Cardiac Fibrosis in Patients With Atrial Fibrillation
Mechanisms and Clinical Implications

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ABSTRACT
Atrial fibrillation (AF) is associated with structural, electrical, and contractile remodeling of the atria. Development and progression of atrial fibrosis is the hallmark of structural remodeling in AF and is considered the substrate for AF perpetuation. In contrast, experimental and clinical data on the effect of ventricular fibrotic processes in the pathogenesis of AF and its complications are controversial. Ventricular fibrosis seems to contribute to abnormalities in cardiac relaxation and contractility and to the development of heart failure, a common finding in AF. Given that AF and heart failure frequently coexist and that both conditions affect patient prognosis, a better understanding of the mutual effect of fibrosis in AF and heart failure is of particular interest. In this review paper, we provide an overview of the general mechanisms of cardiac fibrosis in AF, differences between fibrotic processes in atria and ventricles, and the clinical and prognostic significance of cardiac fibrosis in AF. (J Am Coll Cardiol 2015;66:943–59) © 2015 by the American College of Cardiology Foundation.

The mechanisms of atrial fibrillation (AF) are complex and associated with structural and electrical remodeling in the atria and ventricular myocardium. The key electrophysiological mechanisms of AF include: 1) focal firing due to triggered activity (early and delayed afterdepolarizations); 2) multiple re-entries due to shortening of the action potential; and 3) heterogeneity of impulse conduction caused by atrial fibrosis. Development and progression of atrial fibrosis are the hallmark of structural remodeling in AF and are considered to be the substrate for AF perpetuation. Advanced atrial fibrosis is associated with more frequent paroxysms of AF, transformation of the arrhythmia into a permanent type, and reduced effectiveness of antiarrhythmic drug therapy (1,2).

Despite a large body of experimental and clinical evidence supporting the role of atrial fibrosis in AF, data on fibrotic processes in the ventricles of patients with AF are limited. The available data indicate that ventricular fibrosis may be at least partly responsible for the impaired cardiac relaxation and contractility seen in many patients with AF. Cardiac fibrosis may be implicated in complex interactions between AF and heart failure (HF), each of which can be the cause and the consequence of the other. Given that AF and HF coexist at high frequency, and their clear prognostic significance (e.g., increased risk of hospitalization or death related to HF deterioration), a better understanding of the role of cardiac fibrosis in the pathogenesis of AF and its complications is important (3). The present review focuses on general

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mechanisms of cardiac fibrosis in AF, differences between fibrotic processes in the atria and ventricles, and the clinical and prognostic effect of cardiac fibrosis in AF.

MECHANISMS OF CARDIAC FIBROSIS

Progressive accumulation of fibrotic tissue in myocardium is one of the major components of cardiac remodeling. Formation and redistribution of connective tissue fibers modulate myocardial geometry to adapt to new conditions of (patho)physiological functioning and to prevent or minimize the effects of new mechanical, chemical, and electrical stimuli. This adaptation process involves both the cellular components of the myocardium and the extracellular matrix (ECM), an acellular component of the heart, containing a variety of fibers, with collagen predominant (4).

Excessive ECM production in adults is commonly associated with the pathogenesis of cardiovascular diseases, resulting in abnormalities of cardiac contraction and relaxation, and thus inevitably leading to HF (5).

Although collagen deposition in the healthy heart is restricted to maintenance of heart architecture, during progression of various cardiac disorders, the collagen network undergoes quantitative and qualitative changes leading to excessive accumulation of collagen, either in regions of cardiomyocyte loss (e.g., in myocardial infarction, reparative fibrosis) or diffusely, in areas of the myocardium not involved in the focal injury (e.g., in dilated cardiomyopathy, reactive fibrosis) (4,5).

CARDIAC FIBROBLASTS AND MYOFIBROBLASTS. Both cellular and extracellular components take part in the remodeling process. Cardiac fibroblasts play a pivotal role in formation of the ECM. They are numerous within the myocardium and can account for up to 60% of cells in cardiac muscle (6). Thus, cardiac fibroblasts outnumber even cardiomyocytes, although the latter cells largely determine total myocardial mass.

The population of cardiac fibroblasts in healthy adult hearts is maintained at a relatively low level and is predominantly composed of resident fibroblasts and cells undergoing an epithelial-to-mesenchymal transition. In pathological conditions, fibroblasts dramatically increase in number via differentiation from several cell lineages, including monocytes, endothelial cells, bone marrow-circulating progenitor cells, and pericytes (7–9).

The physiological functions of fibroblasts extend beyond metabolism of the ECM. Tight connections between the fibroblasts, fibers of the ECM, and other cellular components form a multidimensional network that acts as an integral sensor of dynamic changes in the various mechanical, chemical, and electrical stimuli in the myocardium. In response to these stimuli, this complex system adjusts ECM turnover and regulates cardiomyocyte hypertrophy and, to a smaller extent, cardiomyocyte proliferation; it also triggers activation of fibrotic and inflammatory pathways. Of note, cardiac fibroblasts exhibit various phenotypes depending on the surrounding microenvironment (10).

Cardiac fibroblasts might also contribute to electrical remodeling in AF due to their different electrophysiological properties compared with the surrounding cardiomyocytes. Fibroblasts are essentially nonexcitable cells but can transfer currents between cardiomyocytes via connexins in vitro. This action may result in heterogeneity of current conduction, shortening of action potentials, depolarization of resting cardiomyocytes, and induction of spontaneous phase 4 depolarization (11). Consequently, fibroblasts might be directly involved in the occurrence and perpetuation of re-entry, although further research is needed to provide in vivo evidence for this claim. Interestingly, computer modeling found proliferation of myofibroblasts in AF and their electrical interaction with cardiomyocytes to be sufficient for re-entry formation, even in the absence of fibrosis (12).

Myofibroblasts are cells that play a particularly significant role in cardiac fibrosis. They are derived from cardiac fibroblasts but have an ~2-fold higher capacity to synthesize collagen. Compared with cardiac fibroblasts, myofibroblasts do not appear in healthy myocardium, are more responsive to proinflammatory and profibrotic stimuli, and are capable of synthesizing a large variety of cytokines and chemokines (13). Importantly, myofibroblasts contain alpha-smooth muscle actin and adhesion complexes (fibronexus). The latter binds myofibroblast internal microfilaments to ECM proteins that help to provide contractile force to the surrounding ECM.

A range of growth factors, cytokines, and hormones, as well as mechanical stretch and hypoxia, regulate ECM turnover and cardiac fibroblast activity. These factors determine fibroblast gene expression, their differentiation, and the level of collagen synthesis.

TRANSFORMING GROWTH FACTOR-β1 SIGNALING. Among the numerous regulatory factors, angiotensin II and transforming growth factor beta-1 (TGF-β1) (Figure 1)
are the most potent stimulators of collagen synthesis by cardiac fibroblasts (14,15). TGF-β1 produces its effects via binding to the dimerized TGF-β1 receptor (which consists of 2 receptors, TβRI and TβRII) in the extracellular space. Ligand-receptor binding results in a cascade of phosphorylation reactions during which inactive Smad proteins 2, 3, and 4 form the Smad complex (16).

The Smad complex then translocates to the nuclei of target cells, where it regulates expression of genes involved in fibrogenesis (e.g., connective tissue growth factor [CTGF] and periostrin) via appropriate regulatory regions (17,18). This action results in production of the so-called matricellular protein, a profibrotic protein secreted into the ECM. The matricellular protein modulates intercellular and cell-matrix interactions that further stimulate ECM protein synthesis but are not directly involved in ECM structure and mechanical organization or differentiation of cardiac fibroblasts into myofibroblasts (19).

TGF-β-activated kinase 1, an alternative to the Smad pathway for TGF-β1-induced fibrosis, is a member of the mitogen-activated protein kinase family (20). Importantly, apart from activation of fibroblast and collagen synthesis, TGF-β1 can also induce apoptosis of cardiomyocytes (21).

Of note, angiotensin II is not able to induce cardiac hypertrophy and fibrosis in the absence of TGF-β1, but it up-regulates TGF-β1 synthesis, Smad2 phosphorylation, and nuclear translocation of the Smad complex and increases Smad deoxyribonucleic acid–binding activity. TGF-β1, in turn, can directly stimulate expression of angiotensin II type 1 receptor (22). Angiotensin II also predisposes to fibrosis by promoting expression of profibrotic factors, such as endothelin-1. In conjunction with aldosterone, angiotensin II promotes oxidative stress (i.e., excess production of reactive oxygen species) and inflammation, mainly by activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (23,24).

**MATRIX METALLOPROTEINASES AND TISSUE INHIBITORS OF MATRIX METALLOPROTEINASES.** The remodeling and maintenance process of the extracellular space includes not only synthesis but also coordinated degradation of the ECM proteins. Matrix metalloproteinases (MMPs) and their tissue inhibitors, synthesized by cardiomyocytes and cardiac fibroblasts, are intimately involved in the maintenance of ECM homeostasis (25). Indeed, MMP expression increases in a time-dependent manner with left ventricular dysfunction and dilation (26). Overexpression of MMP1 has been shown to cause compensatory hypertrophy and increased collagen concentration within the myocardium. In contrast, targeted deletion...
of MMP2 results in amelioration of left ventricular remodeling (27). Not surprisingly, MMP activity increases in line with TGF-β₁ expression within the myocardium and correlates with the level of inflammation and oxidative stress (28).

Furthermore, collagen and matrix fragments produced by the action of MMP1 themselves form bioactive molecules, so-called matrikines, and release ECM-embedded proinflammatory and profibrotic factors. They promote fibroblast activation and transition to a myofibroblast phenotype, and they effectively stimulate connective tissue synthesis by serving as ligands of leukocyte integrins and other cell-activating receptors (25,29). The latter explains the progression of fibrosis when MMP activity is high, despite the primary MMP function being directed toward matrix degradation. MMP activity is regulated via tissue inhibitors of MMPs and reversion-inducing cysteine-rich protein with Kazal motifs, overexpression of which has been found to blunt angiotensin II–induced MMP activation and cardiac fibroblast migration (30).

**REGULATORY ROLE OF MICRORIBONUCLEIC ACIDS.** Nuclear microribonucleic acids (miRs) play important regulatory roles in cardiac remodeling (31). They are referred to as endogenous, single-stranded, short (~22 nucleotides), noncoding ribonucleic acids. miRs degrade or inhibit the translation of their target messenger ribonucleic acids at the post-transcriptional level, thus regulating gene expression (32).

Several miRs are involved in fibrogenesis. miR-133 and miR-30 regulate cardiac fibrosis by repressing CTGF expression. They were found to be down-regulated in left ventricular hypertrophy associated with increased CTGF expression (33). miR-133 knockout mice developed advanced fibrosis and HF with predisposition to sudden death (34). In contrast, miR-133 overexpression resulted in decreased collagen synthesis by fibroblasts, reduced myocardial fibrosis, and apoptosis (33,35). miR-21 is involved in up-regulation of 1 of the profibrotic pathways (ERK) and promotes MMP2 expression (36,37). Interestingly, it also produces protective effects, including defense against oxidative stress, inhibition of proapoptotic factors, and increased expression of antiapoptotic genes (38). Finally, miR-29 is associated with deposition of collagen types I and III. Up-regulation of miR-29 leads to down-regulation of these proteins and vice versa (39).

**INFLAMMATION.** AF is common in patients with overt inflammatory states of cardiac and noncardiac location (e.g., myocarditis, pericarditis, pneumonia, and inflammatory bowel disease), but low-grade subclinical inflammation (e.g., in coronary heart disease) also contributes to pathogenesis of the arrhythmia (Figure 2) (40). Regardless of whether AF is a cause or consequence of the inflammatory process, it is related to oxidative stress perpetuated by myocardial infiltration with inflammatory cells (e.g., macrophages), which is accompanied by release of reactive oxygen species. Inflammation is further

![Figure 2](image-url)
exacerbated by activation of the renin-angiotensin-aldosterone system, followed by activation of NADPH oxidase. These processes consequently trigger TGF-β1 signaling and structural and electrical remodeling (41). Various inflammatory cytokines and chemokines, such as interleukin-1 and -6, tumor necrosis factor-alpha, and monocyte chemoattractant protein 1, are up-regulated in AF and linked to progression from paroxysmal to chronic AF and AF recurrence post-cardioversion (40).

Inflammation plays a particular role in postoperative AF (e.g., after coronary artery bypass graft, valvular replacement surgery) and post-catheter ablation. In a recent meta-analysis of 925 post-operative patients, serum C-reactive protein was a potent predictor of new-onset AF (42). Similarly, a meta-analysis of 7 studies of post-ablation patients confirmed the predictive role of C-reactive protein for AF recurrence (43).

AGING AND CARDIAC FIBROSIS

The prevalence of AF significantly increases in the elderly. Cardiac aging is a complex process, featuring progressive decline in heart functions and ventricular and atrial remodeling. This process includes reduction in cardiomyocyte numbers, hypertrophy of the remaining cardiomyocytes, alteration of myofibrillar orientation, proliferation of cardiac fibroblasts, and collagen deposition. Progressive fibrosis is a hallmark of the aging heart, as confirmed in animal and human studies showing an increased collagen volume fraction in the myocardium and by result of imaging (44).

Age-related cardiac fibrosis reflects multiple processes that accompany cardiac senescence, chronic activation of the renin-angiotensin-aldosterone axis, excessive beta-adrenergic and endothelin signaling, activation of the TGF-β1 pathway, disruption of intracellular calcium homeostasis, cardiomyocyte apoptosis, recruitment of mononuclear cells and fibroblast progenitors, and down-regulation of the mitochondrial nicotinamide adenine dinucleotide-dependent deacetylase sirtuin-1 (45).

Increased generation of reactive oxygen species and diminished antioxidant capacity are major contributors to age-related myocardial remodeling (Figure 3). Oxidative molecules derive from oxidative phosphorylation processes in mitochondria, increased NADPH oxidase activity, uncoupled nitric oxide synthase function, lipid oxidation within peroxisomes, and up-regulation of cyclooxygenases and xanthine oxidase (46). Chronic oxidative stress leads to the persistence of low-grade inflammation, thus further accelerating cardiac fibrosis. Among the important regulators of aging-related processes is miR-34a, with phosphatase 1 nuclear-targeting subunit (PNUTS), also known as PPP1R10, as the target. Aging-induced expression of miR-34a and inhibition of PNUTS is associated with telomere shortening, deoxyribonucleic acid damage, cardiomyocyte apoptosis, and impaired functional recovery after ischemic injury (47). Hence, profibrotic mechanisms involved in AF pathogenesis are clearly enhanced by aging.

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**FIGURE 3 Oxidative Stress in Cardiac Fibrosis**

ERK — extracellular signal-regulated kinase; JNK — c-Jun N-terminal kinase; MAPK — mitogen-activated protein kinase; NADPH — reduced nicotinamide-adenine dinucleotide phosphate; NOS — nitric oxide synthase; p38 — protein 38; ROS — reactive oxygen species; other abbreviations as in Figure 2.
Close interaction between cardiomyocytes and cardiac (myo)fibroblasts is essential for their function. These interactions are facilitated by multiple paracrine signals, including those predisposing to fibrosis (Central Illustration). Cardiomyocytes, cardiac fibroblasts, and myofibroblasts share many common molecular pathways (mediated by angiotensin II, TGF-β1, endothelin, and cytokines). However, the response to signaling may vary depending on cell type: hypertrophy and reduced cell survival of cardiomyocytes are promoted by angiotensin II-induced release of TGF-β1 and endothelin-1 from fibroblasts, whereas angiotensin II was also found to trigger release of TGF-β1 and endothelin-1 from cardiomyocytes and to stimulate fibroblast proliferation and differentiation to the myofibroblast phenotype and synthesis of ECM components (48). Greater proliferation of fibroblasts was observed around cardiomyocytes expressing angiotensin II receptor type 1 receptors, compared with cells with the angiotensin II receptor type 1 gene knocked out (49).

There are also differences between cardiomyocytes and cardiac fibroblasts in receptor density and receptor kinase activity, which may interfere with the final effects of effector molecules. For example, fibroblasts are known to carry more angiotensin II receptors than cardiomyocytes (49). Multiple other regulatory substances are implicated in the interplay between fibroblasts and cardiomyocytes (e.g., fibroblast growth factor 2, interleukins, natriuretic peptides, and miRs) (48). Some stimuli are attributed predominantly to fibroblasts (e.g., platelet-derived growth factor [PDGF], fibroblast growth factor 2, and activation by mechanical stretching), whereas abnormalities in calcium handling are largely seen in cardiomyocytes (50).

Cardiac remodeling requires fibrosis as an essential component and is a complex process that also incorporates multiple other pathways, such as hypoxia signaling, the osteoprotegerin/RANK/RANKL axis, and Ca^{2+} signaling. A detailed description of these pathways is beyond the scope of the current review.

In summary, the ECM is a macromolecular, metabolically active, dynamic network of fibers (predominantly collagen) and cells (predominantly cardiac fibroblasts with a capacity to differentiate into myofibroblasts) that is essential for normal heart function. Cells surrounding and infiltrating the ECM are linked to the fibrillar component and hence are capable of responding to mechanical stretch and stress, as well as to a variety of autocrine and paracrine stimuli by change in their proliferation, migration, and intensity of collagen synthesis. These processes may have an unfavorable role in cardiac remodeling and the pathogenesis of cardiovascular diseases.

**atrial fibrosis in AF**

A variety of signaling systems are involved in the promotion of atrial fibrosis, as evidenced by numerous human and animal data (Tables 1 and 2).
Atrial fibrosis may develop as part of AF-related structural remodeling, as well as a consequence of other cardiovascular diseases that result in atrial overload and stretch. Conditions associated with atrial fibrosis include hypertension, valvular heart disease, and HF, which cause broadly similar histological changes in the atrial myocardium (51). However, the precise causality between AF and atrial fibrosis may be difficult to establish.

Experimental data have also yielded controversial results. For example, some models of atrial tachyarrhythmia demonstrated marked biatrial dilation with changes in atrial architecture and myocyte characteristics (e.g., loss of myofibrils; accumulation of glycogen; changes in mitochondrial number, shape, and size; fragmentation of sarcoplasmic reticulum; dispersion of nuclear chromatin) while the interstitial space remained unaltered, with no evidence of increased connective tissue content (52). In contrast, more recent studies of rapid atrial pacing demonstrated up-regulation of potent profibrotic factors, such as angiotensin II and TGF-β, (53), and increased collagen content in the atrial interstitium (54). The discrepancy might be attributable to the time required for development of detectable fibrosis after initiation of profibrotic pathways. For example, in a mouse model of HF, there were no signs of histological fibrosis in the left atrium at 8 weeks, despite increased expression of genes related to fibrosis (55). This discrepancy may also suggest that despite the activation of profibrotic genes, other, poorly understood mechanisms of inhibition of fibrosis exist.

Background cardiovascular disease causing HF can be associated with more advanced atrial changes. For example, a model produced by a combination of rapid atrial pacing with mitral regurgitation inevitably resulted in intercellular space expansion in the left atrium and AF (56). This observation is consistent with an HF model of AF caused by ventricular tachypacing, in which connective tissue contained increased numbers of fibroblasts, more collagen, and signs of degeneration and necrosis, compared with an atrial pacing model (57). Cardin et al. (58) noted that ventricular tachypacing led to an ~10-fold overexpression of collagen messenger ribonucleic acid in atrial cardiomyocytes as early as 24 h and progressed further at 2 weeks, compared with atrial pacing. Of note, 8 collagen genes were up-regulated >10-fold, fibrillin was up-regulated 8-fold, and MMP2 was up-regulated 4.5-fold at 2 weeks; however, there were no changes in their expression at 24 h. In addition, TGF-β levels in failing hearts in animals appeared to be higher than in nonfailing hearts (59). Although development of atrial fibrosis associated with HF has been well documented in several animal models of AF, cardiac fibrosis is unlikely to be the sole mechanism of HF, including HF with preserved ejection fraction. For instance, predominant electrical remodeling with minimal (if any) evidence of atrial fibrosis and preservation of ventricular contractility was seen in a sheep model of prolonged persistent AF induced by intermittent atrial tachypacing, but there was no significant tachycardia during the observation period (60). More recently, Martins et al. (61) reported that long-term AF with duration up to 1 year and transition to persistent arrhythmia was accompanied by progressively increasing atrial dilation, mitral valve regurgitation, myocyte hypertrophy, and atrial fibrosis, with no evidence of left ventricular dysfunction.

Thus, atrial remodeling is the mainstay of AF initiation and perpetuation. Atrial structural and functional changes may develop as a result of underlying cardiac conditions, pathological systemic processes, or AF itself. Atrial remodeling also commonly occurs as a part of age-related processes. However, the relationship between the course of AF and atrial fibrosis is complex and nonlinear, meaning that higher levels of collagen deposition within the atria do not always cause more frequent paroxysms of the arrhythmia and its progression toward the persistent or permanent type. A plethora of mechanisms (i.e., hemodynamic alterations, mechanical stretching, changes in hormones, growth factors, and proinflammatory cytokines) modulates the severity of atrial fibrosis. A large body of experimental and clinical data has already provided insights into the key mechanisms of atrial fibrosis.

**EXTRACARDIAC AND GENETIC FACTORS CONTRIBUTING TO ATRIAL FIBROSIS**

Multiple noncardiac factors predispose to fibrosis in AF, including obesity, metabolic syndrome, use of toxic substances, athlete’s heart, obstructive sleep apnea, systemic inflammation, and thyrotoxicosis. All of these factors ultimately affect the myocardium (62). Recently, diabetes, a disease associated specifically with cardiomyopathy and excessive cardiac fibrosis, was shown to triple the risk of AF in obese subjects (63). Obesity leads to electrical and structural atrial remodeling and is associated with diastolic ventricular impairment, atrial dilation, and myocardial lipidosis (64). Obesity in AF is related to delay and significant heterogeneity in atrial conduction, atrial inflammatory infiltration, and interstitial fibrosis. Pathways underlying these changes include activation of TGF-β signaling, oxidative stress, and
<table>
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<tr>
<th>First Author, Year (Ref. #)</th>
<th>n (AF/SR)</th>
<th>Sample Tested</th>
<th>LVEF, % (AF/Controls)</th>
<th>Results (AF vs. Controls) Observed Associations</th>
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<tr>
<td>Adam et al., 2010 (105)</td>
<td>5/5</td>
<td>LAA</td>
<td>61 ± 6/59 ± 6</td>
<td>†collagen, CTGF, NADPHox, Rac1, N-cadherin, connexin 43, Ang II</td>
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<td>Adam et al., 2012 (106)</td>
<td>5/5</td>
<td>LAA</td>
<td>61 ± 6/59 ± 6</td>
<td>†miR-21 with collagen, CTGF, Rac1, LOX, Ang II</td>
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<td>Cao et al., 2013 (107)</td>
<td>48/24</td>
<td>RAA</td>
<td>63 ± 5 (paroxysmal), 64 ± 5 (persistent)/ 64 ± 3</td>
<td>†OPG, RANKL, RANK, RANKL/OPG ratio (In AF) OPG, RANKL, RANKL/OPG ratio with collagen types I and III</td>
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<td>Dawson et al., 2013 (108)</td>
<td>17/30*</td>
<td>Plasma</td>
<td>60 ± 2/69 ± 1</td>
<td>†miR-29b NA</td>
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<td>Dawson et al., 2013 (108)</td>
<td>17/30*</td>
<td>Plasma</td>
<td>60 ± 2/69 ± 1</td>
<td>†miR-29b in chronic AF NA</td>
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<td>Gramley et al., 2007 (109)</td>
<td>42/104</td>
<td>RAA</td>
<td>48 ± 12</td>
<td>†collagen content, activity ↔ MMP2, MMP9 (mRNA and protein levels), †PAI, TIMP1 and 2 (mRNA) with †duration of AF</td>
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<td>42/116</td>
<td>RAA</td>
<td>50 ± 1/47 ± 12</td>
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<td>Gramley et al., 2010 (110)</td>
<td>61/102</td>
<td>RAA</td>
<td>48 ± 11</td>
<td>†collagen content, early † and later † responsiveness to TGF-β1 with † duration of AF: initially †TGF-β1 (mRNA and protein), TIRβ1, phSmad2, Smad4 (protein) followed by a †TIRβ1 phSmad2 (protein) and †Smad7 (protein) NA</td>
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<td>Gramley et al., 2008 (111)</td>
<td>70/20</td>
<td>Serum</td>
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<td>†CITP, CICP, TIMP1 NA</td>
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<td>53 ± 15/44 ± 17</td>
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<td>51 ± 15/63 ± 14/63</td>
<td>†collagen content, TNFα, IL-6 and NFκB activity PiFNκB activity with TNFα, IL-6, and collagen content NA</td>
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<td>Rahmutula et al., 2013 (59)</td>
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<td>RA</td>
<td>NA</td>
<td>†TGFβ1 and TGF-β1 signaling-related proteins (e.g., phSmad2, Smad6, Ang II) PIINKP with AF recurrence; MMP9, TGF-β1, with ablation-induced LA volume reduction; MMP9 with RF energy on ablation NA</td>
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<td>Serum</td>
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<td>34/35</td>
<td>Plasma, RAA</td>
<td>49 ± 89/52 ± 9</td>
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<td>49 ± 12/51 ± 8</td>
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<td>Wang et al., 2015 (122)</td>
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<td>63 ± 7/70 ± 4</td>
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<td>200/0</td>
<td>Plasma</td>
<td>53 ± 10/57 ± 61</td>
<td>NA TGF-β1 with AF recurrence NA</td>
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up-regulation of PDGF and endothelin (65). The pericardial fat envelope could produce a constrictive effect, thus disturbing cardiac relaxation. Some adi- 
up-regulation of PDGF and endothelin (65). Some adi-
up-regulation of PDGF and endothelin (65). Some adi-
up-regulation of PDGF and endothelin (65).

x et al., 2013 (125) 83/52 RAA 62 ± 6/30 ± 5 → RANK, RANKL Fibrocytes with collagen content, LA volume index

Xie et al., 2013 (126) 27/15 LA 55/60 ↑ fibrocytes, collagen I and alpha-SMA Fibrocytes with collagen content, LA volume index

Xu et al., 2009 (127) 27/18 LA, RA 54 ± 9/59 ± 12 ↑ collagen type I, MMP1 and MMP9 (mRNA) with TIMP1 (mRNA)

Collagen type I (mRNA) with atrial diameter; MMP1, MMP9 (mRNA) with TIMP1 (mRNA)

Recurrent AF/nonrecurrent AF. *Chronic AF/AF with subsequent SR recovery.

†↑ = increased; ↓ = reduced; ↔ = not changed; AF = atrial fibrillation; Ang = angiotensin; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CICF = collagen type I C-terminal propeptide; CTIP = collagen type I C-terminal telopeptide; COL1A1 = gene encoding alpha-1 type I collagen; COL1A2 = gene encoding alpha-1 type III collagen; CTGF = connective tissue growth factor; ET = endothelin; ET, R = type A endothelin-1 receptor; ET, A = type B endothelin-1 receptor; HIF = hypoxia-inducible factor; HO-1 = high-sensitivity C-reactive protein; IL = interleukin; KDR = vascular endothelial growth factor receptor 2; LA = left atrium; LAA = left atrial appendage; LOX = lysyl oxidase; LVEF = left ventricular ejection fraction; mR = microborexenic acid; MMP = matrix metalloproteinase; MP = myeloperoxidase; mRNA = messenger ribonucleic acid; NA = not available; NAPDHex = nicotinamide adenine dinucleotide phosphate oxidase; NFκB = nuclear factor kappa B; OPN = osteoprotegerin; PAI = plasminogen activation inhibitor; pHSMA = phosphorylated Smad; PICP = procollagen type I C-terminal propeptide; PIIINP = procollagen type III N-terminal propeptide; pKDR = phosphorylated KDR; RA = right atrium; RAA = right atrial appendage; Rac1 = Ras-related C3 botulinum toxin substrate 1; RANK = receptor activator of nuclear factor kappa B; RANKL = receptor activator of nuclear factor kappa B ligand; RECK = reversion-inducing cysteine-rich protein with Kazal motifs; SMA = smooth muscle actin; Smad = a transcription factor, named by fusion of the Cancers holdfast elegans Sma and Drosophila Mad (mothers against decapentaplegic) proteins, in reference to its homology to these proteins; SR = sinus rhythm; TJR1 = type I transforming growth factor-beta 1 receptor; TJR2 = type II transforming growth factor-beta 1 receptor; TGF-β1 = transforming growth factor beta 1; TIMP = tissue inhibitor of matrix metalloproteinase; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

TABLE 1 Continued

<table>
<thead>
<tr>
<th>First Author, Year (Ref. #)</th>
<th>n (AF/SR)</th>
<th>Sample Tested</th>
<th>LVEF, % (AF/Controls)</th>
<th>Results (AF vs. Controls)</th>
<th>Observed Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xi et al., 2013 (125)</td>
<td>83/52</td>
<td>RAA</td>
<td>62 ± 6/30 ± 5</td>
<td>→ RANK, RANKL</td>
<td>RANK, RANKL, RANKL/OPG ratio with collagen content</td>
</tr>
<tr>
<td>Xie et al., 2013 (126)</td>
<td>27/18</td>
<td>LA, RA</td>
<td>54 ± 9/59 ± 12</td>
<td>↑ collagen type I, MMP1 and MMP9 (mRNA) with TIMP1 (mRNA)</td>
<td>Collagen type I (mRNA) with atrial diameter; MMP1, MMP9 (mRNA) with TIMP1 (mRNA)</td>
</tr>
</tbody>
</table>

AF development and persistence, and it is likely to have a genetic background (73,74). One of the genes involved in atrial development is PITX2. Deficiency of this gene results in formation of enlarged atria with thin walls and prominent deficiency in ion channel expression (75). AF is also related to polymorphisms in genes involved in fibrotic pathways, such as those responsible for modulation of the synthesis of interleukin-1 and -6 (2). Nonetheless, there is presently a lack of robust evidence of target genes directly responsible for AF-related cardiac fibrosis, and further research is warranted.

VENTRICULAR FIBROSIS IN AF

Association of AF with ventricular fibrosis is less established than for atrial fibrosis. Ventricular fibrotic changes are more pronounced in AF patients than in subjects with sinus rhythm, both with magnetic resonance or ultrasound imaging (76,77). In addition, more extensive changes were found in patients with permanent or persistent arrhythmia compared with those with paroxysmal AF (76-78). These reports were confirmed by use of animal data implicating ventricular fibrosis in cardiac remodeling and rate control in AF (79). Avitall et al. (80) observed more extensive ventricular fibrosis in AF when ventricles were not protected from a high atrial rate with atrioventricular node ablation than in ablated animals.

Atrial and ventricular fibrosis in AF is likely to share many common mechanisms, although the extent may vary between the 2 parts of the heart. In transgenic mice with TGF-β1 overexpression, TGF-β1 up-regulation was more pronounced in atria than in ventricles. High TGF-β1 levels were associated with
enhanced expression of only 2 profibrotic genes in ventricles but of 80 genes in atria. Interestingly, TβRII, TβRI, and Smad protein levels were similar in ventricles and atria, but Smad2 phosphorylation was increased only in atria, making them prone to development of selective fibrosis (59). Several mechanisms have been suggested for the different effects of TGF-β1 in ventricles versus atria (Table 3). Importantly, the processes described earlier were reported in intact ventricles. When TGF-β1 overexpression was combined with other pathophysiological stimuli (e.g., those seen in HF), TGF-β1-mediated profibrotic ventricular effects appeared to be enhanced, although atrial fibrosis still predominated. In addition, atrial fibroblasts are more susceptible to PDGF, angiotensin II, and endothelin-1, indicating that their activity is pre-modulated by local atrial factors (81). Hemodynamic changes (e.g., stretch) have a differential effect, and the precise biochemical processes acting on fibroblast activity in ventricles and atria remain unclear at present.

In summary, the cardiac profibrotic microenvironment in AF is unlikely to be strictly limited to the atria, and the ventricular myocardium is also likely to be affected. Even within the atrial myocardium, fibrotic changes take years to become detectable with the diagnostic methods currently available. With the considerably higher myocardial thickness of the ventricles, detectable ventricular fibrosis may require a prolonged time to develop unless amplified by coexisting pathological conditions, such as hypertension, coronary artery disease, and HF.

**IMAGING OF CARDIAC FIBROSIS**

Significant technological advances allow more possibilities for characterization and quantification of focal and diffuse cardiac fibrosis, which was only possible...
with biopsy in the past. The most commonly used late (delayed) gadolinium enhancement cardiac magnetic resonance (DE-CMR) imaging relies on the different abilities of healthy myocardium and areas of fibrotic tissue to clear gadolinium, an agent that shortens T1 relaxation time. Fibrotic tissue is characterized by slowing of gadolinium washout, resulting in greater signal compared with surrounding “reference” tissue. However, finding appropriate reference tissue for quantification of diffuse cardiac fibrosis poses a problem (82,83).

Another cardiac magnetic resonance (CMR)-based method, T1 mapping, was developed to overcome this problem. T1 mapping is a calculation of a post-contrast myocardial T1 time by imaging a given plane with sequentially increasing inversion times; there is no need to compare the results versus normal reference tissue before or after use of a contrast agent. This method allows demonstration of diffuse fibrotic fibers that might appear nearly isointense by using delayed enhancement (82,83).

Despite being the gold standard, CMR is not widely available. Hence, echocardiography remains an alternative for evaluation of cardiac fibrosis on the basis of the dependency of acoustic properties on myocardial composition. Collagen causes ultrasound scattering and attenuation, which can be measured as integrated backscatter (84). Furthermore, with echocardiography, functional assessment as strain peak and strain velocity (parameters that characterize reservoir performance) was found to predict the degree of fibrosis detected in histological specimens and via CMR (85,86).

**CLINICAL IMPLICATIONS AND PROGNOSTIC EFFECTS OF ATRIAL FIBROSIS**

Atrial remodeling, including excessive fibrosis, has major clinical implications in AF. Numerous studies link more extensive atrial interstitial fibrosis to lower effectiveness of AF catheter ablation and the Maze procedure, increased risk of development of post-operative AF, and impaired post-procedural recovery of atrial function (Table 4). Interestingly, delayed enhancement of the atrial myocardium is helpful for evaluation of post-ablation atrial fibrosis and its relation to left atrial reverse remodeling on sinus rhythm (87). Patients undergoing pulmonary vein isolation had a higher AF recurrence rate, with a lesser degree of left atrial and pulmonary vein scarring on DE-CMR (88).

There are limited data on the association of atrial fibrosis with stroke risk in AF patients. An association was found between the percentage of atrial fibrosis assessed via DE-CMR and a higher CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke/transient ischemic attack) score and stroke history (89). Moreover, in this population (n = 387, 36 strokes), adding left atrial fibrosis to the risk model (i.e., CHADS2 but not accounting for previous stroke due to the retrospective nature of the study) improved the C-statistic from 0.58 to 0.72. This outcome was consistent with another study that demonstrated better prediction of left atrial thrombosis or spontaneous echocardiographic contrast by addition of the degree of atrial fibrosis to either the CHADS2 or CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category) scores (90). However, routine use of expensive, and not universally available, DE-CMR for stroke prediction is not practical at present compared with available and recommended stroke risk assessment tools; the approach clearly needs further validation.

Galectin-3 is involved in regulation of fibrosis and was found to be associated with left atrial volume index and AF (odds ratio: 87.5 [95% confidence interval: 6.1 to 1,265.0]). It was also significantly higher in patients with persistent AF than in those with the paroxysmal type of arrhythmia (91).

**CLINICAL IMPLICATIONS AND PROGNOSTIC EFFECT OF VENTRICULAR FIBROSIS**

Ventricular fibrosis has a detrimental effect on both systolic function (due to replacement of apoptotic and necrotized myocardium) and diastolic function (due to increasing stiffness and decreasing compliance) (14). This makes ventricular fibrosis relevant in the context of HF with both preserved and reduced ejection fraction.

Although scarce data are available on the histological assessment of ventricular myocardial fibrosis in patients with AF, a small case series of ventricular biopsy specimens suggests the presence of active myocarditis or nonspecific necrotic/fibrotic changes in patients with lone AF (92). It is probable that most lone AF cases have background myocardial pathology that cannot easily be determined with the use of routine tests and reflect primary electrical disturbances and subclinical cardiomyopathies, likely associated with myocardial fibrosis.

Contemporary markers of ventricular fibrosis (e.g., beta-galactoside-binding lectin galectin-3) are increasingly being studied in patients with HF and have predictive value for adverse outcomes. Their
### TABLE 4  Studies on the Prognostic Significance of Atrial Fibrosis in AF Patients

<table>
<thead>
<tr>
<th>First Author, Year (Ref. #)</th>
<th>n</th>
<th>Duration of Follow-Up</th>
<th>Evaluation of Atrial Fibrosis</th>
<th>Intervention</th>
<th>Study Outcome</th>
<th>Association of Atrial Fibrosis and Study Outcome, OR or HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akoum et al., 2011 (131)</td>
<td>144</td>
<td>283 ± 167 days</td>
<td>DE-MRI</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>Increasing recurrence rate with increasing fibrosis degree</td>
</tr>
<tr>
<td>Canpolat et al., 2015 (132)</td>
<td>41</td>
<td>18 months</td>
<td>DE-MRI, TGF-β1</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>1.127</td>
</tr>
<tr>
<td>den Uijl et al., 2011 (133)</td>
<td>170</td>
<td>12 ± 3 months</td>
<td>IBS</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>2.80 (2.17-3.61)</td>
</tr>
<tr>
<td>Ho et al., 2014 (134)</td>
<td>3,306</td>
<td>10 yrs</td>
<td>Galectin-3</td>
<td>NA</td>
<td>Incident AF</td>
<td>1.19 (1.05-1.36)*</td>
</tr>
<tr>
<td>Kornej et al., 2015 (135)</td>
<td>119</td>
<td>6 months</td>
<td>Galectin-3</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>Higher in AF patients but did not predict AF recurrence</td>
</tr>
<tr>
<td>Kubota et al., 2012 (136)</td>
<td>27</td>
<td>3 yrs</td>
<td>IBS</td>
<td>None</td>
<td>Progression from paroxysmal to persistent AF</td>
<td>HR: 8.74 for patients with IBS ≥20 dB vs. &lt;20 dB</td>
</tr>
<tr>
<td>Kuppahally et al., 2010 (137)</td>
<td>68</td>
<td>1 yr</td>
<td>DE-MRI</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>1.04 (1.01-1.08)</td>
</tr>
<tr>
<td>Ling et al., 2014 (138)</td>
<td>132</td>
<td>1, 3, 6, 12, 18, 24, 30 months</td>
<td>T1 mapping</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>38% of AF recurrence in patients with T1 time &lt;230 ms vs. 25% in patients with T1 time &gt;230 ms</td>
</tr>
<tr>
<td>Malcolme-Lawes et al., 2013 (139)</td>
<td>50</td>
<td>1 yr</td>
<td>DE-MRI</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>Increasing recurrence rate with increasing fibrosis degree</td>
</tr>
<tr>
<td>Marrouche et al., 2014 (140)</td>
<td>272</td>
<td>475 days</td>
<td>DE-MRI</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>1.06 (1.03-1.08)</td>
</tr>
<tr>
<td>McGann et al., 2014 (141)</td>
<td>386</td>
<td>1 yr</td>
<td>DE-MRI</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>4.89</td>
</tr>
<tr>
<td>Oakes et al., 2009 (142)</td>
<td>81</td>
<td>9.6 ± 3.7 months</td>
<td>DE-MRI</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>4.88 (1.73-13.74)</td>
</tr>
<tr>
<td>Olasinska-Wisniewska et al. 2012 (143)</td>
<td>66</td>
<td>12 months</td>
<td>Histology</td>
<td>AF catheter ablation, mitral valve surgery</td>
<td>AF recurrence</td>
<td>1.09 (1.012-1.17)</td>
</tr>
<tr>
<td>Park et al., 2013 (144)</td>
<td>128</td>
<td>1 yr</td>
<td>TGF-β1</td>
<td>Maze procedure</td>
<td>Absence of atrial mechanical contraction</td>
<td>7.47 (1.63-34.4)</td>
</tr>
<tr>
<td>Rienstra et al., 2014 (145)</td>
<td>3,217</td>
<td>10 yrs</td>
<td>Soluble ST2</td>
<td>NA</td>
<td>Incident AF</td>
<td>No association</td>
</tr>
<tr>
<td>Rosenberg et al., 2014 (146)</td>
<td>2,935</td>
<td>8.8 yrs</td>
<td>PIIINP</td>
<td>NA</td>
<td>Incident AF</td>
<td>0.85 (0.72-1.00) and 0.93 (0.88-0.99) at the 10th and 25th percentiles, setting the median as the reference, no association at the 75th and 90th percentiles</td>
</tr>
<tr>
<td>Sasaki et al., 2014 (77)</td>
<td>113</td>
<td>13.8 (8.7-19.9) months</td>
<td>IBS</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>1.04 (1.01-1.07)</td>
</tr>
<tr>
<td>Seitz et al., 2011 (147)</td>
<td>22</td>
<td>NA</td>
<td>DE-MRI</td>
<td>AF catheter ablation</td>
<td>“Difficulty” of AF ablation (time to terminate AF; radiofrequency duration until AF termination; complex fractionated atrial electrogram area/LA surface)</td>
<td>Significant correlation between the fibrosis grade and the electrophysiological substrate indexes</td>
</tr>
<tr>
<td>Wang et al., 2009 (148)</td>
<td>74</td>
<td>NA</td>
<td>IBS</td>
<td>CABG</td>
<td>Post-operative AF</td>
<td>Higher IBS in post-operative AF vs. SR</td>
</tr>
<tr>
<td>Wu et al., 2013 (124)</td>
<td>200</td>
<td>10.9 ± 7.4 months</td>
<td>TGF-β1</td>
<td>AF catheter ablation</td>
<td>AF recurrence</td>
<td>1.31 (1.01-1.22)</td>
</tr>
</tbody>
</table>

*Significant association in univariate analysis only, not significant after adjustment for traditional clinical AF risk factors.

CABG = coronary artery bypass graft; CI = confidence interval; DE-MRI = delayed enhancement magnetic resonance imaging; HR = hazard ratio; IBS = integrated backscatter; OR = odds ratio; other abbreviations as in Table 1.
specific relevance in the context of AF remains to be established (93,94).

Collagen turnover markers of prognostic significance were assessed in hypertensive heart disease, hypertrophic cardiomyopathy, and HF (95,96). However, the major limitation of blood markers of collagen turnover is that they are not cardiac-specific and may not accurately reflect myocardial collagen content. Hence, the results are often conflicting, depending largely on the selection of study cohorts (e.g., exclusion of patients with hepatic and kidney dysfunction, pulmonary fibrosis, osteoporosis, and metastatic bone disease, among others, or measuring the cardiac gradient of collagen markers [i.e., blood from coronary sinus vs. systemic circulation]) (97).

It is even more problematic or even impossible to distinguish between the atrial and ventricular contributions to circulating levels of byproducts of collagen synthesis and degradation. Consequently, attribution of elevated markers of collagen turnover to AF-related atrial fibrosis alone might not be entirely correct.

For example, in the I-PRESERVE (Irbesartan in Heart Failure With Preserved Systolic Function) collagen substudy that included 29% AF patients, procollagen type I amino-terminal peptide and procollagen type III amino-terminal peptide were predictive of all-cause mortality and cardiovascular hospitalizations (98). This association lost significance after adjustment for other confounders, however.

Similarly, the majority of imaging-based studies on the evaluation of ventricular fibrosis focused on patients with arterial hypertension, dilated and hypertrophic cardiomyopathy, and HF; only a few directly addressed patients with AF. Moreover, those few studies with AF included mostly patients referred for AF ablation, which is currently indicated for patients with paroxysmal or persistent arrhythmia resistant to AF ablation, which is currently indicated for patients with paroxysmal or persistent arrhythmia resistant to AF ablation. However, the study had no comparator group with established ventricular fibrosis to assess the effect of sinus rhythm restoration (101). They found that a cutoff level of post-contrast ventricular T1 time <380 ms was associated with better outcome. In a small cohort of patients without left ventricular fibrosis, as evidenced by the absence of late gadolinium enhancement on CMR in patients with systolic HF, significant improvement of left ventricular function was observed after AF catheter ablation. However, the study had no comparator group with established ventricular fibrosis to assess the effect of sinus rhythm restoration (102).

Thus far, similar to atrial fibrosis, it is unclear whether AF triggers profibrotic pathways in the left ventricle, merely a marker of pre-existing fibrotic changes, or both.

**TREATMENT APPROACHES TO REDUCE CARDIAC FIBROSIS**

Angiotensin II is a potent stimulator of profibrotic pathways, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and mineralocorticoid receptor antagonists deemed to reduce fibrosis progression. This was supported by several animal studies but not, thus far, by clinical trials. Retrospective analyses and meta-analyses of randomized trials produced inconclusive results, both for the primary and secondary prevention of AF. It has also been accepted that overall primary prevention of AF with these agents is more feasible than secondary prevention (myocardial fibrosis is more likely to be slowed down than reversed) (103).

Therefore, inhibitors of the angiotensin axis are only recommended for AF management when the arrhythmia is associated with other underlying conditions that are themselves associated with myocardial fibrotic remodeling, such as arterial hypertension with left ventricular hypertrophy and systolic HF, and are not recommended in patients with no apparent cardiovascular disease (e.g., lone AF) (104).

Many other components of profibrotic cardiac pathways (e.g., TGF-β1, PDGF) represent attractive therapeutic targets. Their suppression with either antibody blockade or oligonucleotide interference reduced interstitial fibrosis in animal experiments.
Nonetheless, experience from the animal data must be confirmed by clinical trials, and a better understanding of the details of fibrotic pathways is required (15).

CONCLUSIONS

AF is associated with fibrotic processes both in atria and ventricles. Despite common profibrotic pathways, signaling seems to differ in the ventricular and supraventricular parts of the heart. Atrial fibrosis may precede development of AF, which in turn results in further progression of atrial remodeling. Structural heart disease appears to have a greater effect on both atrial and ventricular fibrosis than arrhythmia per se, but it allows persistent activation of profibrotic stimuli. Although the role of atrial fibrosis in AF is well documented, the implication of ventricular fibrosis in pathogenesis and the outcomes of conditions associated with AF clearly require further research.

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**KEY WORDS** cardiac, extracellular matrix, heart failure, myocytes, myofibroblasts