



Cardiac Resynchronization Therapy in Patients with Atrial Fibrillation - Worth the Effort?

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Abstract

Congestive heart failure (CHF) and atrial fibrillation (AF) are two increasingly common conditions that predispose to each other and frequently coexist. Cardiac resynchronization therapy (CRT) has emerged as an important therapeutic modality for selected patients with end-stage CHF. However, despite the high prevalence of AF in patients eligible for CRT, almost all the randomized clinical trials that validated the benefit of resynchronization therapy excluded patients with preexisting AF. In this review, we examine the available evidence on the benefits and limitations of CRT in patients with AF and discuss recent data that narrowed the knowledge gap on this topic.

Introduction

Cardiac resynchronization therapy (CRT) is now a well established treatment for selected patients with advanced chronic heart failure (CHF), having shown to reduce morbidity and mortality when combined with optimal pharmacotherapy.¹ Since the prevalence of atrial fibrillation (AF) parallels the severity of CHF (from 10% in patients in New York Heart Association (NYHA) class II up to 50% in NYHA class IV),² it is not surprising that many candidates for CRT have AF. Indeed, patients with AF make up 20-30% of CRT recipients in clinical practice.^{3,4} The development of AF in the CHF patient also heralds a worse prognosis, nearly doubling the risk of death,⁵ even though there is no consensus as to whether AF is an independent risk factor or just a marker of more advanced disease. Nevertheless, and despite the high prevalence of this arrhythmia among patients eligible for CRT, almost all the randomized clinical trials that validated the benefit of resynchronization therapy have excluded subjects with preexisting AF. This gap in CRT science is yet to be filled, but was somehow mitigated by several observational studies with encouraging findings,

springing the recent class IIa recommendation for CHF patients with AF who otherwise qualify for CRT.^{6,7} In this review, we examine the available evidence on the benefits and limitations of CRT in patients with AF and discuss recent data that narrowed the knowledge gap on this topic.

Why is Atrial Fibrillation Relevant for Patients Receiving CRT?

AF poses a number of challenges for adequate CRT delivery. Patients with AF have no AV synchrony, precluding coordinated AV pacing with appropriately programmed AV intervals. Moreover, these patients often have highly irregular and fast ventricular rates, particularly during exertion. In these circumstances, spontaneous ventricular rate tends to override biventricular pacing rates, causing a reduction of paced beats precisely when patients most need it.⁸ Special programming features have been developed to overtake spontaneous rhythm in these circumstances,⁹ including Ventricular Rate Regularization™, Ventricular Sense Response™, and Conducted AF Response™. However, some of these programming features increase biventricular pacing at the expense of higher ventricular rates,

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and their benefits remain to be proven. So, the net result of rhythm irregularity and fast ventricular rates is a decrease in biventricular pacing delivery, the cornerstone of resynchronization therapy.

How Important is the Percentage of Biventricular Pacing?

Our knowledge on the relationship between the percentage of biventricular pacing and the clinical benefit of CRT had recent advances. Earlier studies arbitrarily defined adequate biventricular pacing as >85% capture,^{10,11} but it soon became apparent that an even greater degree of biventricular pacing might be required for optimal results. This conclusion stemmed from several observational studies showing that near-maximal biventricular capture is required to realize all the benefits of CRT, both in sinus rhythm and in atrial fibrillation.¹²⁻¹⁷ The largest of these studies followed up a cohort of more than 30,000 patients in a remote-monitoring network.¹⁷ Higher percentages of biventricular pacing were associated with lower mortality and fewer heart failure symptoms. The optimal cut-point that divided the patient population into two pacing groups with maximally different survival patterns was 98.5%. Interestingly, this high cut-point value was also valid for patients with AF (defined here as >0.5% of atrial sensed beats at rates greater than 180 beats/min). This study raised the goal of biventricular pacing even further by showing that subjects with a biventricular pacing percentage above 99.6% experienced a 24% reduction in mortality compared with other quartile groups, while those with <94.8% had a 19% increase in mortality. The reasons behind this brisk decline in CRT benefit when biventricular capture rates drop below near-maximal values are still unclear, but this high threshold emphasizes the need to achieve biventricular pacing as close to 100% as possible. It is interesting to note that both AF and low biventricular pacing rates are independently associated with worse outcomes,^{14,17} thus suggesting that AF may have a dual impact on prognosis, both as a component of more advanced cardiomyopathy and as a determinant of poor biventricular pacing rates that hamper response to therapy.

An important limitation of these analyses (and also a common difficulty in clinical practice) is that even when pacing is delivered, many ventricular

complexes may be fused or pseudo-fused, making pacing capture percentages retrieved from CRT devices inaccurate and an overestimate of effective pacing capture.^{13,18} It is also possible that the loss of biventricular pacing may be a marker of deteriorating cardiac function, since it may be caused by other factors associated with worse outcome, such as nonsustained ventricular tachycardia and premature ventricular contractions. This could help explain why very small reductions in the percentage of biventricular pacing relate to poorer outcomes.¹⁹ Studies in which the actual cause for decreased biventricular pacing can be ascertained and the degree of fusion and pseudofusion accurately quantified are needed to settle these issues.

What is the Impact of AF on the Benefit of CRT? Does AF Preclude Clinical Response to CRT?

Large-scale randomized clinical trials have validated the use of CRT in patients with significant systolic dysfunction, symptomatic CHF despite optimized medical therapy, prolonged QRS duration, and sinus rhythm. The established benefits include improvements in symptoms, exercise capacity, left ventricular systolic function, and ultimately, prognosis.^{1, 20-24} Whether or not these benefits can be extended to patients with AF has been a matter of study and debate in these last few years, encouraged by initial reports showing a beneficial acute effect of CRT on hemodynamic parameters.^{25, 26} In the absence of randomized controlled trials of CRT vs. no CRT in patients with AF, our knowledge on this subject comes essentially from surrogates such as observational studies and comparisons between patients in AF vs. patients in sinus rhythm among CRT recipients. Their findings on mortality and responsiveness to CRT are summarized in Table 1.

A recent meta-analysis of 23 observational studies including a total of 1,912 CRT recipients with a history of AF suggests that, while patients with AF benefit from CRT, they are at increased risk for adverse outcomes when compared to similar patients with sinus rhythm.²⁷ AF was a predictor of all-cause mortality (pooled RR 1.50; 95% CI 1.08-2.09) and was also associated with an increased risk of nonresponse to CRT (pooled relative risk [RR] 1.32; 95% confidence interval [CI] 1.12-1.55), even though the definition of response to CRT

Table 1: Studies reporting the effect of CRT on the functional class of patients with AF, and the impact of AF on mortality and nonresponse to CRT. SR: sinus rhythm; RR: relative risk; NR: not reported. * p<0.05 in all the studies.

Study	Sample Size			% undergoing AVJ ablation	Follow up (months)	NYHA in AF patients *		Impact of AF : RR (95% CI)	
	Year	SR(%)	AF(%)			Baseline	Follow-up	Mortality	Nonresponse
Leclercq	2000	22(59)	15(41)	100%	14	3.3 ± 0.5	2.2 ± 0.7	1.83(0.59-5.73)	NR
Linde	2002	67(51)	64(49)	63%	12	3.0 ± 0.0	2.2 ± 0.5	1.14 (0.54-2.40)	NR
Molhoek	2004	30(50)	30(50)	57%	22	3.3 ± 0.4	2.4 ± 0.8	2.33(0.67-8.18)	1.83(0.78-4.32)
Gasparini	2006	511(76)	162(24)	70%	25	NR	NR	NR	1.28 (0.98-1.68)
Delnoy	2007	162(63)	96(37)	25%	23	2.9 ± 0.6	2.1 ± 0.8	0.72(0.31-1.67)	1.03(0.82-1.31)
Buck	2008	58(51)	56(49)	2%	18	NR	NR	NR	1.33(0.74-2.41)
Ferreira	2008	78(60)	53(40)	49%	29	3.0 ± 0.5	2.2 ± 0.6	7.36(1.68-32.25)	1.56 (0.87-2.81)
Gasparini	2008	1042(81)	243(19)	49%	34	NR	NR	0.98(0.72-1.35)	NR
Khadjooi	2008	209(71)	86(29)	0%	23	3.3 ± 0.5	2.0 ± 0.8	1.24(0.85-1.81)	NR
Tolosana	2008	344 (73)	126 (27)	15%	12	NR	NR	2.16 1.23-3.81)	1.38(1.06-1.79)
Wilton	2011	73 (78)	20 (22)	11%	34	NR	NR	4.46(1.61-12.32)	0.92(0.44-1.93)

differed widely among studies. The effects of CRT on softer endpoints have also been reported in several observational studies including patients with AF. Quality of life was assessed in seven studies reporting changes in the Minnesota Living with Heart Failure (MLWHF) score. All showed improved scores in CRT recipients with AF, even though the pooled mean reduction was 4.1 points less than in those without AF (95% CI 1.7 - 6.6).²⁷ The same was true for exercise capacity, where patients with AF experienced a weighted mean improvement in 6-minute walking distance of 63m, which was 14.1m smaller (95% CI 0.0 - 28.2) than in those without AF.²⁷ Data on hospitalizations for CHF are only available from four studies. Three of these suggest that CRT in patients with AF decreases hospitalization rates,^{11, 28, 29} while another one suggests that patients with AF not submitted to ablation of the atrioventricular junction (AVJ) are at increased risk for hospitalization compared to patients in sinus rhythm.³⁰ Finally, most studies show significant improvements in left ventricular ejection fraction (LVEF)^{10-12, 28, 29, 31-37} which seem independent from heart rhythm, with no consistent difference in LVEF change between pa-

tients with AF and patients with sinus rhythm.²⁷

So, there is some evidence that, even though their prognosis is poorer, patients with AF do benefit from CRT in terms of symptomatic improvement and, possibly, mortality. Nevertheless, it remains unclear whether the worse prognosis of CRT recipients with AF is the result of reduced response to CRT or merely the reflection of greater baseline risk. There are also reasons why CRT might work particularly well in patients with AF, provided that biventricular pacing delivery is assured. Rhythm regularization, rate slowing, simpler programming and the need for less leads are among those reasons. More importantly, the extent to which the benefits of CRT depend upon performing ablation of the atrioventricular junction (AVJ) is still uncertain.

What is the Role of Atrioventricular Node Ablation?

Perhaps the most controversial issue regarding CRT in patients with AF is whether optimal rate control should be achieved pharmacologically

Table 2: Observational studies assessing CRT response according to the use of AVJ ablation. BiV: percentage of biventricular pacing.

Study	Number of AF patients	Number submitted to AVJ ablation (%)	Criteria for AVJ ablation	Timing of AVJ ablation	Benefits of AVJ ablation
Molhoek	30	17 (57)	Not reported	18 ± 6 months pre-CRT	Reduced risk of non-responsiveness
Gasparini	159	114 (70)	BiV <85%	2 months post-CRT	Improvement in functional class and echocardiographic parameters restricted to AVJ ablation group
Ferreira	53	26 (49)	Low BiV or ICD shock due to AF	Pre-, at, or post-CRT	Independently associated with less risk of non-responsiveness, hospitalization and cardiac death
Gasparini	243	118 (49)	BiV <85%	2 months post-CRT	Independently associated with less risk of death (particularly due to HF)
Schutte	36	9 (25)	BiV <90%	Not reported	No effect
Dong	154	45 (29)	Not reported	Median -13 days	Independently associated with less risk of death; Improvement in functional class

or nonpharmacologically by ablation of the AVJ. The potential benefits of AVJ ablation include rhythm regularization by optimizing the alternation of systolic and diastolic phases of the cardiac cycle,³⁸ lower heart rates favoring diastolic performance,³⁹ the avoidance of rate control drugs with potential deleterious effects^{28, 40} and, of course, the nearly complete biventricular capture. The main arguments against AVJ ablation are lifelong pacemaker dependency and the possible restoration of sinus rhythm with prolonged CRT. Six observational studies^{10, 29, 30, 35, 41, 42} followed 675 patients with atrial fibrillation and assessed the response to CRT according to the use of AVJ ablation (Table 2). AVJ ablation was performed in 49% of the patients (ranging from 25% to 70%) based on different criteria. Only one small study found no benefit of AVJ ablation.³⁵ The remainder reported improvements in functional capacity and left ventricular function. One of the largest studies suggested that only patients submitted to AVJ ablation had significant benefit as far as left ventricular ejection fraction (LVEF), left ventricular end-systolic volume and exercise tolerance were concerned.¹⁰ AVJ ablation was also independently associated with a survival advantage in three of these studies.^{30, 41, 42} A recent meta-analysis further underlined the importance of AVJ ablation, associating it with a lower risk of non-response to CRT (pooled RR 0.40, 95% CI 0.28-0.58; P<0.001).²⁷ These findings, taken together with the increasingly recognized importance of near-maximal biventricular capture, suggest that the threshold

for performing AVJ ablation should be low. Nevertheless, robust randomized clinical trials are needed to confirm these results and help us understand who should undergo AVJ ablation and when.⁴³ Meanwhile, it seems reasonable not to perform AVJ ablation systematically at the time of CRT implantation, but instead to perform it a few weeks later if biventricular pacing is suboptimal (<95-99%) despite adequate pharmacological optimization of ventricular heart rate. Holter monitoring and exercise testing can provide accurate and useful information on biventricular pacing rates in order to make informed decisions.^{13, 44} The situation is somewhat clearer for patients with AF and CHF who require conventional pacing for other reasons, including those undergoing ablation of the atrioventricular junction (AVJ) for rate control purposes. The benefit of biventricular pacing in these circumstances has been demonstrated in several randomized clinical trials.^{11, 45-49} Finally, a rhythm control strategy with pulmonary vein isolation should also be considered. There is some evidence that sinus rhythm is desirable in patients with heart failure and that catheter ablation is effective in achieving it and improving the patient's overall condition.⁵⁰ The future may hold a greater role for ablation, as new technology allows faster, more efficient, and safer procedures.⁵¹ For the time being, a recent meta-analysis of AF catheter ablation in patients with systolic left ventricular dysfunction showed significant improvement in LVEF, albeit with considerable heterogeneity among the analyzed studies regarding the

extent of this improvement.⁵² More specifically, the PABA-CHF study was a randomized controlled trial comparing pulmonary vein isolation (PVI) with the combination of AVJ ablation and biventricular pacing for patients with symptomatic AF and an ejection fraction of 40% or less.⁵³ Catheter ablation of AF was superior to CRT with AVJ ablation regarding improvements in LVEF, exercise capacity and quality of life. These results suggest that PVI may be a third option for patients with AF receiving CRT, apart from AVJ ablation and pharmacological therapy. A randomized controlled trial assessing these three alternatives would be most welcome.

Conclusions

Current evidence suggests that CRT is effective in patients with AF, even though its benefits may be less pronounced than in patients without AF. Near-maximal biventricular pacing rates seem crucial to attain the best possible outcome, but these are often difficult to achieve in AF patients unless AVJ ablation is performed or sinus rhythm is restored. Prospective randomized studies to confirm the benefit of CRT in AF patients and assess the roles of AVJ ablation and pulmonary vein isolation are needed.

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