Extracellular matrix alterations in the atria: insights into the mechanisms and perpetuation of atrial fibrillation

Christos A. Goudis, Eleftherios M. Kallergis*, and Panos E. Vardas

Department of Cardiology, University General Hospital, Heraklion, Crete, Voutes 71110, Greece

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Atrial fibrillation is the most common arrhythmia in clinical practice and is associated with increased cardiovascular morbidity and mortality. Atrial fibrosis, a detrimental process that causes imbalance in extracellular matrix deposition and degradation, has been implicated as a substrate for atrial fibrillation, but the precise mechanisms of structural remodelling and the relationship between atrial fibrosis and atrial fibrillation are not completely understood. A large number of experimental and clinical studies have shed light on the mechanisms of atrial fibrosis at the molecular and cellular level, including interactions between matrix metalloproteinases and their endogenous tissue inhibitors, and profibrotic signals through specific molecules and mediators such as angiotensin II, transforming growth factor-β1, connective tissue growth factor, and platelet-derived growth factor. This review focuses on the mechanisms of atrial fibrosis and highlights the relationship between atrial fibrosis and atrial fibrillation.

Keywords
- Atrial fibrosis
- Atrial fibrillation
- Extracellular matrix
- Collagen
- Angiotensin II
- Transforming growth factor-β1

Introduction

Atrial fibrillation is characterized by rapid and irregular activation of the atrium and is associated with increased cardiovascular morbidity and mortality. Electrical, contractile, and structural remodelling have been implicated in the pathology of atrial fibrillation and atrial fibrosis is the hallmark of structural remodelling. Atrial interstitial fibrosis has already been shown to increase with age, mitral valve disease, dilated cardiomyopathy, and myocardial ischaemia. Structural changes in the atria of patients with atrial fibrillation have been identified at the level of cardiomyocytes and extracellular matrix (ECM). Extracellular matrix predominately includes collagen types I and III, fibril, fibronectin, laminin, entactin, and fibromodulin. Extracellular matrix remodelling is the maladaptive response to changes in cardiac structure and function during the progression of heart disease. Degradation and deposition of ECM is a process tightly and dynamically regulated by the delicate balance between matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs).

The process of fibrosis involves reparative fibrosis, which replaces the degenerating myocardial cells, and reactive fibrosis, which causes interstitial collagen deposition. Interstitial fibrosis creates conduction delay causing the electrical impulse to propagate through alternative pathways and eventually to impinge on tissue that has already recovered excitability, causing reactivation and a further increase in the number of re-entrant circuits.

Mechanisms of atrial fibrosis

The precise mechanisms and signalling pathways involved in the development of atrial fibrosis are unknown, but many studies have already revealed complex interactions among neurohumoral and cellular mediators. Triggers for atrial fibrosis include the activation of the renin–angiotensin–aldosterone system (RAAS), inflammation, and oxidative stress.

Profibrotic signals

Multiple fibroproliferative signalling pathways result from profibrotic molecules and mediators in atrial fibrosis. Angiotensin II (Ang II), a known profibrotic molecule, plays a central role in collagen production. Transforming growth factor-β1 (TGF-β1), connective tissue growth factor (CTGF), and platelet-derived growth factor...
(PDGF) also serve as important mediators in the fibroproliferative process.

The RAAS is involved in structural remodelling and development of myocardial fibrosis. Angiotensin II is implicated in several diseases, including heart failure, myocardial infarction, cardiomyopathy, and atrial fibrillation. Angiotensin II type 1 receptor (AT1) receptors of Ang II are responsible for vasoconstriction, sodium and water retention, cardiac hypertrophy, and fibroblast stimulation. After being activated by Ang II, the AT1 receptors induce a phosphorylation cascade that activates mitogen-activated protein kinases (MAPKs), which stimulate proliferation of fibroblasts, cellular hypertrophy, and apoptosis.

The AT1 receptor was found to be up-regulated in the left atria of patients with atrial fibrillation, suggesting an association between increased AT1 activity, enhanced synthesis of ECM components, and the development of atrial fibrillation. In patients with chronic atrial fibrillation, an angiotensin-converting enzyme (ACE)-dependent increase in the amounts of activated extracellular signal-regulated kinase 1/extracellular signal-regulated kinase 2 (Erk1/Erk2) was found. In transgenic mice, cardiac-restricted ACE overexpression causes atrial dilatation with focal fibrosis and atrial fibrillation. Atrial Ang II levels increase early in the course of congestive heart failure induced by rapid ventricular pacing. In contrast, along with ACE, angiotensin-converting enzyme 2 (ACE2) degrades Ang II, while decreased ACE2 expression during atrial fibrillation affects the Ang II-dependent signalling pathway. In addition, atrial fibrillation can be induced by antagonistic regulation between ACE and ACE2 expression.

Angiotensin II treatment in rat hearts has been shown to cause an increase in fibrillin-1. Transforming growth factor β1 is a potent stimulator of collagen-producing cardiac fibroblasts through the Smad and Mad protein signalling pathway. Pathogenic effects of TGF-β1 seem to play a major role in myocardial infarction, hypertrophic and dilated cardiomyopathy, valve disease, and atrial fibrillation. Mice with constitutive expression of TGF-β1 developed selective fibrosis within the atria, but not in the ventricles, suggesting that atrial fibroblasts may be particularly sensitive to the actions of TGF-β1. A similar study, mice with increased expression of TGF-β1 were prone to atrial fibrillation development as a result of raised levels of atrial fibrosis. This finding also suggests that atria seem to be more susceptible than ventricles to the development of fibrosis in response to high TGF-β1. Rapid increases of TGF-β1 have been noticed in congestive heart failure induced by rapid ventricular pacing. Human atrial fibrogenesis in patients with atrial fibrillation is accompanied by a biphasic response, an early increase and later loss of responsiveness to TGF-β1. It appears that fibrosis progresses despite compensatory changes in the TGF-β1-signalling pathway.

High plasma concentrations of TGF-β1 and tissue inhibitors of matrix metalloproteinase (TIMP)-1 are potential non-invasive predictors for electroanatomical remodelling of left atrium in non-valvular atrial fibrillation. A specific polymorphism of TGF-β1 + 915 G → C at codon 25 was associated with the occurrence of atrial fibrillation and serum TGF-β1 level in essential hypertensive subjects. Other TGF-β1 polymorphisms are also involved in the induction of congenital heart block as a result of fibrosis, leading to a predisposition to atrial fibrillation. Transforming growth factor β1 also acts as a mediator of Ang II effects. Angiotensin II regulates TGF-β1 mRNA expression, protein production, and biological activity, while blockade of the AT1 suppresses TGF-β1 up-regulation.

Atrial fibrillation seems to induce profibrotic pathways in the kidney. In a porcine model, brief episodes of atrial fibrillation up-regulated TGF-β1 signalling and down-regulated neutral endopeptidase (NEP), the main enzyme in natriuretic protein metabolism, perhaps accounting for structural changes and alterations of renal function in the long term.

Connective tissue growth factor, a potent profibrotic factor, is a member of the CCN family (cysteine-rich61, CTGF, and nephroblastoma overexpressed) of early intermediate gene. It is implicated in fibroblast proliferation, cellular adhesion, angiogenesis, and ECM synthesis. In vitro, CTGF is induced by TGF-β1 in cardiac fibroblasts and myocytes, while up-regulation of CTGF stimulates fibroblast proliferation. Connective tissue growth factor up-regulation has been found in the failing heart. A recent study has shown that: (i) patients with atrial fibrillation had increased CTGF expression in the right atrium, and atrial dilatation was associated with elevated CTGF expression; (ii) CTGF expression was elevated in both atria of a porcine atrial fibrillation model; (iii) Ang II infusion induced CTGF expression in rat atria but not ventricles; and (iv) both cardiac fibroblasts and cardiomyocytes were responsible for the increased CTGF expression. Tachycardia of atrial myocytes induces paracrine secretion of Ang II and reactive oxygen species (ROS), which, in turn induce expression of CTGF and pro-collagen in co-cultured atrial fibroblasts through increased TGF-β1 expression. The small GTP-binding protein Rac1 is a member of the Rho GTPase superfamily of intracellular signal transducers. Angiotensin II activates CTGF via activation of Rac1 and nicotinamide adenine dinucleotide phosphate oxidase, leading to up-regulation of Cx43, N-cadherin, and interstitial fibrosis, thus contributing to the signal transduction of atrial structural remodelling.

In the left atrial myocardium of patients with atrial fibrillation, Rac1 GTPase mediates up-regulation of fibronectin and CTGF. Transgenic mice with cardiac-specific overexpression of a constitutive active Rac1 mutant (RacET mice) exhibited increased expression of CTGF and interstitial fibrosis, whether or not the mice were in sinus rhythm or atrial fibrillation, suggesting that increased Rac1 activity and not atrial fibrillation precedes atrial remodelling. Endothelin-1 signalling triggers CTGF expression in cultured adult mouse atrial-muscle cells. Diabetes mellitus promotes atrial structural remodelling via activation of the AGE–RAGE system (advanced glycation end-product and the receptor for AGE) with up-regulating CTGF. Further studies are required to determine the exact role of endothelin-1 and AGEs in atrial fibrillation. Although CTGF is widely accepted as a profibrotic factor, there is a lack of in vivo studies clearly linking CTGF overexpression and fibrosis induction. So far, the major evidence for the profibrotic action of CTGF is based on the fact that fibrotic events are accompanied by CTGF up-regulation, while a recent study has shown that CTGF itself does not induce cardiac fibrosis. Certainly, further studies are required to determine the exact mechanisms of CTGF in atrial fibrosis.

Platelet-derived growth factor, a member of the PDGF/vascular endothelial growth factor family, is highly expressed in the
myocardium throughout development and adulthood. It stimulates proliferation, migration, differentiation, and physiological function of mesenchymal cells.66 Development of dilated cardiomyopathy and heart failure has been shown in transgenic mice with cardiac-specific PDGF overexpression.67–69 Mast cells are mediators of immune and allergic responses and are critically involved in atrial fibrillation initiation in stressed mouse hearts. Pressure overload induced mast cell infiltration and fibrosis in the mouse atrium through PDGF-A and enhanced atrial fibrillation susceptibility following atrial burst stimulation.65 The most important trigger for mast cell activation is antigen- and immunoglobulin (IgE)-dependent aggregation of IgE receptor, but mast cells can also be activated by various factors, such as growth factors, cytokines, and hormones.64,65 In addition, interactions between mast cells and connective tissue matrix components have profound influences on the distribution of mast cells in tissues.66–68 Further studies are needed to confirm the importance of mast cell-derived PDGF-A in the pathogenesis of atrial fibrillation.

**Cellular mediators**

Besides profibrotic factors, cellular mediators are involved in cardiomyocyte-fibroblast crosstalk in the promotion of atrial fibrosis. Paracrine and autocrine functions of cardiomyocytes and fibroblasts are implicated in collagen production. Mechanical stretch in cardiac fibroblasts increases Ang II and TGF-β1 expression69 and collagen synthesis.70,71 Cardiomyocytes cannot synthesize collagen by themselves, but stretched cardiomyocytes produce Ang II and TGF-β1, which interact with neighbouring fibroblasts and promote collagen synthesis.72 As a result, atrial dilation contributes to structural remodelling and domestication of atrial fibrillation.73 Tachycardia-paced atrial cardiomyocytes have been shown to secrete factors that cause differentiation to a secretory phenotype in cardiac fibroblasts.74 The current study of cardiomyocyte-fibroblast crosstalk in atrial myocytes from patients with atrial fibrillation has revealed that in diseased atria, myocyte myocytes are in a dedifferentiated state, resembling that of immature muscle cells. Furthermore, in vitro fibroblast proliferation prevents myocytes from redifferentiation and recovery of excitability, indicating that the nature of cell-to-cell contact would seem to play a key role in maintaining the normal structure and function of atrial myocytes.75

**Inflammation**

Inflammation has been implicated in the pathogenesis of atrial fibrillation. Inflammatory mediators, through extracellular signal-regulated kinases (ERKs), c-jun N-terminal kinases (JNKs), MAPKs, and ROS, regulate ECM metabolism and promote collagen synthesis. In a canine model, inflammatory infiltrates and fibrosis were found after pacing-induced sustained atrial fibrillation.76 The first clinical observations pointing to the inflammatory origin of atrial fibrillation were detected in patients with acute perimyocarditis who developed atrial arrhythmias.77 Abnormal atrial histology in terms of leucocyte infiltration, myocyte necrosis, and fibrosis has been observed in tissue samples of patients with atrial fibrillation.78 Leucocytes were found to infiltrate the atrial myocardium both in patients with atrial fibrillation with an underlying structural heart disease and in patients with lone atrial fibrillation.79,80 Indeed, elevated leucocyte counts following coronary artery bypass grafting (CABG) independently predict post-surgery atrial fibrillation, indicating a mechan link between these inflammatory mediators and atrial fibrillation occurrence.81,82 Corroborating this assumption, polymorphonuclear neutrophils (PMN) infiltration is a characteristic feature of the canine sterile pericarditis model, which is the experimental counterpart of post-surgery atrial fibrillation in humans. Pericarditis is induced by surgical opening of the thorax, incision of the pericardium, and irritation of the atrial surface with talcum powder.83 This procedure not only leads to an increase in the systemic inflammatory markers high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6)84 but is also characterized by atrial infiltration by PMNs and myeloperoxidase accumulation.85 Inflammatory response following CABG, in particular elevation of hsCRP levels and activation of the complement cascade also correlated with the occurrence of atrial fibrillation.86,87 The observation that CRP relates to left atrial size and dysfunction lends further support of an association between inflammation and structural remodelling.88 C-reactive protein levels were significantly and independently associated with the development of future atrial fibrillation,89 and patients in persistent atrial fibrillation had higher CRP levels than those with paroxysmal atrial fibrillation and control groups, indicating the possible relationship between CRP levels and the chronicity of the arrhythmia.90 Notwithstanding the fact that hsCRP levels were also elevated in atrial fibrillation patients devoid of other risk factors for the disease91 and were recently identified as prognostic markers of both incidental and recurrent atrial fibrillation after either electrocardioversion or pulmonary vein isolation,92 the above findings were not supported by a recent study, which revealed that there was no difference in CRP levels between patients with lone atrial fibrillation and controls,93 suggesting that CRP is probably not a marker of the arrhythmia, but rather an outcome of the underlying cardiac pathology. Interleukin-6 is a cytokine secreted by both activated leucocytes and fibroblasts that stimulates the Jak/STAT (Janus kinase/signal transducers and activators of transcription) pathway via glycoprotein 130. Tumour necrosis factor-alpha (TNF-α) secreted by macrophages and leucocytes induces activation of the transcription factor nuclear factor (NF)-κB. Interleukin-6, IL-1, and TNF-α can directly decrease collagen synthesis and procollagen mRNA expression in cardiocytes and can increase the breakdown of collagen by increased MMP activity.94–98 High plasma IL-6 levels have been correlated with the presence and duration of atrial fibrillation and increased left atrial diameter.99 Another cytokine, IL-8, is a powerful chemoattractant for neutrophils and was found to be elevated in patients with atrial fibrillation in a recently study by Liuba et al.100 An alteration in the distribution of atrial connexins 40 and 43101 has been associated with inflammation. Abnormal expression of connexin proteins lead to impaired intercellular communication and reduced conductance between neighbouring cells that has been linked to atrial fibrillation.102 Increased endothelial expression of adhesion molecules [vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1)] seems to be an important link between the initiation of proinflammatory and prothrombogenic mechanisms responsible for atrial thrombogenesis. There is evidence that atrial fibrillation increases the expression of VCAM-1 in the
atrial endocardium, and this expression is higher in the left than in the right atrium. The prothrombogenic process of endocardial remodelling can be attenuated substantially by treatment with angiotensin receptor blockers, which suggests that Ang II has a significant pathophysiological role in endocardial remodelling.103

Oxidative stress
Oxidative stress within atrial tissue during atrial fibrillation plays a potential role in structural remodelling of the atrium.104 – 106 Oxidative changes in atrial fibrillation result in mitochondrial DNA damage and up-regulation of NADPH oxidase, an enzyme that catalyzes the production of superoxide from oxygen and NADPH.107,108 Myocardial NADPH oxidase, and to a lesser extent NO synthases (NOSs) and mitochondrial oxidases, contributes significantly to superoxide production in the fibrillating human atrial myocardium.109 Reactive oxygen species (hydrogen peroxide, superoxide anion, hydroxyl radicals, and peroxynitrite) trigger signalling cascades through ERKs, JNK, and MAPKS, resulting in specific redox-regulated modulation and gene expression in both cardiac myocytes and fibroblasts.110 Such redox-sensitive regulation appears to play an important role in the development of several components of the phenotype of the failing heart: for example cardiomyocyte hypertrophy interstitial fibrosis and chamber remodelling.111 Tachypacing in cultured atrial-derived myocytes promotes myofibril degradation through TGF-β1 signalling and increased oxidative stress including up-regulation of NADPH oxidases.112 Reactive oxygen species also directly activate MMPs post-translationally and lead to decreased TIMP levels and collagen synthesis.113,114 Furthermore, ROS have been shown to cause direct activation of MMPs in conditioned media from cardiomyocytes.115 In a canine model with pacing-induced atrial fibrillation, increased oxidative stress due to calcium accumulation in the atria resulted in a cellular redox state that promoted the initiation and maintenance of atrial fibrillation.116 Besides NADPH oxidase, Ang II and inflammatory cytokines also stimulate ROS production. There is evidence that Ang II increases NADPH oxidase-mediated superoxide production through activation of the AT1 receptor, whereas inhibition of Ang II production ameliorates oxidative stress in the vasculature.117 The cDNA microarray technique was proven to be useful for investigating transcription profiles in atrial fibrillation patients and revealed that the gene expression pattern of myocardial tissues can be associated with oxidative stress, resulting in a significant increase in ROS.118 Thus, alteration of the redox status through oxidative-related gene expression promotes atrial remodelling. Hydrogen peroxide significantly alters the electrophysiological characteristics of pulmonary veins and the left atrium through activation of free radicals, which may in turn facilitate the occurrence of atrial fibrillation.119

Although the levels of derivatives of the reactive oxidative metabolites (DROMs) were shown to be higher in patients with persistent atrial fibrillation than in patients with paroxysmal atrial fibrillation, the significance of this finding is uncertain, as it remains unclear at present whether DROMs are the cause or the result of persistent atrial fibrillation. Surprisingly, DROMs do not correlate to left atrial size despite a larger diameter in persistent atrial fibrillation patients and the potential role of oxidative stress on mechanical remodelling.120

Matrix metalloproteinases and atrial remodelling in atrial fibrillation
Additional important contributing factors to ECM remodelling in the heart are MMPs. Matrix metalloproteinases are a family of zinc-dependent endopeptidases that are responsible for degradation of all the matrix components between cells. An abnormal increase in MMP activity results in remodelling of matrix proteins and ECM remodelling,121 – 123 whereas TIMPs directly inhibit the proteolytic activity of activated MMPs by forming tight-binding non-covalent 1:1 stoichiometric complexes with them.124 Cardiac MMP expression and activity increases in a number of pathological conditions, such as heart failure and myocardial infarction.15 Many recent studies focus on altered MMP and TIMP expression and activity in both clinical and animal studies in atrial fibrillation. Matrix metalloproteinase-9 protein level was up-regulated and TIMP-1 protein level was down-regulated in a canine model with atrial fibrillation compared with controls.127 The activity of MMP-9 was also selectively and significantly increased by ~50%, and the level of complexed TIMP-4 protein was significantly decreased by ~50%, in samples from dogs after rapid pacing-induced atrial failure.128 In another canine model of heart failure, MMP inhibition attenuated atrial remodelling and vulnerability to atrial fibrillation.129 Up-regulation of MMP-9, TIMP-1, and TIMP-3 was reported in a porcine model after rapid atrial pacing-induced atrial fibrillation130 and, besides collagen, changes in other ECM proteins such as fibrillin or fibronectin were also found to be associated with the development of atrial fibrillation in pigs.131 In a canine model of atrial fibrillation, ECM-related transcripts in atria, after ventricular tachypacing-induced congestive heart failure, are consistent with a fibrotic pathophysiology.132 In patients with atrial fibrillation, an increase in the expressions of MMP-1, -3, -7, -9, and TIMP-1, -2, -3, -4 in atrial tissue was reported that contributed to atrial structural remodelling and atrial dilatation.133 Atrial ECM remodelling manifested by the selective down-regulation of TIMP-2, along with up-regulation of MMP-2 and collagen volume fraction in the atrium, was associated with the development of sustained atrial fibrillation in patients with cardiomyopathy and heart failure.8 Enhanced MMP-9 activity, along with selective down-regulation of TIMP-1 expression in atrial fibrillation, promotes the process of atrial structural remodelling.134,135 Decreased plasminogen activator inhibitor (an inhibitor of a potent activator of many MMPs) and tissue metalloproteinase inhibitor expression may promote increased metalloproteinase activity with increasing duration of human atrial fibrillation.136 Collagen content seems to be greater within the atrial myocardium and lower in the ventricular myocardium in patients with atrial fibrillation and heart failure. The presence of atrial fibrillation in these patients may modulate MMP and TIMP levels and ECM composition in the atrial myocardium.137

Perpetuation of atrial fibrillation
Even though it now constitutes common understanding that ‘atrial fibrillation begets atrial fibrillation’, the progressive nature of atrial fibrillation is often further demonstrated by patients who initially present with paroxysmal atrial fibrillation and who then progress to persistent and eventually develop permanent atrial fibrillation.
It has also long been established that both electrophysiological alterations and anatomical substrates are critical for atrial fibrillation generation, maintenance, and perpetuation. The term electrical remodelling refers to the alterations in ion channel gene expression which produce shortening of the effective refractory period and loss of rate adaptation, in response to even brief episodes of rapid atrial rates, thus facilitating the appearance of multiple re-entrant wavelets increasing the likelihood of atrial fibrillation initiation and perpetuation. However, pure electrical remodelling has not been able to fully explain the development of sustained atrial fibrillation. Since atrial fibrillation-induced effective refractory period alterations recover completely before atrial fibrillation becomes sustained, other factors must be involved in the perpetuation of the arrhythmia, suggesting that structural, rather than ionic, remodelling may be the primary contributor to atrial fibrillation stabilization. Fibrosis refers to an excessive deposition of ECM due to both increased collagen synthesis and unchallenged or decreased collagen degradation as a result of mechanical overload of the tissue or tissue damage. Augmented interstitial fibrosis modifies the pattern of myocyte apposition, rearranges atrial myocyte connections, and alters cell-to-cell interaction and communication. The combination of normal and diseased atrial fibres in conjunction with local fibrosis results in spatial dispersion of atrial refractoriness and causes inhomogeneous localized conduction abnormalities, including intra-atrial conduction block and slow conduction. Moreover, fibrosis of the atrial tissue can facilitate the development of ectopic pacemakers and late potentials as a result of inhomogeneous stimulus conduction, and can also lead to fluctuations in membrane potentials. Thus, atrial fibrosis can change a homogeneously activated atrium into a discordant, inconsistent, and fragmented architecture. Augmented interstitial fibrosis may increase atrial susceptibility to atrial fibrillation, since it is known that atrial re-entrant arrhythmias are facilitated by impairment of atrial conduction and by the presence of adjacent atrial regions with disparate refractory periods. Furthermore, according to the current definition of atrial fibrillation, it results from multiple re-entrant circuits of various size and conduction velocities that propagate randomly through the atria and can be initiated by triggers, such as premature atrial contractions arising from focally discharging cells located most commonly in the myocardial sleeves extending from the left atrium into the pulmonary veins. The ability of a single extrastimulus to initiate atrial fibrillation has been associated with the existence of a susceptible underlying substrate, which is characterized by local inhomogeneities in conduction and refractoriness. Changes in ECM composition may constitute a background for these electrophysiological alterations, facilitating the induction of atrial fibrillation by appropriate triggers. In post-operative atrial fibrillation, transient factors related to surgery (sympathetic stimulation, inflammation, and oxidative stress) contribute to the occurrence of the arrhythmia. Among these transient predisposing factors, sympathetic activation appears to be more relevant than inflammation and oxidative stress. Despite the importance of transient surgery-induced factors, the majority of post-operative atrial fibrillation cases occur in atria with a pre-existing atrial fibrillation substrate due to a long-lasting structural remodelling process. Atrial dilatation, a known risk factor for the initiation and sustainability of atrial fibrillation, has also been associated with fibrosis and subsequent heterogeneity of conduction. The original concept of mechanoelectric feedback described electrophysiological changes induced by acute stretch. However, chronic stretch describes a different kind of mechanoelectric feedback characterized by signalling pathways known to stimulate fibroblast proliferation, promote cellular hypertrophy, and to activate matrix protein synthesis leading to fibrosis. A Disintegrin And Metalloproteinase (ADAM) form a large family of membrane-bound glycoproteins that function in proteolysis, signalling, adhesion, and fusion. Because of their disintegrin and metalloproteinase activity, ADAMs are known to regulate cell—cell and cell—matrix interactions and may thereby influence the architecture of cardiac tissue. Enhanced ADAM-dependent disintegrin and metalloproteinase activity suggests a molecular mechanism that also contributes to the dilatation of fibrillating human atria.

Conclusion

Atrial fibrillation plays a key role in the development and persistence of atrial fibrillation. The increase in ECM deposition results in abnormal conduction through the atria, thus creating a substrate for atrial fibrillation. The molecular pathways involved in atrial fibrosis are beginning to emerge. Renin—angiotensin system, TGF-B1, CTGF, PDGF, inflammation, and oxidative stress, through structural remodelling, are particularly involved in the pathogenesis of atrial fibrillation, suggesting possibilities for evolving upstream therapies and new therapeutic approaches in the management of the arrhythmia. Renin—angiotensin—aldosterone system inhibitors, statins, and possibly n-3 polyunsaturated fatty acids, beyond their conventional indications, may modify the arrhythmia substrate responsible for atrial fibrillation. This effect may be due to prevention or possibly reversal of structural changes in the atrial myocardium, and treatment of the underlying cardiovascular disease that promotes the development of atrial fibrillation. In the secondary prevention, however, upstream therapies have failed, so far, to demonstrate any effect on atrial fibrillation recurrences or major cardiovascular outcomes. Several key issues in which fibrosis alters atrial function and interacts with other pathophysiological mechanisms to promote the initiation and maintenance of atrial fibrillation need to be resolved.

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References


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