Reduction in Myocardial Collagen Cross-Linking Parallels Left Ventricular Dilatation in Rat Models of Systolic Chamber Dysfunction

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Background—The transition from compensated left ventricular hypertrophy (LVH) to heart failure is associated with alterations in the myocardial interstitium. We hypothesized that LV dilatation is associated with modifications in collagen cross-linking.

Methods and Results—We studied 2 rat models of LV dilatation: (1) pressure-overload hypertrophy with heart failure (POH-F) induced by suprarenal abdominal aortic banding and (2) LVH induced by 7 months of isoproterenol (ISO, 0.04 mg · kg⁻¹ · d⁻¹) administration. In POH-F rats and in rats receiving ISO, LV dilatation and a reduced systolic chamber performance were noted. Myocardial hydroxyproline concentrations ([HPRO]) were increased in the POH-F rats, whereas in rats receiving ISO, [HPRO] was decreased. In POH-F rats, the ratio of myocardial collagen type I to type III was increased, but in rats receiving ISO, myocardial collagen I/III was unchanged. In contrast to the diverse changes in myocardial collagen concentrations and phenotypes observed in the 2 models of LV dilatation, the ratio of myocardial insoluble to soluble (relationship between cross-linked and non–cross-linked) collagen was decreased in both the POH-F and ISO groups. Moreover, administration of captopril (0.22 mmol · kg⁻¹ · d⁻¹), which inhibited the ISO-induced reduction in myocardial insoluble/soluble collagen but not the reduction in [HPRO], prevented the ISO-induced alterations in LV dimensions and performance.

Conclusions—Because decreases in the ratio of myocardial insoluble to soluble collagen parallel LV dilatation in rats, reductions in myocardial collagen cross-linking may be an important mechanism contributing to LV dilatation in heart disease. (Circulation. 2001;103:155-160.)

Key Words: collagen ■ systole ■ diastole ■ mechanics ■ remodeling

Left ventricular (LV) dilatation (remodeling) accompanies a reduction in systolic chamber function in a number of cardiac conditions.¹⁻³ The fundamental mechanisms that contribute to chamber remodeling remain unclear. Growing evidence suggests that LV myocardial collagen matrix disorganization and changes in the fibrillar collagen network contribute to the progression of LV chamber dilatation and dysfunction.⁴⁻⁵ Matrix disorganization associated with LV dilatation has in turn been attributed to an enhanced collagen degradation through changes in matrix metalloproteinases (MMPs) or their tissue inhibitors.⁶⁻⁻⁸ Increases in the activity of MMPs⁵ may reduce the amount of collagen available for fibril formation.⁴ However, despite increased activities of MMPs,⁶⁻⁸ LV dilatation is more frequently associated with normal or increased myocardial collagen concentrations,⁵,⁹,¹⁰ effects ascribed to an enhanced collagen expression. The question of how an augmented matrix degradation but a concomitant increase in myocardial collagen available for fibril repair leads to matrix disorganization has not been adequately addressed. It is feasible that qualitative changes in newly synthesized myocardial collagen prevent efficient repair of dysfunctional fibrils, an effect that contributes to LV dilatation. Indeed, an excess proportion of thin collagen fibrils in LV dilatation may represent either more type III collagen⁵ or a reduction in collagen cross-linking.¹⁰,¹¹

Because all models of LV systolic dysfunction exhibit chamber remodeling, it is conceivable that among the expected diverse alterations in the composition of the myocardial matrix, a common qualitative collagen characteristic would be apparent. To test this supposition, myocardial collagen characteristics were compared in 2 rat models of LV hypertrophy (LVH) that progress to LV dilatation: pressure-overload hypertrophy (POH)¹ and isoproterenol (ISO)-induced LVH.³ Moreover, because ACE inhibitors produce

Received May 11, 2000; revision received July 18, 2000; accepted July 20, 2000.
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beneficial effects in various forms of LV dilatation, we reasoned that the same common qualitative collagen characteristic would be a target of captopril (CAP) therapy in the rat model with reduced collagen concentrations (ISO model).

**Methods**

**Experimental Groups**

The experiments were approved by the Institutional Animal Care and Use Committee of the University of Massachusetts Medical School and the Animal Ethics Committee of the University of the Witwatersrand (clearance No. 96/48/3).

**ISO-Induced LVH**

Initially, a dose-titration study was performed to establish the highest dose of ISO that could be administered for prolonged periods without producing sudden cardiac death. Subsequently, 50 male 4-month-old Sprague-Dawley (SD, outsource from OLAC, UK) rats weighing 250 to 300 g were randomly assigned to 5 groups. ISO (Imuprel, Adcock Ingram) was administered at a dosage of 0.04 mg·kg⁻¹·min⁻¹ for 7 months. To determine the effect of CAP on ISO-mediated cardiac changes, rats from 1 of the ISO-treated and 1 of the vehicle-treated groups also received CAP (Fluka BioChemika) at 0.22 mmol·kg⁻¹·min⁻¹ in the drinking water for 7 months. Rats in the fifth group, which received no therapy, were euthanized after 1 month of administration of the vehicle of ISO to evaluate the effects of age (5 versus 11 months) on myocardial collagen concentrations.

**Pressure-Overload Hypertrophy**

Harlan Sprague Dawley (Hsd:SD, Charles River, Wilmington, Mass) rats weighing 150 to 200 g underwent either aortic banding or sham surgery as previously described. All surviving rats were studied 20 weeks after surgery. Because the purpose of the present study was to determine whether changes in collagen cross-linking parallel LV dilatation in POH, we grouped POH rats according to the presence or absence of pulmonary congestion. Of the 57 banded rats that survived 20 weeks, 25 rats had a lung weight/body weight ratio >2 SD above the mean for the control group. These rats were classified as having decompensated POH with evidence of heart failure (POH-F). The remaining banded rats (n=32) were called POH without failure (POH-NF).

**Echocardiographic Studies**

Echocardiographic was performed as previously described on all ISO-treated rats and their controls at the end of the experimental period (72 hours after the last dose of ISO) and in POH rats and their controls 20 weeks after surgery. Fractional endocardial shortening was calculated from end-diastolic diameter (EDD)−end-systolic diameter (ESD)/(EDD×100)

**Isolated Perfused Heart Preparation**

Rats were anesthetized and hearts were excised and immediately rinsed in an ice-cold physiological saline solution as previously described. Hearts were perfused retrogradely at a constant flow with 37°C physiological saline solution. The coronary flow rate was calculated from [end-diastolic diameter (EDD)−end-systolic diameter (ESD)]/(EDD×100).

LV developed pressure and LV diastolic pressure were determined by use of a water-filled balloon-tipped cannula coupled to either a Gould P50 (ISO study) or a Statham P23 (POH study) pressure transducer inserted via the left atrium into the LV cavity. A thin-walled latex balloon with a zero pressure filling volume beyond maximum LV lumen capacities was selected for this study to avoid the stiffness of the balloon wall contributing to LV pressure at higher filling volumes. The volume of the balloon wall was assessed with a water-displacement technique, and the same balloon was used throughout each of the studies. LV and coronary perfusion pressures were recorded with either a Hellige (ISO study) or a Gould model RS 3400 (POH study) polygraph. A micromanipulator was used to gradually increase LV volumes to values that resulted in no further change in LV developed pressure. LV pressures were determined at as many multiple small increments in volume as were practically possible to improve the accuracy of curve fitting during later analysis.

LV systolic chamber performance was determined from the slopes of LV developed pressure-volume (P-V) relations (systolic elastance, E). LV diastolic remodeling was assessed from the relationship between LV diastolic pressure and LV volume. Statistical comparisons of LV diastolic P-V relations were made from the slopes of the linearized relations (LV chamber k) and the volume intercepts (V₀) of these relations (see Statistical Analysis section).

**Myocardial Collagen**

Samples of LV tissue from all rats were weighed and stored between −70°C for tissue analysis. Myocardial hydroxyproline concentration (HPRO) was determined by the method of Stegemann and Stalder after acid (HCl) hydrolysis. Myocardial collagen was extracted and digested with cyanogen bromide (CNBr) according to the procedure described by Mukherjee and Sen. Using a portion of the CNBr-digested collagen sample, polyacrylamide gel electrophoresis was performed on vertical gels with stacking and separating gel concentrations of 3% and 12.5%, respectively, as previously described. The type I/III collagen ratio was determined after gel scanning. The amount of type I collagen in the myocardium was determined from the product of (area scanned on the gel corresponding to type I collagen/area for type I and type III) and myocardial [HPRO]. The type III collagen concentration was determined similarly. The remaining portion of the CNBr-digested collagen sample was subjected to acid hydrolysis and [HPRO] determination. The amounts of non−cross−linked (soluble) and cross−linked (insoluble) collagen in the myocardium were determined from the product of the percentage of collagen soluble to CNBr digestion and the total myocardial collagen concentration and the difference between the total collagen concentration and soluble collagen concentration, respectively. The relationship between insoluble and soluble collagen was used as an index of the degree of collagen cross-linking.

**Histology**

Before cardiac tissues obtained from rats receiving ISO and their controls were stored for biochemical assessment, a longitudinal slice of the LV from the apex to the base through both the anterior and posterior LV walls was stored in formalin for subsequent histology. LV tissue was processed routinely for light microscopy, and 50-μm-thick sections of the long-axis circumference were cut through the full thickness of the LV wall. Ten slices were obtained at 1-mm intervals and stained with Masson’s trichrome from which hematoyxin was omitted. A pathological grade (modified from Teerlink et al) was assigned to each slice as follows: 0, no damage; 1, patchy fibrosis in 1 to 5 areas (<20% of the field). In rats receiving ISO there was no evidence of either patchy fibrosis in >20% of the field, diffuse, contiguous subendocardial, or transmural fibrosis. The grades for individual slices were summed and then divided by the number of slices to produce a single average pathological score. Scoring was done on coded samples by an independent observer blinded to the identity of the rat from which the sample was obtained.
Analysis

Regression analysis was used to determine the lines of best fit for the cardiac function relations. The systolic LV P-V relations were found to best fit a linear function. The LV diastolic P-V relations were found to best fit the exponential function: LV diastolic pressure = b \cdot e^{-t \cdot LV \ diastolic \ volume}, which was linearized: ln LV diastolic pressure = ln b + mL(LV diastolic volume) for statistical analysis. Differences in LV geometry, hemodynamics, pathological score, and myocardial collagen biochemical analysis between POH-F, POH-NF, and control groups and between ISO, Control, ISO, and ISO+CAP, and CAP groups were assessed by 1-factor ANOVA followed by Tukey post hoc tests. All values in the text are represented as mean ± SEM.

Results

Body, Heart, and Lung Weights

Rats with POH-F and POH-NF had increased LV weights but similar body weights compared with sham-operated control rats (Table 1). However, compared with POH-NF and control rats, rats with POH-F exhibited marked pulmonary congestion (as indicated by the greater lung weights) and right ventricular hypertrophy (Table 1). Chronic ISO administration produced an increase in LV and right ventricular weight, but body weights were not different (Table 1). CAP treatment of a group of rats receiving ISO prevented the development of cardiac hypertrophy (Table 1).

LV Systolic Chamber Performance

Aortic banding produced a decrease in fractional endocardial shortening (Table 2), a right shift in the LV systolic P-V relation (Figure 1), and a decrease in the slope of this relation (LV E, Table 2) when there was evidence of pulmonary congestion (POH-F) but not in the POH-NF group. Chronic ISO administration produced an effect on indexes of LV systolic chamber function similar to the changes noted in POH-F rats (Table 2, Figure 1). CAP therapy of a group of rats receiving ISO prevented the ISO-mediated decrease in endocardial shortening (Table 2), the right shift in the systolic P-V relation (Figure 1), and the decrease in the slope of this relation (LV E, Table 2). Administration of CAP to control rats failed to influence systolic chamber function (LV E, 735 ± 40 mm Hg/mL). Similar coronary flow rates were obtained in POH-NF and POH-F compared with control rats (coronary flow rate in mL \cdot \min^{-1} \cdot g^{-1}: POH-F, 12.6 ± 1.0; POH-NF, 12.8 ± 0.9; control, 12.2 ± 1.7).

LV Remodeling

In POH-F but not in POH-NF rats, LV end-diastolic and end-systolic internal dimensions were increased (Table 2), and a marked right shift (Figure 2), decreased slope (Table 2), and increase in volume intercept (Table 2) of LV diastolic P-V relations occurred. ISO produced an effect on indexes of LV remodeling similar to the changes noted in POH-F rats (Table 2, Figure 2). CAP prevented the increase in LV internal dimensions (Table 2) and the right shift, decreased slope, and increased volume intercept of the diastolic P-V relation (Figure 2, Table 2) produced by ISO.

### Table 1. Body, Heart, and Lung Weights in Rats With POH and in Rats Receiving ISO

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>POH-NF</th>
<th>POH-F</th>
<th>ISO</th>
<th>ISO+CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>455 ± 10</td>
<td>444 ± 7</td>
<td>421 ± 10</td>
<td>595 ± 15</td>
<td>583 ± 10</td>
</tr>
<tr>
<td>LV wet weight, g</td>
<td>1.19 ± 0.04</td>
<td>1.69 ± 0.03*</td>
<td>1.79 ± 0.04*</td>
<td>1.10 ± 0.03</td>
<td>1.49 ± 0.04*</td>
</tr>
<tr>
<td>LV dry weight, g</td>
<td>0.24 ± 0.01</td>
<td>0.34 ± 0.01*</td>
<td>0.36 ± 0.01*</td>
<td>0.20 ± 0.01</td>
<td>0.26 ± 0.01</td>
</tr>
<tr>
<td>RV weight, g</td>
<td>0.26 ± 0.01</td>
<td>0.29 ± 0.01</td>
<td>0.39 ± 0.03†</td>
<td>0.41 ± 0.01</td>
<td>0.48 ± 0.02*</td>
</tr>
<tr>
<td>Lung weight, g</td>
<td>1.99 ± 0.07</td>
<td>2.0 ± 0.05</td>
<td>4.18 ± 0.3†</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

RV indicates right ventricle; ND, not done.

*P < 0.01 vs the control or control and ISO+CAP groups; †P < 0.01 vs control and POH-NF groups.

### Table 2. LV Performance and Dimensions in Rats With POH and in Rats Receiving ISO

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>POH-NF</th>
<th>POH-F</th>
<th>ISO</th>
<th>ISO+CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocardial shortening, %</td>
<td>39 ± 2 (n=8)</td>
<td>44 ± 3 (n=10)</td>
<td>30 ± 0.5 (n=8)*</td>
<td>37 ± 3 (n=10)</td>
<td>28 ± 2 (n=11)*</td>
</tr>
<tr>
<td>End systolic diameter, mm</td>
<td>5.42 ± 0.27 (n=8)</td>
<td>5.16 ± 0.47 (n=10)</td>
<td>7.84 ± 0.39 (n=8)*</td>
<td>4.66 ± 0.26 (n=10)</td>
<td>5.54 ± 0.16 (n=11)*</td>
</tr>
<tr>
<td>ED diameter, mm</td>
<td>8.68 ± 0.29 (n=8)</td>
<td>8.77 ± 0.36 (n=10)</td>
<td>11.4 ± 0.29 (n=8)*</td>
<td>8.02 ± 0.15 (n=10)</td>
<td>8.86 ± 0.09 (n=11)*</td>
</tr>
<tr>
<td>ED posterior wall thickness, mm</td>
<td>1.56 ± 0.12 (n=8)</td>
<td>1.99 ± 0.12 (n=10)†</td>
<td>1.91 ± 0.07 (n=8)†</td>
<td>1.73 ± 0.1 (n=10)</td>
<td>1.84 ± 0.1 (n=11)</td>
</tr>
<tr>
<td>LV E, mm Hg/mL</td>
<td>598 ± 48 (n=12)</td>
<td>493 ± 41 (n=26)</td>
<td>291 ± 9 (n=20)†</td>
<td>722 ± 45 (n=10)</td>
<td>427 ± 10 (n=11)*</td>
</tr>
<tr>
<td>LV chamber k, mm Hg/mL</td>
<td>18.1 ± 1.3 (n=12)</td>
<td>18.1 ± 1.4 (n=26)</td>
<td>13.3 ± 0.95 (n=20)†</td>
<td>17.5 ± 1.1 (n=10)</td>
<td>10.5 ± 0.73 (n=11)</td>
</tr>
<tr>
<td>LV V0,m L</td>
<td>0.23 ± 0.01 (n=12)</td>
<td>0.25 ± 0.01 (n=26)</td>
<td>0.34 ± 0.02 (n=20)*</td>
<td>0.20 ± 0.01 (n=10)</td>
<td>0.27 ± 0.02 (n=11)*</td>
</tr>
</tbody>
</table>

ED indicates end diastole; E, systolic chamber elastance; k, diastolic stiffness; and LV V0,m, LV volume intercept of the LV diastolic P-V relation. Sample numbers are in parentheses.

*P < 0.01 vs the other 2 groups; †P < 0.01 vs the control group.
Myocardial Collagen and Fibrosis

The POH-F group had an increased myocardial [HPRO] (Figure 3), and rats receiving ISO had a markedly decreased myocardial [HPRO], compared with their respective control groups (Figure 4). CAP therapy failed to influence the ISO-induced decrease in [HPRO] (Figure 4). Administration of CAP to control rats did not modify myocardial [HPRO] ([HPRO] in mg/mg LV dry wt, 6.26 ± 0.35). The greater [HPRO] values in the control rats used for the ISO study (Figure 4) compared with those used for the POH study (Figure 3) may reflect a change in [HPRO] related to both the age and the strain of the rat (SD for the ISO study and Hsd:SD for the POH study). Control SD rats euthanized at 5 months of age had decreased [HPRO] compared with control SD rats 6 months older ([HPRO] in 5-month-old SD rats in mg/mg LV dry wt, 3.14 ± 0.15, P < 0.01 versus [HPRO] in 11-month-old SD rats). In a separate study, we were able to show that at an equivalent age of 11 months, myocardial [HPRO] varies according to the strain of rat studied ([HPRO] in μg/mg LV dry wt: Sprague-Dawley, 6.39 ± 0.28; Long-Evans, 4.19 ± 0.22; Wistar-Kyoto, 3.17 ± 0.09; P < 0.01 between all 3 rat strains).

Seven months of ISO administration resulted in minor and insignificant histological evidence of discrete (patchy) myocardial fibrosis (pathological score: Control, 0.20 ± 0.13; ISO, 0.55 ± 0.21; not significantly different from controls). Six rats receiving ISO had patchy fibrosis in <20% of the field, in contrast to evidence of patchy fibrosis in <20% of the field in 2 control rats. Three rats receiving both CAP and ISO had evidence of patchy fibrosis (pathological score, 0.27 ± 0.14).

The POH-F group of rats exhibited a marked increase in type I collagen content but no change in type III collagen (Table 3), resulting in an increase in the ratio of type I/III collagen (Figure 3). However, ISO administration produced no changes in collagen phenotypic ratios (Figure 4), because both type I and type III myocardial collagen concentrations were decreased to a similar extent (Table 3). CAP failed to modify type I/III collagen ratio in either the ISO (Figure 4) or the control (I/III for control CAP, 3.5 ± 0.26) group.

In contrast to the lack of consistent change in myocardial [HPRO] or collagen phenotypes in rats receiving ISO compared with POH-F rats, both the ISO and the POH-F groups had a decreased collagen cross-linking, as evidenced by a reduction in insoluble/soluble collagen (Figures 3 and 4). Furthermore, in rats receiving ISO, the decreased collagen cross-linking was prevented by CAP administration (Figure 4).

Discussion

Our results show that abnormalities of myocardial collagen cross-linking but not other quantitative or qualitative collagen features parallel chamber dilatation in 2 rat models of LV systolic dysfunction. This conclusion is supported by the findings that (1) alterations in collagen cross-linking, but not phenotypic ratios, parallel LV dilatation irrespective of changes in collagen content in both POH-F and ISO-induced LV systolic dysfunction and (2) CAP-mediated prevention of LV dilatation in a rat model with a reduced myocardial collagen content is associated with an attenuation of the
decrease in collagen cross-linking but not with an effect on collagen concentrations.

**Collagen Concentrations and Phenotypic Ratios**

Myocardial collagen concentrations changed in opposite directions in the 2 models of LV systolic dysfunction examined in this study. Collagen concentrations increased in the POH-F group, whereas in the ISO group, myocardial collagen content decreased. Our results demonstrating increased myocardial collagen concentrations in POH are consistent with previous reports. However, a β-adrenoceptor agonist–induced decrease in myocardial HPRO concentrations is in apparent contrast to previous studies on interstitial effects of β-adrenoceptor agonists. Our data are likely to differ from those of authors reporting on increases in myocardial collagen concentrations after administration of ISO, because we used far lower doses of ISO.

In the POH-F group, the ratio of collagen type I/III was increased, as previously reported, whereas ISO administration produced no effect. Hence, it is unlikely that myocardial collagen phenotypic ratios contribute to LV dilatation and dysfunction in rodent models.

**Collagen Cross-Linking Versus Content**

Our results showing a decrease in myocardial collagen cross-linking associated with detrimental cardiac chamber remodeling and subsequent systolic dysfunction in 2 animal models of LV dilatation are supported by similar findings in tachycardia-induced heart failure and idiopathic dilated cardiomyopathy. Gunja-Smith and colleagues demonstrated a marked reduction in the concentration of mature collagen cross-linked collagen despite increased myocardial collagen concentrations in patients with idiopathic dilated cardiomyopathy. Similarly, Spinale and coworkers showed a reduction in collagen cross-linking in tachycardia-induced heart failure, although myocardial collagen concentrations were decreased. The results obtained in idiopathic dilated cardiomyopathy, tachycardia-induced heart failure, POH (this study), and ISO-induced LV dysfunction (this study), when taken together, suggest that alterations in myocardial collagen cross-linking may be responsible for the effects of matrix remodeling (loss of structural integrity) and LV dilatation.

The relationship between myocardial collagen concentrations and changes in LV function in POH is well established. However, no mechanism(s) by which enhanced myocardial collagen concentrations (which should improve myocyte support) in POH could lead to LV dilatation has been proposed. The results obtained in the present study suggest 1 possible mechanism. An enhanced collagen synthesis may lead to an altered relationship between cross-linked and non–cross-linked collagen in favor of a reduction in

**TABLE 3. Myocardial Collagen Characteristics in Rats With POH and in Rats Receiving ISO**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=18)</th>
<th>POH-NF (n=32)</th>
<th>POH-F (n=25)</th>
<th>Control (n=10)</th>
<th>ISO (n=11)</th>
<th>ISO + CAP (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I collagen content, μg/mg LV dry wt</td>
<td>2.44±0.17</td>
<td>2.70±0.11</td>
<td>3.57±0.20*</td>
<td>4.92±0.26</td>
<td>4.04±0.23†</td>
<td>3.78±0.38†</td>
</tr>
<tr>
<td>Type III collagen content, μg/mg LV dry wt</td>
<td>1.3±0.11</td>
<td>1.44±0.08</td>
<td>1.48±0.10</td>
<td>1.47±0.10</td>
<td>1.17±0.06†</td>
<td>0.98±0.07†</td>
</tr>
<tr>
<td>Soluble collagen, μg/mg LV dry wt</td>
<td>0.88±0.10</td>
<td>0.96±0.07</td>
<td>1.50±0.09*</td>
<td>1.75±0.12</td>
<td>2.29±0.19*</td>
<td>1.36±0.2</td>
</tr>
<tr>
<td>Insoluble collagen, μg/mg LV dry wt</td>
<td>2.86±0.29</td>
<td>3.16±0.20</td>
<td>3.48±0.32</td>
<td>4.64±0.23</td>
<td>2.92±0.38*</td>
<td>3.42±0.33</td>
</tr>
</tbody>
</table>

*P<0.01 vs the other 2 groups; †P<0.01 vs the control group.
cross-linked collagen. This, in turn, may impair extracellular matrix integrity.\textsuperscript{21,22} The structural support provided by the fibrillar collagen matrix is an important determinant of myocyte shape and alignment and the transduction of myocyte shortening into overall myocardial ejection.\textsuperscript{23} Hence, a loss of collagen support due to increased degradation of mature collagen with replacement by newly synthesized collagen with decreased cross-linking may contribute directly to LV dilatation and systolic dysfunction.

The present study demonstrates that CAP prevented the decrease in collagen cross-linking as well as the LV remodeling effect induced by administration of ISO. Previous studies in various models of heart failure have reported beneficial effects of ACE inhibition on myocardial collagen structure and composition.\textsuperscript{24,25} Thus, it is possible that the maintenance of collagen cross-linking by CAP in rats receiving ISO would conserve the structural integrity of the myocardial matrix, thereby preventing LV dilatation and dysfunction.\textsuperscript{21,22}

No mechanism(s) that explains the decrease in myocardial collagen cross-linking in either idiopathic dilated cardiomyopathy,\textsuperscript{10} tachycardia-induced heart failure,\textsuperscript{11} POH-F (this study), or ISO-induced ventricular remodeling (this study) has been elucidated. One possibility is that the activity of lysyl oxidase may be decreased, which would result in a reduction in collagen cross-linking. Alternatively, an increased turnover of collagen could reduce the time available for newly synthesized collagen to form stable cross-links and hence structurally adequate fibrils. An increased collagen turnover could result from the enhanced activity of MMPs reported in idiopathic dilated cardiomyopathy,\textsuperscript{16} tachycardia-induced heart failure,\textsuperscript{7,11} and POH.\textsuperscript{8} Indeed, elevations in serum markers of collagen turnover have been reported in patients with idiopathic dilated cardiomyopathy.\textsuperscript{26}

In conclusion, we have shown that irrespective of changes in myocardial collagen concentrations, a decrease in collagen cross-linking parallels LV dilatation in 2 rat models of LV dysfunction. These results suggest that a decrease in myocardial cross-linked collagen relative to non–cross-linked collagen contributes to matrix disorganization and LV dilatation.

Acknowledgments

This research was supported by the Medical Research Council of South Africa; the University Research Council of the University of the Witwatersrand, South Africa; the 1997 Young Researchers’ and 1998 Vice-Chancellor’s Research Award of the University of the Witwatersrand conferred on Dr Norton; and the Scientific Council of the University of Massachusetts. We also acknowledge the excellent technical support of R. McGinn and E. Somya.

References


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Circulation. 2001;103:155-160
doi: 10.1161/01.CIR.103.1.155

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Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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