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Atrial Fibrillation and Heart Failure Parallels: Lessons for Atrial Fibrillation Prevention

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Abstract

Heart failure (HF) and atrial fibrillation (AF) are two of the most common cardiovascular diseases encountered in clinical practice, and the prevalence of these diseases continues to grow world-wide with the aging of the global population.

While recognizing that AF is a heterogeneous disorder, we submit that the parallels between AF and HF may arise because many cases of AF and HF result from the cumulative exposure of the atria and ventricles to a common set of systemic cardiovascular risk factors. Over time, exposure to risk factors promotes development of atrial and ventricular structural and functional abnormalities via activation of several biological pathways in concert: up-regulation of neurohormonal signaling cascades, release of inflammatory mediators, programmed cell death and fibrosis. Cardiac structural remodeling occurs in concert with electrophysiologic remodeling, both of which contribute to atrial and ventricular rhythm disturbances, including AF.

AF and HF, instead of representing distinct disease processes, often represent different endpoints along a disease continuum. By reviewing some of the mechanistic parallels between AF and HF, we hope to emphasize the connection between established cardiovascular risk factors, cardiac remodeling and AF, with a view to promoting strategies for AF prevention.

Keywords

atrial fibrillation; heart failure; atrial fibrillation prevention; epidemiology

Introduction

In his Shattuck lecture, Dr. Eugene Braunwald identified two epidemics of cardiovascular disease that continue to emerge despite advances in cardiovascular medicine: heart failure (HF) and atrial fibrillation (AF).[1] AF is now the most common arrhythmia encountered in clinical practice.[2] The prevalence of AF increases dramatically with age and it is present in 9% of individuals by the age of 80 years.[3] AF is associated with a lower quality of life,

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increased hospitalization rates, and a greater risk of stroke and mortality.[4] HF is also highly prevalent and is a major cause of morbidity and mortality worldwide.[5] Like AF, HF incidence increases with age and the condition is associated with substantial morbidity, mortality, and an impaired quality of life.[2]

HF and AF frequently coexist and each condition predisposes to the other.[2] AF is exceedingly common in HF, affecting 30% of all individuals with HF.[6] Men and women with AF have a 3- and 11-fold increased risk, respectively, of the combined endpoint of HF and all-cause mortality when compared to those in sinus rhythm.[2,5] Conversely, the development of HF is associated with a 4.5–5.9 fold increased risk of future AF.[5,6] As with HF, the increase in new cases of AF is attributable in part to the aging of the population and a concomitant increase in the prevalence of comorbidities, including the burden of cardiovascular risk factors.

The striking epidemiological similarities between AF and HF are mirrored by experimental and clinical studies that suggest significant mechanistic connections between AF and HF.[2,5,7,8] These similarities may be explained by the fact that many cases of AF and HF arise from cumulative exposure of the atria and ventricles, respectively, to a common set of cardiovascular risk factors (Figures 1 and 2).[9] These risk factors lead to atrial and ventricular sub-clinical structural and electrophysiological remodeling via activation of several biological pathways in concert: up-regulation of neurohormonal signaling cascades, release of inflammatory mediators, metabolic stress, programmed cell death and myocardial fibrosis.[7,8] The direct mechanisms linking sub-clinical cardiac remodeling to clinical AF are poorly defined, but structural atrial remodeling clearly facilitates AF in many patients.

While the pathophysiology of AF is still debated, significant discoveries have increased our understanding of this arrhythmia by highlighting the importance of focal triggers in initiating AF.[9] These observations have led to the development of new therapies for individuals with AF, including percutaneous and surgical AF ablation.[10] It is notable, however, that anti-arrhythmic and ablative therapies have greater efficacy in younger patients with paroxysmal AF than in older patients with multiple cardiovascular risk factors and persistent AF,[11] possibly because AF is a heterogeneous disorder with complex initiating and perpetuating mechanisms.[12,13] Pathological atrial structural remodeling often precedes development of AF and the presence of atrial enlargement is strongly associated with increased AF risk.[14] While enhanced automaticity plays a key role in triggering AF, pathological atrial remodeling also contributes substantially to AF initiation and maintenance in many individuals.

The conventional paradigm of regarding AF and HF as distinct disorders is challenged by the important epidemiological and mechanistic similarities between these disorders. In patients with sub-clinical ventricular remodeling, HF is often the clinical manifestation of underlying ventricular myopathy. Likewise, AF is often the clinical manifestation of atrial myopathy, especially in older individuals and those with cardiovascular disease risk factors. The interplay between genetic factors and the nature, chronicity and severity of risk factor exposure may help to explain why all individuals with AF do not develop HF, and vice versa. The purpose of this work is to review the genetic, mechanistic and epidemiological parallels between HF and AF, and to emphasize the strong connections between these diseases and cardiovascular risk factors. In contrast to prior reviews examining the dual epidemics of AF and HF,[7,8] we have drawn from the available literature in order to promote strategies for AF prevention in the community (Table 1).

AF and HF: Shared risk factors

AF shares strong epidemiologic associations with other cardiovascular diseases (CVD) and risk factors such as coronary artery disease, valvular heart disease, diabetes mellitus hypertension, obesity and obstructive sleep apnea (OSA).[15–18] These factors have been termed “upstream” risk factors, but the relationship between concomitant CVD and AF is incompletely understood and complex. In the Framingham Heart Study, history of myocardial infarction (MI) increased the risk for AF in men by 40%.[19] AF occurs often in post-MI patients and is independently associated with increased short- and long-term mortality in this setting.[20] History of valvular heart disease confers a 1.8- and 3.4-fold increased risk of AF in men and women, respectively.[19] Similarly, a 20-mmHg increase in pulse pressure confers a 26% increased risk of AF.[21] Diabetes mellitus and hypertension may have a synergistic effect on likelihood of developing AF, as diabetes has been associated with a 49% increased risk of AF in individuals with hypertension.[22] Obesity is another significant risk factor for AF, with each unit increase in body mass index conferring a 4% increased risk of AF.[17] Importantly, the association between obesity and AF appears to be mediated by atrial enlargement. It is also significant that, even after adjustment for body mass, OSA remains associated with a 2.2-fold increased risk of incident AF.[18]

Many of the conditions associated with AF also predispose to HF.[23] Hypertension confers a 2- to 3-fold increased risk of HF.[23] History of MI is associated with a 2-fold increased risk of HF.[23] Diabetes mellitus is associated with up to a 5-fold increased risk of HF.[24] As with AF, valvular heart disease is a risk factor for HF, accounting for about 1 in 10 cases.[23] Evidence suggests that obesity is also associated with increased risk of HF, with each unit increase in body mass index conferring a 5% and 7% risk of HF for men and women, respectively.[25] After adjustment for body mass, sleep apnea remains associated with a 2.4-fold increased risk of prevalent HF.[26]

AF and HF: Shared intermediate phenotypes

Cardiovascular risk factors impose hemodynamic, inflammatory, catecholaminergic, neurohumoral and metabolic stress on the atria and the ventricles. Sub-clinical phenotypes such as ventricular hypertrophy or atrial enlargement develop in response to these stressors and serve as useful markers of increased HF and AF risk, respectively. These intermediate phenotypes may appear to be initially adaptive, enabling the heart to compensate for increases in afterload and/or preload, or decreased contractility. With the passage of time, however, these initially compensatory mechanisms become maladaptive, leading to a decline in atrial and/or ventricular function. As the atria and ventricles are inexorably linked, any functional abnormality of one chamber may affect the other.

Echocardiographic and electrocardiographic measures of ventricular and atrial remodeling provide support for the hypothesis that AF and HF share common intermediate phenotypes.[27,28] Left ventricular wall thickness and electrocardiographic left ventricular hypertrophy, two well-established markers of hypertensive ventricular remodeling and HF, are also strongly associated with atrial enlargement and AF.[27] Left ventricular dilatation and systolic dysfunction post-MI predict future HF and also predict AF.[27,28] Pressure and volume-overload in left-sided valvular heart disease are associated with both ventricular and atrial enlargement.[29] Dilatation of either the atria or the ventricles in valvular as well as coronary heart disease predicts AF, HF and mortality.[30,31] In sum, ventricular remodeling, regardless of etiology, is associated with increased AF risk just as atrial enlargement is associated with increased HF risk.[32,33]

AF and HF: Shared neurohormonal signaling pathways

Structural remodeling seen in atria of individuals with AF is similar to that seen in myopathic ventricles from individuals with HF.[34–37] Chronic intra-atrial or intra-ventricular pressure overload activates common stress signaling pathways, most notably the renin angiotensin-aldosterone system (RAAS), which results in impaired myocardial vascular growth, myocyte apoptosis and interstitial fibrosis.[38]

Chronic RAAS activation has been shown to contribute to fibrosis and chamber remodeling in both AF and HF experimental studies.[35–37,39] Angiotensin-converting enzyme, Angiotensin II (AII) and transforming growth factor-beta 1 (TGF-β1) are up-regulated in a systemic and tissue-specific manner in response to atrial and ventricular stretch.[40] Mechanical stretch also induces fibroblasts to synthesize AII and TGF-β1.[41] AII and TGF-β1 induce downstream factors that promote local extracellular ventricular and atrial fibrosis.[42] AII and TGF-β1 also promote atrial and ventricular myocyte apoptosis and chamber dilatation. Experimental data suggest that the RAAS may also affect potassium channel function, action potential duration, and facilitate intra-atrial re-entry. In this fashion, the RAAS may directly promote AF independent of its effect on atrial structure or function.[43]

AF and HF: Shared mechanisms of inflammation and oxidative stress

Inflammation and oxidative stress play an important role in the pathogenesis of AF.[42] Histologic changes consistent with inflammation are seen in two-thirds of patients with AF and these changes are often seen prior to the onset of AF.[43] Over-expression of tumor necrosis factor-α (TNF-α), a well established inflammatory mediator, has been associated with atrial fibrosis, abnormal calcium handling, altered ion channel function, prolonged action potential duration and increased susceptibility to AF.[43] Circulating levels of C-reactive protein and interleukin-6, two other systemic inflammatory cytokines, are also predictive of future AF.[43]

It is well established that pro-inflammatory cytokines also contribute to the pathogenesis of ventricular dysfunction and HF.[44] Circulating levels of these cytokines independently predict worsened functional class and mortality in individuals with HF.[45] As is true in individuals with AF, TNF-α and interleukin-6 are important regulators of ventricular myocyte cell death in individuals with left ventricular remodeling and HF.[45]

AF and HF: Shared mechanisms of extracellular fibrosis

Atrial fibrosis is the predominant pathologic abnormality seen in AF-related structural remodeling and the degree of fibrosis has clinical significance.[14] Fibrosis results from increased deposition of dense, disorganized collagen in the extracellular space and occurs in the setting of myocyte atrophy and apoptosis.[14] Atrial fibrosis is mediated by altered expression of matrix metalloproteinases (MMPs) in response to neurohormonal signaling, inflammation and oxidative stress.[35–37] Increased MMP activity correlates with both degree of fibrosis and duration of AF.[46] Atrial interstitial fibrosis increases AF vulnerability in animal and transgenic models for selective fibrosis.[46] Atrial fibrosis often precedes development of AF and the degree of fibrosis correlates with AF persistence.[46] The severity of fibrosis also correlates with the duration of AF as well as with the likelihood of restoration of sinus rhythm with cardioversion.[47]

As in AF, accumulation of extracellular collagen and fibrosis play important roles in both ventricular dilatation and hypertrophic ventricular remodeling in HF.[48] Fibrosis typically occurs in a localized fashion in ischemic cardiomyopathy and diffusely in pressure-overload and hypertrophic cardiomyopathies. MMPs have also been shown to mediate ventricular

remodeling in HF.[48] Increased MMP expression predicts transition from hypertrophy to HF and is inversely correlated with ventricular function.[48]

AF and HF: Electrophysiological Parallels

Pacing-induced HF models have yielded valuable information about how atrial structural remodeling affects the electrophysiological properties of the atrium.[49] These models have convincingly demonstrated that atrial ion channel expression, distribution and function are profoundly linked to ventricular structure and function.[50] Atrial fibrosis develops in these models and disrupts atrial cell-to-cell junctions and myocyte coupling, causing regional electrical silence, abnormal calcium handling, decreased atrial refractoriness, and dispersion of the atrial refractory period.[50,51] Atrial fibrosis causes localized conduction slowing and unidirectional block, thereby increasing conduction heterogeneity and providing a substrate for both macro-reentrant and focal tachyarrhythmias.[14] Mechanical stretch may directly modulate atrial myocyte electrical activity via a pro-arrhythmic mechanism known as mechano-electric feedback and indirectly by up-regulation AII expression.[52] Another pro-arrhythmic mechanism seen in HF models is the dysregulated expression of ion channels and modulator proteins in the atrium. This results in shortening of the atrial effective refractory period, promotion of multiple wave reentry and facilitation of AF.[53,54] Atrial structural remodeling promotes atrial electrical anisotropy, thereby facilitating AF and providing a plausible electrophysiologic mechanism linking risk factors to AF as well as justification for AF prevention through risk factor modification.

AF and HF: Common Genetic Associations

Parental history of HF is associated with an almost 70% increase in HF risk and parental history of AF is associated with an almost two-fold increase in AF risk among offspring.[55,56] Traditional mapping and cloning studies have shown that mutations in ion-channel genes, including several encoding sodium and potassium channels, explain a small proportion of AF cases.[57] Case-control and genome-wide association studies suggest that a much larger proportion of AF cases may be explained by common variation in a small number of genes.[57] Interestingly, a number of these genetic polymorphisms occur in genes controlling the production of angiotensin converting enzyme, the AII receptor, interleukin-6, and endothelial nitric oxide synthase.[57] As has been discussed previously, these gene products are involved in myocardial fibrosis, inflammation and cardiac remodeling, respectively. Importantly, many of these genes and gene products have also been associated with ventricular hypertrophy, ventricular enlargement and HF.[58] Ongoing genome-wide association research promises to yield further insight into the genetic predictors of AF and HF. Genetic polymorphisms may help to explain the considerable variance in clinical presentation seen among patients exposed to cardiovascular risk factors.

AF: Lessons for AF Prevention from HF epidemiology

Several schemes have been proposed for the classification of AF, but none fully account for all aspects of AF.[59] Characterization of AF based on presence or absence of symptoms, duration or response to cardioversion, while clinically relevant, do not adequately describe the underlying mechanisms of this arrhythmia. The limitations of these descriptors make individualized treatment and clinical trial design as well as interpretation difficult. For example, a patient with paroxysmal and symptomatic AF may have as severe an atrial myopathy as another patient with persistent and asymptomatic AF.

When thinking about AF prevention and treatment, it may be helpful to consider the HF disease model proposed by the American College of Cardiology/American Heart Association in 2001 (Figure 1).[60] The advantage of this pathophysiological model is that it

recognizes the importance of cardiovascular risk factors for the development of HF and emphasizes that risk factors evolve over the adult life course. Like HF, AF is often a phenotypic manifestation of exposure of the heart to cardiovascular risk factors. Though AF develops suddenly, underlying atrial electrical and structural remodeling often precedes clinical AF and is strongly linked to cardiovascular risk factors (Figure 2). As was recently emphasized by an expert panel, AF prevention has received relatively little attention despite an increasing prevalence.[61] Parallels between AF and HF would suggest that an effort should be made to develop AF prevention strategies that focus on patients with cardiovascular risk factors and/or intermediate phenotypes associated with AF. Adaptation of current conceptual models of AF to accommodate the existence and importance of AF risk factors and intermediate phenotypes may enhance disease prevention efforts through more aggressive risk factor modification in at-risk individuals. Although existing data have not yet convincingly demonstrated that treatment of hypertension, diabetes or coronary artery disease modifies the natural history of AF, the risk signals are sufficiently strong to justify enhanced attention to guideline-directed therapies for these conditions as a plausible way of reducing the incidence of AF.

Limitations

It is clear that while AF results from structural and electrophysiologic remodeling in many patients, the complexity of this arrhythmia dictates recognition that this is not the case for all patients with AF. The disease model proposed by the American College of Cardiology/ American Heart Association for HF has limited value when applied to those patients with AF due exclusively to enhanced pulmonary vein automaticity. Though the electrocardiographic manifestation of AF may be similar in the patient with AF but no structural heart disease and the patient with AF and structural heart disease, patients with truly isolated AF likely have a distinct electrophysiologic disorder strongly linked to familial predisposition. While lone AF has been associated in some patients with development of ventricular myopathy and HF, the majority of these patients do not have significant atrial myopathy.

Conclusions

AF is likely to affect 3% of the population by 2050. One in four individuals 40 years of age and older will develop AF during their lifetime.[2] The weight of current evidence suggests that most cases of AF and HF result from exposure of the heart to a common set of systemic cardiovascular risk factors and that HF and AF share common genetic predictors as well as mechanisms of structural and electrophysiologic remodeling.[2,7,8] Early identification and treatment of these risk factors may help to slow or prevent the onset of AF. Reframing AF as a disease process that develops over the life course of an individual may add a useful dimension to our thinking by helping to emphasize that established risk factors and cardiac remodeling are essential for the development and maintenance of AF in many patients. Further investigation is needed to evaluate the role of CV risk modification, particularly treatment of hypertension, on the development of future AF.

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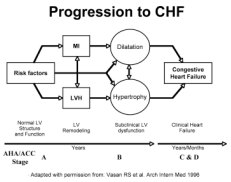

Figure 1.
Model of Progression to HF
LV = left ventricle, MI = myocardial infarction

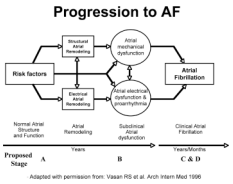

Figure 2.
Model of Progression to AF
AF = Atrial Fibrillation

Table 1

Mechanisms and Features Common to both Atrial Fibrillation and Heart Failure

Common Cardiovascular Risk Factors	Age, hypertension, diabetes, valvular disease, MI
Common Genetic Associations	Parental history, variation in angiotensin converting enzyme, angiotensinogen, angiotensin II type I receptor, IL-6, endothelial nitric oxide synthase genes
Common Morphologic and Hemodynamic Features	Increased intra-atrial and intra-ventricular volume and pressure, reduced CO
Common Intermediate Phenotypes	LV hypertrophy, LV enlargement, LA enlargement, reduced LV and LA EF
Common Mechanisms of Electrophysiologic Remodeling	
Stretch-related Mechanisms	Abnormal calcium handling, shortened action potential duration, decreased refractoriness, dispersion of the refractory period
Fibrosis-related Mechanisms	Disrupted cell-cell junctions, areas of delayed conduction, facilitation of re-entry
Independent Mechanisms	altered ion channel expression and density
Common Mechanisms of Structural Remodeling	
Neurohormonal signaling mechanisms	Renin-angiotensin-aldosterone system, TGF-β1, sympathetic nervous system
Tissue-level inflammatory mediators	CRP, TNF-α, IL-6
Factors associated with extracellular remodeling	Increased collagen deposition, increased MMP activity
Cellular oxidative stress response	Myocyte apoptosis, myolysis

MI = myocardial infarction, CO = cardiac output, LV = left ventricular, EF = ejection fraction, LA = left atrial, TGF = tissue growth factor, CRP =C-reactive protein, TNF = tumor necrosis factor, IL = interleukin, AII = angiotensin II, MMP = matrix metalloproteinase