Cardiac resynchronization therapy and atrial fibrillation. Do we have a final answer?

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This editorial refers to ‘Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation’ by M. Gasparini et al., on page 1644

Cardiac resynchronization therapy (CRT) has been extensively studied in a variety of clinical trials including >4000 patients in stable sinus rhythm (SR).1 The recently issued European Society of Cardiology guidelines for cardiac pacing and CRT strongly recommend the latter for patients in SR who present with moderate to severe heart failure (HF), left ventricular (LV) systolic dysfunction, and a wide QRS complex, with a view to lower mortality and morbidity. These guidelines assigned a class I, level of evidence A, for the implantation of a CRT pacemaker, and level of evidence B for a CRT intracardiac cardioverter defibrillator (ICD).1 Surprisingly, despite the high prevalence of permanent atrial fibrillation (AF) observed among patients suffering from moderate to severe HF, CRT has not been tested in a large, randomized clinical trial dedicated to patients in permanent AF. The likelihood of co-existent AF and chronic HF is strongly related to the severity of the disease.2 The prevalence of AF in New York Heart Association (NYHA) functional class I is estimated at 5%, compared with up to 40% in class IV.3 For instance, Baldassarini et al. reported a 20% prevalence of AF in a population presenting in NYHA functional class II–IV and with left bundle branch block on surface ECG.3 In that Italian database, the prevalence of AF was 30% among patients in NYHA functional class III or IV with left bundle branch block, who are typical candidates for CRT.3 In various published registries, ~20% of CRT recipients were in permanent AF.4,5 Gasparini et al. report the results of a noteworthy, large, observational study designed to (i) assess the effects of CRT on mortality; (ii) compare the outcomes of 1042 patients in SR vs 243 patients in permanent AF; and (iii) in the latter group evaluate the effects of atrio-ventricular (AV) node ablation on their survival rate.6

**CRT in the presence of AF**

**Observational studies**

The efficacy of CRT in patients with permanent AF was first ascertained in a short-term haemodynamic study, which showed a significant improvement in haemodynamics during biventricular stimulation.7 Several additional, small, observational studies of patients in SR or AF similarly showed that biventricular stimulation improves cardiac function, manifested by a lowering of NYHA class, better quality of life (QoL), and higher exercise capacity.8,9 In right ventricular (RV) pacemaker recipients who have undergone AV node ablation for permanent AF, various studies have shown that upgrading from single RV to biventricular stimulation decreased NYHA class, and increased exercise capacity and LV ejection fraction (EF) significantly.10 In 2006, Gasparini et al. reported the results of a study conducted at two medical centres, which included 723 CRT system recipients, of whom 561 were in SR, and 162 were in permanent AF.11 All patients were treated with drugs to control the heart rate, and the percentage biventricular stimulation was measured 2 months after device implantation. The 114 patients with <85% biventricular stimulation underwent AV node ablation to create complete heart block and allow incessant biventricular stimulation, while the remaining 48 patients, in whom the mean percentage biventricular stimulation was 88 ± 3%, did not undergo AV node ablation. Over a mean follow-up of 25 ± 18 months, highly significant and similar (i) increases in functional capacity, magnitude of reverse remodeling, and LV systolic function; and (ii) decrease in NYHA functional class were observed in patients in SR, as well as patients in AF. The rate of responders; defined as a ≥10% decrease in LV end-systolic volume (ESV) was 69% in patients in SR, and 60% in patients in AF (P = 0.166). While the baseline characteristics of the patients in AF who did, vs those who did not, undergo AV node ablation were similar, the significant increases in LVEF, LVESV, and exercise capacity were limited to the group of patients who had undergone the ablation procedure. The magnitude of increase in LVEF and

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LVESV, and decrease in NYHA functional class, was significantly greater in patients whose AV node had been ablated. The proportion of responders at 12 months was also significantly higher ($P < 0.001$) in that group (68%) than in the group who did not undergo AV node ablation (18%). It is noteworthy that when the analysis was limited to survivors, the difference in the proportion of responders between these two groups of patients remained highly significant ($P < 0.001$).11

**Randomized trials**

MUSTIC AF, OPSITE, and PAVE are the only published randomized trials that were designed to assess the efficacy of CRT in patients in AF.12 In MUSTIC AF, 59 patients in drug-refractory NYHA HF functional class III, and in permanent AF, who had LV systolic dysfunction and a $>200$ ms QRS duration during RV pacing, were randomly assigned to 3 months of RV, vs 3 months of biventricular stimulation, in a crossover study design.12 By intention to treat, no significant difference was observed between the two study periods in (i) distance covered during a 6 min hall walk (the primary study end-point); or (ii) several secondary end-points, including NYHA functional class, QoL, peak VO$_2$, and hospitalization for worsening HF. However, in patients whose percentage biventricular stimulation was $>85\%$, CRT alleviated symptoms, increased exercise capacity, improved QoL, decreased the rate of re-hospitalizations, and promoted reverse LV remodelling significantly.13 It is noteworthy that these therapeutic effects conferred by $>85\%$ biventricular stimulation in patients with AF remained stable for at least 2 years of follow-up.12 While MUSTIC AF pointed to the importance of a high percentage of biventricular stimulation to optimize CRT in patients with AF, the power of the trial was limited by a higher than expected drop-out rate. The results of the long-term phase of the OPSITE study showed that, in patients with AF who had undergone AV node ablation, LV or biventricular stimulation had no, or only modest effects on QoL and exercise capacity, compared with RV pacing.12 This study was also strongly limited by a 32% drop-out rate and a heterogeneous population. Finally, the PAVE trial compared the effects of biventricular vs single RV stimulation in patients presenting with permanent AF who needed AV node ablation, regardless of LV systolic function or NYHA functional class, a population dissimilar from the typical CRT candidates. Only 30% of the patients were in NYHA functional class III, and the mean LVEF was 45 ± 15%. At 6 months of follow-up, biventricular stimulation had significantly increased exercise capacity and LVEF, and improved QoL.12 Interestingly, the therapeutic effects of CRT appeared greatest in patients with an LVEF <45% or in NYHA HF functional class II or III.12 A meta-analysis of these three trials found that all-cause mortality in patients assigned to CRT was 7.1%, vs 14% in controls, corresponding to a relative risk of 0.51, and a 99% confidence interval between 0.22 and 1.16 ($P < 0.001$).12

Gasparini et al. have reported the survival rate of 1285 recipients of CRT systems implanted in four European medical centres between 1995 and 2004, including 243 patients with permanent AF, the largest number reported thus far.6 The first observation made in this non-randomized study was, over a median follow-up of 34 months (range: 10–40 months), a similar performance of CRT with respect to all-cause and cardiac mortality among patients who were in SR and among all patients who were in AF, whether or not they had undergone AV node ablation. However, the baseline characteristics of the patients in SR vs AF were dissimilar, blurring the interpretation of the results. Patients in AF were significantly older than patients in SR, a clear disadvantage, though they had a significantly shorter QRS duration and higher LVEF, both of which are associated with a better prognosis.13 Finally, despite similar HF management recommendations in both groups, the patients in AF were more likely to be treated with digitals and amiodarone, and less likely to undergo cardioverter defibrillator implantation, which might have influenced their outcomes.6 Consequently, the comparison of the performance of CRT in patients in SR vs patients in AF made in that study must be interpreted very cautiously. In particular, it would be risky to extrapolate to patients in AF the results of CARE-HF and COMPANION, the two main randomized trials that examined the morbidity and mortality of CRT recipients, all of whom were in SR.1 The second observation, as noteworthy as the first, was a markedly higher survival of patients in AF, who had undergone AV node ablation because of a <85% biventricular stimulation rate, assessed 2 months after implantation of the CRT system. The differences in death rates, including death from all causes, cardiac death, and death from end-stage HF, between patients who had, vs patients who had not undergone AF ablation, were remarkable. Uninterrupted and complete biventricular capture is probably a warrantor for the success of CRT, as suggested by the MUSTIC trial. While it can easily be achieved during SR by programming an appropriate AV delay, it is not as easily accomplished during AF, because of marked variations in ventricular rate. Special pacing algorithms have been developed to suppress the spontaneous rhythm consistently. However, their performance might not be consistent, or they may require rapid pacing, which, in the long term, might cause tachycardia-induced cardiomyopathy. Furthermore, even when a stimulus is delivered, the complex may be fused or pseudo-fused, which may lead to an overestimation of the percentage of biventricular captures retrievable from statistics stored in the device’s memory. The authors plausibly attributed the survival benefit observed in their study to the combination of biventricular stimulation and AV node ablation. AV node ablation (i) ensures that CRT is flawlessly delivered, without fusion or pseudo-fusion; (ii) eliminates the risk of uncontrolled ventricular rate; and (iii) regularizes the heart rate, a combination of effects particularly beneficial in patients presenting with AF and HF.14 One other indirect benefit conferred by AV node ablation might be the discontinuation of drugs that may negatively influence morbidity and mortality in patients suffering from HF, such as digoxin and amiodarone. Regardless of CRT and compared with drugs, AV node ablation is probably a wise means of controlling the heart rate, and reliable CRT delivery together with effective rate control is a clinically beneficial combination.

This large, observational and important study has methodological limitations. For instance, a single assessment of the percentage of biventricular stimulation may be inaccurate or non-representative. The study was not randomized and the baseline characteristics of the patient groups were dissimilar. In the AV node ablation group, QRS duration, an independent predictor of mortality in patients with HF, was significantly shorter than in
the other group. Furthermore, the decision to ablate the AV node might have been prompted by factors, which, a priori, identified responders to CRT. Finally, the relationship between survival and reverse remodelling was not examined because echocardiographic data were rigorously collected in only 50% of patients.

Large, well-conducted, randomized trials are needed to ascertain the role of CRT in patients in AF and HF, and determine whether the best strategy includes AV node ablation. While it is likely to facilitate the delivery of therapy, this strategy has potential adverse effects, pacemaker dependency in particular. Furthermore, AF ablation has been suggested as another option for patients suffering from chronic HF and permanent AF. The preliminary results of PABA-CHF, an as yet unpublished, small, randomized trial, suggest that AF ablation might be superior to ‘ablate and pace’ in combination with CRT in patients with permanent AF and LV dysfunction.

Much remains to be accomplished in testing these various strategies. In the meantime, we need to follow the 2007 European Society of Cardiology guidelines for cardiac pacing and CRT. Based on a consensus of experts, these guidelines have assigned a class IIa and level of evidence C indication for CRT, for patients with an LVEF <35%, who remain in NYHA HF functional class III or IV despite optimal drug treatment, and who have permanent AF and an indication for AV node ablation. Therefore, as currently framed, the guidelines point to AV node ablation as the starting point of therapy, as suggested by the results of the PAVE trial. Whether patients presenting with HF and permanent AF have an indication first for CRT and secondly for AV node ablation remains an open question. The results of the study by Gasparini et al., which are concordant with those of prior registries and small studies, should prompt the design of a properly powered, randomized trial to ascertain the merits of CRT in patients in permanent AF, and give us an answer based on evidence.

Conflict of interest: none declared.

References


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