Atrial Fibrillation and Congestive Heart Failure

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ABSTRACT. Atrial fibrillation (AF) and congestive heart failure (CHF) are common conditions which predispose each other, share risk factors, and are associated with morbidity and mortality. They share common pathophysiology, including structural and electrical remodeling, intracellular calcium dysregulation, and neuroendocrine mechanisms, and also have genetic basis. Despite better survival in patients with sinus rhythm than those with AF, rhythm control has not been found to be superior to rate control. The role of non-antiarrhythmic therapy is also being explored. Catheter ablation and device-based therapy with pacemaker and cardiac resynchronization therapy may also benefit patients with AF and CHF.

KEYWORDS. ablation, antiaryrrhythmic drugs, atrial fibrillation, genetics, heart failure.

Introduction

In an analysis of Framingham Heart Study, atrial fibrillation (AF) and congestive heart failure (CHF) have been found to be associated with each other, and the presence of either one increases the risk of developing the other and also increases the mortality risk associated with the other. Both the incidence and the prevalence of AF are increasing, even after adjustment for aging of the population, and the prevalence of CHF is increasing primarily as a result of improved survival after its onset due to improved treatment. Both AF and CHF are modern epidemics in cardiovascular disease. In the ATRIA (Anticoagulation and Risk Factors In Atrial Fibrillation) study, 2.3 million adults in the United State were estimated in 1996 to suffer from AF and the number is expected to increase to 5.6 million in 2050. The lifetime risk of developing AF after age 40 is 26% for men and 23% for women, and its presence increases the risk of stroke, dementia, and death. CHF afflicts 5.3 million adult Americans, with a lifetime risk after age 40 of more than 20%. The burden of health-care expenditure related to these two conditions is profound, with CHF alone accounting for almost $35 billion.

Temporal relation of AF and CHF

In a large cohort of patients from the Framingham Heart Study, at first diagnosis of AF, 26% of patients had a prior or concurrent diagnosis of CHF, and 16% of the remaining patients developed the condition during the follow up period of 5.6 years (Figure 1a). Among patients who developed CHF, 24% had a prior or concurrent diagnosis of AF, and 17% developed AF during the follow up period of 4.2 years (Figure 1b). Patients with a previous diagnosis of AF were found to develop CHF at a rate of 3.3% per year, and the ones with previous CHF developed subsequent AF at a rate of 5.4% per year. The coexistent presence of AF and CHF worsens both symptoms and mortality (Figure 2) than either disorder alone in most large studies. There are conflicting data as to whether AF is an independent predictor of mortality in patients with CHF, with the largest experience coming through subset analyses of the SOLVD (Studies of Left Ventricular Dysfunction), CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) and V-HeFT trials. A retrospective analysis of the SOLVD analyzed 3-year follow up of 6,517 patients with AF having asymptomatic
and symptomatic left ventricular (LV) dysfunction. In SOLVD, AF was associated with significant increases in all-cause mortality (RR 1.34, 95% CI 1.12–1.62, p < 0.01), CHF-related mortality (RR 1.42, 95% CI 1.09–1.85, p < 0.01), and the death and hospitalization for CHF (RR 1.26, 95% CI 1.03–1.42, p < 0.02). This was largely due to increased mortality from pump failure (16.7% versus 9.4%). There was no increase in mortality from arrhythmia. The CHARM trial included 7,599 patients with symptomatic CHF, both with reduced and preserved LV ejection fraction (LVEF) out of which 18% had AF at baseline. After a follow-up of 38 months, AF was associated with an increased risk for all-cause mortality in patients with either a low LVEF (<40%) (RR 1.29, 95% CI 1.14–1.46, 37% versus 28%) and preserved LVEF (RR 1.72, CI 1.45–2.06, 24% versus 14%). V-HeFT I and II trials included 1,427 patients with New York Heart Association (NYHA) Class II–III, out of which 14% had AF. There was no significant difference in major morbidity or mortality at 2 years in either V-HeFT I or II when comparing patients with versus those without AF.

**Common risk factors for AF and CHF**

**Genetics**

Epidemiological data point towards a heritable contribution to the development of AF. In the Framingham Heart study, the odds ratio of developing AF over 4 years among participants with a history of parental AF was 1.85. In a study conducted in Iceland of more than 5,000 patients, the relative risk of developing AF was 1.77 in those with an affected first-degree relative. Genes encoding potassium and sodium channels as well as atrial natriuretic peptide have been associated in patients with familial AF. More recently, somatic mutations in the connexin 40 gene leading to a defect in gap junction proteins have been identified in patients with idiopathic AF. In genome-wide association studies, two variants on chromosome 4q25 and chromosome 16q22 within the ZFHX3 gene have been associated with AF. In a large number of genes have been implicated in the development of cardiomyopathy (both dilated and idiopathic) compared with AF. Over 300 mutations have been described related to the development of hypertrophic cardiomyopathy, and often they are unique to families. Familial dilated cardiomyopathy is associated with mutations in a variety of proteins related to the sarcomere and cytoskeleton as well as ion channels and regulatory proteins. In most cases, familial forms of AF...
and CHF have an earlier age of onset than acquired forms.

Possible shared biologic mechanisms between AF and CHF have been described. In some patients with familial cardiomyopathy and AF, mutations involving the cardiac sodium channel gene (SCN5A) are the underlying abnormality, which is also associated with the long QT syndrome. Also, a mutation in a nuclear envelope protein gene has been identified in patients with familial dilated cardiomyopathy that is often preceded by the development of AF. The mechanisms by which such mutations cause arrhythmias and cardiomyopathy are not yet fully understood.

Acquired risk factors

Although known genetic variants play an important role in the development of AF and CHF in many individuals, the majority of cases of AF and CHF are secondary to other medical and cardiac conditions. Age, male gender, hypertension, metabolic syndrome, diabetes, alcohol ingestion, smoking, neurohormonal activation, inflammation, hyperthyroidism, and surgery are common general medical conditions which can increase the risk for the development of AF and CHF. Cardiac risk factors include: 1) ischemic heart disease (with all of the risk factors for coronary artery disease); 2) valvular heart disease; 3) LV systolic and diastolic dysfunction; and 4) myocarditis and infiltrative cardiomyopathies. Coronary artery disease leading to myocardial ischemia and infarction is the greatest single contributor to systolic ventricular dysfunction in developed nations. Age, diabetes, and hypertension are strongly associated with diastolic dysfunction. Systolic dysfunction is more common in men whereas diastolic dysfunction is especially common in women, although there is considerable overlap. Independent risk factors for AF also include elevated CRP and homocysteine levels along with subclinical and clinical hyperthyroidism and asymptomatic LV dysfunction. AF and CHF have many shared risk factors that extend beyond predisposing conditions. Complex cellular, molecular, neurohormonal, structural, and electrophysiological processes have been revealed which can increase the risk for both conditions.

Structural changes

In an experimental model, chronic or persistent atrial tachyarrhythmia achieved by rapid pacing leading to marked elevation of ventricular rate leads to dilation of the ventricles, thinning of the ventricular wall, and decreased contractility, ultimately resulting in ventricular dysfunction and CHF. It is also noted to reduce myocardial compliance, impeding ventricular filling, and causing shortened filling times. An overall decrease in myocardial collagen content along with altered extracellular collagen distribution has been noted with persistent tachycardia leading to dilation of the ventricular walls and decreased contractility. Underlying mechanisms for this are not yet fully understood. In animal models, the severity of CHF progresses with increasing heart rates and duration of tachycardia. Structural changes during this time include cytoskeletal alterations with increased actin and tubulin. In CHF, atrial volume and pressure overload contribute to the development of atrial enlargement along with altered atrial refractory properties and interstitial fibrosis, which then lead to heterogeneity of atrial conduction thereby predisposing to development of AF.

Molecular events

Prolonged rapid atrial pacing in animals has been found to decrease L-type Ca$^2+$ current and transient outward K$^+$ current, resulting in shortening of action potential duration as well as atrial refractory period. Intracellular accumulation of glycogen, decreased connexin, progressive mitochondrial injury, and depletion in cytochrome oxidase and creatinine kinase activity lead to abnormal cellular energetics and depletion of high-energy phosphate levels with resulting sarcomere loss and atrial remodeling. These changes lead to an environment more conducive to further AF—hence “AF begets AF” as suggested by Wijffels et al. Heart failure leads to reductions in ionic transmembrane currents including the L-type Cal current, delayed rectifier and transient outward K$^+$ current and increase in the Na$^+$/Ca$^2+$ exchanger current. The cumulative effect of these changes on atrial action potential duration is minimal at slow heart rates but increased at rapid rates. Interestingly, a combination of AF and CHF produce effects on ionic current densities different from either disorder alone. CHF-induced AF also results in dysregulation of Ca$^2+$ load in atrial sarcoplasmic reticulum because of reduction in ryanodine receptor and calquestrin expression. In addition, atrial contraction is decreased because of reductions in protein kinase A and C. This creates a state of atrial intracellular Ca$^2+$ overload leading to generation and maintenance of AF and a similar ventricular diastolic Ca$^2+$ overload contributes towards CHF.

Neurohormonal mechanisms

Inflammation and oxidative stress have been implicated in the genesis of CHF and AF. In experimental CHF, local angiotensin II production precedes the development of atrial fibrosis. In fact, upregulation of the RAAS (renin angiotensin aldosterone system) is considered to be one of the important factors leading to development and maintenance of both CHF and AF. Activation of the RAAS system leads to upregulation of the transforming growth factor beta-1 pathway provoking myocardial fibrosis and unleashing a vicious circle causing self-propagation of AF and CHF. A rapid heart rate in patients with AF can result in increased sympathetic activity, which seems to be independent of hemodynamic changes seen in AF. Also, studies have revealed increased cathecholamine levels in experimental atrial tachycardia-induced cardiomyopathy. This again suggests a possible link between AF and CHF at the hormonal level.
Reversibility

Shinbane et al.,37 in their review of animal models and clinical studies in tachycardia-induced cardiomyopathy, noted that cardiac output becomes reduced in as little as 24 h of tachycardia, with induction of CHF within 1 month and resolution of the tachycardia leading to improvement in CHF within 48 h. During a time period of 4–6 weeks of rapid ventricular pacing in a canine model, the inducibility of AF and increase in atrial dimensions increased markedly with the induction of CHF but decreased proportionately to the improvement in hemodynamic function during a recovery period of 5 weeks.53 Resolution of tachycardia by rate or rhythm control results in improvement of EF and other signs of CHF, but with recurrence of tachycardia an abrupt decline in LVEF and an increased risk of sudden death has been noted.54 Interestingly, even with normalization of EF, pathologic remodeling, i.e. atrial fibrosis and ventricular dilation, may persist after treatment of tachycardia-induced cardiomyopathy.55,56 Hence there is at least partial reversibility in pathological mechanisms underlying AF and CHF.

AF and CHF: therapeutic approaches

Rate or rhythm control

Based upon the expectation that CHF would be more easily managed in AF patients if they could be kept in sinus rhythm, it has been postulated that restoration and maintenance of sinus rhythm would be of specific importance in such patients. The presence of sinus rhythm as opposed to AF was associated with improved survival in the AFFIRM trial, but antiarrhythmic treatments designed to maintain sinus rhythm were not associated with improved survival when compared with rate control strategy in AFFIRM.57 Similarly, the SAFE trial emphasized the benefits of sinus rhythm over AF, showing an improved quality of life with the presence of sinus rhythm compared with AF.58 Similar to AFFIRM, however, SAFE along with Strategies of Treatment of AF (STAF) study and HOT CAFÉ (Polish How To Treat Chronic AF) demonstrated no advantage of a rhythm control strategy comprising antiarrhythmic drug therapy and electrical cardioversion over a rate control strategy in terms of morbidity or mortality.59,60 A meta-analysis of the STAF study, PIAF (Pharmacological Intervention in AF) trial and HOT CAFÉ trial revealed a reduction in the combined endpoint of all-cause death or thromboembolic stroke with a rate control compared with a rhythm control strategy.61 In fact, there were fewer adverse events including stroke with rate control than rhythm control, which appears to be related to greater discontinuation of anticoagulation in the rhythm control arm. A post hoc analysis of ATHENA (A placebo controlled double blind trial with Dronedarone to prevent Hospitalization or Death in patients with Atrial Fibrillation) involving 4,628 patients (with persistent or paroxysmal AF with at least one risk factor for cardiovascular hospitalization and receiving usual care with antithrombotic and rate control therapy) revealed that dronedarone reduced the risk of stroke from 1.8% per year to 1.2% per year (hazard ratio 0.66, 95% CI 0.46–0.96, p=0.027). The effect of dronedarone was similar whether or not patients were receiving oral anticoagulant therapy, and there was a significantly greater effect of dronedarone in patients with higher CHADS2 score.62 This suggests that the failure to demonstrate stroke reduction with antiarrhythmic therapy in previous rate versus rhythm control studies was due to discontinuation of anticoagulation, although it is also possible that this result in ATHENA could also reflect a pharmacologic difference between dronedarone and other antiarrhythmic agents. Evidence of the adverse effects of dronedarone therapy in patients with AF and CHF comes from the results of the ANDROMEDA trial (Antiarrhythmic Trial with Dronedarone in moderate to severe CHF evaluating morbidity decrease), which was discontinued prematurely because of a significant increase in the incidence of death in patients assigned to dronedarone due to worsening heart failure.63 Dronedarone causes an increase in serum creatinine without affecting creatinine clearance, and it is possible (but currently unproven) that the adverse outcomes associated with dronedarone in this trial may have related to higher discontinuation of angiotensin-converting enzyme inhibitors (ACE-Is) in the dronedarone arm due to higher serum creatinine.64,65 At the current time, dronedarone is contraindicated in patients with severe heart failure based on the results from ANDROMEDA.

In a study of Danish Investigations of dysrhythmia and mortality on Dofetilide (DIAMOND) trial and in CHF-STAT (Congestive heart failure-Survival Trial of Antiarrhythmic Therapy) the subgroup of heart failure patients who maintained sinus rhythm demonstrated reduced mortality.66,67 The Atrial Fibrillation in Congestive Heart Failure (AF-CHF) trial, a large multicenter prospective randomized trial, involving 1,376 patients which assessed cardiovascular mortality among patients with concomitant AF and CHF treated with a rate or rhythm control strategy, did not describe any morbidity or mortality benefit or any improvement in secondary outcome (Figure 3) of rhythm over rate control.68 SWORD (Survival With Oral d-Sotalol), a trial of d-sotalol (a relatively pure Class III agent) in patients with LVEF ≤40% post myocardial infarction demonstrated increased mortality with d-sotalol use compared with placebo.69 SWORD was not a trial looking specifically at AF patients, but does raise concern about the use of this class of antiarrhythmic drugs in patients with CHF post myocardial infarction.

Antiarrhythmic therapy

Class I agents: sodium channel blockers

These are commonly used for patients with structurally normal hearts and AF but avoided in patients with CHF and ischemic heart disease as they may increase mortality.70
Class III agents: potassium channel blockers

The CHF-STAT study showed that amiodarone (which has action on multiple cellular ionic currents) did not increase mortality in CHF patients and could be safely initiated in the outpatient setting. Amiodarone has been shown to be more efficacious than sotalol in preventing recurrent AF. Dronedarone, a deiodinated derivative of amiodarone, showed great promise in reducing toxicity.

The European Trial in atrial fibrillation or flutter patients receiving dronedarone for maintenance of sinus rhythm (EURIDIS) confirmed dronedarone’s superior safety profile in AF than amiodarone. Dofetilide was found to be safe in CHF patients in the DIAMOND-CHF trial but it requires inpatient QTc monitoring for 72 h, and dosage adjustment is necessary for renal function to reduce the risk of torsades de pointes. Sotalol was...
Rate control

As discussed in the reversibility section, control of ventricular rate is important to mitigate the negative hemodynamic consequences of AF. The goal heart rate has been suggested to be 60–80 bpm at rest and 90–115 bpm during moderate exercise, with variation according to the age of the patient. Beta-blockers are effective in controlling the ventricular response to AF and also provide benefit in decreasing morbidity and mortality from CHF and are indicated in all stable CHF patients. Digoxin is ineffective as monotherapy to control heart rate during exercise, but in combination with beta-blockers it can lower the ventricular rate during AF and has been used for rate control in patients with CHF. Digoxin concentrations increase all-cause and cardiovascular mortality, which may be related to intracellular Ca²⁺ overload leading to an increase in oxygen consumption and arrhythmogenesis. Non-dihydropyridine calcium channel blockers are also effective rate-controlling agents, but can worsen CHF because of their negative inotropic effect. Amiodarone can also lower the ventricular rate during AF and has been used for rate control when other pharmacological agents have been unsuccessful or are contraindicated. The myriad non-cardiac toxicities of amiodarone limit its utility as a rate control strategy.

Other drug therapies

Medical treatment of AF and CHF is also focused towards factors that can induce atrial arrhythmogenesis in heart failure, atrial remodeling and fibrosis, local conduction disturbances, etc., which can promote further AF. Clinical studies on RAAS blockade in CHF has shown significant reduction in incidence of AF and improved outcomes with both ACE-I and ARB (angiotensin receptor blocker), most likely targeting AF neurohormonal modulation and probably improvements in ventricular function and atrial pressures, although not all studies with these agents have shown a reduction in AF. Statins have also been reported in some studies to reduce the incidence of AF, although the mechanism for this effect is not clear and may relate to antioxidant and anti-inflammatory properties, which might exert a stabilizing effect on the cardiac membrane and prevent atrial remodeling. The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardio-Heart Failure (GISSI-HF) trial showed a reduction in mortality and hospitalization with fish oil but no such data is documented for AF.

Anticoagulation

The risk of stroke in patients with AF is increased in those with CHF and hence anticoagulation with warfarin is recommended; CHF is included in the CHADS2 stroke risk scale for patients with AF. Multiple agents are currently under investigation as alternatives to warfarin. Dabigatran has recently been approved in the United States for this purpose and has been included in the recent guidelines as a reasonable alternative to warfarin. Because approximately 90% of embolic strokes in AF are believed to originate from the left atrial appendage, left atrial appendage occlusion devices are undergoing clinical trials as an alternative to anticoagulation.

Recently a closed-chest approach in the canine model has been developed in which a catheter-based snare delivery device achieved safe and reliable ligation of the entire LAA, and may provide an alternative to warfarin or to endovascular device implants in patients with non-valvular AF for the prevention of embolic events originating from LAA. This has been reported to be feasible in humans and may be appropriate for patients with AF who are ineligible for anticoagulation, although these agents are currently investigational.

Device-based therapy

Ablation and pacing

Ablation of the AV node and placement of a pacemaker to regulate heart rate is an option for patients with AF refractory to medical therapies. This may improve exercise duration and quality of life. But right ventricular pacing may cause or aggravate mitral regurgitation and lead to worsening of heart failure in patients with pre-existing LV dysfunction and cause an increase in mortality in this subset of patients. Mechanisms underlying this finding have been attributed to increased vulnerability for ventricular arrhythmias secondary to lower heart rates and pacing-related prolongation of repolarization and change in the ventricular activation sequence. Hence for patients with uncontrolled AF who also have LV dysfunction, cardiac resynchronization therapy (CRT) device implantation has been found to improve both LV systolic function and functional status and also decreases mortality. Although most large randomized CRT studies focused primarily on patients in sinus rhythm, a meta-analysis has suggested that the benefits of CRT are similar among patients in AF compared with those in sinus rhythm. For these reasons, patients with AF and CHF who require a ventricular pacing system appear to benefit from biventricular pacing. Criteria for choosing CRT pacemakers or defibrillators in patients with AF are otherwise the same.
as for patients in sinus rhythm, and generally require an LVEF of 30–35% or less (depending on the NYHA heart failure functional class) and a broad QRS complex. In some cases, patients with AF may have a tachycardia-mediated cardiomyopathy due to uncontrolled rapid ventricular rates during AF as the cause of CHF. If this is suspected, attempts should be made to control the ventricular rate over a period of time to see if the cardiomyopathy improves prior to making a decision about CRT implantation.

**Catheter and surgical ablation**

The observation of Haissaguerre et al. 101 that ectopic beats originating from the pulmonary veins could trigger AF opened a new approach to possibly eliminate these foci by ablation. 102 With procedural improvements since the first attempts to identify and ablate these foci, successful maintenance of sinus rhythm can be achieved in approximately 70–80% of patients, although more than one ablation procedure may be required in a significant number of patients. 103, 104 Ablation strategies vary between centers and operators, and may include electrical isolation of pulmonary veins by continuous ablation lesions around the pulmonary vein ostia 105 or creation of large circumferential lesions around the pulmonary veins, with or without the requirement of electrical isolation in both atria. 106, 107 as well as targeting of complex electrograms and the creation of lines of ablation within the left and right atria. Multiple studies have been reported with improvement in EF in CHF patients after successful AF ablation and decreased need for antiarrhythmic agents. 108–112 Catheter ablation of AF was found to be superior to treatment with antiarrhythmic drugs in the maintenance of sinus rhythm, improvement of exercise tolerance and quality of life. 113, 114 Complications of catheter ablation of AF include pulmonary vein stenosis, cerebrovascular accident, pericardial effusion, tamponade, and a very small periprocedural mortality rate. 115, 116

The PABA-CHF (Pulmonary vein Antral isolation versus Atroventricular Node ablation with Biventricular pacing for treatment of AF in patients with CHF) trial found catheter ablation of AF superior to AV nodal ablation and biventricular pacing in regard to exercise capacity, quality of life, and LV function after a 6-month follow up. 117

**Conclusion**

AF and CHF are highly prevalent diseases in modern society, with considerable morbidity and mortality. Each disorder predisposes to the other, and both share common molecular and physiologic mechanisms. A variety of treatments, both pharmacologic and nonpharmacologic, have demonstrated benefit in the treatment of AF and CHF, and future therapies are on the horizon that may allow us better treatment for these common cardiac conditions.

**References**


