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Atrial Fibrillation in Congestive Heart Failure

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Synopsis

Atrial fibrillation and congestive heart failure are morbid conditions that share common risk factors and frequently coexist. Each condition predisposes to the other, and the concomitant presence of the two identifies individuals at increased risk for mortality. Recent data have emerged which help elucidate the complex genetic and non-genetic pathophysiological mechanisms that contribute to the development of atrial fibrillation in individuals with congestive heart failure. Clinical trial results offer insights into the noninvasive prevention and management of these conditions, though the emergence of newer technologies, such as catheter ablation for atrial fibrillation, have yet to be studied extensively in patients with congestive heart failure.

Keywords

Atrial fibrillation; congestive heart failure; genetic mutations; etiology; pathophysiology; management

Introduction

Atrial fibrillation (AF) and congestive heart failure (CHF) are among the most common medical conditions and are associated with significant morbidity. These two conditions share similar risk factors, frequently coexist, and have additive adverse effects when occurring in conjunction. Much evidence has amassed regarding the nature of the relations between AF and CHF. In this review we will discuss AF in the context of CHF, with a particular emphasis on the underlying pathophysiological mechanisms and genetic basis of AF. We will also address

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the proper management of AF when it occurs in conjunction with CHF, on the basis of recent clinical trials and practice guidelines.

Epidemiology

AF is the most common arrhythmia seen in clinical practice, and is responsible for significant morbidity (1). Over 2.3 million individuals in the United States currently have AF (2), and as many as 5.6 to 12.1 million individuals are projected to be affected by 2050 (2,3). The lifetime risk of developing AF after the age of 40 is 26% for men, and 23% for women (4). The presence of AF confers a five-fold increased risk of stroke (5), a significantly increased risk of dementia (6), and an almost two-fold increased risk of death (5). Moreover, the incidence of AF is rising (7), and thus presents a significant healthcare burden as it accounts for an increasing proportion of hospitalizations (8). Health care costs are approximately five times greater for individuals with AF than for those without AF (9).

CHF has a similar prevalence affecting over 5 million individuals in the United States (10). After the age of 40, the lifetime risk of developing CHF is over 20% (11). CHF portends a grave prognosis, with over half of individuals dying within five years of diagnosis (12), though some estimates indicate that survival may be improving (12,13). CHF accounts for a significant proportion of the healthcare budget, with an estimated cost of $34.8 billion in 2008 (10).

Prevalence of comorbid AF and CHF

As both AF and CHF occur frequently, the simultaneous presence of these two conditions is common. The prevalence of AF in patients with systolic left ventricular dysfunction and CHF ranges from 6% for asymptomatic patients or for those with minimal symptoms (14), to between 15% and 35% for patients with New York Heart Association (NYHA) class II–IV symptoms (15–23). In two large epidemiologic studies (24,25), the prevalence of AF was greater in CHF patients with preserved ejection fractions than in those with left ventricular systolic dysfunction, though the rates of AF were similar in patients with systolic as compared to diastolic CHF in one clinical trial (20).

The concomitant presence of both AF and CHF in many patients may be explained by shared underlying risk factors and mechanisms, or a causal relation between the entities. Indeed, many risk factors for AF have been recognized as leading risk factors for CHF (Table). The shared risk factors include hypertension, diabetes mellitus, ischemic heart disease, and valvular heart disease (26). Additionally, evidence of myocarditis, one potential cause of dilated cardiomyopathy and CHF, has also been implicated in the genesis of AF (27,28). In one series, AF was directly attributable to CHF in 5% of cases (29).

Temporal relations of AF and CHF

The temporal relations of AF and CHF were examined in a study of 1470 patients with new onset AF or CHF from the Framingham Heart Study (30). The average follow-up was 5.6 years after the development of AF, and 4.2 years after the development of CHF. Among patients who developed AF, 26% had a prior or concurrent diagnosis of CHF, and 16% of the remaining patients subsequently developed CHF during the follow-up period. Among patients who developed CHF, 24% had a prior or concurrent diagnosis of AF, and 17% developed AF during the subsequent follow-up period. For patients diagnosed with AF, the incidence of developing CHF was 33 per 1000 person-years. Conversely, among individuals diagnosed with CHF, the incidence of developing AF was 54 per 1000 person-years.

The association between AF and the development of CHF was also analyzed in a study of 3288 patients diagnosed with AF at the Mayo Clinic (7). Twenty-four percent developed CHF during a mean follow-up of 6.1 years, with an incidence of 44 per 1000 patient-years. A spike in the

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incidence of CHF was seen early after the diagnosis of AF, with 7.8% of cases occurring within the first 12 months, and approximately 3% per year thereafter. Patients with lone AF fared well, as only about 2% developed CHF within 5 years of being diagnosed with AF (7).

Prognosis of comorbid AF and CHF

Whereas substantial morbidity and mortality is attributable to each of these individual conditions, the concomitant presence of AF and CHF identifies individuals with a higher risk for death than with either condition alone. The prognostic impact of incident AF or CHF among individuals diagnosed with the other comorbid condition was assessed by investigators from the Framingham Heart Study (30). The development of AF in individuals with CHF was associated with a hazard ratio for death of 1.6 in men, and 2.7 in women, during follow-up of 4.2 years. Similarly, the development of CHF among individuals with AF was associated with a hazard ratio for death of 2.7 in men, and 3.1 in women, over a follow-up of 5.6 years.

The clinical consequences of AF are derived from the loss of organized atrial activity and absence of coordinated atrial mechanical function. Impaired contraction of the atria may cause blood stasis and the potential for thrombus formation, particularly in the left atrial appendage, with a resultant risk of stroke. This risk of stroke is increased in patients with CHF (31). Hundreds of electrical impulses arrive at the atrioventricular node and are variably transmitted, resulting in fast or slow heart rates and irregular ventricular depolarization. Patients may experience symptoms such as palpitations, dyspnea, or fatigue. The electrical and mechanical features of AF may also have hemodynamic consequences. A reduction in cardiac output is attributable to both the irregularity of ventricular contractions and the loss of atrial mechanical activity, which impairs ventricular filling (32,33). In fact, restoration of sinus rhythm results in a roughly 30% increase in cardiac output (34), though the significance of atrial contribution to cardiac output has been controversial in patients with preexisting elevations in left atrial pressure (35,36). Persistent tachycardia due to poor rate control has also been reported to result in a cardiomyopathy (37).

Thus, AF and CHF commonly coexist, share a similar risk factor profile, and have adverse hemodynamic effects. The simultaneous presence of both diseases identifies individuals at substantially increased risk of cardiovascular events and death.

Pathophysiology of AF in CHF

The pathophysiologic basis of AF is complex and incompletely understood (38). Initial mechanistic explanations for AF cited reentry as a principal factor (39–42). The multiple wavelet hypothesis, proposed by Moe and Abildskov,(41) stated that the development of AF depended on the perpetuation of a sufficient number of “randomly wandering wavelets” created as a normal occurrence due to heterogeneous repolarization. The hypothesis maintained that adequate atrial mass, short refractory periods, and conduction velocities slow enough to permit temporal disparities in depolarization and repolarization in the atria favored the development of these reentrant wavelets.

This argument is predicated on the concept that the wavelength of an electrical signal also represents the minimal pathway length that must be present to sustain a reentrant circuit. If a pathway is shorter, then a reentrant electrical stimulus will encounter refractory tissue upon completing the circuit and terminate. In contrast, if the pathway is longer then the electrical signal may encounter excitable tissue upon completing the circuit, thereby perpetuating the previous cycle. The wavelength, and thus the pathway length, is proportional to both the refractory period of the tissue, as well as the conduction velocity. This model explains precipitants of AF that shorten the atrial effective refractory period or decrease conduction velocity.

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The focal automaticity theory was an early competing hypothesis that explicitly challenged the role of reentrant rhythms in the genesis of AF, instead proposing that repetitively firing foci serve as the driving factor (43). In fact, a contemporary paradigm acknowledges complexity in the development of AF, recognizing the role of both susceptible atrial substrate, which may foster reentry, as well focal electrophysiologic triggers (Figure 1) (44).

Susceptible atrial substrate

Fibrosis—Atrial fibrosis is commonly observed in patients with AF, both with and without underlying organic heart disease, and is considered a major factor contributing to the development and maintenance of AF (27,28,45). Fibrosis results from increased interstitial collagen deposition, which may disrupt cell-to-cell coupling and thereby alter signal conduction. Indeed, areas with decreased conduction velocities and heterogeneous conduction have been observed in animal models of AF and fibrosis (46,47).

Fibrosis accompanies aging and is observed both with ischemia and myocyte stretch (48,49). Activation of the renin-angiotensin-aldosterone system provokes myocardial fibrosis, which appears to be mediated through upregulation of the TGF-β1 pathway (50). Indirect evidence of the contributory role of atrial fibrosis provoked by the renin-angiotensin-aldosterone neurohormonal axis is derived from clinical trials that have documented a significant reduction in the risk of new-onset or recurrent AF with angiotensin converting enzyme inhibitors or angiotensin receptor blockers (51,52).

Myocyte stretch—Myocyte stretch is another important factor contributing to AF susceptibility. Indeed, several pathological conditions associated with increased left atrial pressure are closely linked to the development of AF, including hypertension, mitral valve disease, and CHF. Myocyte stretch stimulates collagen deposition by fibroblasts, in part mediated via angiotensin II and TGF-β1 pathways (48). Additionally, stretch causes acute alterations in electrophysiological properties that are favorable to the development and maintenance of AF via mechanoelectric feedback mechanisms (53).

Electromechanical remodeling

Experimental models in goats demonstrate that prior AF promotes an environment favorable to subsequent episodes of AF through both electrophysiological (54) as well as structural remodeling (55). Intracellular calcium overload causing a reduction of L-type calcium currents may contribute to atrial remodeling (56). Additional mechanisms of atrial remodeling may include intracellular glycogen accumulation accompanied by sarcomere loss (55), and diminished myocyte energy reserves (53). Accompanying proarrhythmic electrophysiological changes have been observed, such as decreases in myocyte resting potential, shortening of the atrial effective refractory period, and characteristic alterations in the morphology of the action potential (54,56). Grossly, structural changes resulting from AF may manifest as left atrial enlargement (57), which predisposes to recurrent AF.

Elements promoting susceptible atrial substrate are often interrelated, underscoring the difficulty of identifying discrete mechanisms that result in AF. For example, both myocyte stretch and prior AF have been linked to atrial fibrosis (48).

Focal triggers

In addition to the role of susceptible atrial substrate, recent evidence has emerged which supports a critical role for focal triggers in the development of AF in many patients with this arrhythmia. These focal triggers most commonly arise from within the pulmonary veins (58, 59), and conduct to the left atrium through sleeves of muscular tissue in the pulmonary veins (60). The importance of these triggers has been underscored by the success of pulmonary vein

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isolation in preventing recurrences of AF in many patients (61,62). The mechanisms resulting in these triggers remain unclear, though automaticity, triggered activity, and microreentry have all been implicated (63). The observation that myocyte stretch increases pulmonary vein foci firing once again illustrates the interdependence of mechanisms contributing to AF (64). Ectopic foci have also been identified in other areas of the heart such as the posterior left atrium, coronary sinus, superior vena cava, and ligament of Marshall (65). Additionally, atrioventricular nodal reentrant tachycardias (66), as well as atrioventricular bypass tracts may also trigger AF (67).

Modulating factors

In addition to susceptible atrial substrate and electrophysiologic triggers, modulating factors such as autonomic tone have been identified in the development of AF (68,69). Vagal denervation has been explored for the prevention of recurrent AF with promising initial results (69). Inflammation may also be associated with the development of AF in patients with concomitant cardiovascular disease (70). In fact, treatment with corticosteroids in addition to beta blockade during the postoperative period reduced the risk of developing postoperative AF by roughly 50% among patients undergoing cardiac surgery without any preexisting history of AF (71).

Role of Genetics

An abundance of epidemiological data implicates a heritable contribution to the development of AF. In a prospective cohort study encompassing patients from the Original and Offspring cohorts from the Framingham Heart Study, the odds ratio of developing AF over 4 years among participants with a parental history of AF was 1.85, and increased to 3.23 when limiting the analysis to parents and offspring who developed AF under the age of 75 (72). Other studies have confirmed that up to approximately one-third of individuals with AF have a positive family history of the condition (73–76). In a study encompassing over 5000 patients diagnosed with AF in Iceland, the relative risk of developing AF was 1.77 among members with an affected first-degree relative, and declined with each successive degree of relation (77).

Analyses of patients with familial AF have exposed mutations in genes encoding potassium (78–84) and sodium (75,76,85–87) channels (Figure 2), as well as atrial natriuretic peptide (88), and have identified several loci associated with AF (89–92). Mutations in ion channels may contribute to AF by their effect on the atrial action potential, which is comprised of multiple tightly coordinated electrical currents. The majority of identified potassium channel mutations result in a gain of channel function. Such an increase in an outward potassium current would produce more rapid repolarization of atrial myocytes, shorten the atrial effective refractory period, and thus predispose to reentry(78–81,83,84,93). Interestingly, a loss-of-function mutation in the ultrarapid delayed rectifier potassium current (I_{Kur}) has been identified which prolongs the action potential and facilitates early after depolarizations, particularly under adrenergic stimulation (82). As discussed below, prolongation of the action potential has been observed in patients with CHF, suggesting that triggered activity may play an important role in initiating AF in this setting (94). Some loss-of-function mutations in sodium channels decrease ionic current, prolong the atrial action potential duration, and may predispose to AF in a similar manner.(95)(85). More recently, somatic mutations in gap junction proteins have been identified in patients with idiopathic AF (95), but the prevalence of such mutations is unknown. Despite mechanistic insights gleaned from identification of these mutations, ion channel mutations are rare causes of AF (96).

In some cases, identification of genes implicated in cardiomyopathies has shed light on possible shared biological mechanisms between CHF and AF. In some patients with a familial cardiomyopathy and AF, mutations have been identified in *SCN5A*, or the cardiac sodium

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channel gene also associated with the Brugada and long QT syndromes (97,98). Similarly, mutations in the laminin A/C gene, a nuclear envelope protein, have been identified in patients with familial dilated cardiomyopathy that is preceded by the development of AF (99,100). The mechanisms by which such mutations cause arrhythmias and a cardiomyopathy remain unclear.

Most mutations identified thus far have been discovered by linkage or candidate gene analysis. More recently, genome-wide association studies have been employed to search for genetic variation that may underlie common diseases such as AF (101,102). Genome-wide association studies can identify genetic variants associated with a particular phenotype by scanning for hundreds of thousands of single nucleotide polymorphisms in patients both with and without the condition of interest. The identified variants may have a direct pathogenic role in the development of the condition; however, in most cases, such variants are simply serving as a marker of a genetic region associated with a risk of the condition. Genome-wide association studies represent a major advance owing to the fact that they provide rapid assessment of thousands of markers throughout the genome and are not constrained by existing understanding of physiology.

A recent genome-wide association study in Iceland has identified two variants on chromosome 4q25 associated with AF (101). Replication in three additional cohorts of European ancestry reproduced the associations, while replication in a cohort of Chinese descent confirmed the association with one of the variants (101). No known gene is present in the genomic block containing the two variants, though two potential candidate genes, *PITX2* and *ENPEP*, are located in close proximity. *PITX2* plays an important role in cardiac development by directing asymmetric morphogenesis of the heart (103). Knockout of *PITX2* in a mouse model suppresses the default pathway for sinoatrial node formation in the left atrium (104,105). *ENPEP* encodes an aminopeptidase responsible for breakdown of angiotensin II in the vascular endothelium. Knockout of *ENPEP* in a mouse model resulted in systemic HTN but no arrhythmias (106). Investigation of the causal mechanisms by which these variants are related to AF is ongoing. In two subsequent genome-wide association studies, a second common AF susceptibility locus was identified on chromosome 16q22 within the ZFHX3 gene.(107,108)

Specific implications in CHF

Thus it is clear that electrical triggers, susceptible substrate, and modulating factors are important for the promotion of AF. Genetic factors may promote AF by increasing susceptibility to reentry, triggered activity, disrupting cell-to-cell communication, and through other currently as yet undefined mechanisms. Several of the discussed pathophysiological mechanisms are of particular importance in patients with CHF (Figure 1).

Increased atrial refractoriness has been observed in CHF patients that develop AF, suggesting that the origins of the arrhythmia in this patient population may differ from those classically described (94). A variety of ion channel current abnormalities have been reported in experimental CHF models, including a reduction in L-type Ca^{2+} current (I_{Ca}), transient outward K+ current (I_{to}), and slow delayed rectifier current (I_{Ks}) (109). Notably, CHF is accompanied by an increase in the Na^{+}/Ca^{2+} transmembrane exchange channel current, which exchanges three monovalent sodium ions for every one divalent calcium ion. This net positive intracellular imbalance can predispose to delayed after depolarizations, resulting in arrhythmias initiated by triggered activity. Indeed, data from a pacing-induced animal model of CHF demonstrate that abnormalities in calcium handling prolong the atrial action potential and foster AF through triggered activity (110). Adrenergic stimulation occurs in CHF, and is a well-known cause of triggered activity. The role of adrenergic stimulation in the genesis of AF is not clear (111). In parallel to ion channel remodeling present in patients with CHF, heterogeneous distribution of connexins, which form gap junctions, has been observed in both animal models of atrial hemodynamic overload as well as in humans with a history of CHF (112).

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Elevations in left atrial and pulmonary venous pressure present in CHF promote AF as well. Myocyte stretch increases firing from ectopic foci such as the pulmonary veins through mechanoelectrical feedback (64). Additionally, increased fibrosis results from myocyte stretch. Gross evidence of structural remodeling includes left atrial enlargement, which predisposes to AF (113,114). Although increased atrial refractoriness has been observed clinically in patients with CHF, shortening of the atrial refractory period has been reported in experimental models of left atrial stretch, suggesting that many competing processes may be occurring simultaneously in these patients (115).

Neurohormonal activation is another principal feature of CHF that also promotes AF. Upregulation of both the renin-angiotensin-aldosterone and adrenergic systems causes myocardial fibrosis, which impairs impulse propagation (46,116). Fibrosis is thought to play a prominent role in the development of AF in patients with CHF. In an experimental pacing model of CHF, fibrosis, rather than ion channel remodeling, produced lasting effects that correlated with the maintenance of induced AF (117). Nonetheless, angiotensin II may have independent effects on ion currents which promote AF (118).

Treatment

Thromboembolism prophylaxis

Thromboembolism prophylaxis, ventricular rate control, and restoration of sinus rhythm when indicated, are the goals of AF therapy (1). The risk of cerebral thromboembolism in patients with AF is increased in those with CHF (31). Annual stroke risk can be estimated using validated scoring schemes (31,119), and guidelines provide a recommended approach to the prevention of thromboembolism in patients based on their underlying risk. Generally, warfarin is advisable for the prevention of ischemic cerebrovascular events in patients with CHF and an additional stroke risk factor (1).

Rate and rhythm control

Recent controlled trials of patients with predominantly persistent and asymptomatic AF demonstrated no advantage of a rhythm control strategy comprised of antiarrhythmic drug therapy and electrical cardioversion over a rate control strategy in terms of survival or morbidity (120–124). A meta-analysis of these trials demonstrated a reduction in the combined endpoint of all-cause death or thromboembolic stroke with a rate control strategy (125).

However, rhythm control strategies in these trials were only moderately successful, with the maintenance of sinus rhythm ranging from 23% to 64% over variable periods of follow-up. Post-hoc analyses of these and other trials demonstrate that achievement of sinus rhythm is associated with improved survival (126) and quality of life (127,128). The observation that non-cardiovascular deaths were greater in the rhythm control arm than in the rate control arm of the AFFIRM trial has provoked speculation that the benefits of maintaining sinus rhythm were offset by the harmful effects of antiarrhythmic drug therapy (129).

These trials were not adequately powered to assess the optimal management strategy of AF in patients with CHF. More recently, the results of the Atrial Fibrillation and Congestive Heart Failure Trial (AF-CHF) were reported (130). This randomized controlled trial assessed cardiovascular mortality among patients with concomitant AF and CHF treated with either a rate or rhythm control strategy. Over 1300 patients were enrolled, with a mean left ventricular ejection fraction of 27%. One third of patients had NYHA class III or IV symptoms, and over two-thirds had persistent AF. Over 80% of patients randomized to the rhythm control arm were treated with amiodarone, and 40% underwent electrical cardioversion. During a mean follow-up period of 37 months, sinus rhythm was documented in 75–80% of patients in the rhythm control arm by 12-lead electrocardiogram at each follow-up visit, whereas sinus rhythm was

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present in 30–40% of patients in the rate control arm at each visit. No difference was observed in cardiovascular mortality between strategies during the follow-up period. These data suggest that a rhythm control strategy consisting of pharmacologic and electrical cardioversion for stable patients with concomitant AF and CHF does not improve cardiovascular survival. These results may not pertain to patients that are hemodynamically unstable as a result of AF. Additionally, the impact of other rhythm or rate control strategies, such as catheter ablation for AF, or atrioventricular node ablation with pacing, was not assessed adequately in this or other trials comparing rate and rhythm control strategies. In a smaller trial of 61 patients randomized to rhythm control with amiodarone and direct cardioversion or rate control and followed for one year, an improvement in left ventricular function and some quality of life parameters was observed among those in the rhythm control arm.(131)

Catheter ablation

Catheter ablation for AF, specifically pulmonary vein isolation, has become an increasingly popular therapy for the treatment of AF. Recent controlled trials suggest that in carefully selected patients, catheter ablation is superior to a medical rhythm control strategy for the prevention of recurrent disease during short-term follow-up, with success rates ranging from 56–87% (132). Yet subjects in these trials predominantly were healthy, had paroxysmal rather than persistent or permanent AF, and were typically without structural heart disease.

Catheter ablation for AF was assessed in 58 patients with CHF in one non-randomized controlled trial (133). Sinus rhythm was present in 78% of patients following ablation after approximately one year, although repeat ablations were required in half of the patients. Improvements in functional status, symptoms, and ejection fraction were noted with ablation.

Similarly, in a prospective cohort study, sinus rhythm was achieved in 73% of patients with left ventricular systolic dysfunction who underwent pulmonary vein isolation at approximately 14 months of follow-up, as compared to 87% of patients with preserved left ventricular function (134). Sixty-eight percent of the patients with left ventricular systolic dysfunction had NYHA class III symptoms.

Despite promising initial results, there are presently no data that demonstrate that catheter ablation improves survival in patients with CHF. Moreover, results from studies of catheter ablation for AF must be interpreted in the context of the study designs, which often were not randomized, involved few patients, and provided only short-term follow-up.

Atrioventricular nodal ablation and pacemaker placement

Ablation of the atrioventricular node with implantation of a single right ventricular lead for permanent pacing, also referred to as the “ablate and pace” approach, is effective for the achievement of rate control in patients with AF and rapid ventricular response, and results in greater symptom control than pharmacologic therapy aimed at controlling the ventricular rate in patients with left ventricular systolic dysfunction and CHF (135). Yet right ventricular pacing can be associated with progressive left ventricular dysfunction, whereas biventricular pacing results in reduced morbidity and mortality in systolic CHF patients with NYHA class III or IV symptoms in sinus rhythm and with a prolonged QRS (136). In a prospective cohort study of patients with conventional indications for biventricular pacemaker implantation, the benefits of biventricular pacing in a subgroup of patients with AF were maximized when biventricular pacing was induced nearly 100% of the time by atrioventricular node ablation (137). Improvements in the ejection fraction and functional capacity were seen when compared to patients who received biventricular pacing less than 85% of the time. Other data demonstrate improvements in a variety of functional and symptomatic parameters in patients with AF and systolic CHF with a wide QRS who are treated with biventricular pacemakers (138). The

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Atrioventricular Junction Ablation Followed by Resynchronization Therapy in Patients with CHF and AF trial (139) trial will compare pharmacologic rate control therapy to atrioventricular node ablation with biventricular pacemaker implantation in patients with symptomatic permanent AF and CHF, irrespective of underlying QRS duration.

While the ablate and pace approach achieves rate control, it does not restore sinus rhythm and necessitates permanent implantation of a mechanical pacemaker. AV nodal ablation with biventricular pacing was compared to AF ablation in a pilot study of 35 subjects with CHF and systolic left ventricular dysfunction (140). In the Pulmonary Vein Isolation Versus AV Nodal Ablation With Biventricular Pacing for Patients With Atrial Fibrillation With Congestive Heart Failure (PABA CHF) study, pulmonary vein isolation was associated with greater improvement in symptoms and ejection fraction as compared with the ablate and biventricular pacing group.

Definitive trials assessing the effectiveness of AF ablation as compared with an ablate and ventricular pacing strategy are warranted. In the meantime, atrioventricular node ablation and ventricular pacing remains a reasonable option for the management of patients in whom the achievement of adequate rate control with pharmacologic therapy is inadequate (1).

Renin-angiotensin-aldosterone axis inhibitors and beta-blockers

Importantly, pharmacological agents commonly used in the management of patients with systolic CHF both prevent incident AF and reduce recurrences in patients with concomitant AF and CHF, again reinforcing the shared mechanisms of these diseases. Both angiotensin converting enzyme inhibitors and angiotensin receptor blockers are effective in preventing the onset of AF. In one meta-analysis of randomized trials assessing the use of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, the relative risk of developing AF among patients treated with either medication was reduced by 28% (51). Patients with CHF enjoyed a relative risk reduction of 44%, with a greater benefit seen among those with more severe left ventricular systolic dysfunction. In another meta-analysis, the overall risk reduction for the development of new onset AF among patients treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker was 18%, and patients with a history of CHF had a particular benefit with a risk reduction of 43% (52).

Further, a systematic review of randomized placebo-controlled trials in patients with CHF demonstrated that the addition of beta-blockers in addition to ACE-I therapy was associated with a relative risk reduction of 27% in the incidence of AF over an average follow-up of 1.35 years (141). However, no preventative effect of beta-blockade was observed in the SENIORS trial, which studied the use of nebivolol in elderly patients (≥70 years old) with either diastolic or systolic CHF.

Conclusion

AF and CHF share many risk factors, frequently coexist, and identify individuals at high risk of cardiovascular morbidity. The pathophysiological mechanisms of AF in patients with CHF are complex and potentially involve elements of reentry, triggered activity and enhanced automaticity. Therefore, it is unlikely that a treatment strategy aimed at any one of these mechanisms alone will restore sinus rhythm. A rhythm control strategy consisting of antiarrhythmic drugs and electrical cardioversion in stable patients with AF and CHF adds no benefit to a rate control strategy. Newer therapies aimed at restoring sinus rhythm, such as catheter ablation for AF, and rate control therapies such as atrioventricular nodal ablation with biventricular pacing, have emerged as potential alternatives to conventional rhythm and rate control strategies. Future trials will be necessary to delineate the role for such techniques in the multitude of patients with these morbid conditions.

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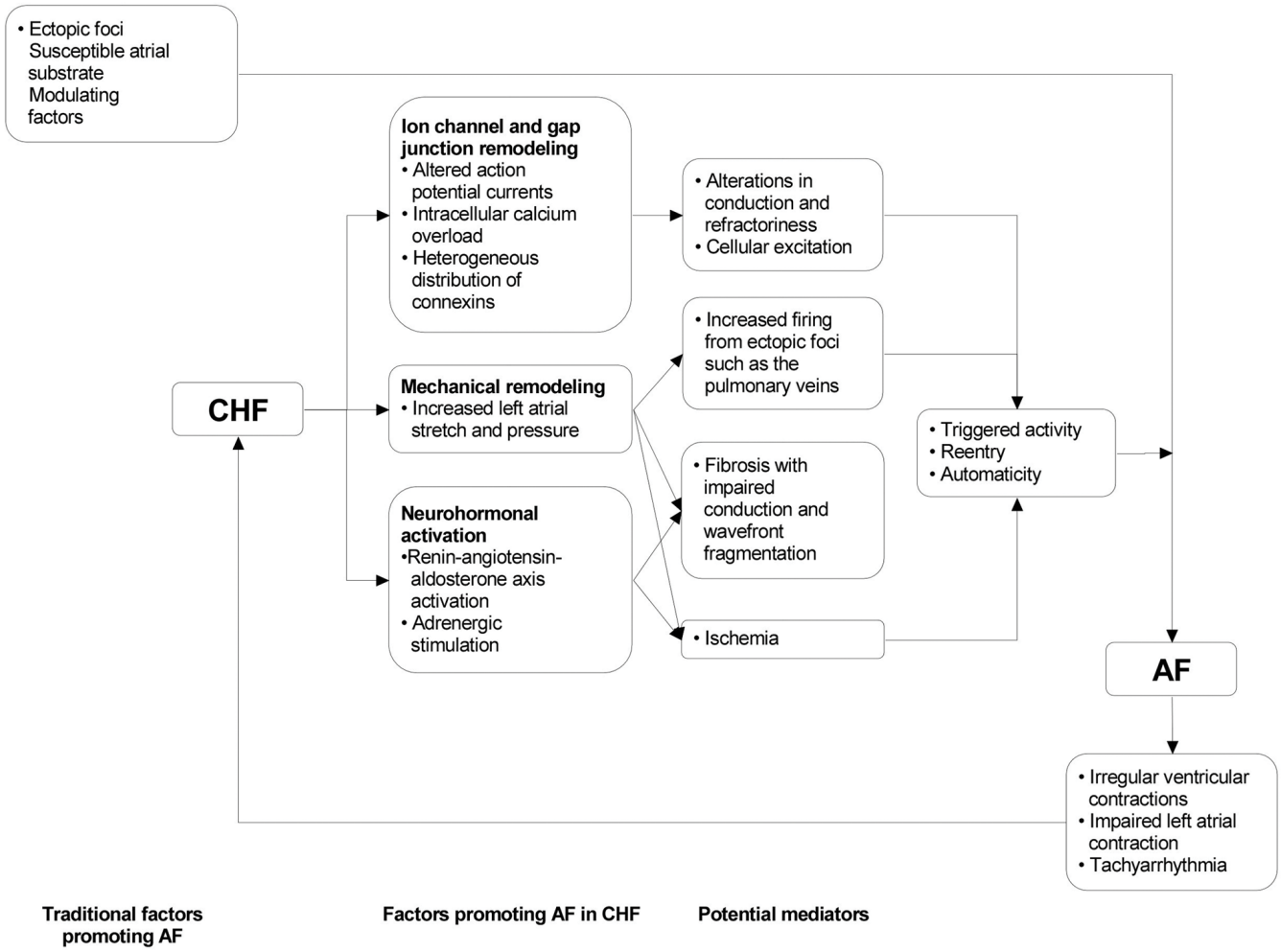

Figure 1.

Mechanisms promoting atrial fibrillation in congestive heart failure.
AF = atrial fibrillation, CHF = congestive heart failure

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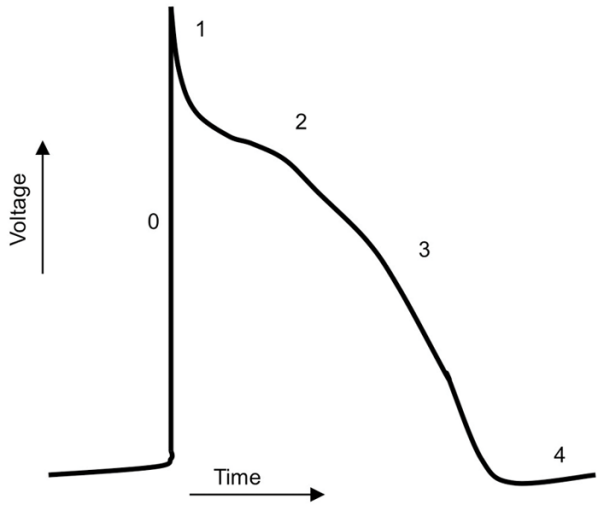

Ionic current	Predominant active phase	Gene	Gain or loss of function	Predicted effect on ARP	Reference
I_{Na}	0	*SCN5A*	Loss	None	[85, 98]
I_{to}	1	*KCND3/KCNIP2*	-	-	-
I_{Kur}	2	*KCNA5*	Loss	↑	[82]
I_{CaL}	3	*CACNA1C*	-	-	-
I_{Kr}	3	*KCNH2/KCNE2*	Gain	↓	[80]
I_{Ks}	3	*KCNQ1/KCNE1*	Gain	↓	[78, 79, 83, 84, 94]
I_{NCX}	3		-	-	-
I_{K1}	4	*KCNJ2*	Gain	↓	[81]

Figure 2.
Genetic mutations affecting ionic currents that underlie the atrial action potential.
ARP = atrial refractory period, GOF = gain of function mutation, LOF = loss of function mutation.

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Table

Shared risk factors for atrial fibrillation and congestive heart failure.

Non-modifiable risk factors
Aging
Male gender
Genetic predisposition
Modifiable risk factors
Hypertension
Diabetes mellitus
Obesity
Hyperthyroidism
Smoking
Excessive alcohol consumption
Heart disease
Ischemic heart disease
Valve disease
Infiltrative cardiomyopathies
Myocarditis
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Subclinical disease
Electrocardiographic left ventricular hypertrophy
Neurohormonal activation
Inflammation