CRT-D Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation

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The number of patients with atrial fibrillation and congestive heart failure has steadily increased in the United States. The presence of atrial fibrillation increases morbidity and mortality for patients with left ventricular dysfunction. The emergence of cardiac resynchronization therapy to improve symptoms and survival from congestive heart failure may provide benefits for those with atrial fibrillation; we review the pathophysiology of atrial fibrillation in the presence of left ventricular dysfunction and the promise of cardiac resynchronization therapy to improve symptoms for the for these patients.

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Atrial fibrillation in the patient with left ventricular dysfunction presents unique challenges to the physician and patient. The emergence of cardiac resynchronization therapy, or CRT, through biventricular pacing has been an important advance in the management of congestive heart failure, and recent studies have demonstrated improved quality of life and survival benefit that will certainly expand its use.

The role of CRT in patients with atrial fibrillation and congestive heart failure is not as well established as for those in sinus rhythm. We will review mechanisms of the mutually detrimental effects of atrial fibrillation and congestive heart failure, their impact on morbidity and mortality, and the physiologic concepts that could form the basis for using CRT in patients with congestive heart failure and atrial fibrillation.

EPIDEMIOLOGY OF ATRIAL FIBRILLATION AND CONGESTIVE HEART FAILURE

Atrial fibrillation affects approximately 2 million people in the United States, making it the most common cause of hospitalization for cardiac arrhythmias in the United States.[1] Congestive heart failure affects approximately 5 million people in the United States[2] with an incidence that has risen by 155% over the past 20 years. Currently, the prevalence of atrial fibrillation ranges from 1 percent to those under 50 years of age to approximately 9% in those over 80 years of age. An analysis of a national hospital admissions records from 1996 to 2001 showed that primary admission for atrial fibrillation accounted for 1% of all admissions, with admissions increasing 34% over this study period.[3] Like other forms of heart disease, more men than women develop atrial fibrillation at a younger age, but the incidence for women approaches that of men in older populations. Congestive heart failure is listed as a secondary diagnosis in 22% of admissions for atrial fibrillation, second only to hypertension. Conversely, for patients with atrial fibrillation as a secondary diagnosis, congestive heart failure is listed as the most common primary diagnosis across all age groups.[4]

Congestive heart failure and atrial fibrillation have a mutually adverse effect on mortality and morbidity. Data from the Framingham population show that patients with congestive heart failure that go on to develop atrial fibrillation have almost twice the mortality rate as those with a normal rhythm.[5]

Based on these findings, it stands to reason that restoration of sinus rhythm in patients with congestive heart failure would have beneficial effects not only on quality of life but survival as well. Unfortunately, previous attempts to use antiarrhythmic

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drugs to maintain sinus rhythm were unsuccessful or associated with increased mortality from proarrhythmia. In a subset analysis of the CHF-STAT trial, patients treated with amiodarone that spontaneously converted to sinus rhythm had a higher survival rate than those who did not convert.[6] Nonpharmacologic approaches have been used to restore and maintain sinus rhythm as well. Hsu and others found that patients with congestive heart failure and atrial fibrillation that underwent curative radiofrequency ablation for atrial fibrillation demonstrated improvements in ejection fraction, exercise capacity, and quality of life.[7]

THE MUTUAL PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION AND LEFT VENTRICULAR DYSFUNCTION

Atrial fibrillation has significant hemodynamic effects that are even more compromising to patients with diminished cardiac function and compliance. The loss of atrial kick in late diastole has long been known to increase mitral and tricuspid regurgitation, reduce diastolic filling and thus decrease cardiac index. The irregularity of atrial fibrillation also diminishes left ventricular filling time, further compromising cardiac output.[8]

Atrial natriuretic peptide, or ANP, is a peptide released from atrial tissue in response to atrial pressure overload or atrial stretch. This neurohormone has significant vasodilator and diuretic properties that may contribute to the lightheadedness and diuresis when elevated in the presence of atrial fibrillation.[9] With persistent or chronic atrial fibrillation, ANP levels decrease, allowing unopposed activation of the renin–angiotensin axis, causing further hemodynamic compromise.[10] Tuinenburg et al. evaluated the levels of several neurohormones in 267 patients with sinus rhythm and atrial fibrillation.[11] In patients with congestive heart failure and atrial fibrillation there were significant increases in plasma concentrations of ANP and the potent vasoconstrictor, endothelin. The investigators found no such increases in epinephrine, dopamine, renin, and aldosterone levels.

Congestive heart failure exerts its own influence on the initiation and sustainability of atrial fibrillation. Experimental models of congestive heart failure demonstrate a distinct cellular milieu compared to tachycardia-induced atrial fibrillation. Li et al. observed atrial hypertrophy in a canine model in which heart failure was induced with prolonged rapid ventricular pacing.[12] In this model, there were significant decreases in L-type calcium current, transient outward potassium current, and slowly rectifying potassium current.

There may also be an important role for atrial stretch receptors in the development of atrial fibrillation. These nonspecific cation receptors respond to passive stretch from elevated atrial pressure by including rapid atrial tachycardias that can lead to atrial fibrillation. Bode et al. used tarantula peptide in a rabbit model to illustrate the importance of these receptors. Atrial fibrillation inducibility and duration steadily increased with increasing atrial pressures in this model. When stretch receptors were exposed to the peptide, initiation of atrial fibrillation was completely suppressed even at the highest atrial pressures used in the control group.[13]

THE ROLE OF CARDIAC RESYNCHRONIZATION THERAPY IN CONGESTIVE HEART FAILURE

Cardiac resynchronization is achieved by correction of electromechanical dyssynchrony caused by a combination of left ventricular dilatation and aberrant ventricular activation. This dysynchrony is chiefly manifest by paradoxical septal motion during systole that reduces stroke volume. All this leads to diastolic mitral regurgitation, which further exacerbates the vicious cycle of left ventricular dilation and dysynchrony.

CRT corrects dysynchrony by producing a more physiologic left ventricular activation sequence. This is achieved by pacing the heart from two ventricular sites: the right ventricular apex and the lateral left ventricular wall. This, coupled with optimization of the atrioventricular delay and interventricular timing, increases diastolic filling time and reduces paradoxical septal motion and diastolic mitral regurgitation. Ultimately, this has been shown to reduce left ventricular dimensions and improve ejection fraction.

Early clinical trials showed improvements in exercise tolerance and quality of life.[14] Recent larger trials attempted to identify a survival benefit with CRT. The COMPANION trail randomized 1520 patients to optimal medical therapy versus CRT versus CRT with defibrillator capabilities (CRT-D).[15] Both CRT treatment groups achieved significant reductions in the combined primary endpoint of death or hospitalizations from heart failure. Patients in the CRT-D group had a significant 34% reduction in all-cause mortality, while the CRT group demonstrated a 24% reduction, approaching

but not reaching statistical significance. The CARE-HF study randomized 813 patients to medical therapy or CRT pacing.[16] Patients in the CRT group had a 34% reduction in the primary endpoint of death or cardiovascular events and significant reductions in all-cause mortality. This was the first study to show significant reductions in mortality from CRT without support of an implantable defibrillator.

Permanent atrial fibrillation is especially burdensome to patients with congestive heart failure. Many of these patients are managed with a strategy of rate control to reduce symptoms attributed to accelerated ventricular rates. Unfortunately, the negative inotropic effects of many rate-controlling drugs limit their use. Ablation of the atrioventricular node to maintain a regular and controlled ventricular rate has been shown to improve quality of life and exercise tolerance in many patients. However, right ventricular pacing causes dysynchronous left ventricular activation. The clinical impact of this was demonstrated in the DAVID trial, which evaluated 508 patients with implantable defibrillators randomized to dual chamber (DDD) pacing or back-up single chamber (VVI) pacing at 40 beats per minute.[17] In this trial, patients randomized to the back-up pacing mode had significant reductions in the primary endpoint of death or hospitalization. The study demonstrated that chronic right ventricular pacing has detrimental effects on survival and heart failure hospitalizations in patients with left ventricular dysfunction.

The results of the DAVID trial are very relevant to patients with left ventricular dysfunction who have undergone ablation of the atrioventricular node for atrial fibrillation with rapid ventricular rates, since they are pacemaker-dependent. The role of CRT has been studied in several small studies in this population. Leon et al. evaluated 20 consecutive patients with chronic atrial fibrillation and New York Heart Association Class III heart failure who had undergone atrioventricular nodal ablation for chronic atrial fibrillation.[18] In this study, there were significant improvements in NYHA class, quality of life, ejection fraction, and left ventricular dimensions after upgrade from a right ventricular pacemaker to CRT. Garrigue compared biventricular pacing with left ventricular-only pacing and found similar benefits with biventricular pacing over left ventricular pacing.[19] A recent report compared outcomes of CRT in patients with chronic atrial fibrillation and sinus rhythm.[20] In this study, 30 patients with a CRT device and sinus rhythm were compared to 30 patients treated with CRT who had permanent atrial fibrillation. Both groups had comparable improvements in left ventricular ejection fraction, 6-minute walk and quality of life scores. Interestingly, half of the atrial fibrillation patients had undergone atrioventricular nodal ablation, and their outcomes were similar to the outcomes in patients who did not have an ablation.

Since many of the early CRT trials excluded patients with atrial fibrillation, the role of cardiac resynchronization therapy in reducing atrial fibrillation burden has yet to be explored. The hemodynamic and autonomic benefits of CRT may create a substrate with less atrial stretch and fewer alterations in ion current density, thereby reducing atrial fibrillation. There are few case reports citing examples of spontaneous restoration and maintenance of sinus rhythm after treatment with CRT.[21,22] One trial is underway that is designed to evaluate the efficacy of an algorithm to suppress atrial fibrillation incorporated into a CRT-D device.[23] The AF-CHF trial will randomize patients to a rate control versus rhythm control strategy to determine the best way to treat patients who have cardiomyopathy and atrial fibrillation.[24]

In conclusion, the interplay between atrial fibrillation and congestive heart failure has deleterious effects. The use of CRT is gaining acceptance for patients that are pacemaker-dependent in the presence of spontaneous or intentional complete heart block, in order to avoid the deleterious effects of chronic right ventricular pacing. What is currently unknown is whether patients with congestive heart failure and paroxysmal or persistent atrial fibrillation can expect reductions in the arrhythmia burden from the hemodynamic improvements derived from CRT. Clinical trials that attempt to address this specific question would be most welcome.

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