Cardioreparative Effects of Lisinopril in Rats With Genetic Hypertension and Left Ventricular Hypertrophy

Christian G. Brilla, MD, PhD; Joseph S. Janicki, PhD; and Karl T. Weber, MD

Background. In genetic and acquired hypertension, a structural remodeling of the nonmyocyte compartment of the myocardium, including the accumulation of fibrillar collagen within the interstitium and adventitia of intramyocardial coronary arteries and a medial thickening of these vessels, represents a determinant of pathological hypertrophy that leads to ventricular dysfunction.

Methods and Results. To evaluate the benefit of angiotensin converting enzyme inhibition in reversing this interstitial and vascular remodeling in the rat with genetic spontaneous hypertension (SHR) and established left ventricular hypertrophy (LVH), we treated 14-week-old male SHR with oral lisinopril (average dose, 15 mg/kg/day) for 12 weeks. Myocardial stiffness and coronary vascular reserve to adenosine (800 µg/min) were examined in the isolated heart; myocardial collagen and intramural coronary artery architecture were analyzed morphometrically. In lisinopril-treated SHR compared with 14-week-old baseline or 26-week-old untreated SHR and age- and sex-matched Wistar-Kyoto (WKY) controls, we found 1) a regression in LVH and normalization of blood pressure, 2) a complete regression of interstitial fibrosis, represented by a decrease of interstitial collagen volume fraction from 7.0±1.3% to 3.2±0.3% (p<0.025; WKY, 2.8±0.5%), 3) normalization of myocardial stiffness constant from 19.5±0.9 to 13.7±1.3 (p<0.025; WKY, 13.8±2.2), 4) a reversal of intramural coronary artery remodeling, including a decrease in the ratio of perivascular fibrosis to vessel lumen size from 1.4±0.2 to 0.4±0.1 (p<0.025; WKY, 0.6±0.1) and medial thickening from 12.3±0.6 to 7.4±0.5 µm (p<0.005; WKY, 7.4±0.4 µm), and 4) a restoration of coronary vasodilator response to adenosine from 12.3±0.9 to 26.0±1.4 ml/min/g (p<0.005; WKY, 21.8±2.2 ml/min/g). Thus, in SHR with LVH and adverse structural remodeling of the cardiac interstitium, lisinopril reversed fibrous tissue accumulation and medial thickening of intramyocardial coronary arteries and restored myocardial stiffness and coronary vascular reserve to normal.

Conclusions. These cardioreparative properties of angiotensin converting enzyme inhibition may be valuable in reversing left ventricular dysfunction in hypertensive heart disease. (Circulation 1991;83:1771–1779)

In arterial hypertension, a disproportionate accumulation of fibrillar collagen in the interstitial space of the hypertrophied left ventricle (LVH) has been held responsible for abnormal myocardial stiffness and for the impaired pumping capacity of the heart.1–8 In addition, the observed perivascular fibrosis and medial thickening of intramyocardial coronary arteries may account for abnormal coronary vasodilator reserve, which is commonly seen in the hypertensive heart.9–11 Therefore, this remodeling of the nonmyocyte compartment of the myocardium is considered a major determinant of pathological hypertrophy on which the appearance of ventricular dysfunction and, ultimately, symptomatic heart failure is based.12 Several lines of evidence suggest that circulating and tissue renin-angiotensin systems may be involved in this remodeling of the nonmyocyte compartment,13,14 including the cardioprotective effects of angiotensin converting enzyme (ACE) inhibition that served to prevent myocardial fibrosis in the rat with renovascular hypertension.15 We further reasoned that ACE inhibition may have cardioreparative properties that would reverse the remodeling of the cardiac interstitium in the hypertrophied myocardium. Accordingly, this study was undertaken to determine whether the ACE inhibitor,
lisinopril, was able to restore myocardial structure and function to normal in rats with established LVH and myocardial fibrosis due to genetic spontaneous hypertension (SHR). In SHR, although arterial pressure does not appear to depend on the circulating renin-angiotensin system, tissue ACE activity may be contributory. We specifically sought to determine whether 1) interstitial fibrosis with abnormal myocardial stiffness of the left ventricle could be reversed and 2) perivascular fibrosis and medial thickening of intramyocardial arteries with impaired coronary vasodilator response to adenosine could be reversed.

Methods

Experimental Model

Fourteen-week-old male SHR and their normotensive genetic controls, Wistar-Kyoto rats (WKY), weighing 265–325 g at the onset of the study, were in the following manner: 1) 14-week-old SHR (n=14) and WKY (n=13), observed in our colony since 12 weeks of age and showing stable blood pressure during this 2-week period, were killed for physiological and morphological studies (groups, SHR-C14, WKY-C14), 2) untreated 14-week-old SHR (n=11) and WKY (n=9) were observed for 12 additional weeks and killed at 26 weeks of age (groups, SHR-C26, WKY-C26), 3) 14-week-old SHR (n=9) and WKY (n=3) were treated with lisinopril (20 mg/kg body wt/day) in their drinking water for 12 weeks and killed at 26 weeks (groups, SHR-L26, WKY-L26). This dose inhibits ACE and normalizes elevated blood pressure in SHR. Adjustments in lisinopril dosage were made according to the blood pressure response; after 3 weeks, this included a reduction to 15 mg lisinopril/kg body wt/day and after 9 weeks a reduction to 10 mg/kg body wt/day. Blood pressure was measured weekly in all animals by the standard tail cuff method. In groups WKY-C26 and SHR-L26 two rats died suddenly while the weekly blood pressure was being measured and were, therefore, not considered in further analyses and are not included in the number of animals listed for these groups. No rat died in group WKY-L26 and in the other experimental groups. To minimize the number of animals that needed to be killed, we examined only three rats in group WKY-L26 because this group was less important for the overall objective of this study. All rats were fed with standard rat chow and water ad libitum.

Physiological Studies

Animals were anesthetized (methohexital 50 mg/kg i.p.), and a carotid artery was cannulated. Arterial pressure was recorded in the lightly anesthetized state. After additional anesthesia, the animals were intubated and mechanically ventilated. The chest was opened by median sternotomy, and the heart and lungs were removed en bloc. Within seconds, the ascending aorta was cannulated, and retrograde perfusion commenced with 37°C crystalloid (modified Krebs-Henseleit) perfusate as previously reported. The pulmonary artery was cannulated, and coronary venous flow was measured by a Doppler probe (Transonic Inc., Ithaca, NY). Thebesian drainage into the left ventricle is negligible (<5% of total coronary blood flow in either rat strain) and was not included in the coronary flow measurements. A compliant balloon was positioned in the left ventricle by way of the mitral orifice and was secured at the apex, which was punctured to permit the egress of Thebesian drainage. The other end of the balloon was fixed to a short catheter with an outer diameter approximating that of the mitral annulus, thereby preventing regurgitation of the balloon. The catheter was connected with a stopcock to a syringe (to allow volume changes) and to a Statham pressure transducer (Gould-Statham, Oxford, Calif.). Coronary perfusion pressure was optimized, as reported elsewhere, and averaged 113±3 mm Hg for normotensive and 124±6 mm Hg for hypertensive rats. Atrial pacing maintained heart rate at 200 beats/min.

Steady-state left ventricular pressure was recorded from isovolumetrically beating hearts during increments (0.02 ml) in balloon volume over the left ventricular end-diastolic pressure range of 0–25 mm Hg. For each heart, two sets of pressure-volume data were recorded. Reproducible (±10%) results were combined for analysis of the systolic and diastolic stress-strain relations. In five preparations (WKY-C14, two; SHR-C14, one; WKY-C26, one; SHR-C26, one) the results were not reproducible, and therefore, their functional data were not included in the analysis.

To normalize pressure-volume relations for hearts of different left ventricular weight and size, stress (σ, dynes/cm²), tangent elastic modulus (E, dynes/cm²), and strain (ε) for the midwall at the equator of the left ventricle were calculated by assuming spherical geometry and by considering the midwall equatorial region as representative of the remaining myocardium: σ=(V×P)/W×(1+[4(V+W)/[V¹/³+(V+W)¹/³]]); E=3[V×P/W−σ+[(σ/V)+(W×σ−V×P)/W(V+W)]/P×dP/dV]×[(V¹/³+(V+W)¹/³)/[V−²/³]²]; ε=ln (L/Lo);

where V is chamber volume (ml), L is midwall equatorial circumference (cm), Lo is circumference at end-diastolic wall stress of 0 dynes/cm², W is left ventricular wall volume (=0.943 ml/g×LV weight in grams), and P is end-diastolic or peak systolic pressure (dynes/cm²=7.5×10⁻⁴ mm Hg). We derived the slope c (dynes/cm²) describing the relation between peak-systolic wall stress and end-diastolic strain in the isovolumetrically beating heart. Myocardial diastolic stiffness was calculated with the stiffness constant (k, dimensionless), that is, the slope of the linear relation between tangent elastic modulus, ε, and end-diastolic wall stress, σ. The slope of the systolic stress-strain and the E−σ relations were obtained by regression line analysis.
Baseline coronary blood flow was measured in all hearts at a perfusion pressure of 100 mm Hg, heart rate of 200 beats/min, and a left ventricular volume that coincided with an end-diastolic pressure of 0 mm Hg. Thereafter, maximal coronary vasodilation was induced by infusing adenosine (800 μg/min). This dosage of adenosine abolishes the hyperemic response that accompanies a 10-second occlusion of coronary perfusate in each heart.\(^8\) Maximal coronary blood flow (ml/min) for the same coronary perfusion pressure, heart rate, and filling pressure as at baseline was measured and normalized to total ventricular weight (ml/min/g). Coronary vascular resistance was calculated with the ratio of coronary perfusion pressure and coronary flow, assuming 0 mm Hg downstream pressure. The total duration of the physiological study was 30 minutes or less.

After the coronary blood flow measurements were obtained during adenosine-mediated maximal vasodilation, the hearts were immediately perfusion fixed at 100 mm Hg with 2.5% buffered glutaraldehyde (pH 7.4) for 15 minutes. The atria and great vessels were then trimmed away, and the ventricles were separated and weighed.

**Morphology and Morphometry**

Coronal sections of the left ventricle, obtained from its equator, were prepared for light microscopy as previously reported.\(^4\) The collagen-specific stain, Sirius Red F3BA (Pfaltz & Bauer, Stamford, Conn.), was used on 5-μm thick, paraffin-embedded sections. One entire cross-section of the left ventricular myocardium was used for the morphometric analysis. The equator was selected as representative for the whole left ventricle. Our previous studies\(^24\) did not demonstrate a localized heterogeneity in the fibrous tissue response.

Collagen volume fraction was determined with an automatic image analyzer (Quantimet 520, Cambridge Lab., Inc., Cambridge, Mass.) and was calculated as the sum of all connective tissue areas of the coronal section, divided by the sum of all connective tissue and muscle areas in all fields of the section. Perivascular collagen, excluded from this measurement, was treated separately (vide infra). We previously showed that total collagen volume fraction (including perivascular collagen), as determined by this morphometric approach, is closely related to hydroxyproline concentration of the left ventricle.\(^24\)

The ratio of perivascular collagen area to vessel luminal area was also determined with the image analyzer. For each left ventricle, an average of 10 nonpapillary coronary arteries was found suitable (i.e., cross-sectional cut) for morphometric analysis. One average value for the perivascular collagen area ratio and medial wall thickness was calculated for each specimen. The fibrillar nature of collagen within the interstitial space and surrounding intramural coronary arteries was examined using direct and polarized light as previously reported.\(^25\)

Average medial thickness of intramyocardial coronary arteries, ranging in diameter from 15 to 150 μm, was calculated as \(\left[\frac{VA+MA}{\pi}\right]^{1/2} - \left(\frac{VA}{\pi}\right)^{1/2}\), where VA is vessel luminal area, and MA is medial area.

**Statistical Analysis**

The main purpose of the study was to compare mean values of histological parameters in the different experimental groups. Therefore, data are expressed as mean±SEM and were compared by the following sequential procedure: analysis of variance (F test) of the omnibus hypothesis; if the omnibus hypothesis could be rejected, post hoc pairwise group comparisons were undertaken with Bonferroni bounds by considering the following comparisons between the different experimental groups: SHR-C\(_{14}\) versus WKY-C\(_{14}\), SHR-C\(_{26}\) versus WKY-C\(_{26}\), SHR-L\(_{26}\) versus SHR-C\(_{26}\), SHR-L\(_{26}\) versus WKY-C\(_{26}\), and WKY-C\(_{26}\) versus WKY-L\(_{26}\). Data regarding left ventricular function, that is, the linear relations between tangent elastic modulus and end-diastolic wall stress and between peak-systolic wall stress and end-diastolic strain, were compared by multiple linear regression analysis. Regression lines are shown with 95% confidence limits. All reported \(p\) values were corrected for the number of comparisons, and the significance level was assumed at a \(p\) value less than 0.05.

**Results**

**Blood Pressure and Hypertrophy**

At the beginning of the study, systolic blood pressure in the different SHR and WKY groups was not significantly different within a strain. In comparison

### Table 1. Hemodynamics and Left Ventricular Hypertrophy

<table>
<thead>
<tr>
<th></th>
<th>SHR-C(_{14})</th>
<th>SHR-C(_{26})</th>
<th>SHR-L(_{26})</th>
<th>WKY-C(_{14})</th>
<th>WKY-C(_{26})</th>
<th>WKY-L(_{26})</th>
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<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>221±6(^*)</td>
<td>218±12(^*)</td>
<td>121±12(^*)</td>
<td>129±7</td>
<td>124±4</td>
<td>128±1</td>
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<tr>
<td></td>
<td>(n=14)</td>
<td>(n=11)</td>
<td>(n=9)</td>
<td>(n=13)</td>
<td>(n=9)</td>
<td>(n=3)</td>
</tr>
<tr>
<td>c×10(^{-4}) (dynes/cm(^2))</td>
<td>141.3±6.8</td>
<td>144.9±7.3</td>
<td>136.6±6.2</td>
<td>137.8±4.3</td>
<td>141.7±12.7</td>
<td>137.5±2.7</td>
</tr>
<tr>
<td>LV/RV</td>
<td>5.2±0.2(^*)</td>
<td>5.2±0.2*</td>
<td>3.7±0.1(^*)</td>
<td>3.9±0.2</td>
<td>3.7±0.2</td>
<td>3.6±0.1</td>
</tr>
<tr>
<td>LV/BW (mg/g)</td>
<td>3.3±0.1(^*)</td>
<td>3.2±0.1*</td>
<td>2.3±0.1(^*)</td>
<td>2.6±0.1</td>
<td>2.5±0.1</td>
<td>2.4±0.1</td>
</tr>
<tr>
<td>RV/BW (mg/g)</td>
<td>0.64±0.02</td>
<td>0.63±0.03</td>
<td>0.60±0.01</td>
<td>0.63±0.02</td>
<td>0.64±0.03</td>
<td>0.71±0.01</td>
</tr>
</tbody>
</table>

SHR, spontaneously hypertensive rats; WKY, Wistar-Kyoto rats; C, control; L, lisinopril treatment; subscripts refer to age of rats; SBP, systolic blood pressure; c, slope of the systolic stress-strain relation; LV/RV, ratio of left to right ventricular weight; LV/BW, left ventricular weight normalized to body weight; RV/BW, right ventricular weight normalized to body weight.

\(^*p<0.005\) SHR-C\(_{14}\) vs. WKY-C\(_{14}\); SHR-C\(_{26}\) vs. WKY-C\(_{26}\); SHR-L\(_{26}\) vs. SHR-C\(_{26}\).
to their age- and sex-matched genetic counterpart, SHR-C14 were hypertensive with a systolic blood pressure of 221±6 mm Hg (p<0.005) and had LVH (Table 1) when expressed as either a significantly increased ratio of left to right ventricular weight (5.2±0.2, p<0.005) or LV weight normalized to body weight (3.3±0.1 mg/g, p<0.005). Right ventricular weight normalized to body weight was no different between all groups. Although systolic blood pressure remained elevated at hypertensive levels in untreated SHR throughout the experimental 12-week-period, blood pressure decreased significantly to values seen in normotensive WKY controls in all SHR treated with lisinopril, and it remained at normotensive levels throughout the experiment.

At the end of the study, SHR-C26 had the same degree of hypertension and LVH as SHR-C14. In contrast, arterial pressure (121±12 mm Hg), the ratio of ventricular weights (3.7±0.1), and normalized LV to body weight (2.3±0.1 mg/g) showed no evidence of hypertension or LVH in SHR-L26 and these variables were not different from those of WKY-C26.

**Interstitial Collagen Volume Fraction**

The interstitial collagen volume fraction of the left ventricle (Figure 1) was significantly elevated in SHR-C14 compared with WKY-C14 (5.4±1.0% versus 3.3±0.6%, p<0.05), showing established interstitial fibrosis at the beginning of the study, and it was also significantly increased in SHR-C26 compared with WKY-C26 (7.0±1.3% versus 2.8±0.5%, p<0.025). After 12 weeks of oral administration of lisinopril, interstitial collagen volume fraction was normalized in SHR-L26 (3.2±0.3%) to values seen in WKY-C14 and WKY-C26; that is, no significant difference between SHR-L26 and WKY-C26 was found. Lisinopril treatment in WKY did not affect interstitial collagen volume fraction.

**Myocardial Stiffness and Systolic Function**

To compare hypertrophied and nonhypertrophied left ventricles in the various groups, pressure-volume data were normalized for mass and size and presented as the derived linear relation between tangent elastic modulus and end-diastolic wall stress (Figure 2). The regression line analysis of wall stress and tangent elastic modulus, of which the latter is the slope of the exponential relation between end-diastolic stress and strain, showed that SHR-C26 was significantly different from SHR-L26 and WKY-C26. No difference between lisinopril-treated SHR and the WKY control group was found. Myocardial diastolic stiffness, as measured by the stiffness constant k (Figure 3), which is the slope of the linear relation between tangent elastic modulus and end-diastolic wall stress, was significantly elevated in SHR-C14 compared with WKY-C14 (20.6±0.8 versus 15.5±0.9, p<0.05), whereas the slope c (Table 1) of the systolic stress-strain relation was unaffected (multiple regression analysis). After 12 weeks of lisinopril treatment, diastolic stiffness constant decreased significantly to 13.7±1.3 in SHR-L26 (p<0.025) and was not different from that of WKY-C26. The slope c of the systolic stress-strain relation in SHR-L26 tended to be reduced compared with that during pretreatment and in WKY-C26 but was not significantly different. In WKY, lisinopril treatment did not affect myocardial stiffness.

**Intramural Coronary Artery Remodeling**

Perivascular collagen area normalized to vascular luminal area was significantly elevated in SHR-C26.
compared with WKY-C26 (1.4±0.2 versus 0.6±0.1, p<0.05) and decreased after 12 weeks of lisinopril treatment to 0.4±0.1 (p<0.005), which was not different compared with that of WKY-C26 (Table 2).

Average medial wall thickness associated with maximal vasodilatation was significantly increased in SHR-C14 9.7±0.7 μm (p<0.05) and in SHR-C26 12.3±0.6 μm (p<0.005) compared with age-matched WKY (Figure 4). After 12 weeks of lisinopril treatment, it decreased significantly in SHR-L26 to 7.4±0.5 μm (p<0.005) and was not different from WKY-C26 (7.4±0.4 μm). No change in the thickness of the tunica media occurred during lisinopril treatment in WKY. The average luminal radius of all analyzed vessels in each group was no different from one another.

**Coronary Vasomotor Reactivity**

Minimal coronary vascular resistance (Table 2) was increased in SHR-C14 and SHR-C26 (7.1±0.8 and 8.3±0.6 mm Hg/ml/min/g, respectively, p<0.05) compared with age-matched WKY (4.6±0.5 and 4.6±0.4 mm Hg/ml/min/g, respectively). Accordingly, coronary vasodilator reserve, as defined by the mean coronary blood flow normalized to ventricular weight after adenosine (Figure 5), was diminished in SHR-C14 and SHR-C26 (14.5±1.4 and 12.3±0.9 ml/min/g, respectively, p<0.05) compared with age-matched WKY (22.1±2.2 and 21.8±2.2 ml/min/g, respectively). After 12 weeks of lisinopril treatment, coronary vasodilator reserve increased to 26.0±1.4 ml/min/g (p<0.005) in SHR-L26 parallel to a reduction (p<0.025) of minimal coronary vascular resistance to 3.9±0.2 mm Hg/ml/min/g and was not significantly different from that in WKY. Coronary blood flow in WKY-L26 remained unaffected.

**Discussion**

The longitudinal study conducted during the past 30 years in Framingham, Massachusetts, has convincingly demonstrated that systemic hypertension is the most important etiological factor associated with the appearance of symptomatic heart failure, and LVH is the major risk factor associated with its appearance. The risk of developing heart failure increases...
inhibition may relate to its influence on the remodeling of the myocardium after infarction.20

In this 12-week treatment trial in 14-week-old SHR having LVH with myocardial fibrosis and intramural coronary artery involvement, we addressed the “cardioprotective” effects of ACE inhibition. Our aim was to determine whether the abnormal remodeling of the extracellular space could be restored to normal. We further sought to determine whether the consequences of this remodeling (that is, abnormal myocardial stiffness and impaired coronary vascular reserve) would likewise be returned to normal.

Before we initiated the study, our primary concern was to estimate the appropriate duration of a regression trial with an ACE inhibitor in SHR. Previous studies demonstrated that a regression in LVH can be obtained after 6–11 weeks of drug treatment.30–32 Evidence has been presented to suggest that myocardial collagen synthesis can be decreased in SHR with an ACE inhibitor.33 Whether this would hold true for a regression in myocardial fibrosis was unclear. We chose a 12-week treatment period for three reasons: 1) myocardial collagen degradation was shown to be very slow, 1.01±0.23%/day in the left ventricle,34 2) in SHR treated with the ACE inhibitor captopril, myocardial collagen synthesis was shown to be reduced from 776±145 to 365±77 pg/mg protein for 3 hours,33 which corresponds to a reduction of 53%, and 3) untreated 14-week-old SHR in our colony had a 40% increase in interstitial collagen volume fraction compared with age- and sex-matched WKY (5.4±1.0% versus 3.3±0.6%). Assuming an unchanged daily rate of collagen degradation of 1% during treatment with an ACE inhibitor and an accompanying 50% reduction in collagen synthesis with lisinopril, 80 days are required to remove the 40% excess myocardial collagen.

Regression of Hypertrophy and Blood Pressure Control

ACE inhibitors, such as captopril,35,36 enalapril,37 and lisinopril30 reduce left ventricular mass when LVH is present in SHR, the rat with renovascular hypertension, or in the Dahl salt-sensitive rat. Our results confirm that a complete restoration in myocardial mass, expressed as either the ratio of left ventricular body to weight or the ratio of left to right ventricular weight, can be achieved with 12 weeks of ACE inhibition in SHR. We also found that oral administration of lisinopril, a non-sulfhydryl-containing ACE inhibitor, normalized arterial pressure in these animals. Whether arterial pressure would have remained normal with a discontinuation of lisinopril therapy is uncertain and would depend on whether this agent favorably influenced both the structural remodeling of systemic arteries and arterioles and the yet unknown stimulus to hypertension in SHR.

Regression of Interstitial Fibrosis and Abnormal Myocardial Stiffness

Myocyte growth is but one aspect of the hypertrophic remodeling of the myocardium. Nonmyocyte
cell growth, for example, cardiac fibroblast proliferation with enhanced collagen accumulation, is another. Previous studies demonstrated that various agents that oppose the adrenergic system, including α-methyldopa, clonidine, and propranolol when given alone or in combination, may induce a regression in myocardial mass in 12-week-old SHR with LVH.\textsuperscript{33,38} However, myocardial collagen concentration was found to rise with the regression in LVH and reduction in myocyte size. Hence, the regression in LVH mediated by these agents led to an even greater heterogeneity in myocardial structure. Whether the disproportionate increase in collagen concentration would adversely influence myocardial stiffness was not examined in the above studies. However, previous findings indicate strongly an interrelation between myocardial stiffness and fibrillar collagen.\textsuperscript{4–6,15} The interstitial fibrosis seen in SHR\textsuperscript{2} or the rat with aortic banding\textsuperscript{1} was shown to be responsible for abnormal cardiac muscle stiffness. By introducing hydralazine therapy at 4 weeks of age, it was possible to prevent LVH in SHR; however, the interstitial and perivascular fibrosis continued unabated, and at 36 weeks of age, myocardial stiffness was abnormal.\textsuperscript{39} Moreover, because the calculation of stress normalizes for differences in mass, alterations in myocardial stiffness are not related to changes in myocardial mass. In returning collagen volume fraction to normal levels with lisinopril in this study, we were able to restore diastolic myocardial stiffness to normal; this did not occur spontaneously in SHR-C\textsubscript{26}, and the administration of lisinopril to WKY controls did not alter diastolic stiffness or collagen volume fraction. Last, O’Brien and Moore\textsuperscript{40} showed that after collagenase digestion, the distensibility of the rabbit ventricle was increased and that this did not occur after trypsin or elastase digestion. Each of these findings also lends further support that in humans with LVH and systemic hypertension, the observed increase in collagen concentration is likely responsible for the presence of left ventricular diastolic dysfunction with symptomatic heart failure.\textsuperscript{41}

Although we were able to completely regress myocardial fibrosis, that is to restore interstitial and perivascular collagen to that of the level of genetic controls, the findings of other investigators have been inconsistent. Sen et al\textsuperscript{31} showed that myocardial hydroxyproline content decreases in SHR treated with oral administration of captopril and that this was associated with a reduction in collagen synthesis. However, less-favorable results were obtained with 6 weeks of oral administration of captopril in rats with renovascular hypertension, in which a rise in collagen concentration accompanied the regression in LVH.\textsuperscript{36} The explanation for these differences in response between genetic and acquired hypertension is unknown. Potential considerations include differences in the duration of therapy, in which a regression in myocyte size occurs more quickly with a reduction in blood pressure, whereas collagen degradation is a slower process, or include differences in drug dosage. In addition, trophic factors involved in promoting fibroblast growth and collagen synthesis may differ in genetic and acquired hypertension.

**Regression of Perivascular Fibrosis and Medial Thickening and Abnormal Coronary Vasodilator Reserve**

Enhanced collagen deposition is seen within the adventitia of intramyocardial coronary arteries in genetic hypertension and renovascular hypertension.\textsuperscript{2,6,42} In addition, vascular smooth muscle cell growth leads to medial thickening of these vessels. Such intramural coronary artery remodeling may compromise the vasomotor reactivity of intramural vessels to exogenously administered vasodilators, such as dipyridamole or adenosine. This abnormality, termed “impaired coronary vasodilator reserve,” is frequently observed in LVH with hypertension.\textsuperscript{43,44}

Herein, we found that 12 weeks of treatment with oral lisinopril could eliminate the perivascular fibrosis of intramural vessels leaving the normal amount of collagen in the adventitia of these vessels. We also found that lisinopril promoted a regression in medial thickening of these vessels to values found in WKY. The regression in perivascular fibrosis and medial thickening of intramural vessels was associated with a restoration in coronary vasodilator reserve to adenosine that resembled values seen in WKY. A spontaneous resolution of the abnormality in vascular reserve was not seen at 26 weeks of age in untreated SHR, whereas 12 weeks of lisinopril treatment did not alter vasomotor reactivity to adenosine in WKY. Our findings further support the observations of Anderson et al,\textsuperscript{9} who recently reported that 12 weeks of oral administration of hydralazine will regress medial thickness in 32-week-old SHR and will improve coronary reserve to adenosine and of Canby and Tomanek,\textsuperscript{45} who reported a return in coronary vascular resistance in 24-week-old SHR after 12 weeks of oral administration of captopril. In unrelated but relevant studies, Limas et al\textsuperscript{52} and Michel et al\textsuperscript{46} each reported that captopril and perindopril, respectively, would regress the structural remodeling of afferent arterioles within the kidney of rats with renovascular or genetic hypertension.

**Clinical Implications**

It is widely recognized that the survival of patients with advanced, symptomatic heart failure is severely compromised despite treatment with diuretics, digoxin, and vasodilators. These agents, however, are prescribed to attenuate the consequences of heart failure and, therefore, are palliative. More remedial therapy is needed that restores the structural remodeling and attendant functional abnormalities of the hypertrophied myocardium to normal. The nature of the desired cardio reparative process will, no doubt, vary according to the etiological basis of remodeling and hypertrophy. In this connection, the search for pathogenetic mechanisms must continue, including
the identification of trophic factors that mediate myocyte and nonmyocyte growth.

The results of this study indicate that the ACE inhibitor lisinopril may represent such remedial therapy. Lisinopril in young adult SHR with LVH was associated with a decrease in interstitial fibrosis as well as in the medial thickening and perivascular fibrosis of intramyocardial coronary arteries that appeared with the hypertrophic process. Furthermore, and presumably as a result of these cardio-protective effects, abnormal myocardial stiffness and impaired coronary vascular reserve were returned to normal.

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