Remodeling After Myocardial Infarction in Humans Is Not Associated With Interstitial Fibrosis of Noninfarcted Myocardium

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Objectives. This study was specifically designed to evaluate whether noninfarcted hypertrophic myocardium in patients with end-stage heart failure after myocardial infarction (MI) is associated with an increase in interstitial fibrous tissue.

Background. Postinfarction remodeling consists of complex alterations that involve both infarcted and noninfarcted myocardium. The question arises whether ventricular dysfunction is due to physical events, such as inadequate myocardial hypertrophy to compensate for increased tangential wall stress, or is caused by the development of progressive interstitial fibrosis in noninfarcted myocardium.

Methods. Fifteen hearts were obtained as cardiac explants (n = 13) or at autopsy (n = 2) from patients with end-stage coronary artery disease. Sixteen normal hearts served as reference hearts. Samples were taken from the left ventricular (LV) wall that contained the infarcted area, the border area and noninfarcted myocardium remote from scar areas. Collagen was quantified biochemically and microdensitophotometrically. Collagen type I and III ratios were analyzed by using the cyanogen bromide method and immunohistochemical staining, followed by microdensitophotometric quantification.

Results. In noninfarcted myocardium remote from the scar areas, total collagen levels and collagen type I/III ratios did not differ statistically from those in reference hearts. These observations contrasted with high total collagen content and high collagen type I/III ratios in scar and border areas.

Conclusions. Remodeling of LV myocardium after MI in patients with end-stage heart failure is not necessarily associated with interstitial fibrosis in noninfarcted hypertrophic myocardium remote from scar areas. This finding raises questions regarding therapeutic interventions designed to prevent or retard the development of interstitial fibrosis.

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Myocardial infarction (MI) impairs ventricular pump function because of loss of myocardial cells. In the immediate postinfarction state, systolic dysfunction leads to an increase in ventricular volume, both end-systolic and end-diastolic, in association with chamber dilation, which basically acts as a compensatory mechanism to increase ventricular stroke volume (1). At the structural level, volume load hypertrophy of the remaining viable and noninfarcted myocardium compensates for the loss of muscle and helps to restore ventricular function (2). In some patients, however, the infarct may show thinning and disproportionate lengthening, causing regional ventricular dilation, a phenomenon known as "infarct expansion" (3,4). This occurs early, usually within hours after the onset of infarction, only in patients with transmural infarction and predominantly in those with a large anterior infarction (5,6). Adaptive hypertrophy of the noninfarcted myocardium will readily occur, but it appears inadequate to fully compensate for the increased volume load and related elevation in diastolic wall stress, thus causing structural chamber dilation (7). The complex alterations in ventricular architecture that take place, which involve both infarcted and noninfarcted myocardium, are collectively named "ventricular remodeling."

Clinical studies (5,6,8–10) have shown unequivocally that early infarct expansion and ventricular chamber dilation are indicative for progressive ventricular enlargement and eventual heart failure. The question arises why progressive deterioration occurs under these circumstances. Some investigators (1,11) have suggested that chamber dilation with an increase in diastolic and systolic wall stresses would stimulate further ventricular enlargement and, hence, a vicious cycle leading to heart failure. Other investigators have emphasized that an increase in interstitial collagen in the noninfarcted hypertrophic myocardium plays a role. This concept is based largely on experimental studies in animals (see Weber et al. [12] for review) and a few studies in humans (13–16). According to these investigators, interstitial myocardial fibrosis develops throughout the noninfarcted myocardium, thus producing progressive myocardial stiffening with further impairment of systolic and diastolic ventricular function. At present, the concept of interstitial fibrosis as an intrinsic component of remodeling of noninfarcted myocardium seems widely accepted (12,16,17). Indeed, current experimental studies (12,17–19) are directed

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
LV = left ventricle; left ventricular
MI = myocardial infarction

toward the regulation of ventricular loading conditions to prevent development of interstitial fibrosis.

In view of the clinical importance of the concept of remodeling, in this study we quantified not only total collagen content, but also the ratio between types I and III collagen, with particular emphasis on the noninfarcted myocardium, in explanted and autopsy hearts of patients with chronic heart failure due to ischemic heart disease.

Methods

Heart specimens. The hearts studied were obtained from 15 patients (3 women, 12 men) with end-stage MI. Severe, long-standing (>12 months) and progressive heart failure had developed in all patients. All were in New York Heart Association functional class IV; all were treated with a similar regimen of diuretic drugs, inotropic drugs and angiotensin-converting enzyme (ACE) inhibitors; and all were selected for heart transplantation. Blood pressure had been elevated in some patients, but none had been treated specifically for hypertension. The hearts were sampled as cardiac explants (n = 13) or were obtained at autopsy (n = 2). The autopsy hearts became available within 10 h after death. The patients ranged in age from 33 to 70 years (mean 51). Hearts from 16 age-matched adult patients (8 women and 8 men, mean age 52 years) who died of noncardiovascular-related disease served as a reference group.

The cardiac explants were obtained from three centers: the Academic Hospital in Utrecht, The Netherlands (n = 8); Harefield Hospital, Middlesex, England, United Kingdom (n = 3) and St. George's Hospital, London, England, United Kingdom (n = 2). The five cardiac explants from the United Kingdom were processed according to protocol as follows. A cross-section was made of the left ventricle (LV), perpendicular to the ventricular long axis, at the level of the papillary muscles; in the unfixed state a transmural block from the left lateral wall was snap-frozen in isopentane cooled in liquid nitrogen. An adjacent block was fixed in 4% buffered formalin.

The eight cardiac explants from The Netherlands were available intact. Examination of the coronary arteries revealed extensive three-vessel obstructive atherosclerotic disease in each. The LV myocardium, in particular, showed extensive replacement of viable myocardium by scar tissue. The latter presented in part as regional transmural and often bandlike fibrous scars and in part as patchy areas of replacement fibrosis. Each heart showed an estimated infarct size of ~40% to 60% of the initial LV myocardium. The hearts were further processed according to protocol as follows. A cross section of
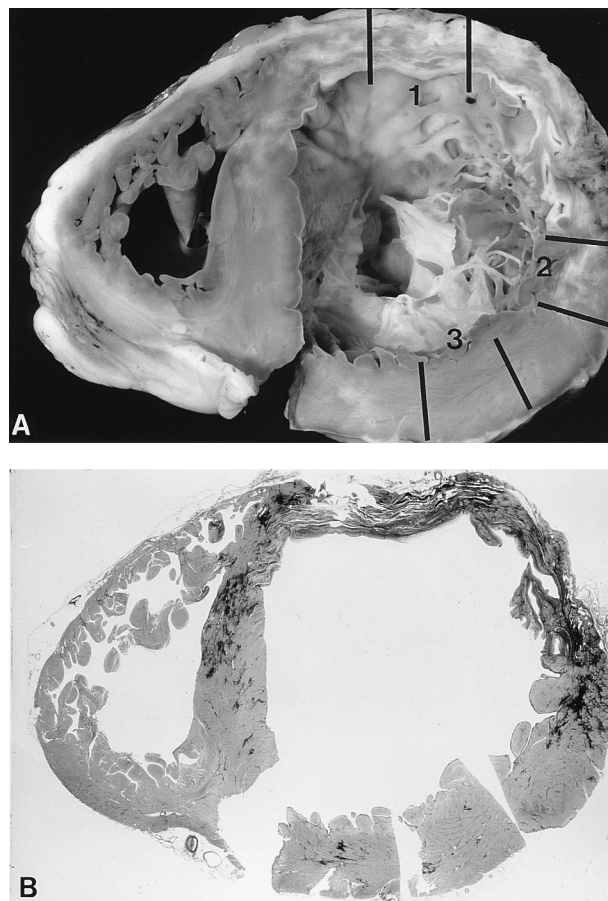

Figure 1. Cross sections perpendicular to the left ventricular long axis of a heart with end-stage ischemic heart disease. **A,** Gross specimen. The heart is dilated and contains a large transmural infarct scar in the anterior wall, extending into the upper part of the ventricular septum and far laterally almost to the base of the posteromedial papillary muscle. The noninfarcted hypertrophic myocardium reveals a few patches of scar tissue (compare with **B**). The sites where blocks have been taken are indicated: 1 = scarred area; 2 = border area; 3 = noninfarcted myocardium as it appears grossly. **B,** Histologic section corresponding to the cross section shown in **A,** stained with Sirius red. Small scars within otherwise noninfarcted myocardium are distinct and more readily identified than in the gross specimen.

the heart, similar to that obtained in the hearts from the United Kingdom, was taken (see above); a transmural block from the left lateral wall of the left ventricle was snap-frozen; the heart was then fixed in 4% buffered formalin; subsequent blocks were taken from the fixed heart to include the scar area, the immediate border area and noninfarcted myocardium remote from the scar (see example in Fig. 1). The two autopsy hearts of patients with MI were similarly processed.

Collagen. Collagen was quantified by using a biochemical and a histochemical technique. The biochemical method (hydroxyproline analysis) allows quantification of total collagen, which is expressed in μg collagen/mg tissue. The histochemical method uses Sirius red to stain all fibrillar collagens, which are quantified spectrophotometrically. Hence, the absolute figures are not the same, but comparisons between the two techniques are valid with respect to trends.

Hydroxyproline analysis. Eight heart specimens with MI and 16 reference hearts were used. Formalin-fixed blocks from the scar area, the border area and the noninfarcted myocardium—as indicated previously—were frozen in liquid nitrogen. Sections were cut at 20-μm thickness and collected in a cold Eppendorf test tube, and the exact wet weight of the tissue was determined. Total collagen concentration was determined by measuring the hydroxyproline levels according to the method of Stegemann and Stalder (20), and the data were expressed as μg collagen/mg wet weight of tissue (20).

Sirius red staining. Sirius red specifically stains all types of fibrillar collagen (21). The same eight cardiac explants with MI and 10 reference hearts were used. Tissue samples were taken from the same three sites selected for the hydroxyproline analysis. The advantage of the Sirius red staining method is that the sections of noninfarcted myocardium, remote from the scar, could be screened microscopically for the presence of small areas of replacement fibrosis, unnoticable to the naked eye, before microspectrophotometry (Fig. 1). In this way we felt confident that the total amount of fibrillar collagen was quantified in truly noninfarcted myocardium.

All samples were embedded in paraffin, sectioned at 5-μm thickness and stained with Sirius red (0.1% Sirius red F3BA dissolved in saturated picric acid, pH 2.0).

The total amount of fibrillar collagen and that of all proteins was quantified spectrophotometrically by using a Vickers M85A scanning and integrating microdensitometer (22,23). The maximal absorption for Sirius red is at a wavelength of 557 nm, and that for total bound picric acid is at 434 nm. From each section 20 nonoverlapping areas were measured at a wavelength of 557 nm and 10 at a wavelength of 434 nm. For each section the mean of the measurements at 557 nm was calculated and divided by the mean of the 10 readings at 434 nm and multiplied by 100 (22,23). The integrated absorbance readings were converted into arbitrary units of the mean integrated absorbance values.

Types I and III collagen. For determination of the type I/type III collagen ratio, only frozen tissue samples could be used (blocks from the LV lateral wall, snap-frozen in isopentane cooled in liquid nitrogen). Two techniques were employed: a biochemical technique (cyanogen bromide analysis), using spectrophotometric quantification, and an immunohistochemical method that allowed identification of the tissue components before microdensitophotometric quantification.

Cyanogen bromide analysis. Eight heart specimens with MI and 10 reference hearts were used. Cryostat sections were cut at 20-μm thickness, collected in an Eppendorf test tube and treated with 2% sodium dodecyl sulfate in 0.1 mol/liter Tris HCl buffer (pH 7.2) for 24 h at room temperature. The homogenates were centrifuged at 4,000 rpm for 10 min. The pellet was resuspended in 250 μl 70% vol/vol formic acid and 5 μl cyanogen bromide crystals (stock solution 100 μg/μl). The digestion time was 24 h under mixing conditions at 30°C. The residue was vacuum dried. The resulting peptides were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis. For reference purposes, types I and III collagen

standards were prepared from human leiomyoma tissue, as described by ChandraRajan (24). When gel electrophoresis was completed, the gel was removed and stained for 30 min by gentle shaking in an aqueous solution containing 0.125% Coomassie blue R250, 50% methanol and 10% acetic acid. The gel was destained by continuous shaking using a solution of 10% acetic acid and 50% methanol in distilled water. Gels were scanned by using a LKB laser spectrophotometer. The areas beneath the peaks were calculated by computerized integration. The al(III)CB3.6.8 peptide was used to quantify the percentage of type III collagen (25), based on the following calculation:

$$\% \text{ Type III} = \frac{\text{Area al(III)CB3.6.8} \times 100}{\% \text{ Area type III standard} \times \text{Total area all peaks}}.$$

The results were expressed as the type I/type III collagen ratio.

Immunohistochemical analysis. Fifteen heart specimens with MI and 16 reference hearts were used. Cryostat sections were cut at 6-μm thickness mounted on organosilan-coated glass slides, dried overnight at room temperature and fixed in cold acetone for 10 min at 4°C.

Types I and III collagen were immunostained with mouse anti-type I collagen and mouse anti-type III collagen (clone I-8H5, immunoglobulin G2a and clone III-53, immunoglobulin G1, respectively; both gifts of Dr. K. Iwata, Fuji Chemical Industries Ltd., Toyama, Japan). The method applied was a two-step indirect immunoalkaline phosphatase technique. The end product was visualized with fast red, and types I and III collagen were quantified with a microdensitophotometer at a wavelength of 500 nm (26). Leiomyoma tissue, known to have a type I/type III collagen ratio of ~1 (27), was used to establish the appropriate dilutions of the anticollagen antibodies to achieve identical optical densities, and it served as a reference to correct the ratio obtained for the collagens. The results were expressed as the type I/type III collagen ratio.

Statistical methods. The results obtained for scar areas, border zones and noninfarcted myocardium, remote from the scars, were analyzed by Student t test. The statistical significance of the calculated ratios of collagen types I and III was analyzed by both Student t test and Mann-Whitney test.

Results

Collagen. *Hydroxyproline analysis (Table 1).* The 16 adult reference hearts had a mean value ($\pm$ SD) of collagen of 5.8 ($\pm$ 1.5) μg/mg wet weight of tissue in the LV. Collagen values showed no relation with patient age or gender. Each of the eight hearts with MI used in this analysis showed a high total collagen content in the scar area; in seven of the eight hearts, values were lower in the border zone. Values in noninfarcted myocardium remote from the scar were much lower in all eight hearts. The mean value of the total collagen amount in noninfarcted myocardium did not differ statistically from that of reference hearts.

Sirius red staining (Table 2). Microscopic foci of replacement fibrosis were present in all sections, all of which were

Table 1. Total Collagen, Quantified by Hydroxyproline Analysis, in 8 Hearts With Myocardial Infarction and 16 Reference Hearts

Hearts With MI			
Scar Area	Border Area	Noninfarcted Myocardium	Reference Hearts
48.90	33.80	7.10	5.00
81.20	87.20	10.70	6.80
64.00	30.00	6.80	3.90
26.70	17.70	10.50	6.50
29.40	18.80	8.60	4.60
41.40	26.70	5.30	5.10
45.70	10.70	4.00	5.10
85.40	14.30	5.00	6.60
			4.30
	$p < 0.05$		
			6.20
		$p < 0.05$	
			1.50
			7.10
			6.80
			6.00
			5.00
			9.50
		$p = NS$	

Data are presented as μg/mg tissue wet weight. MI = myocardial infarction.

sampled from the same sites selected for the hydroxyproline analysis. As stated, such foci were excluded from spectrophotometric quantification. The total fibrillar collagen amount is shown in Table 2. The amount of fibrillar collagen related to

Table 2. Total Fibrillar Collagen, Measured With Sirius Red Staining and Microdensitophotometry, in Eight Hearts With Myocardial Infarction and Nine Reference Hearts

Hearts With MI			
Scar Area	Border Area	Noninfarcted Myocardium	Reference Hearts
0.21	0.09	0.03	0.05
0.24	0.12	0.06	0.05
0.20	0.09	0.05	0.05
0.23	0.09	0.04	0.04
0.23	0.09	0.06	0.06
0.21	0.11	0.05	0.07
0.19	0.100	0.07	0.06
—	0.07	0.05	0.04
			0.05
			0.05
	$p < 0.05$		
	$p < 0.05$		$p = NS$

Data are expressed as arbitrary units of the mean integrated absorbance values. The eight postinfarction hearts are the same as those in Table 1. MI = myocardial infarction.

Table 3. Percent of Collagen Type III and Ratio of Type I to Type III Collagen, Quantified by Cyanogen Bromide Analysis, in 8 Hearts With Myocardial Infarction and 10 Reference Hearts

Hearts With MI		Reference Hearts	
Type III Collagen (%)	Type I/Type III Collagen Ratio	Type III Collagen (%)	Type I/Type III Collagen Ratio
64.20	0.56	58.00	0.72
41.80	1.39	61.10	0.64
62.20	0.61	60.30	0.66
54.90	0.82	52.90	0.89
47.00	1.13	64.20	0.56
44.10	1.27	67.80	0.47
48.50	1.06	74.20	0.35
38.00	1.63	63.70	0.57
		63.20	0.58
		62.20	0.61
	$p < 0.05$*		

*By both Student t test and Mann-Whitney test. MI = myocardial infarction.

total protein is highest in scar areas and declines markedly in the border areas and in noninfarcted myocardium. The total fibrillar collagen amount in noninfarcted myocardium is similar to that in reference hearts.

Types I and III collagen. *Cyanogen bromide analysis.* Table 3 shows the calculated percentages of type III collagen and the type I/type III collagen ratio for reference hearts and the LV lateral wall of hearts with MI. Hearts with MI showed a mean ($\pm$ SD) type I/type III collagen ratio of 1.06 ± 0.38; in reference hearts this value was 0.60 ± 0.14 ($p < 0.05$ by both Student t test and Mann-Whitney test). The wide range of mean values for type I/type III collagen ratio in hearts with MI relates to the fact that some blocks contained mostly scar and border areas, whereas others contained substantial areas of noninfarcted myocardium. The cyanogen bromide method does not allow identification of these differences before analysis. However, we know that these differences were present because they became apparent when the same blocks were used for immunostaining for collagen types I and III (see Immunohistochemical analysis; Fig. 2).

Immunohistochemical analysis (Table 4). The mean corrected type I/type III collagen ratio was 0.54 ± 0.11 in reference hearts versus 0.83 ± 0.25 in hearts with MI ($p < 0.05$ by both Student t test and Mann-Whitney test).

Of the 15 blocks obtained from the LV lateral wall, 11 showed scar tissue intermingled with viable myocardial cells throughout the microscopic sections. In only four blocks a distinct difference could be seen between noninfarcted myocardium and scar tissue within the same microscopic section. These four cases allowed us to distinguish between measurements made at sites of scar tissue and those obtained at noninfarcted areas.

Quantification of the type I/type III collagen ratio in these four sections with distinct noninfarcted myocardium, without microscopic scars, showed a corrected ratio of 0.44, 0.77, 0.66
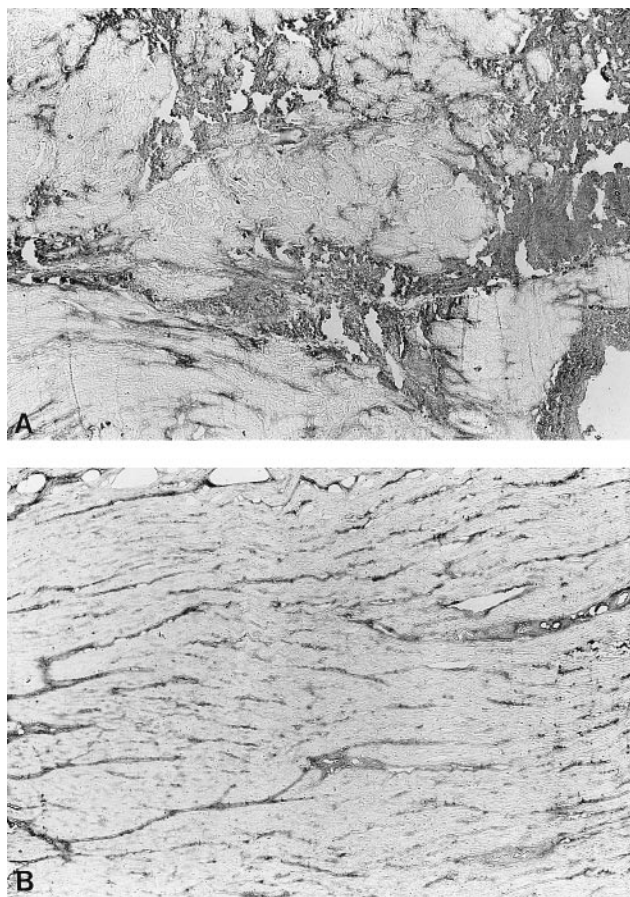
Figure 2. Frozen sections of tissue blocks used to quantify the type I/type III collagen ratio. Both sections were obtained from the left ventricular lateral wall. Both blocks were used for biochemical quantification and immunostaining. The sections shown are stained for type I collagen. **A**, Marked fibrosis is evident. **B**, There is a mild increase in collagen. These differences underlie the wide range of results obtained with the biochemical technique. Original magnification ×35.

Table 4. Type I/Type III Collagen Ratio Quantified Spectrophotometrically in 15 Hearts With Myocardial Infarction and 16 Reference Hearts

Hearts With MI	Reference Hearts
0.71	0.45
0.71	0.56
0.87	0.56
1.01	0.59
0.88	0.36
1.25	0.58
1.31	0.45
0.63	0.41
0.56	0.56
0.73	0.68
0.51	0.38
1.15	0.69
0.70	0.43
0.56	0.60
0.72	0.74
0.82	0.58

$p < 0.05$*

*By both Student t test and Mann-Whitney test. Data are expressed as mean value of the corrected type I/type III collagen ratio. MI = myocardial infarction.

and 0.45, respectively. Thus, the mean corrected ratio of these four sections (0.58 ± 0.16) was similar to that seen in reference hearts. Measurements at sites with scars, but in the same sections, showed a corrected ratio of 0.71, 0.87, 1.01 and 0.88, respectively, and hence, a higher type I/type III collagen ratio (mean 0.87 ± 0.12).

Discussion

Two important aspects emerge from this study. First, noninfarcted hypertrophic myocardium, remote from the site of myocardial scar tissue, does not show an increase in interstitial fibrous tissue. In fact, the endomysial collagen network at these sites presents the same ratio between types I and III collagen seen in reference hearts. Second, at the site of the scar the ratio between types I and III collagen is greater than the ratio that occurs normally in endomysial and perimysial sites.

Remodeling. It is currently in vogue to consider postinfarction remodeling of LV myocardium in terms of a myocyte and a nonmyocyte compartment (12,17,28,29). Indeed, functional integrity of myocardium is highly dependent on structural characteristics of the extracellular matrix. The collagen network, composed largely of types I and III fibrillar collagen, is a major constituent for the preservation of myocardial architecture and chamber geometry. It is of interest in this context that factors that promote myocyte growth are largely different from those that contribute to changes in the collagen network. In the setting of postinfarction myocardial remodeling the prime stimulus for hypertrophy of noninfarcted myocardium is volume overload. This type of ventricular hypertrophy is not associated with an increase in interstitial collagen, in contrast to pressure overload hypertrophy, which is accompanied by an increase in collagen and structural and biochemical remodeling of the collagen matrix (28). The fibrogenetic factors involved are still under investigation, but it appears that elevated levels in circulating angiotensin II and aldosterone may play a role, as well as local tissue factors such as endothelins and bradykinin (30). Once interstitial fibrosis develops it will increase myocardial stiffness and, therefore, will have a negative effect on diastolic and systolic ventricular function. At this stage hypertrophy of myocardium can no longer be considered a physiologic adaptation, but rather a pathologic condition that may set the stage for a vicious cycle leading to overt heart failure. It has been stated (15,16) that this provides the structural basis for end-stage heart failure postinfarction cardiac remodeling.

Remodeling and fibrosis. The observations in the present series of hearts are pertinent to this concept. All patients included in the study had end-stage MI. The cardiac explants all showed extensive scarring (see Methods), in accordance

with the clinical course, and all showed distinct global LV chamber dilation with extensive hypertrophy of noninfarcted myocardium (see Fig. 1). In other words, in all instances the condition fit the description of remodeling. However, none of these hearts had an increase in interstitial fibrous tissue in noninfarcted myocardium. The total collagen content, measured biochemically and quantified by using microdensitophotometry, was not greater than that in reference hearts and the ratio between types I and III collagen was also normal.

At the site of the scar, however, the ratio between both collagen types had shifted, with an increase in type I over type III collagen. This observation is in keeping with wound healing processes in general, since the usual scar contains a similar increase in type I over type III collagen (31). In human hearts, this phenomenon may have adverse effects. Type I collagen is found principally in thick collagen fibers, such as those in tendons, and is generally associated with tensile strength. Type III collagen, in contrast, is found in thin fibers and relates to elasticity. Therefore, the change in type I/type III collagen ratio in myocardial scar tissue may cause undue stiffness with a negative net effect on myocardial performance.

Myocardium in the immediate border zone of the scar, made up of connective tissue extensions of the scar intermingling with viable myocardium, showed an increase in total collagen and also an increase in type I over type III collagen. When the levels were quantified, they were below those obtained within the scar but significantly higher than those found at sites of noninfarcted myocardium remote from the scar. We encountered one exception (Case 2, Table 1) in which hydroxyproline analysis revealed almost the same high levels of collagen in the scar as in the immediate border zone. Because the technique does not allow for visual identification of the tissue components, the only explanation that we can offer is that both sites represented excessive replacement fibrosis. We feel strengthened in this view, because the adjacent tissue block, used for Sirius red staining and microdensitophotometric quantification (Case 2, Table 2), revealed a decrease in collagens in the border area as in other cases.

Comparison with previous studies. The present observations are at variance with recent reports (13–16) claiming that postinfarction remodeling is associated with an increase in interstitial fibrous tissue in noninfarcted myocardium. These reports differ among themselves and to some extent are even inconsistent. For instance, Bishop and coworkers (13) found enhanced deposition of predominantly type I collagen, whereas Mukherjee and Sen (14) found increased deposition of type III collagen. The first group of investigators stated specifically that they avoided regions that were macroscopically replaced by scar tissue, whereas the second group stated that they removed tissue from the LV apex, avoiding the infarcted area of the myocardium. Both groups studied collagen by using biochemical analysis only, without microscopic verification of the tissue architecture. Apart from the conflicting results, the question arises whether other factors may have played a role in the data obtained. Because both groups took full thickness blocks of myocardium, one may consider the option that

endocardial thickening, likely to be present in a heart with chronic dilation, may have affected the outcome.

Volders and associates (15) stated that "myocardial tissue from the interventricular septum was routinely sampled during autopsies." They studied hearts with a transmural infarct in the anterior, posterior or lateral part of the LV, excluding hearts with an interventricular septal infarct. They quantified collagen by using the Sirius red staining technique, as in our study. However, they found a significantly greater amount of collagen in the septum of patients with infarction than in the control group without infarction. It may be relevant to this point that patients with end-stage heart failure after MI usually have a large infarct, and streaks of scar tissue that often extend into adjacent noninfarcted myocardium, far beyond the scar readily distinct to the naked eye (see Fig. 1). Therefore, it may well be that the "routinely" sampled site in the interventricular septum contained extensions from the neighboring scar or isolated small areas of replacement fibrosis. This option is strengthened by their Figure 1A (15), which clearly shows replacement fibrosis. We also frequently encountered microscopic patches of replacement fibrosis (microscopic scars) in the apparent noninfarcted myocardium, but we excluded such areas from our measurement of the interstitial compartment of noninfarcted myocardium.

Finally, Beltrami and associates (16) produced an extensive study on the ventricular characteristics in cardiac explants of patients with end-stage coronary artery disease. They reported diffuse interstitial fibrosis of myocardium at sites remote from the infarcted region (see their Fig. 3B). Their observations were based on six randomly chosen embedded tissue blocks, stained with a trichrome stain, and the volume fraction of the nonmyocyte compartment was estimated by using a point counting system. In other words, they measured the total extracellular matrix and, given their staining technique, did not specifically measure collagens. Thus, the increase found could be anything affecting the nonmyocyte compartment, such as an increase in water content. Moreover, they did not specifically select blocks from noninfarcted areas. In fact, they stated that the randomly selected blocks did contain extensive scarring, as well as patchy areas of replacement fibrosis, and it remains unclear whether any of these blocks contained no scar tissue at all. We wonder, therefore, whether the blocks are truly representative for noninfarcted myocardium.

Study limitations. All patients enrolled in our study had been treated with ACE inhibitors, known to decrease fibrogenesis (14). One could argue, therefore, that the absence of interstitial fibrosis in noninfarcted myocardium, remote from the scars, was due to this medication. However, each patient had extensive myocardial scar formation, with compensatory hypertrophy of viable myocardium and global LV dilation, and each had progressive LV dysfunction with overt heart failure; in other words each met the criteria for ventricular remodeling, generally considered to be associated with an increase in interstitial fibrosis. Nevertheless, in this study, interstitial fibrosis in noninfarcted myocardium was not greater than that in reference hearts, despite the fact that the gross anatomic and

clinical findings all fitted with progressive postinfarction LV dysfunction. Indeed, according to current concepts, the absence of an increase in interstitial fibrosis should have led to a stable rather than to a deteriorating clinical condition. We wonder, therefore, whether the beneficial effects of ACE inhibitors are truly due to their inhibiting effects on fibrogenesis.

Conclusions. We feel confident that the noninfarcted myocardium of the hearts with MI that we studied contained no increase of collagens in the nonmyocyte compartment. We therefore believe that the basic structural processes of postinfarction remodeling of LV myocardium are replacement fibrosis of necrotic myocardium, leading to scar tissue, and myocardial hypertrophy of noninfarcted myocardium without interstitial fibrosis. The mechanisms that cause progressive LV dysfunction in some patients may well relate to physical effects (1,11). In patients in whom remodeling is associated with an increase in interstitial fibrosis of the noninfarcted myocardium, other processes known to increase interstitial fibrous tissue may be at work. An increase in pressure load, added to an increase in volume load, could be one of those factors (18).

These considerations are relevant clinically. Because postinfarction remodeling with progressive LV deterioration is not necessarily due to progressive interstitial fibrosis, it may be necessary to reconsider therapeutic attempts to prevent the fibrosis or reduce its severity.

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