Atrial Fibrillation
Research Article

The Pathophysiology of Atrial Fibrillation in Heart Failure

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Introduction

Atrial fibrillation (AF) and heart failure are the emerging epidemics of cardiovascular diseases. Both are responsible for considerable morbidity and mortality. AF and heart failure are frequently encountered together. In a large cohort of patients from the Framingham Heart Study, at first diagnosis of AF, 26% of patients had a previous or concurrent diagnosis of heart failure. Similarly, at first diagnosis of heart failure, 24% had a previous or concurrent diagnosis of AF. In the long-term follow-up, they found that AF preceded heart failure with approximately the same frequency that heart failure preceded AF.1

There are complex interactions between AF and heart failure. Both conditions frequently co-exist, partly because of common risk factors, including age, diabetes, hypertension, coronary artery disease, and valvular heart disease.2,3 However, the relationship between AF and heart failure is not simply coincidental. Clinical and experimental data have defined multiple pathophysiological mechanisms to explain how either condition contributes to the new development of the other. This is a vicious cycle in which AF begets heart failure and heart failure begets AF. The development of AF in the setting of heart failure, and vice versa, is associated with clinical deterioration and worsening prognosis, which indicates the need for an improved understanding of the clinical and pathological relationships between these two conditions.

Mechanisms of AF-induced heart failure

AF can cause the worsening of heart failure in those already affected by the condition; also, it can cause the new development of heart failure, so-called tachycardia-induced cardiomyopathy.

How does AF contribute to the development of heart failure?

Tachycardia is associated with an overall decrease in myocardial collagen content and altered extracellular collagen distribution, both of which contribute to dilation and thinning of the ventricular walls and decreased contractility. Depletion of myocardial energy stores has been proposed as one of the mechanisms that contribute to ventricular dysfunction in tachycardia-induced cardiomyopathy.4–6 Furthermore, a rapid, irregular heart rate in patients with AF can result in increased sympathetic nerve activity, which seems to be independent of the hemodynamic changes observed in AF (Figure 1).7,8 In animal models, after resolution of tachycardia, changes induced by tachycardia can persist. Pathologically, an increased density of collagen in the extracellular matrix and thickening of collagen fibers develops leading to an increase in left ventricular mass and myocardial stiffness and a decrease in ventricular relaxation.5 These changes

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suggest that permanent diastolic dysfunction is possible regardless of an improvement in systolic function with therapy.

The natural history of tachycardia-induced cardiomyopathy is not clearly elucidated as most studies in humans are observational. Furthermore, “pure” tachycardia-induced cardiomyopathy is relatively uncommon and its presence can be difficult to establish. However, in clinical experience, the treatment of AF-related heart failure has been shown to resolve ventricular dysfunction and the symptoms of heart failure, which underlines the importance of clinical recognition and treatment of patients with tachycardia-induced cardiomyopathy.9

Mechanisms of heart failure-induced AF

The presence of heart failure is the strongest risk factor for AF. The prevalence of AF in heart failure increases according to New York Heart Association (NYHA) class, ranging from 4% in NYHA class I to 50% in patients who are in NYHA class IV.10 Subgroup analyses from several large clinical trials showed that that the presence or development of AF in patients suffering from heart failure is associated with a higher mortality.11,12 Understanding the pathophysiology of AF in heart failure will enhance opportunities for discovering effective AF prevention and treatment strategies.

Although the pathophysiology of AF remains incompletely understood, the role of the pulmonary veins in AF initiation and the role of atria in AF maintenance are well established. It has been shown that various mechanisms, including rapid local ectopic activity, single-circuit re-entry, and multiple-circuit re-entry, can cause AF. The re-entry mechanisms need an appropriate substrate on which a triggering ectopic beat acts to initiate re-entry.

Paroxysmal AF often progresses into persistent AF, and the longer AF persists the more difficult it becomes to maintain sinus rhythm after cardioversion. In 1995, Wijffels et al13 made the now-classical observation that AF modifies atrial properties by shortening of atrial
effective refractory period so that AF maintains itself more readily, a phenomenon called electrical remodeling and described as “AF begets AF,” as observed in atrial tachycardia model. However, even without a decrease in effective refractory period, the presence of local conduction abnormalities, such as tissue fibrosis, can stabilize re-entry by producing conduction barriers, allowing AF to be sustained.14

Pathophysiology of AF in heart failure

Although various mechanisms can cause AF, the distinct mechanisms of AF may be more common in different populations. Numerous experimental and clinical observations suggest that both the triggers and electrophysiological substrates of AF in patients with heart failure are different from those present in patients without structural heart disease.

The study from Chen’s group showed that heart failure enhanced PV arrhythmogenesis in an animal model. Compared with the control group, PV cardiomyocytes in heart failure rabbits had a faster spontaneous activity and higher incidence of delayed afterdepolarization (DAD).15,16 The increased PV arrhythmogenecity may partly contribute to the development of AF in heart failure.

Like atrial tachycardia model, heart failure causes remodeling of atrial ionic current and transport mechanisms. However, the ionic remodeling caused by heart failure involves a more balanced decrease in the inward current and the outward, resulting in no change or an increase in action potential duration.17 This finding is opposite to that in the atrial tachycardia model, where action potential duration is shortened. Thus, the ionic current changes in heart failure do not alter the atrial action potential duration in a way that favors atrial re-entry. On the other hand, heart failure also upregulates the Na⁺–Ca²⁺ exchanger (NCX), which potentially produces measurable DADs. The DAD-related activity induced by the increase in NCX activity may account for the occurrence of focal atrial tachyarrhythmias in heart failure.18
Furthermore, the key regulators of intracellular Ca\(^{2+}\), including the ryanodine receptor and the sarcoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA2a), are downregulated in heart failure.\(^{19,20}\) These effects may create a state of atrial intracellular diastolic Ca\(^{2+}\) overload, which contributes to the generation and maintenance of AF.

Although AF inducibility can be increased either by heart failure or by rapid atrial pacing, the electrophysiological mechanisms appear to be different in these situations. Rapid atrial pacing induces substantially greater decreases in atrial refractory periods than heart failure. In contrast, heart failure causes greater atrial interstitial fibrosis than does rapid atrial pacing, leading to heterogeneity of atrial conduction and regions of slow electrical conduction (Figure 2).

Fibrosis is a hallmark of arrhythmogenic structural remodeling in heart failure.\(^{21}\) Although the responsible mechanisms behind atrial fibrosis in heart failure have been incompletely determined, the renin–angiotensin system (RAS) appears important in structural remodeling and the development of myocardial fibrosis in heart failure.\(^{21,22}\) Interventions that inhibit activation of the RAS, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have shown to prevent tissue fibrosis and development of AF in animal models. Previous studies showed that enalapril and candesartan decreased the percentage of atrial fibrosis in heart failure animals.\(^{23,24}\) In human studies, the ACEIs and ARBs have been studied in both primary and secondary prevention of AF. In primary prevention of AF, meta-analysis has shown that ACEIs and ARBs reduce the risk of new-onset AF in patients with significant underlying heart disease. The effect was most pronounced in heart failure, and only significant in hypertension when associated with left ventricular hypertrophy.\(^{25}\) In secondary prevention of AF, several small prospective studies, mainly open-label and no placebo group, have demonstrated that therapy with ACEIs or ARBs conferred an additional benefit on risk of recurrent AF.\(^{26,27}\) However, subsequent large randomized, double-blind, placebo-controlled trials in patients with non-permanent AF failed to demonstrate the benefits of RAS blockade on risk of recurrent AF.\(^{28,29}\)

It is possible that ACEIs or ARBs might prevent the development of the atrial electrical and structural remodeling that is required to provide the substrate for AF in normal atrial substrate. However, once the atrial fibrosis already exists, the RAS blockade may not be able to reverse this structural remodeling, leading to the failure of this therapy in secondary prevention of AF. The atrial electrical and structural remodeling associated with paroxysmal AF may be reversible or preventable if therapy aimed at substrate remodeling is initiated early rather than later in the course of the disease. Another possibility, the follow-up duration in large randomized controlled studies with ARB therapy was relatively short. Some data suggest that RAS blockade may promote the regression of atrial fibrosis. However, over the course of the brief follow-up period in those clinical trials, it may not be possible that ARB therapy could have modified the substrate for AF sufficiently to improve the clinical outcome.

Conclusions

There is complex interplay of AF and heart failure. Alterations in neurohormonal activation, electrophysiological parameters, and mechanical factors conspire to create an environment in which heart failure predisposes to AF and AF exacerbates heart failure. Each condition has deleterious effects on the other. Development of AF in a patient with heart failure often leads to symptomatic deterioration, predisposes to episodes of worsening heart failure, increases the risk of thromboembolic episodes, and worsens long-term outcome. In the management of heart failure patients with AF, the potential precipitating factors and secondary causes of AF should be identified and if possible corrected and background heart failure treatment should be optimized.

References


