EDITORIAL COMMENT

Matrix Metalloproteinases and Atrial Structural Remodeling*

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Atrial fibrillation (AF) is a common arrhythmia, affecting approximately 5% of the population older than 65 years; the arrhythmia is associated with significant morbidity and mortality, and it is challenging and often frustrating to treat (1,2). There is a tendency for AF to become chronic and more resistant to cardioversion with increasing duration of the arrhythmia (3). Although the details are poorly understood, persistence of AF is thought to result from the atrial remodeling that occurs.

ATRIAL REMODELING

Remodeling of the atrium may refer to changes in structure and function (structural or mechanical remodeling) or electrophysiologic properties (electrical remodeling; ionic and gap junction remodeling) that occur in response to a pathologic stimulus (most commonly, rapid atrial or ventricular pacing). Because of the disparities in the time course of tachycardia-induced electrical remodeling and recovery of atrial function (4,5), it is likely that structural (and not electrical) remodeling is responsible for the substrate that favors AF persistence and the prevention of AF by prompt cardioversion. However, whether structural remodeling is simply a marker for the electrophysiologic changes, or is in some way causal, or is important only for final stabilization of the arrhythmia remains uncertain.

Atrial fibrosis has been demonstrated to provide a morphological substrate for AF both in the setting of left ventricular (LV) dysfunction and in mitral valvular disease (6,7). Unlike the atrial remodeling associated with rapid atrial pacing, which promotes AF maintenance by reducing the wavelength for reentry and increasing the regional disparity of refractoriness, rapid ventricular pacing alters the heterogeneity of conduction velocity and is associated with interstitial fibrosis, increased atrial angiotensin II levels, and prolonged episodes of AF (6,8). Moreover, treatment with an angiotensin-converting enzyme (ACE) inhibitor reduces the duration of AF and attenuates the structural remodeling seen in this model; these data are consistent with the reduced relapse rate of AF after cardioversion in patients pretreated with lisinopril (9), and the increased incidence of AF in control versus trandolapril-treated patients in the TRACE study (10). Novel genetic models of AF in the mouse provide further insights (11,12); for example, connexin-40 knockout mice have slower atrial conduction velocity compared to wild-type mice and increased vulnerability to atrial arrhythmia (11), and constitutive TGF-β overexpression produces increased atrial fibrosis and episodes of inducible AF (12). In addition to their contributions to understanding the pathophysiology of AF, these data and others in murine models challenge the hypothesis that a critical atrial mass is necessary for the maintenance of AF (13).

FIBROSIS OF THE LEFT ATRIUM DURING PROGRESSION OF HEART FAILURE IN THE RAT

In this context, the report by Boixel et al. (14) in this issue of the Journal is of particular interest. Twelve weeks after LV infarction in rats, dilation, interstitial fibrosis, and altered expression of matrix metalloproteinases (MMPs) were noted in the left atrium. Animals with “severe” heart failure (increased heart weight, right ventricular weight, and left atrial weight-to-body-weight ratios, increased plasma ANP [atrial natriuretic peptide], and urinary cGMP [guanosine 3′,5′-cyclic monophosphate]), had increased expression of MMP-7 and MMP-2 localized to myocytes and the interstitial space, respectively; MMP-7 alone was increased in animals with severe heart failure. Injections of MMP-13, the major rodent interstitial collagenase, were not statistically significant in either group, and there were no differences in the protein expression of endogenous tissue inhibitors of matrix metalloproteinases (TIMPs). Fibrosis was present in both compensated and decompensated infarctions. However, these structural changes were unaccompanied by atrial arrhythmia, either supporting the contention that structural changes precede and are in some fashion causal in, or that the milieu and size of the atrium (critical mass hypothesis) are insufficient for, the maintenance of AF. A linear relation between the amount of atrial fibrosis in right atrial appendages taken at the time of open-heart surgery and the incidence of postoperative AF was recently demonstrated (15). Unfortunately, in the study by Boixel et al. (14), fibrosis was not quantified.

An apparent paradox is that an increase in MMP activity induced fibrosis, whereas a decrease in the amount of collagen might have been expected. This is because the total matrix collagen content is a function of both synthesis and degradation, and degraded products of matrix proteins serve as a stimulus for collagen synthesis; this in turn may result in increased deposition of poorly structured fibrotic tissue (16). Therefore, the MMPs result in collagen deposition and denaturation, and hence a change in both the content and quality of collagen.

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MMPs AND ATRIAL REMODELING

Matrix metalloproteinases (MMPs) comprise a large multigene family of structurally and functionally homologous neutral proteinases that play a critically important role in extracellular matrix turnover and are implicated in the pathogenesis of a variety of cardiovascular disease (17). The MMPs consist of three highly conserved domains: an amino-terminal propeptide, a catalytic domain containing zinc and calcium ions, and a hemopexin-like domain at the carboxy-terminal, which binds substrate and interacts with the endogenous tissue inhibitors of MMPs (TIMPs) (18).

The MMPs are secreted by fibroblasts, smooth muscle cells, endothelial cells, and myocytes as inactive zymogens, requiring cleavage of the pro-peptide by proteolysis for activation. The MMPs are classified according to substrate specificity (although several MMPs can degrade a number of matrix components) and domain organization, and they classically are subdivided into the interstitial collagenases (MMP-1, MMP-8, MMP-13), the gelatinases (MMP-2, MMP-9), the stromelysins (MMP-3, MMP-10), and an unclassified group (membrane-type, MMP-7, MMP-11, MMP-12). Regulation of MMPs is complex and occurs by gene transcription, protein activation, and inhibition by one of four TIMPs.

Activation of MMPs and disruption of the collagen struts and fibers are proposed to play important roles in subsequent cell slippage, eccentric hypertrophy, and changes in ventricular geometry after myocardial infarction (MI) and remodeling of the left ventricle in cardiomyopathy (19–22). Although there is rapidly accumulating data with respect to the role of MMPs in ventricular remodeling, aside from the study by Boixel et al. (14), there are few published data existing for the atrium. Recent data from our laboratory suggest that activation of MMPs is responsible for the structural remodeling of the left atrium in response to rapid atrial pacing (23). In that study, left atrial myocardium was examined from dogs with rapid pacing-induced atrial failure (400 beats/min for 6 weeks) and from control dogs. Activation of MMPs was measured using gelatin and casein zymography, and levels of the cardiac specific tissue inhibitor of metalloproteinase-4 (TIMP-4) and the TIMP-4/MMP complex were measured with Western blot analysis. In contrast to the study by Boixel et al., the activity of MMP-9 was selectively and significantly increased by ~50%, and the level of complexed TIMP-4 protein was significantly decreased by ~50% in samples from dogs with atrial failure. Differences in species and experimental models may be responsible for the disparate findings.

The ADAMs (a disintegrin and metalloproteinase) are transmembrane proteins that function (largely in unknown fashion) in a wide variety of biological processes (24). Although collagen degradation provides new integrin-binding sites that are necessary for cell survival, a complete loss of integrin signaling due to detachment from the extracellular matrix results in apoptosis, dilation, and failure—all features of the remodeling process (25,26). We recently identified increased levels of an ADAM and decreased levels of TIMP-4 in human heart end-stage failure (27). In addition, expressions of ADAM10 and ADAM15 were increased in atrial tissue from patients with chronic AF, and ADAM expression was correlated with the amounts of integrins β1 and β3 (28). These early data suggest that ADAMs may also be involved in the pathogenesis of atrial remodeling and fibrillation.

CAUTIONARY NOTES

Boixel et al. (14) suggest that atrial fibrosis results from hemodynamic loading, but in their model the roles of local and systemic neurohormonal stimuli, such as angiotensin II, bradykinin, and endothelin, remain uncertain. The renin-angiotensin system is considered to be important in producing the fibrotic changes that comprise structural remodeling (29). In addition, increased systemic aldosterone levels are noted in failing ventricles and in patients with AF (30,31), and may contribute to the atrial fibrosis in this model. It is also important to remember that remodeling involves many processes, and it is influenced not only by hemodynamic load, wall stresses, and neurohormonal activation, but also by apoptosis and changes in cytokines, nitric oxide production, and oxidative stress (32).

Remodeling is also a dynamic process, and activation of MMPs, like apoptosis, is time-dependent; however, in the study by Boixel et al. (14), MMPs and TIMPs were assessed only at a single time point. Moreover, MMPs are differentially activated and expressed according to the nature of the loading stimulus (e.g., pressure vs. volume overload) and the temporal profile (e.g., acute vs. chronic) (33). For example, in the rat, MMP/TIMP regulation evolves differentially during the 16 weeks after infarction; MMP-13 predominates in the early postischemic period, whereas MMP-14 increases during later remodeling. Protein levels of MMP-2, -9, -13, and -14 are post-transcriptionally increased in the ventricle. Although the time course of collagenolytic activity after MI suggests a correlation between such activity, ventricular remodeling, and systolic function (19), the details of the time course of atrial mechanical remodeling are not as well characterized, and these may have important implications for the termination of AF, atrial stunning after cardioversion, and the maintenance of sinus rhythm.

Conspicuously absent in the study by Boixel et al. (14) is an assessment of left atrial function, admittedly a daunting task in rodents. The cardiac interstitium and its fibrillar collagen matrix play a critical role in determining cardiac performance (34). Cardiac collagen maintains the structural integrity and overall geometry of the heart; but in addition, the extracellular matrix tethers and aligns individual myocytes and myofibrils, enabling optimal transduction and coordination of force generated during cardiac contraction. Although the mechanism is not clear, matrix alterations may produce an added hemodynamic stress, or may disturb
signaling between myocytes. The MMP activation may be linked to mechanical dysfunction in an additional manner: in situ zymography of explanted cardiomyopathic hearts demonstrated that gelatinases (MMP-2 and -9) were physically associated with the sarcomeres; and, in vitro, myosin heavy chain was digested by the gelatinases (35).

Conclusions. The MMPs can be regarded as potential etiologic agents in atrial remodeling for several reasons. First, there is biologic plausibility; the extracellular matrix is physically and biochemically in close communication with the cytoskeleton (e.g., β1 integrins). Second, defects in the dystrophin–dystroglycan–laminin complex produce dilated cardiomyopathy. Finally, and most convincingly, studies with MMP inhibitors in animal models and genetically engineered mice demonstrate salutary effects of MMPs on the course of cardiac dilation and heart failure (20,36–38). We wholeheartedly agree with Boixel et al. that studies with specific MMP inhibition in well-defined models of AF and structural remodeling are warranted.

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