

## EDITORIAL COMMENT

## Cardiac Dyssynchrony in Congestive Heart Failure and Atrial Fibrillation

### Integrating Regularization and Resynchronization\*

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Congestive heart failure (HF) is associated with electrical and conduction abnormalities. Aside from the higher risk for sudden cardiac death, patients often present with atrial fibrillation (AF) and left ventricular (LV) conduction abnormalities. The prevalence of atrial fibrillation increases with the severity of heart failure and worsens its course by loss of atrial contraction, poor rate control, and irregular rhythm. Cardiac resynchronization therapy (CRT) improves symptoms and exercise tolerance in patients with congestive heart failure and cardiac dyssynchrony. These effects are paralleled by reverse LV remodeling, improve LV function, and translate into an improved prognosis on top of the optimal medical treatment (1). Clinical benefits are consistent across the multiple studies, and the therapy has evolved into the class I indication for HF patients with a broad QRS complex, severely depressed LV function, and sinus rhythm (2).

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In this issue of the *Journal*, Upadhyay et al. (3) bring to our attention CRT in HF patients with permanent AF. In a meta-analysis of 5 cohort studies, they found slightly greater improvement in LV ejection fraction but a smaller functional benefit measured from exercise tolerance or quality of life in these patients compared with patients with sinus rhythm. However, the meta-analysis included observational studies in the absence of sufficiently powered randomized trials. The only randomized data available were

from the subpopulation of the MUSTIC (MULTisite STimulation In Cardiomyopathies) trial (4), which was a crossover study with rather small numbers, significant drop-outs, and changes in the mode of pacing. In general, the meta-analysis of observational studies is rather unusual, and presented studies used surrogate end points of reverse LV remodeling and function. Therefore, it is encouraging that the meta-analysis is corroborated by 2 recent studies (5,6). Although still being nonrandomized, they included a relatively large number of patients and reported long-term clinical follow-up with mortality as the primary end point. In both studies, Khadjooi et al. (5) and the report of the MILOS (Multicentre Longitudinal Observational Study) group (6) showed that CRT led to a similar benefit in CRT candidates with AF compared with patients with sinus rhythm. Thus, we can agree with Upadhyay et al. (3) that the analysis of the existing observational data is timely and may serve as a hypothesis-generating effort relevant for the design of the future randomized trials.

What should be addressed in these trials? The resynchronization with consistent biventricular capture, the prerequisite for the CRT benefit (7), is often difficult to achieve because of irregularity and intermittent fast ventricular rates in AF. It is controversial whether optimal medical rate control should be achieved pharmacologically or nonpharmacologically by ablation of the atrioventricular junction (AVJ). Studies with the pharmacological strategy of rate control suggested that when adequate CRT delivery can be achieved with rates of biventricular pacing (BVP) of approximately 85% to 90%, the benefits are comparable to patients with sinus rhythm (5,4,8). In case of inadequate rates of BVP <85%, nonpharmacological AVJ ablation has been advocated (6,9). It ensures that CRT is correctly delivered without fusion or pseudofusion, eliminates the risk of uncontrolled ventricular rate, and regularizes the heart rate, all effects that might be particularly beneficial in patients presenting with HF and AF (10,11). The “ablate and CRT” strategy was also applied prospectively in the previously mentioned multicenter MILOS study (6) and resulted in a strikingly superior impact on survival compared with patients with the optimal medical rate control. This supports the initiation of a prospective randomized trial to test the postulate that AVJ ablation is a fundamental adjunct to ensure adequate CRT delivery. However, the poor survival in patients with medical rate control despite adequate BVP capture is at odds with earlier studies reporting a beneficial outcome on surrogate end points (4,5,8). It should be pointed out that in the MILOS study (6), the decision to ablate was already performed at 2 months after CRT implantation. Although the decision seems to be justified on the basis of inadequate BVP capture, no information is provided on the CRT effect on LV remodeling and doses or combinations of negative chronotropic drugs. Multiple drug regimens are frequent in these patients, and homogeneity

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and optimization of the medical therapy should be critically reviewed in the trials.

Nevertheless, the rapid translation from the suboptimal rate control to ablate and pace strategy may be justified by the withdrawal of negative chronotropic drugs. It is noteworthy that digoxin and amiodarone were discontinued in the ablative arm (6,9), and differences in the medical regimen might have impacted the survival, possibly by reducing the pro-arrhythmic risks (12).

Atrioventricular junction ablation is considered safe, but one should keep in mind the potential adverse effects. Given the sizable proportion of nonresponders to CRT, one could wonder whether it is acceptable to ablate all patients with AF and make them pacemaker dependent for the rest of their lives. Likewise, a small but significant risk of higher mortality exists if patients are paced at lower heart rates (13), and higher pacing rates in the initial period after AVJ ablation should be considered. Recently, catheter ablative techniques with either pulmonary vein isolation or the more extensive maze-like procedure and targeted ablation of areas with low-amplitude potentials in HF patients with paroxysmal or symptomatic AF have emerged as an effective treating strategy (14–16). Although the therapy is now rapidly adopted in clinical practice and may be attractive to consider as an alternative to the conventional AVJ ablation, long-term survival data are lacking. A properly powered randomized study should ascertain the merits of CRT in HF patients with AF treated either pharmacologically, by AVJ, or by catheter ablation strategy.

It is interesting that the rates of nonresponders in patients with AF are similar to those in patients with sinus rhythm. The reasons for lack of response are multifactorial. One factor is the selection of CRT candidates. The use of QRS duration as inclusion criteria outperformed various tissue Doppler imaging indexes in the recent PROSPECT (Predictors of Response to CRT) trial (17). However, this trial did not consider the impact of interventricular dyssynchrony in combination with the intraventricular delay. Although sophisticated echocardiographic parameters may be difficult to assess at an irregular heart rate, the incorporation of this parameter for identification of the responders could be helpful (18).

In addition, a prospective algorithm aimed at optimization of the CRT programming in nonresponders should be incorporated in future trials. A V-V interval adaptation should be considered at regular follow-up intervals (19,20). Given the rate dependency of the optimal V-V interval (20), the development of a rate-adaptive V-V interval algorithm in patients with AF is desired. Finally, the design of the studies should consider such factors as location of scar in patients with ischemic etiology, consistency in the lead position, concomitant mitral valve regurgitation, and duration of AF, as well as extracardiac causes of AF. In analogy to the relationship between the atrial tissue remodeling and AF (21), future studies should also address whether thera-

peutic response after CRT may be related to the remodeling at the molecular level (22,23).

In summary, what should we as clinicians do today in patients with congestive heart failure presenting with AF and broad QRS? The 2007 European Society of Cardiology Guidelines for Cardiac Pacing and CRT have assigned a class IIA and level C indication for CRT in such patients who have an indication for AVJ ablation (1). Before that is considered, most important is the maximal effort to restore the sinus rhythm. Recompensation, control of extracardiac causes of AF, and an attempt for cardioversion under an appropriate drug regimen are the primary goals for the treating cardiologist. The CRT can be considered after optimal rate control if cardioversion has failed. The decision to “ablate and CRT” remains individual and depends on the careful risk–benefit considerations, including patient age and comorbidity, as well as access and experience with ablative techniques including the transseptal catheter-based approach. For the time being, the AVJ ablation should be considered in patients with documented poor biventricular capture despite optimal medical rate control.

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