Fibrosis of the Left Atria During Progression of Heart Failure Is Associated With Increased Matrix Metalloproteinases in the Rat

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OBJECTIVES

The purpose of this study was to determine the pathogenic factors and molecular mechanisms involved in fibrosis of the atria.

BACKGROUND

Fibrosis is an important component of the pathophysiology of atrial fibrillation, especially when the arrhythmia is associated with heart failure (HF) or atrial dilation.

METHODS

We used a rat model of myocardial infarction (MI) complicated by various degrees of left ventricular dysfunction and atrial dilation to study fibrosis and matrix metalloproteinase (MMP) activity in the left atrial (LA) myocardium by means of histologic, Western blot, zymographic, and immunohistologic techniques.

RESULTS

Three months after surgical ligature of the left coronary artery, 27 rats had a large MI, 12 were in mild HF, and 15 in severe HF. Both groups had LA enlargement at the echocardiography. Masson’s trichrome and picrosirius staining of tissue sections revealed marked fibrosis at the periphery of trabeculae and also surrounding myolytic myocytes, in both mild and severe HF. In mild HF, the activity and expression of the matrilysin MMP-7 were increased (122%), whereas in severe HF, both MMP-7 (211%) and the gelatinase MMP-2 (187%) were up-regulated. There were no changes in the expression or activity of MMP inhibitors, TIMP-1, -2, and -4. Immunostaining of cryosections showed that MMP-2 was present in the interstitial spaces, whereas MMP-7 accumulated in myolytic myocytes.

CONCLUSIONS

Hemodynamic overload of the atria is an important pathogenic factor of fibrosis; MMP-7 appears to be involved in the early stage of this tissue remodeling process. (J Am Coll Cardiol 2003;42:336–44) © 2003 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most frequent form of arrhythmia in clinical practice (1). Its pathophysiology is complex and usually combines triggering by focal extrasystoles, activation of the nervous system, and a substratum that allows micro-reentry of the electrical impulse. The substratum is characterized by functional and structural alterations of the myocardium, including action potential shortening and hypertrophied and dedifferentiated myocytes showing extensive myolysis (2–4). When AF complicates heart failure (HF), fibrosis becomes a predominant component of atrial remodeling. For instance, in the canine model of pacing-induced HF, marked fibrosis of the atrial myocardium contributes to local impairment of electrical conduction and, in turn, to AF persistence (5). Tissue alterations with fibrosis are also present in the right atria (RA) of patients in sinus rhythm during HF or with a dilated atrium, suggesting that hemodynamic factors participate in atrial myocardium remodeling (4,6,7).

Matrix metalloproteinases (MMPs) play a crucial role in extracellular matrix homeostasis in a number of physiologic and pathologic situations, including during HF (8–12). These proteolytic enzymes are regulated at transcriptional levels and by endogenous physiologic inhibitors such as tissue inhibitors of metalloproteinases (TIMPs) (8,10,12). During HF, there is increased activity of various MMPs such as: 1) collagenases that degrade fibrillar collagens; 2) gelatinases that degrade type IV and fibrillar collagens as well as non-collagenous constituents of the basement membrane (9,10,12). Moreover pharmacologic inhibition of MMPs prevents left ventricle (LV) dilation and pump dysfunction (11,13,14).

In the present study, we used the rat model of myocardial infarction (MI) characterized by various degrees of systolic and diastolic LV dysfunction (15–17) to address the following questions: 1) is chronic alteration of the working conditions of the atria an important pathogenic factor for fibrosis, and 2) how are MMPs and their inhibitors...
planted intraperitoneally with electrodes placed in a "lead 2-like" position. The one-channel electrocardiographic signal (1 kHz) was digitized, amplified and emitted with a radiofrequency carrier. Rats were housed in a cage placed on a receiver that captured the signal independently of animal activity. Acquisition and analysis were performed using the software Chart v4.1.2’ (PowerLab, AdInstruments, Colorado Springs, Colorado).

**Immunohistochemistry.** Cryosections (7 μm) of LA were used for double indirect immunofluorescence labeling as previously described (4). The following primary antibodies were used: mouse anti-rabbit sarcomeric alpha-actinin antibody (1/400, Sigma Chemical Co, St. Louis, Missouri); polyclonal chicken anti-human MMP-2 (5 μg/ml; Chemicon, Euromedex, Souffleweyersheim, France) or polyclonal rabbit anti-human MMP-7 (10 μg/ml; Chemicon). As secondary antibodies we used Texas-red-conjugated sheep anti-mouse IgG (1/20 Amersham Biosciences), FITC conjugated donkey anti-rabbit IgG (1/20; Amersham Biosciences, Orsay, France) and FITC conjugated donkey anti-chicken IgG (1/50; Jackson ImmunoResearch, Baltimore, Maryland). Slides were examined with a fluorescence microscope.

**ANP and cGMP assays.** Plasma concentrations of atrial natriuretic peptide (ANP) were measured after solid-phase extraction on Bond Elut cartridges by radioimmunoassay with anti-atrial natriuretic factor antibodies (personal products), standard atrial natriuretic factor (1-28, Sigma Aldrich, Lyon, France), and iodinated atrial natriuretic peptide (ANP) (REN Life Science, Courtaboeuf, France). Urinary and extruded cGMP levels were measured with a radioimmunoassay kit (3H cyclic guanosine monophosphate assay, Amersham, London, UK) (18). The day before euthanasia, rats were placed in metabolic cages for collection of 15-h urine samples in order to normalize cGMP concentration with urine output (nmol/ml).

**MMP zymography and TIMP reverse zymography.** Proteins were extracted from frozen atrial tissues, crushed and homogenized on ice in 0.05 mol/l Tris-HCl, pH 7.5, containing 0.01 mol/l CaCl$_2$, 2 mol/l guanidium chloride, and 0.2% Triton X-100, dialyzed against 0.05 mol/l Tris-HCl, pH 7.5, and 0.2% Triton X-100 for 48 h at 4°C. The amount of protein was determined using the Bradford assay. Ten micrograms of proteins were subjected to SDS-PAGE gels containing 0.1% gelatin or alpha-casein (Sigma Aldrich) for MMP-2 and MMP-7 analysis, respectively. For TIMP-1 and TIMP-2 measurements, 160 ng/ml proMMP-2 (Euromedex, France) were added in gelatin gels; for TIMP-4, 320 ng/ml proMMP-7 were added in casein gels. A solution of TIMPs was used as reference. Quantification was performed by densitometry analysis with the NIH Image 1.61 program. A sample used as a standard was loaded in each gel in order to normalize density values, and data were expressed as arbitrary units (AUs). The specificity of the protease activity was checked by incubating gelatin and casein gels with EDTA (30 mmol/l) or Pefabloc

**Abbreviations and Acronyms**

AF = atrial fibrillation  
ANP = atrial natriuretic peptide  
AU = arbitrary unit  
HF = heart failure  
LA = left atria/atrial  
LV = left ventricle  
MI = myocardial infarction  
MMP = matrix metalloproteinase  
RA = right atria/atrial  
TIMP = tissue inhibitor of metalloproteinase

(TIMPs) regulated during the atrial myocardial remodeling associated with LV pump dysfunction?

**METHODS**

**Experimental MI.** Animal care complied with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research, and the study was authorized (#006235) by the French Agriculture Ministry. Myocardial infarction was induced in 10-week-old male Wistar rats (Charles River, France) by left coronary artery ligation, as previously described (15). Briefly, animals were anesthetized with 2% Rompun solution (Bayer-Pharma, Puteau, France) and 10 mg/kg Imalgene 500 (Mériel, Lyon, France), then intubated and ventilated. After left thoracotomy, the ligation of the descending anterior left coronary artery was performed. This procedureinfarcted about 30% to 40% of the LV. A sham operation was performed in eight rats (Sh) by evertting the heart from the thorax without performing coronary artery ligature. Three months after surgery, the rats were euthanized, and their left atria (LA) were frozen in liquid nitrogen for biochemical and immunohistochemistry studies or fixed for 24 h in buffered formalin before being embedded in paraffin for histologic examination.

**Echocardiographic study.** Transthoracic echocardiography was performed in rats anesthetized with 2% isoflurane aerosol in air enriched with 50% $O_2$ using an echocardiograph (Toshiba Powervision 6000, SSA 370 A) equipped with an 8- to 14-MHz linear transducer. The LV and the aorta and the posterior wall of the LA (16).

**Histologic study.** Sections (7 μm thick) of fixed LA (10% formol) were stained with picrosirius red F3BA or Masson’s trichrome.

**Holter monitoring.** A hermetically sealed transmitter (DataScience International, St. Paul, Minnesota) was implanted intraperitoneally with electrodes placed in a “lead 2-like” position. The one-channel electrocardiographic signal (1 kHz) was digitized, amplified and emitted with a radiofrequency carrier. Rats were housed in a cage placed on a receiver that captured the signal independently of animal activity. Acquisition and analysis were performed using the software Chart v4.1.2’ (PowerLab, AdInstruments, Colorado Springs, Colorado).
MMP-2, -7, -13, and TIMP-1, -2, and -4 (Chemicon) sites were blocked with 4% BSA. Antibodies against lane). Proteins were transferred to polyscreen PVDF mem-

phoresis was performed as described by Laemmli on 10% polyacrylamide gel in non-reducing conditions (30 °C). Western blot.

protease activities, respectively (19,20). (VWR, Fontenay, France) to block MMP and serine

Western blot. The same procedure was used to extract proteins for Western blot and zymography studies. Electro-

guidance from a long-axis heart view revealed atrial dilation

increased. They were considered to be in mild HF (M).

urinary cGMP concentrations were not significantly in-

operative rats, but less than in the S; their plasma ANP and

weight ratio was enhanced compared with the sham-

physical signs of congestive HF. Their heart weight/body

were increased in keeping with urinary accumulation of

remained 15 infarcted rats showed no

were increased in both M and S rats. Of note, the RA

in S rats (Table 2, Fig. 1). The LA weight/body weight ratio

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shaped by Masson’s trichrome procedure. In control

sections of atria from both M (n = 4) and S (n = 4) rats

large increase in connective tissue that accumulated between

This was clearly revealed by picrosirius staining, which

showed that myocytes were entirely surrounded by collage-

in tortuous strips (Fig. 2B). In both M and S, there was a

there was a large increase in connective tissue that accumulated between bundles of fibers. The collagen also accumulated within the trabeculae in the intercellular spaces, forming large septa.

Marked structural alteration of atrial myocardium of

in infarcted rats. Figures 2A and 2B show tissue sections of LA stained with Masson’s trichrome procedure. In control

Mild Heart Failure

Severe Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Mild Heart Failure (M)</th>
<th>Severe Heart Failure (S)</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>15</td>
<td>12</td>
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<tr>
<td>BW, g</td>
<td>624 ± 2</td>
<td>611 ± 4</td>
<td>574 ± 4*‡</td>
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<td>HW/BW, mg/g</td>
<td>2.7 ± 0.02</td>
<td>3.2 ± 0.03</td>
<td>4.3 ± 0.04*‡</td>
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<td>LVW/BW, mg/g</td>
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<td>0.9 ± 0.07*‡</td>
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<tr>
<td>LAW/BW, mg/g</td>
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<td>0.1 ± 0.02*</td>
<td>0.2 ± 0.04*‡</td>
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<tr>
<td>RAW/BW, mg/g</td>
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<td>0.14 ± 0.01*</td>
<td>0.15 ± 0.02*</td>
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<tr>
<td>(HW-LVW)/BW, mg/g</td>
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<td>1.10 ± 0.04*</td>
<td>1.43 ± 0.03*</td>
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<td>ANP, pmol/ml⁻¹</td>
<td>52.8 ± 1.1</td>
<td>76.9 ± 2.9</td>
<td>175.6 ± 9.0‡</td>
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<tr>
<td>Urinary cGMP, nmol/ml</td>
<td>5.7 ± 0.7</td>
<td>6.1 ± 0.3</td>
<td>19.1 ± 3.6‡</td>
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</table>

All values are means ± SEM. n = the number of animals in each group; significant difference vs. sham, *p < 0.05, †p < 0.001; significant difference vs. M, ‡p < 0.05. ANP = atrial natriuretic peptide; BW = body weight; cGMP = cyclic guanosine monophosphate; HW = heart weight; LAW = left atrial weight; LVW = left ventricular weight; RVW = right ventricular weight.

in S rats (Table 2, Fig. 1). The LA weight/body weight ratio was increased in both M and S rats. Of note, the RA

Clinical, morphologic, and biologic characteristics of

Three months after surgery, 12 rats showed

signs of severe HF (S) including body weight loss, increased

heart and right ventricle weights and, often, pleural effusion

(Table 1). In this group, plasma concentrations of ANP

were increased in keeping with urinary accumulation of
cGMP (15,18). The remaining 15 infarcted rats showed no

physical signs of congestive HF. Their heart weight/body

weight ratio was enhanced compared with the sham-

operated rats, but less than in the S; their plasma ANP and

urinary cGMP concentrations were not significantly in-

creased. They were considered to be in mild HF (M).

M-mode echocardiograms obtained with two-dimensional
guidance from a long-axis heart view revealed atrial dilation

in both M and S groups compared to Sh, more pronounced

Table 1. Morphologic and Biologic Parameters

Table 2. Echocardiographic Parameters

<table>
<thead>
<tr>
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<th>Sham</th>
<th>Mild Heart Failure (M)</th>
<th>Severe Heart Failure (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4</td>
<td>10</td>
<td>6</td>
</tr>
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<td>LAD, mm</td>
<td>5.7 ± 0.3</td>
<td>7.1 ± 0.2*</td>
<td>9.7 ± 0.1*†</td>
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<tr>
<td>LVDD, mm</td>
<td>7.5 ± 0.3</td>
<td>9.4 ± 0.5*</td>
<td>12.9 ± 0.7*‡</td>
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<tr>
<td>LVDS, mm</td>
<td>5.1 ± 0.1</td>
<td>6.8 ± 0.1</td>
<td>10.7 ± 0.4*‡</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>32 ± 1</td>
<td>27 ± 3*</td>
<td>17 ± 6*‡</td>
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</tbody>
</table>

All values are means ± SEM; n = the number of animals in each group. Significant difference vs. sham, *p < 0.05; significant difference vs. M, †p < 0.05. LAD = left atrial diameter; LVDD = end-diastolic left ventricle diameter; LVDS = end-systolic left ventricle diameter.
control atria, the staining was organized in a regularly striated network that filled the entire cell body, whereas myocytes in diseased atria showed extensive myofibrillar disruption (Fig. 2F).

**Up-regulation of MMPs in diseased atria.** Figure 3A shows that when zymogram studies were performed with gelatin as the proteolytic substrate, a proteolytic activity was detected at around 72 kD, corresponding to gelatinase A (MMP-2) (the guanidium of the extraction buffer induced activation of MMP-2, explaining that both proform and active forms of the MMP were visible; the three bands were used for quantification) (Fig. 3A). MMP-2 activity was detected in all samples and was significantly increased only in atria from S rats (8.9 ± 0.9 AU vs. 3.1 ± 0.7 AU in Sh (n = 4) and S (n = 4), respectively; p < 0.05).

The main proteolytic activity detected on casein zymogram was at around 28 kD, corresponding to the matrilysin MMP-7 (Fig. 3A). MMP-7 activity was barely detectable in sham-operated animals (0.9 ± 0.09 AU [n = 4]), while a strong band was obtained with the atria of M rats (2.0 ± 0.4 AU, [n = 4]; p < 0.05) and an even stronger band in the S group (2.8 ± 0.3 AU [n = 4]; p < 0.001). No other proteolytic activity was observed with gelatin and casein zymograms.

Changes in MMP activities ran parallel to changes in MMP-2 and MMP-7 protein expression, as shown with Western blots performed with antibodies directed against 72 kD MMP-2 and 28 kD MMP-7 (Fig. 3B). Densitometric analysis of the blots showed a significant increase in MMP-2 expression in the S group only (62.3 ± 10.3 AU vs. 166.9 ± 3.8 AU, in Sh [n = 4] and S [n = 4] rats; p < 0.05). Faint MMP-7 protein was detected in Sh (19.9 ± 1.3 AU, n = 4), while its expression was markedly enhanced in both M (60.5 ± 12.5 AU [n = 4]; p < 0.05) and S (66.6 ± 12.9 AU [n = 4]; p < 0.05) animals. There was also a trend towards an increase in the expression of interstitial collagenase MMP-13 in atria of infarcted rats (3.8 ± 0.6 AU in Sh (n = 5); 12.2 ± 4.3 AU in M (n = 4); 6.8 ± 2.8 AU [n = 5] in S; p = NS) (Fig. 3B).

**Lack of changes of TIMP activity in atria from infarcted rats.** The regulation of TIMPs was first examined by studying the MMP inhibitory activity of protein samples by reverse zymography. In gels containing gelatin and proMMP-2, two bands were detected at around 28 and 26

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**Figure 1.** Two-dimensional echocardiographic image (parasternal long-axis view) of the heart in sham-operated (A) and infarcted (severe heart failure) (C) rats. M-mode echocardiograms were obtained from the two-dimensional long-axis views, with a cross-section at the level of the aortic valve in sham-operated (B) and infarcted (D) rats. Ao = aorta; LA = left atria; LV = left ventricle.
kD, corresponding to TIMP-1 and TIMP-2, respectively (Fig. 3C). When zymogram analysis was performed with casein as substrate supplemented with proMMP-7 (21), only a weak inhibition of proteolytic activity corresponding to TIMP-4 (24 kD) was detected (data not shown). There was no significant difference in the intensity of three bands between groups of rats. Western blots performed with anti-TIMP-1 and -TIMP-2 antibodies, detected bands at their expected molecular weight: 100 and 98 kD, respectively (Fig. 3D). After reduction of protein samples with beta-mercaptoethanol in order to suppress TIMP-MMP complexes, there was no significant difference in band intensity between groups.

**MMP-7 accumulated in atrial myocytes of infarcted rats.** As shown in Figures 4A and 4B in both normal and diseased myocardial samples, positive MMP-2 staining was observed at the periphery of trabeculae. In diseased atria, the staining was also seen around bundles of fibers (Fig. 4B).
We then examined the tissue localization of the matrilysin MMP-7 in sections of the same specimen. Sections of control atria showing a typical regular cross-striated organization of sarcomeric alpha-actinin (Fig. 4C) were entirely negative with anti-MMP-7 antibody (Fig. 4E). In contrast, sections of diseased atria stained positively with anti-MMP-7 antibody. The staining was observed in most of the myolytic myocytes, and was distributed irregularly throughout the cell body and at the cell periphery (Fig. 4F). Note that the interstitial space was negative with MMP-7 staining.

DISCUSSION

After experimental MI in the rat, and despite the lack of arrhythmia, the progression of LV dysfunction had a marked impact on the LA, with fibrosis and numerous enlarged myocytes with myolysis as the main features. The metalloproteinases MMP-2 and MMP-7 appear to be involved in this extracellular matrix remodeling.

Hemodynamic overload of the atria is an important pathogenic factor of fibrosis. Our finding of an important fibrosis during the atrial remodeling associated with LV dysfunction is reminiscent of the accumulation of interstitial tissue observed in the fibrillating atria of dogs with pacing-induced HF or mitral valve stenosis (5,22). In contrast, it conflicts with the lack of extracellular matrix remodeling observed in experimental AF induced by atrial pacing (3). Marked fibrosis around dystrophic myocytes is also observed in RA of patients with chronic AF that often complicates HF or valve diseases, and also in those in sinus rhythm with a hemodynamic overload and dilated atria (4,6,7,23). Altogether, these studies point to a specific role of atrial loading conditions in fibrosis. The RA of infarcted rats also exhibits a fibrotic remodeling that was probably the indirect consequence of LV dysfunction via pulmonary circulation adaptation and hemodynamic overload of the right side of the heart (24). Hypertrophied myocytes with extensive myolysis.

Figure 3. MMP and TIMP activities in atrial myocardium. (A) Gelatin (MMP-2) and casein (MMP-7) zymogram showing the proteolytic activity in sham-operated (Sh), and infarcted rats in mild (M) or severe (S) heart failure. (B) Western blot of proteins from Sh, M, and S rats probed with anti-MMP-2, anti-MMP-7, and anti-MMP-13 antibodies. Analysis of TIMP-1 and -2 activity by reverse zymography (C) and (D) Western blot performed with anti-TIMP-1, anti-TIMP-2 in Sh, M, and S rats.
can be also the consequence of the hemodynamic overload of the atria (3,6), together with oxidative injury (25). In addition to local changes in the loading conditions of the atria, various neuromediators or hormones probably play an important role in this extracellular matrix remodeling. For instance, the renin-angiotensin system is up-regulated during HF, and there is an increased density of angiotensin type-2 receptors in fibrillating human atrial myocardium (26). Moreover, it has been shown that angiotensin-converting enzyme inhibition attenuates atrial remodeling and fibrosis in the experimental dog model of HF (27,28).

Different patterns of MMP expression during atrial remodeling. Matrix metalloproteinases appear to be key actors in interstitial tissue alterations of diseased atrial myocardium. However, the up-regulation of the gelatinase MMP-2 was observed only in animals with severe congestive HF, possibly because at this stage, factors known to stimulate MMP-2, such as mechanical stress, endothelin-1, the renin-angiotensin system, or cytokines accumulate (8,10,12,29).

We also observed marked up-regulation of the matrilysin MMP-7 in both groups of infarcted rats. This MMP, which is produced by various tissues (30), has the widest range of substrates, including all fibrillar collagens (31) and components of the basement membrane (32), which are required for cell–cell cohesion and alignment. Overloaded rat atrial myocardium showed marked fibrosis between myocytes and the loss of myocyte cohesion that may be associated with alterations of the basement membrane, as observed during the atrial remodeling during feline cardiomyopathy (33). In dilated atria, enlarged myocytes with myolysis appear to be an important source of MMP-7. The expression of this protease may be either one component of the process of cell hypertrophy and dedifferentiation (3,6), as reported in denervated muscle cells (34), or the consequence of changes in cytoskeletal architecture of myocytes (20). The interstitial space of atrial myocardium where fibroblasts are present was negative for the MMP-7 immunostaining. However, we have recently observed that isolated rat atrial fibroblasts

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**Figure 4.** Frozen atrial sections stained with anti-alpha-actinin sarcomeric (red), anti-MMP-2 (green) (A, B), and anti-MMP-7 (green) (E, F) from sham (A, C, E) and infarcted (B, D, F) rats in severe heart failure. Arrow in panel F indicates peripheral cell staining. Note that distinct magnifications were used in panel A, B (×20) and C to F (×40); Bar = 20 μm.
maintained 24 h in culture secrete large amounts of both MMP-2 and MMP-7, indicating that in some circumstances, these cells can also be a source of MMPs (unpublished data). Both the marked fibrosis surrounding trabeculae and bundles of myofibers and the trend towards an increase in the MMP-13 expression indicate that interstitial collagenases are also likely to be key actors in this remodeling process.

The observation that MMPs are up-regulated in the atria three months after MI suggests that a large part of the extracellular matrix remodeling of the LA is due to the progression of HF. In the LV after MI, in addition to early activation of MMP-1, -2, -3 and -9, there is also a delayed activation of MMPs, including the MT-MMP, that is probably involved in the remodeling of the myocardium (11).

The MMP up-regulation observed here was not matched by changes in TIMPs that bind specifically to the catalytic domain of MMPs and form an important control system for overall MMP activity (10,12). Thus, the lack of TIMP up-regulation and, in turn, the altered MMP/TIMP stoichiometry, could result in a loss of control of MMP activity and thereby contribute to the increase in MMP activity in diseased atria (35). A similar lack of adaptive TIMP responses to increased MMP activity has been reported in diseased atria (35). A similar lack of adaptive TIMP activity and thereby contribute to the increase in MMP activity in diseased atria (35). A similar lack of adaptive TIMP activity and thereby contribute to the increase in MMP activity in diseased atria (35). A similar lack of adaptive TIMP activity and thereby contribute to the increase in MMP activity in diseased atria (35). A similar lack of adaptive TIMP activity and thereby contribute to the increase in MMP activity in diseased atria (35).

Potential clinical significance. Changes in extracellular matrix may have a profound impact on atrial electrical and mechanical properties (37–39). Fibrosis in the intercellular spaces that form collagenous septa could alter the conduction of electrical influxes such as the transverse conduction velocity (5,38) and contribute to the loss of myocyte-myocyte coordination. None of the infarcted rats of the present study had an AF. This may be because the size of the rat atria, even during HF, is not sufficient for the constitution of circuits of reentry of the electrical impulse in keeping with the wavelength theory, or because some triggering factors are lacking. The lack of episodes of AF in this model indicates that the structural remodeling that is believed to constitute part of the substratum of AF can be present in the absence of the arrhythmia. This may provide an explanation for the vulnerability to AF observed in clinical settings associated with atrial hemodynamic overload. Thus, study of effects of pharmacologic MMP inhibition on the progression of atrial remodeling and the occurrence of AF is warranted.

REFERENCES


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