Cardiac resynchronization therapy (CRT) has become an integral treatment modality for patients with heart failure (HF), diminished left ventricular ejection fraction, and a wide QRS complex, conferring symptomatic relief, functional improvement, and survival benefit to the majority of recipients.\textsuperscript{1-4} CRT indications\textsuperscript{5} were initially restricted to patients in sinus rhythm, yet as atrial fibrillation (AF) is the most common sustained arrhythmia in patients with HF, with a prevalence that increases with more advanced HF symptoms,\textsuperscript{6} much attention has focused on expanding the CRT indications to patients with permanent AF.

Despite the fact that approximately a quarter of patients with HF eligible for CRT therapy have permanent AF,\textsuperscript{6} the overwhelming majority of multicenter, randomized CRT trials have only included patients in sinus rhythm.\textsuperscript{1-4} The majority of our knowledge regarding the role of CRT in patients with permanent AF is, therefore, based on nonrandomized, observational data.

There are special considerations that are pertinent to CRT patients with permanent AF. First, in the absence of large, randomized, prospective trials of CRT versus no CRT in the AF population, it is not firmly established whether patients with AF derive survival, symptomatic, and structural benefits from CRT and if these benefits do occur, whether they are comparable in magnitude to those seen in patients with sinus rhythm. Second, it is not completely established how best to ensure a high burden of biventricular pacing in CRT recipients who also have AF, although the role of atrioventricular nodal ablation in this context seems to be widely accepted.\textsuperscript{7,8}

From a survival perspective, there are no randomized, prospective trials examining the effect of CRT on mortality in patients with AF. Early prospective, nonrandomized, observational data,\textsuperscript{9} however, showed no difference in total mortality after CRT in 96 patients with permanent AF compared with 167 patients in sinus rhythm. A retrospective analysis of the Cardiac Resynchronization-Heart Failure (CARE-HF) trial\textsuperscript{10} identified 124 of 813 (15%) patients with a diagnosis of AF, in whom the presence of AF did not diminish the decrease in all-cause mortality conferred by CRT. A more recent meta-analysis,\textsuperscript{10} however, suggested an attenuated survival benefit from CRT in patients with AF compared with patients in sinus rhythm.

From a symptomatic perspective, CRT seems to benefit patients with AF. In the Multisite Stimulation in Cardiomyopathy-Atrial Fibrillation (MUSTIC-AF) trial,\textsuperscript{11} 41 patients with slow, permanent AF of >3-month duration and a paced QRS duration of >200 ms were randomized in a single-blinded, crossover study design (3 months for each phase) to right ventricular versus biventricular pacing. At the end of 6 months, 85% of patients who were blinded to their pacing mode preferred biventricular pacing to right ventricular pacing. With the preferred mode of pacing adopted for the following 6 months, patients had significant improvement in their 6-minute walk tests, quality of life scores, and New York Heart Association HF class compared with baseline values. Other studies have also documented improved symptoms in HF patients with permanent AF and chronic right ventricular pacing after undergoing device upgrade to biventricular pacing.\textsuperscript{12,13} A more recent meta-analysis\textsuperscript{10} suggests, however, an attenuated symptomatic response to CRT in patients with AF compared with patients in sinus rhythm.

As documented by echocardiography, CRT also improves systolic function and induces reverse remodeling in patients with permanent AF and diminished left ventricular function. Prospective, nonrandomized, observational data\textsuperscript{9} demonstrated similar rates of left ventricular reverse remodeling (defined as >10% decrease in left ventricular end-systolic volume) between CRT patients with permanent AF versus sinus rhythm. Similarly, in patients with HF chronically paced in the right ventricle, upgrading to CRT increased left ventricular ejection fraction\textsuperscript{12} and reduced left ventricular end-systolic diameter and the severity of mitral regurgitation.\textsuperscript{13} A more recent meta-analysis,\textsuperscript{10} however, suggests an attenuated echocardiographic response to CRT in patients with AF compared with patients in sinus rhythm.

Preventative CRT also seems to be beneficial in patients with permanent AF and normal left ventricular function undergoing radiofrequency ablation of the atrioventricular node. In this population, CRT after atrioventricular nodal ablation seems to prevent a decline in left ventricular ejection fraction and improve measures of the 6-minute walk test and peak myocardial oxygen consumption compared with right ventricular pacing.\textsuperscript{14} Compared with right ventricular pacing, CRT in patients with permanent AF was also recently shown in a small, prospective, randomized trial\textsuperscript{7} to reduce the rates of worsening of HF, as well as HF hospitalizations when performed after atrioventricular nodal ablation.

In patients with AF, it is imperative to ensure a high rate of biventricular pacing for the patient to extract maximum benefit from CRT.
benefit from CRT. Unlike in sinus rhythm, this task may be challenging in patients with AF. Relying on the percent biventricular pacing data stored in the CRT device may be misleading, because these rates include fusion and pseudofusion between pacing from the device and intrinsic atrioventricular conduction. This is one of the reasons implicated in the improved outcomes of CRT patients with AF with atrioventricular nodal ablation compared with rate control with medications. Other mechanisms implicated in the improved outcomes after atrioventricular ablation include more complete rate control and regularization without the need for high doses of medications that may induce fatigue and exacerbate other symptoms of HF.

In this issue of Circulation: Heart Failure, Healey et al examined the effect of CRT in patients with permanent AF enrolled in the Resynchronization for Ambulatory Heart Failure Trial (RAFT). In 229 patients equally divided between CRT defibrillator versus regular defibrillator, the study demonstrated no difference in total mortality rates between the 2 study groups but it did demonstrate a strong trend toward a 42% decrease in HF hospitalizations with CRT, closely missing statistical significance with a P value of 0.052. Other end points, such as the Minnesota Living with Heart Failure score, also showed a strong trend toward improvement in the CRT group compared with the non-CRT group, although the 6-minute walk test results were negative. It is worth noting that this study by Healey et al constitutes to date the largest, randomized report examining the role of CRT in patients with permanent AF, as the RAFT trial stratified randomization by AF status. The authors should, therefore, be commended for publishing these important results. Unfortunately, however, the lack of true statistical significance in the strong trends toward decreased rates of HF hospitalizations and improved quality of life scores suggests that the subgroup of patients in RAFT with permanent AF was not powered to detect differences in these end points.

Of particular concern in this RAFT subanalysis is that optimal biventricular pacing (>95%) was achieved in only one third of the patients, because only 1 patient underwent atrioventricular nodal ablation, whereas the rest of the patients with AF randomized to the CRT arm had the unproven Conducted AF Response feature activated. Furthermore, Healey et al do not report any follow-up echocardiographic data in their study. Favorable effects of CRT on structural and functional echocardiographic parameters, if present, may add insight into whether CRT may actually be clinically beneficial in patients with permanent AF.

So do patients with permanent AF extract any benefit from CRT? The answer is probably yes. They do derive symptomatic benefit and experience reverse remodeling from CRT as previously shown in the MUSTIC-AF trial and other studies. These data have formed the basis for the current American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines published in 2008 that recommend (with a class IIa indication) the use of CRT pacing in AF in patients meeting other accepted criteria. Although underpowered and lacking optimal CRT delivery, the present study by Healey et al further supports the benefit of CRT in patients with permanent AF as far as reducing HF hospitalizations, albeit with a level of certainty reaching 94.8% as opposed to 95%, which is conventionally used as the threshold cutoff for statistical significance.

Does it then matter to the resynchronized ventricles that the atria are fibrillating? Another way of asking the same question is do patients in AF extract similar benefits compared with those in normal sinus rhythm when their ventricles are resynchronized? The best available data to date suggest a lesser benefit from CRT in the presence of AF compared with normal sinus rhythm, particularly when biventricular pacing is used without concomitant atrioventricular nodal ablation.

The study by Healey et al is a welcome addition to the growing literature on the role of CRT in permanent AF. Because of its important shortcomings, however, it has failed to answer definitively whether patients with permanent AF benefit from CRT. Taken in the context of the growing literature on this subject, our conclusion, contrary to that of Healey et al, is that CRT does benefit patients with AF when biventricular pacing is ensured. We do agree with the authors in their assertion that further randomized trials are needed in the sizable group of patients with HF who also have permanent AF.

Disclosures

None.

References


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The Atria Are Fibrillating: Does it Matter to the Resynchronized Ventricles?
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