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EDITORIAL COMMENT

The Class I–Cardiac Resynchronization Therapy Effect?*

Angel Rodrigo Leon, MD, FACC
Atlanta, Georgia

Objections from die-hard skeptics notwithstanding, cardiac resynchronization therapy (CRT) improves symptoms, ventricular performance, functional capacity, quality of life, and survival in patients with moderate to severe congestive heart failure (CHF). Now, Yannopoulos et al. (1) propose that CRT also decreases the frequency and duration of atrial arrhythmia. The authors, in the current issue of the *Journal*, present evidence collected from implanted devices documenting a diminished atrial arrhythmia burden after converting the implanted device from conventional pacing to one providing cardiac resynchronization. The improvement in arrhythmia burden parallels an improvement in ventricular function and geometry. If these initial observations prove consistent, we might have to add an atrial antiarrhythmic effect to the list of benefits of cardiac resynchronization.

See page 1246

Clinical observations suggest a physiologic link between deterioration in ventricular function and increased atrial fibrillation (AF) and flutter. Historically, CHF increases the risk of AF (2). Mitral regurgitation also commonly leads to atrial arrhythmia. Logic follows that increased left ventricular filling pressure and mitral regurgitation produce atrial stretch that accelerates fibrosis, apoptosis, and heterogeneity in atrial conduction that create a substrate for atrial arrhythmia. Experimental models support this association (3). As cardiac function and geometry worsen, the likelihood of AF increases; the loss of atrial transport with compromised ventricular filling and pre-load in turn aggravate an already tenuous hemodynamic state, perpetuating a vicious cycle fraught with adverse consequences (4,5). Furthermore, a history of CHF and left ventricular dysfunction in a patient with AF increases the risk of thromboembolic stroke. Thus recurrent atrial arrhythmia not only marks the worsening of ventricular dysfunction but also contributes further to symptoms and undesirable outcomes, including death, increased hospital stays, a need for cardioversion and antiarrhythmic drug therapy, and a requirement for warfarin anticoagulation.

Clinicians have few tools to effectively combat AF in the heart failure patient. The risk of proarrhythmia in patients with left ventricular dysfunction precludes the use of Class I antiarrhythmic agents. The Class III drugs approved for use by the U.S. Food and Drug Administration (sotalol and dofetilide) might be safer but have limited efficacy in maintaining sinus rhythm in CHF; use of each requires in-hospital initiation of therapy, and the beta-blocking effect of sotalol might interfere with use of proven standard beta-blockade. The old stand-by, amiodarone, lacks U.S. Food and Drug Administration approval for this purpose and carries a substantial risk of organ toxicity with prolonged use. In practice, it might remain the most frequently used antiarrhythmic drug for treating AF in the CHF population. Recent reports on the efficacy of catheter ablation in selected patients with CHF and left ventricular dysfunction raise enthusiasm for this technique (6,7). However, primary ablation must stand the test of time and more controlled study before one can advocate its widespread use in patients with moderate to sever heart failure, particularly by operators with limited expertise. Catheter ablation of the atrioventricular junction provides rate control for the patient with persistent or permanent AF and rapid ventricular conduction, and ventricular function might improve after rate control. However, the loss of atrial transport and obligatory right ventricular pacing after ablation might actually worsen CHF in individuals with AF and left ventricular dysfunction not due to inadequate rate control. Therefore, in most CHF patients, our treatment of AF consists of warfarin anticoagulation, antiarrhythmic drug therapy (usually with amiodarone) and direct current cardioversion to maintain sinus rhythm in those with paroxysmal or persistent arrhythmia, or controlling atrioventricular conduction in those with persistent/permanent AF who have no other choice.

A reduction in arrhythmia represents a significant bonus from any therapy that improves cardiac function. Ventricular reverse remodeling resulting from afterload reduction and/or beta-receptor blockade could also promote reverse atrial remodeling and decrease atrial arrhythmia. However, the large multicenter trials of afterload-reducing drugs and beta-blockers in heart failure could not systematically analyze the effect on atrial arrhythmia, given the absence of implanted devices with monitoring capability. Theoretically, less atrial arrhythmia could account for some of the reduction in the frequency of hospital stays and improvement in symptoms seen in those studies, but such a conclusion would be highly speculative. The effect of CRT on ventricular arrhythmia remains unclear. Stored data from devices implanted in patients enrolled in the Contak-CD and

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From Emory University School of Medicine, Cardiology, The Carlyle Fraser Heart Center, Atlanta, Georgia.

InSync-ICD clinical evaluations showed no difference in overall ventricular tachycardia/ventricular fibrillation events between active therapy and control groups (8). Yet, others reported a decrease in ventricular arrhythmia (9). Certainly the impressive effect of CRT on survival demonstrated in the CARE-HF (Cardiac Resynchronization-Heart Failure) trial suggests that improving ventricular function reduces the long-term risk of sudden death (10).

Although the CRT trials used devices with some capability to detect and count atrial arrhythmia, almost all multicenter trials excluded patients with significant baseline atrial arrhythmia. Even in patients with atrial arrhythmia, not knowing the pre-implant arrhythmia burden prevents a meaningful assessment of the impact of CRT. Nor can we adequately compare the effect of CRT against a control without an implanted device to gather post-implant arrhythmia data. Therefore, an analysis of AF from CARE HF could not adequately assess a change in arrhythmia burden, given the absence of pre-implant data and the lack of an implanted device to collect data in the control group (11). The many CRT trials focused on functional status, exercise capacity, ventricular geometry and function, and eventually mortality but not on atrial arrhythmia as a primary or secondary end point. Surely any future CRT trial would not likely include a period of observation for atrial arrhythmia during inactive left ventricular stimulation for a comparison of active CRT against a control. Thus, the data from observational studies with longitudinal comparisons, like the one discussed here, might provide the only opportunity to examine the effect of CRT on atrial arrhythmia.

The results reported by Yannopoulos et al. (1) demonstrate an impressive reduction in the frequency of atrial arrhythmia after CRT. The observed effect might have important clinical implications and raise other questions. The potential for a reduction in atrial arrhythmia should prompt postponement of atrioventricular junction ablation or perhaps primary AF ablation for at least 3 months after implant in order to determine whether CRT alone might reduce the atria fibrillation burden. One might also wish to reconsider the use of previously ineffective antiarrhythmic therapy and cardioversion to prolong intervals of sinus rhythm in patients otherwise thought destined to remain in persistent atria fibrillation. Conversely, CRT could also potentially reduce anti-arrhythmic drug use in heart failure patients with paroxysmal AF who previously required drug therapy to remain in sinus rhythm. This study did not systematically test the effect of reducing antiarrhythmic drugs after an observed reduction in arrhythmic events after CRT. That would require prospective study in patients with paroxysmal AF indicated for CRT, and it might provide interesting and valuable data. Could the apparent elimination of AF after CRT obviate the need for warfarin anticoagulation in those patients with AF and CHF? The number of patients enrolled in this study and the duration of follow-up do not provide the opportunity for a proper answer. But, the ability to catalog the presence or, more importantly, the absence of AF or flutter might allow reconsideration of the need for anticoagulation. As we move forward, should we adopt automatic arrhythmia detection by implanted devices as the best way to measure the success of therapies for AF, particularly when considering the discontinuation of anticoagulation as a potential goal of a particular therapy?

Although the reduction in atrial arrhythmia seems impressive, one cannot yet consider an ancillary antiarrhythmic benefit of CRT as an independent indication for its increased use in patients with CHF. The indications for CRT will still rest on its effect on ventricular function, mortality, and functional improvement. However, data such as those presented by the authors allow one to conclude that the bonus effect of improving ventricular function through cardiac resynchronization might provide an unanticipated but highly desirable anti-arrhythmic therapy. So, with apologies to Vaughn-Williams, should we call it the Class I–CRT effect?

Reprint requests and correspondence: Dr. Angel Rodrigo Leon, Emory University School of Medicine, Cardiology, The Carlyle Fraser Heart Center, 6th Floor MOT, 550 Peachtree Street, NE, Atlanta, Georgia 30308. E-mail: angel_leon@emoryhealthcare.org.

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