125 µl PIB at 4°C. Gel segments initially swelled and then reached diffusion equilibrium ~18–24 h later. The gel segments were then carefully removed, leaving behind ~90 µl of eluant (with renin present, if the enzyme had focused in the corresponding gel segment).

Each 90 µl of eluant was then combined with 30 µl of plasma from 48-h anephric rats as an angiotensinogen source. The total 120 µl was then incubated at 37°C for 1–24 h, with longer incubation times used as necessary for samples with relatively little renin activity. The ANG I generated in the substrate represent background error, which is then subtracted from all gel segments containing renin activity. This background error correction was determined from gel slices that clearly contained no sample renin activity due to their correspondingly high or low isoelectric points (for example, gel slices 50–60 in Fig. 3). The background error is exactly equivalent to the sample blanks for the plasma and myocardial renin assays. Subtraction of background and calculation of the five major renin glycoform proportions resolved in the gels were performed as previously reported (11, 14).

**RESULTS**

Fourteen rats survived coronary ligation with myocardial infarction sizes that were calculated to include 45.9 ± 4% of the left ventricular circumference. An additional eight sham-operated animals were also studied. Initial body weight of the infarct animals was 270 ± 11 g. This was not different from the sham controls and did not change significantly over the 10-day period after myocardial infarction. After 10 days, heart weight-to-body weight ratio in the infarct animals was 3.8 ± 0.6 and was not statistically different from that calculated in the sham animals (2.8 ± 0.5) than in the sham controls (3.4 ± 0.1 mg/g).

Ten days after myocardial infarction, plasma renin concentration (PRC) was almost fourfold higher in the infarcted animals than the shams (26.8 ± 3.1 vs. 7.5 ± 1.9 ng ANG I · ml plasma· h· 1, P < 0.003; Fig. 1). Similarly, left ventricular renin concentration in the infarcted hearts was increased almost fourfold compared with shams (8.7 ± 1.6 vs. 2.5 ± 0.1 ng ANG I · g myocardium· h· 1, P < 0.008; Fig. 1). Note the log scale of the renin activity axis in Fig. 1. The ratio of plasma to left ventricular renin concentration in the infarcted animals was 3.8 ± 0.6 and was not statistically different from that calculated in the sham animals at 2.8 ± 0.5. Myocardial renin was always significantly and positively correlated with plasma renin, whether for all animals grouped together (r = 0.7, P = 0.0003), for sham animals (r = 0.79, P < 0.02), or for myocardial infarction animals alone (r = 0.55, P < 0.04) (see Fig. 2, top). In addition, myocardial renin was significantly and positively correlated with infarct size (r = 0.62, P < 0.02), as shown in Fig. 2, bottom. Infarct sizes ranged from as low as 18% to as high as 64% of the left ventricular circumference.

The same five major active renin glycoforms (renin forms I-V) were always detected in plasma and myocardium of both myocardial infarction and sham rats, with corresponding isoelectric points of 5.7, 5.4, 5.2, 5.0, and 4.8. Renin glycoforms I plus II accounted for 41.5 ± 5% of the renin activity in the plasma of infarct animals. This was not different from the percentage of renin glycoforms I plus II in the hypertrophied myocardium of the same animals (48 ± 5%) or the plasma (41.4 ± 3%) or normal myocardium (47.5 ± 2%) of the sham.
controls. Figure 3 is a representative figure showing the active renin glycoform profiles for both a sham and myocardial-infarcted animal.

Centrifugation (100,000 g for 1 h) of myocardial homogenates from either infarct or sham animals resulted in pelleting of 12 ± 6% of homogenate renin. However, after the pellet was washed in PIB and again centrifuged at 100,000 g for 1 h at 4°C, all original pellet renin activity was present in the supernatant, and none could be measured in the recentrifuged pellet with or without the presence of 1% Triton X-100.

Angiotensinogen concentration in the plasma of 10-day infarcted animals was significantly lower than that of sham controls (1.1 ± 0.08 vs. 2.03 ± 0.06 nM/ml, P < 0.0001), as shown in Fig. 4. In contrast, left ventricular homogenate angiotensinogen concentrations did not differ between infarcted animals and sham controls (0.081 ± 0.008 and 0.070 ± 0.004 nM/g, respectively) (see Fig. 4). The ratio of plasma to myocardial angiotensinogen in the infarcted animals was 13.5 ± 0.75, significantly lower (P < 0.0001) than the ratio in sham animals of 29.5 ± 1.5, indicating a significantly increased distribution of myocardial angiotensinogen relative to plasma angiotensinogen in infarcted animals. Myocardial angiotensinogen was positively correlated with plasma angiotensinogen in the infarcted animals (r = 0.72, P < 0.004) but was not correlated with infarct size, as shown in Fig. 5.

In five additional animals, renin and angiotensinogen concentrations were determined separately on infarcted (scarred) and noninfarcted myocardium harvested from the same hearts. There were no differences in the concentrations of renin or angiotensinogen between paired infarcted and noninfarcted myocardial samples. Infarcted myocardial renin concentration was 5.4 ± 1.4 vs. 5.9 ± 1.1 ng ANG I·g⁻¹·h⁻¹ for neighboring noninfarcted myocardium. The angiotensinogen concentration of infarcted myocardium was 0.080 ± 0.014 vs. 0.075 ± 0.004 nM/g for noninfarcted myocardium.

To provide a comparative reference, a separate group of seven BNX animals without coronary ligation or sham surgery was also studied. Forty-eight hours after BNX, PRC decreased by 99%, and myocardial renin concentration decreased by 92% when compared with sham infarct animals (Fig. 1). These same animals displayed a significant 2.3-fold increase in both plasma and myocardial angiotensinogen concentration compared with shams (Fig. 4).

**DISCUSSION**

Experimental myocardial infarction due to coronary ligation elicits left ventricular hypertrophy (LVH) within...
10 days and is accompanied by a fourfold increase in both plasma and myocardial renin concentration. The observed increase in PRC after experimental myocardial infarction is consistent with previous reports (8, 9, 22, 30); however, the corresponding response of myocardial tissue renin has not been previously reported. The current study demonstrates that myocardial renin concentration rises significantly after infarction and is positively correlated with both myocardial infarct size ($r = 0.62, P < 0.02$) and corresponding PRC ($r = 0.55, P < 0.04$). A parallel rise in both cardiac tissue and PRC may have general relevance to common pathophysiological conditions, since chronically increased plasma renin has been observed in both animals and patients with severe left ventricular dysfunction (22, 29–31, 34).

Previous studies have inferred an increase in cardiac RAS activity after experimental myocardial infarction, as increases in mRNA for renin, angiotensinogen, ACE, and ANG II receptors as well as increased ANG II receptors themselves have been demonstrated in the myocardium (8, 18, 21, 27, 28, 37). However, the current direct measurement of increased myocardial renin activity after myocardial infarction now also documents increased local myocardial activity of this critical RAS enzyme.

We chose to evaluate the myocardial RAS response to infarction at the 10-day time point to exclude confounding plasma RAS activation by acute responses to surgery. Because the RAS may be a key regulator of LVH after myocardial injury (16, 24, 33, 37), the 10-day time...
point was also adequate to permit the myocardium to begin to compensate by developing LVH (measured as a significant increase in heart weight to body weight) after infarction. However, the response to myocardial infarction begins immediately after injury and progresses well after 10 days; thus the present study is somewhat limited in scope. Another study limitation is that no direct measurement of heart failure was made, and therefore, we do not know if larger infarcts or heart size were accompanied by more extensive heart failure. Finally, the use of a moderate sodium-restricted diet may have influenced the size of the infarcts measured in this study. However, in a previous study (15), sodium restriction had no effect on cardiac renin glycoform distribution or plasma-to-left ventricular ratio for renin or angiotensinogen, with plasma and cardiac renin and angiotensinogen all increasing between 10 and 50% due to moderate sodium restriction.

In this study, the plasma-to-left ventricular renin ratio was 2.9 ± 0.5 in the sham group and 3.8 ± 0.6 in the coronary ligation group. The two ratios were not significantly different and approximate the expected range for renin diffusion equilibrium between plasma and the myocardial interstitium (7, 15). Because both groups underwent a thoracotomy, pericardial injury, and handling of the heart, the left ventricular interstitial space may have been altered by these perturbations. In previous studies from our lab using normal rats from which cardiac tissue was collected without prior thoracotomy or pericardial injury, the plasma-to-left ventricular renin ratio was ~4 to 4.8 (7, 15).

The plasma-to-left ventricular renin ratios measured in the present study may have included renin bound to either the coronary vascular wall or myocardial cell membranes. In general, bound myocardial active renin would lower the plasma-to-left ventricular ratio below the range of 4–5 predicted for diffusion equilibrium between plasma and the cardiac interstitial space. Thus our results do not rule out renin tissue binding, especially in the infarcted animals. We attempted to measure membrane-bound renin activity, since it has been suggested that ~12% of myocardial homogenate renin may be associated with cardiac membranes (4).

In addition, more recent studies have suggested that infused renin may bind to the vascular surface (6) and that plasma renin binding to cardiac tissue membranes may play a role in myocardial renin distribution (5). In the present study, we were unable to demonstrate membrane-associated renin activity in sham or infarcted hearts, a result that corresponds to previous work in normal rat hearts (15) and myocytes (7). However, our experimental preparation includes coronary saline perfusion used to prepare blood-free myocardium for subsequent renin and angiotensinogen measurements. This perfusion step might remove bound renin from coronary vessels or cardiomyocytes. Other methodological differences could also account for loss of renin binding, such as the proteolytic inhibitor buffer employed in this study, which could have displaced bound renin due to its ionic strength or other solute considerations not present in previous studies demonstrating possible cardiac renin binding (4–6, 32).

Our results indicate that most myocardial renin may be derived from plasma renin and that both normal and hypertrophied myocardium include renin that has diffused from the plasma into the myocardial interstitium. The possibility that most myocardial tissue renin may be localized to the myocardial interstitium is supported by our previous work (7, 15) and by complimentary findings using renin infusions into modified Langendorff perfused rat hearts (6).

In addition, Danser et al. (5) found a cardiac tissue-to-plasma renin ratio of 30% (equivalent to a plasma-to-left ventricular ratio of ~3.3) from human subjects with dilated cardiomyopathy. Kwong and Egan (17) found cardiac tissue-to-plasma albumin ratios of 6–16% and ratios of ~30% for smaller solute molecules in the heart. Because both renin and angiotensinogen are smaller than albumin and all three molecules have a net negative charge, renin and angiotensinogen are capable of crossing the coronary capillaries into the cardiac interstitium.
Although the major source of myocardial renin appears to be uptake of renal renin from the plasma (3, 4, 15, 35), myocardial renin gene expression has been reported (1, 10, 19), including increased expression around the infarcted area after coronary artery ligation (28). Cardiac renin synthesis is not required to explain the myocardial renin levels observed in the present study, since myocardial renin appears to be a direct function of plasma renin both before and after infarction. However, an increase in cardiac renin mRNA and subsequent elevated renin expression in a very localized infarct border zone would have gone undetected in the present study, since we only assessed total hypertrophied noninfarcted ventricle and scarred ventricular tissue renin. It is also possible that any increased border zone renin activity may have equilibrated with the plasma 10 days after infarction.

In addition, this study is essentially in agreement with the previous finding indicating low to undetectable renin mRNA in hypertrophied noninfarcted myocardium (28), since our reported increased renin activity in hypertrophied noninfarcted myocardium appears to be in equilibrium with plasma renin and may very well be derived from the plasma.

Because ~8% of control myocardial renin remained after 48 h BNX in the reference group, it is possible that the remaining renin activity was due to local renin synthesis. It is also possible that the remaining renin activity did not have enough time to diffuse out of the myocardium, or was perhaps bound to the myocardium. However, another possibility is that the remaining renin after BNX was due to reninlike activity from cathepsin D, in which case ~8% of myocardial reninlike activity measured in this study may not have actually been renin.

Circulating active renin is composed of five major glycoforms (I-V) in the rat, each with similar enzymatic specific activities and differing oligosaccharide attachments. The chronic low-salt diet used in this study has been previously shown not to influence the proportions of circulating rat renin glycoforms (12, 15). In general, only acute changes in renin secretion stimuli are known to cause proportional changes in renin glycoforms (12, 13, 26). In this study, the plasma renin and myocardial renin glycoform profiles were identical, indicating that all major forms of active renin, regardless of charge or oligosaccharide content, are present in the myocardium in the same proportions before and after coronary ligation and subsequent development of myocardial hypertrophy. Thus cardiac remodeling associated with LVH after infarction did not alter the distribution of myocardial renin glycoforms.

Prevention of potential renin and angiotensinogen measurement errors employing the present methods has been recently summarized (7, 15). A previously unmentioned potential artifact is the possible inadvertent activation of prorenin. This seems unlikely since acidic conditions favoring prorenin activation are completely avoided (pH 7.5 in all homogenization and assay steps), and the convertase enzyme responsible for activation of prorenin (a thiol protease or possibly a metalloprotease) would be inhibited by the proteolytic inhibitors in the PIB.

Plasma angiotensinogen concentrations were lower after myocardial infarction than sham surgery, perhaps reflecting consumption of angiotensinogen substrate secondary to the accompanying fourfold increase in PRC. However, there was no difference in myocardial angiotensinogen concentration between sham and infarct groups. This was a somewhat surprising result, because increased myocardial renin would be expected to consume and thus decrease myocardial angiotensinogen after infarction. Such an inverse relationship between cardiac renin and angiotensinogen has been documented from cardiac tissue taken from a combined group of human heart donors and patients with dilated cardiomyopathy (5). In addition, the accompanying decreased plasma angiotensinogen after infarction would also tend to reduce myocardial angiotensinogen, since distribution of plasma angiotensinogen within the myocardial interstitium has been previously postulated to be a source of myocardial angiotensinogen (4, 15, 20). Because angiotensinogen levels were not reduced in myocardial tissue after infarction, there may have been infarct-induced myocardial angiotensinogen synthesis. Increased cardiac angiotensinogen gene expression after infarction was reported in one study (21) but was not observed in another (28). Alternatively, an increased myocardial volume of distribution for angiotensinogen due to structural alterations of the hypertrophied myocardium may have occurred. Lack of a change in myocardial angiotensinogen after infarction is not because the assay was incapable of detecting changes in myocardial angiotensinogen. Angiotensinogen measurements in the BNX reference group (Fig. 4) show that myocardial angiotensinogen levels increase significantly after 48 h of BNX, at a time when plasma angiotensinogen is elevated and myocardial renin is low.

The relatively high plasma-to-left ventricular angiotensinogen ratio, compared with the lower plasma-to-left ventricular renin ratio, may be due to limited angiotensinogen access into the myocardial space secondary to its larger molecular size (15, 17). In addition, destruction of myocardial angiotensinogen by myocardial renin would further result in relatively high plasma-to-left ventricular angiotensinogen ratios, especially if plasma angiotensinogen permeability into the myocardium is low due to its large molecular weight.

Myocardial renin or angiotensinogen measurements in infarcted hearts must be interpreted in view of the fact that portions of the myocardium are infarcted (scarred) and other portions are noninfarcted. After coronary ligation in the rat, infarcted myocardium contains necrotic cardiomyocytes, increased numbers of myofibroblasts and inflammatory cells, as well as increased collagen, hyaluronic, and interstitial fibrosis. The noninfarcted tissue displays myocyte hypertrophy and increased interstitial collagen (2, 23, 36). In this study, there was no difference in renin or angiotensinogen concentration between scarred and nonscarred myocardium when expressed per gram wet weight.
Therefore, renin and angiotensinogen concentrations from whole infarcted hearts appear to be equally relevant for both the infarcted and noninfarcted areas. However, the local distribution of renin or angiotensinogen in these two areas need not be identical, since the infarct region may contain a higher water content and radially different intracellular and extracellular spaces (36).

In conclusion, myocardial renin concentrations vary directly with the PRC in normal myocardium, at sites of myocardial injury, and in neighboring hypertrophied cardiac tissue. Myocardial renin levels also correlate with infarct size, suggesting that plasma and myocardial renin may be dependent on the severity of cardiac injury. The distribution of active renin glycoforms is identical between plasma and myocardium in both control animals and after myocardial infarction. Therefore, cardiac remodeling associated with the significantly increased LVH seen after infarction does not favor redistribution of any specific renin glycoform into the hypertrophied myocardium. Myocardial angiotensinogen levels do not fall after experimental myocardial infarction despite a significant increase in myocardial renin concentration and a fall in plasma angiotensinogen concentration.

We thank Lynn M. Forbis for expert technical assistance.

This study was supported by the American Heart Association (Minnesota Affiliate), Hennepin Faculty Associates, and National Heart, Lung, and Blood Institute Vascular Disease Academic Award HL-03435–01.

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References


