Atrial Fibrillation and Ventricular Dysfunction

A Vicious Electromechanical Cycle

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Case Presentation: A 44-year-old man with a history of hypertension presented with New York Heart Association class IV congestive heart failure (CHF) and atrial fibrillation (AF) with rapid ventricular response (160 beats per minute) and unknown onset. Transthoracic and transesophageal echocardiography demonstrated severe global left ventricular (LV) dilatation, LV ejection fraction (LVEF) of 20%, and a mobile thrombus in the left atrial appendage but no evidence of coronary artery disease or valvular heart disease. After treatment with furosemide, digoxin, metoprolol, lisinopril, and warfarin, a repeat transesophageal echocardiogram 4 weeks later showed resolution of the thrombus. Subsequent attempts at cardioversion were unsuccessful despite treatment with sotalol hydrochloride and amiodarone. An average heart rate of less than 80 beats per minute was achieved after treatment with diltiazem hydrochloride, metoprolol, and digoxin. Three months later, the patient’s LVEF was 55% with mild LV enlargement.

Prevalence

AF and CHF are recognized as 2 major epidemics of cardiovascular disease in the 21st century. In 1995, AF was reported to be the most common cardiac arrhythmia, affecting more than 2 million people in the United States alone. According to 2001 estimates, CHF affects more than 4 million Americans. The prevalence of CHF increases from 0.8% among persons 50 to 59 years of age to 6.6% among persons 80 to 89 years of age. Similarly, the prevalence of AF more than doubles with each decade of age, from 0.5% at age 50 (50 to 59 years) to 9% at age 80 (80 to 89 years). Thus, these burgeoning populations can be attributed at least in part to the changing composition of the overall US population with its growing number of elderly persons. However, a study in Olmsted County, Minnesota, found a 3-fold increase in prevalence of AF between 1960 and 1989 that was not totally attributable to age.

CHF and AF are closely linked. CHF is the strongest risk factor for development of AF. However, several studies during a 50-year period have provided persuasive evidence that AF may precipitate or exacerbate LV dysfunction, giving rise to AF-induced cardiomyopathy. To what extent AF is a cause or a consequence of ventricular dysfunction and CHF is a subject of ongoing investigation.

Congestive Heart Failure as a Consequence of Atrial Fibrillation

Evidence and Frequency

That AF impairs cardiac efficiency was first recognized by Mackenzie almost a century ago. This entity was only rediscovered in the past 10 to 15 years. Its frequency continues to be underestimated. LVEF of 40% or less was observed in 105 of 282 patients (37%) who had atrioventricular node ablation for AF that was refractory to medical therapy. Of 56 patients who had repeat echocardiography after ablation, 16 (29%) had LVEF that improved to near normal values (≥45%), and 22 (39%) had partial improvement after ablation (LVEF ≤45%), which suggests that about 10% overall had AF-induced cardiomyopathy (Figure 1). These observations convey a strong message that AF-mediated systolic dysfunction frequently occurs with AF, reduced LVEF, or CHF.

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Mechanisms
The mechanisms responsible for tachycardia-induced cardiomyopathy are not clearly understood. In experimental models, chronic tachycardia invariably results in LV dilatation and systolic dysfunction, whereas in humans, systolic dysfunction occurs less consistently. In animal models, there have been reports of myocardial energy depletion, myocardial ischemia, abnormalities of calcium regulation, or extracellular matrix remodeling. Exacerbation of LV dysfunction also may be due to AF irregularity, because impaired hemodynamics and sympathetic activation are found in patients paced at irregular rhythms.

Congestive Heart Failure as a Cause of Atrial Fibrillation
Evidence and Frequency
LV dysfunction is associated with an increased risk of AF in men (4.5-fold) and women (5.9-fold). In a contemporary heart failure cohort, AF is less prevalent in African Americans (19.7%) than in Caucasians (38.3%). The prevalence of AF is related to the extent of LV dysfunction and the patient’s heart failure status. AF occurs in about 10% of patients with New York Heart Association functional class I or class II heart failure and in about 50% of patients with class IV. In patients with preexisting LV dysfunction, AF may further aggravate CHF symptoms.

Like the documented association between AF and CHF caused by systolic dysfunction, the association between heart failure with preserved EF and AF is well established. Indeed, 25% to 30% of patients who present with new-onset diastolic heart failure have recent onset of AF with rapid ventricular response. Patients with impaired diastolic function depend on filling by atrial contraction and need a long diastolic period to fill the LV at normal atrial pressures. After onset of AF, the loss of atrial contribution to filling and the rapid rate with shortened diastolic filling times mandate elevated atrial pressures to maintain cardiac output. Conversely, diastolic dysfunction leads to elevated filling pressures and atrial remodeling, predisposing to AF. Almost 10% of patients with abnormal LV diastolic function have new-onset AF during 4 years of follow-up. The risk of AF is proportional to the severity of LV diastolic dysfunction as defined by echocardiography (abnormal relaxation [hazard ratio, 3.3], pseudonormal relaxation [hazard ratio, 4.8], and restrictive LV diastolic filling [hazard ratio, 5.3]). In this study, both left atrial volume and the extent of diastolic dysfunction provided independent predictive value.

Mechanisms
The pathophysiology of AF is linked to the pathophysiology of CHF in several ways.

Mechanoelectrical Feedback
Acute atrial stretch is associated with increased dispersion of refractoriness and alterations in anisotropic and conduction properties facilitating AF. LV diastolic dysfunction and systolic dysfunction lead to left atrial dilatation, which may stimulate stretch-activated channels and increase vulnerability to AF. Blockade of stretch-activated channels reduces the propensity for AF despite elevated atrial pressure or volume or both. Sustained atrial overload in CHF causes atrial enlargement that may facilitate the stability and persistence of atrial fibrillation.

Neurohumoral Modulation
In CHF, neurohumoral modulation with elevated concentrations of catecholamine and angiotensin II may promote atrial fibrosis, thus changing atrial conduction properties and promoting AF.

Atrial Ionic Channel Remodeling
A substantial amount has been learned in the last few years about the role of ion channels in atrial substrate remodeling due to CHF. Atrial I\textsubscript{CaL} downregulation, although it occurs in CHF, is much less marked compared with changes after atrial tachycardia. I\textsubscript{Ks} density is not affected by atrial tachycardia but is decreased in experimental CHF. The mechanisms by which atrial ionic remodeling affects the occurrence and persistence of AF in subjects with CHF remain to be determined.

Prognosis
In the Framingham study, AF was an independent predictor of mortality at all ages in men and women. AF is also a marker for some patient subsets of other comorbid conditions that may increase cardiovascular mortality and morbidity (eg, hypertension and aortic and cerebral atherosclerosis).

The prognosis of AF-induced cardiomyopathy without preceding LV dysfunction has not been defined, but among patients undergoing atrioventricular node ablation, the survival
with LV dysfunction that subsequently improved (LVEF ≥45%) was comparable to the survival of age- and sex-matched controls and was better than that noted in patients with persistent LV dysfunction.13

In patients with preexisting CHF or LV dysfunction, AF might be expected to increase morbidity and cardiovascular mortality. Nonetheless, the data are discordant in that some studies (eg, Vasodilator Heart Failure Trial [V-HeFT] and Prospective Randomized study of IbopaMine and Efficacy [PRIME] trial)29–31 did not demonstrate an independent effect of AF on mortality, whereas other studies suggested the converse.32–35

In the Studies Of Left Ventricular Dysfunction (SOLVD) prevention and treatment trial,32 AF at baseline was an independent predictor of mortality and morbidity, primarily related to pump failure, death, or rehospitalization for heart failure. The lack of association between AF and arrhythmic death implies that AF was not simply a marker of sicker patients, because sudden cardiac death generally is strongly associated with the severity of symptoms and hemodynamic status.32 In a sub-study of the Danish Investigators of Arrhythmia and Mortality ON Dofetilide (DIAMOND) trial35 of patients with an ejection fraction of 35% or less, the maintenance of sinus rhythm at 1 year was strongly and independently associated with survival, either with placebo or dofetilide (Figure 2). Further evidence that AF causes hemodynamic deterioration in patients with underlying LV dysfunction was provided by a study of 344 patients with compensated CHF who were followed for 19 months. The development of AF in 8% of these patients was followed by an increase in left atrial size and by mitral regurgitation, reduction in cardiac index, or deterioration in symptom status.36

**Patient Management**

**Management of Congestive Heart Failure**

When AF persists in patients with CHF, therapeutic strategies are directed at restoring sinus rhythm or achieving rate control and optimizing therapy for CHF.

Theoretically, many standard CHF therapies could have favorable effects on the electrical and structural properties of the atria, which could favorably influence the arrhythmic milieu. Inhibition of angiotensin-converting enzyme or angiotensin-II receptor not only exerted beneficial effects on ventricular remodeling but also reduced atrial fibrosis. Diuretics and natriuretic peptides may reduce atrial stretch by unloading action on pressure and volume overload. Aldosterone antagonists may be beneficial through their potassium-sparing effects, reduction of oxidative stress, antifibrotic effects, and reverse remodeling.37 The modification of fluctuations in autonomic tone by β-blockers could benefit patients whose sympathetic overactivity plays a role in the genesis of AF. Thyrotoxicosis as a potential cause of AF and exacerbation of CHF should not be overlooked. Patients with AF and systolic dysfunction are at increased risk of thromboembolism, and full anticoagulation with warfarin may be indicated. Whereas early and optimal CHF therapy may help prevent AF, the magnitude of impact on the timing and extent of CHF therapy is poorly quantified.

**Management of Atrial Fibrillation**

Contemporary trials provide objective evidence and general guidelines about the competing strategies of rate versus rhythm control.38–40 No significant difference in mortality was found between the 2 strategies, but a trend in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and in RAte Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) favored rate control in the composite end points of death, stroke, and recurrent hospitalization.

Extrapolating from these trials should be done with caution. In general, they comprised older patients or younger patients with risk factors for stroke who were sufficiently tolerant of AF to be randomized. Thus, patients with AF and severely symptomatic heart failure are underrepresented. Other trials confined to patients with LV dysfunction are ongoing (Figure 3). Of interest is that rate control in patients without CHF in the AFFIRM trial was statistically superior to rhythm control, whereas the 2 approaches seemed similar in patients with CHF. Further analyses are needed to address the complex interaction of CHF and AF management strategies, in particular the impact of antiarrhyth-

**Figure 2.** Effect of sinus rhythm on mortality in patients with LV dysfunction. Survival rates of patients treated with dofetilide or placebo who converted or did not convert to sinus rhythm. MI indicates myocardial infarction; RR, risk ratio; and SR, sinus rhythm. Modified from Pedersen et al.,35 with permission of the American Heart Association.
Atrial Fibrillation – Management
Issues Under Resolution

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AFFIRM – completed*  
PAAF – completed*  
RACE – completed*  
STAF – completed*  
AF-CHF – ongoing

Figure 3. Management strategy: Rate control versus maintenance of sinus rhythm in atrial fibrillation. AF-CHF indicates Atrial Fibrillation and Congestive Heart Failure trial; PAAF, Pharmacological Intervention in Atrial Fibrillation; and STAF, Strategies of Treatment of Atrial Fibrillation.

Rhythm Control
CHF patients whose AF onset is associated with severe hemodynamic deterioration require an initial attempt at maintaining sinus rhythm. The cornerstone of antiarrhythmic therapy is amiodarone, sotalol, or dofetilide under close monitoring. The increased prevalence of coronary artery disease in patients who have CHF restricts the use of class IA and IC (Singh-Vaughan Williams classification) antiarrhythmic agents. In patients whose onset of AF is not clearly associated with increased symptoms, treatment should be individualized. The AFFIRM data indicate that either rate control or rhythm control may be appropriate, but further analysis is needed in the subset of patients with CHF.

Rate Control
Optimal rate control cannot be determined by the resting ECG and should be assessed instead with a 24-hour Holter monitor or with the chronotropic response to exercising on a treadmill or walking. Adequate rate control is defined by a resting heart rate of 80 or fewer beats per minute, a peak heart rate on a 6-minute walk of fewer than or equal to 110 beats per minute, or an average heart rate of less than 100 beats per minute. Digoxin alone is frequently inadequate because heightened sympathetic tone easily overrides the vagomimetic effects of digoxin. β-Blockers are a pivotal component of pharmacological rate control but must be titrated upward slowly in patients who have CHF. Use of calcium channel blockers is complicated because they are associated with adverse outcomes in patients with CHF or reduced systolic function. If tachycardia-related cardiomyopathy is strongly suspected, their use to control heart rate is appropriate. In other patients, strategies such as atrioventricular node ablation and implantation of a permanent pacemaker should be used to control rate if β-blockers and digoxin are ineffective. Accumulated data suggest that such an approach is associated with improved quality of life, exercise tolerance, and LV function. Long-term survival after atrioventricular node ablation is comparable to that of patients having medical therapy. Nevertheless, several issues require further study, including the potential detrimental effects of desynchronization of LV contraction by pacing from the right ventricular apex, the ideal pacing modality, the use of concomitant adjunctive atrial pacing techniques, and the role of implantable cardioverter-defibrillator placement. The role of focal pulmonary vein isolation and ablation remains to be determined in patients with AF and CHF, particularly given the frequent presence of underlying structural heart disease and a diffuse atrial arrhythmogenic substrate.

Conclusions
AF can cause severe, reversible LV dysfunction in patients without structural heart disease (AF-induced cardiomyopathy) and should always be considered when patients present with newly recognized CHF or AF. Milder degrees of improved LV dysfunction with rhythm or rate control also are frequently noted. The case example presented in this review illustrates the need to maintain a heightened sense of awareness of this potentially reversible condition.

In patients with underlying structural heart disease and LV dysfunction, AF is a harbinger of increased hemodynamic deterioration and increased mortality. Efforts to maximize CHF therapy should be an integral part of the management strategy for AF; recognition also should be given to the special issues involved in treating AF in patients who have CHF.

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