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CLINICAL RESEARCH

Triple-site pacing for cardiac resynchronization in permanent atrial fibrillation: follow-up results from a prospective observational study

Pedro Marques*, Miguel Nobre Menezes, Gustavo Lima da Silva, Tatiana Guimarães, Ana Bernardes, Nuno Cortez-Dias, Luis Carpinteiro, João de Sousa, and Fausto J. Pinto

Cardiology Department, Santa Maria University Hospital (CHLN), Lisbon Academic Medical Centre, Cardiovascular Centre of the University of Lisbon, Faculty of Medicine, Av. Prof. Egas Moniz, 1649-035 Lisboa, Portugal

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Aims Cardiac Resynchronization Therapy (CRT) is associated with a particularly high non-response rate in patients with atrial fibrillation (AF). We aimed to assess the effectiveness of triple-site (Tri-V) pacing CRT in this population.

Methods and results Prospective observational study of patients with permanent AF who underwent CRT implantation with an additional right ventricle lead in the outflow tract septal wall. After implantation, programming mode (Tri-V or biventricular pacing) was selected based on cardiac output determination. Patients were classified as responders if NYHA class was reduced by at least one level and echocardiographic ejection fraction (EF) increased ≥ 10%, and as super-responders if in NYHA class I and EF ≥ 50%. Forty patients (93% male, mean age 72 ± 10 years) were included. Thirty-three were programmed in Tri-V. The following results pertain to this subgroup. At baseline, 58% were in NYHA class III and 36% NYHA class II. At 1 year follow-up, Minnesota QoL score was reduced (36 ± 23 vs. 8 ± 6; $P = 0.001$) and the 6MWT distance improved (384 ± 120 m to 462 ± 87 m, $P = 0.003$). Mean EF increased (26% ± 8 vs. 39 ± 10; $P < 0.001$ at 6 months and 41 ± 10; $P < 0.001$ at 12 months). Responder rate was 59% at 6 months and 79% at 12 months. Super-responder rate was 9% at 6 months and 16% at 12 months. One year survival free from heart failure hospitalization was 87.9%.

Conclusion Tri-V CRT yielded higher response and super-response rates than usually reported for CRT in patients with permanent AF using clinical and remodeling criteria.

Keywords Cardiac resynchronization therapy • Multi-site pacing • Triple-site pacing • Heart failure • Atrial fibrillation • Cardiac output • QRS duration • Ejection fraction • Responder • Super-responder

Introduction

Cardiac resynchronization therapy (CRT) is associated with a significant non-response rate of up to 30%.[1] A significant proportion of the patients eligible for this therapy have atrial fibrillation (AF).[2] Yet, this subgroup of patients has been much less studied, and the results of CRT in this population are less consistent.[2]

To reduce the rate of non-response to CRT and improve clinical outcome, multi-point and multi-site pacing are emerging as new forms of CRT. Yet, few studies have yet been undertaken, and only one in the setting of AF.[3]

Thus, considering the paucity of CRT studies in AF, and the worse results this therapy has had in this subset of patients, investigating new modalities of CRT in AF is of utmost importance. In this study, we tested the usefulness of triple-site pacing by means of an additional right ventricle lead. We have previously published the results pertaining to the acute-phase, which demonstrated superior acute hemodynamic performance of this type of CRT.[4] In this paper, we present the clinical follow up results.

* Corresponding author. Tel: 21 780 5356; fax: 21 780 5610. *E-mail address*: pedroncmarques@gmail.com

What's new?

- This is the first study to evaluate multi-site pacing with 2 RV leads in patients with permanent atrial fibrillation
- This study provides important scientific data to consider triple-site pacing as means of improving CRT response in patients with permanent atrial fibrillation
- The results of this study may warrant consideration for a larger randomized trial

Methods

Objective

The aim of this follow-up study was to assess the safety, clinical, and remodeling impact of triple-site (Tri-V) cardiac resynchronization therapy by use of two right ventricle (RV) leads in patients with atrial fibrillation.

Patient selection

Patients were selected if all the following inclusion criteria were met: (1) permanent atrial fibrillation; (2) ejection fraction <35% with heart failure NYHA ≥ II despite adequate medical treatment and baseline QRS >120 ms; or need for anti-bradycardia pacing with an anticipated percentage of ventricular pacing >40% in patients with an ejection fraction <40%; and (3) cognitive capacity to understand the study and thereby give informed consent.

Implantation and connection method

One conventional RV lead was implanted in the RV apex (a defibrillation lead in the case of CRT-D). A second RV lead was implanted in the RVOT septal wall meeting fluoroscopic criteria combined with ECG criteria,[5] ensuring avoidance of the RVOT anterior or free wall. A third coronary sinus lead for left ventricle (LV) pacing was implanted per conventional CRT pacing (i.e. a postero or lateral meso-basal position). The RV apical lead was connected to the RV channel. If the LV lead was bipolar, with a pacing threshold below 2.5 V with no diaphragmatic stimulation, the LV lead was connected to the atrial channel and the RVOT lead was connected to the LV channel. If the LV lead was quadripolar, if the pacing treshold was over 2.5 V, the use of specific LV vector programming was necessary, or if there was any type of diaphragmatic stimulation, then the LV lead was connected to the LV channel and the RVOT lead to the atrial channel on the generator. Any device and lead brand could be used. Programming was set to DDDR with the shortest possible AV interval (25–40 ms depending on device brand) and a VV interval of 0 ms.

Hemodynamic evaluation and pacing mode selection

Details of the hemodynamic evaluation have been previously published.[4] Up to 1 month after implantation, all patients underwent minimally invasive hemodynamic evaluation by placement of a radial arterial line and the use of the Vigileo™/FloTrac III™ (Edwards Lifesciences, Irvine, USA) transducer system. Cardiac output and systolic volume were assessed at 70 beats per minute in both Tri-V and conventional biventricular (Bi-V) configurations with 100% pacing. The final pacing mode was selected based on the configuration with the best hemodynamic performance.

Baseline and follow-up assessment

At baseline, 6 months, and 12 months patients underwent clinical assessments with determination of NYHA class, 6-minute walk test (6MWT) and the Minnesota Living With Hear Failure Questionaire (MLHFQ). Heart failure hospital admissions and mortality were assessed at each follow-up. An ECG and echocardiogram were also performed.

Electrocardiographic evaluation

All patients underwent standard 12-lead ECG evaluation. The QRS duration was measured by two blinded operators.

Echocardiographic evaluation

The echocardiographic study was performed with a Vivid 7 device (General Electrics®). The LV ejection fraction was estimated by the Simpson biplane method determined from the cineloops acquired in two-dimensional mode, with measurement of end-diastolic and late systolic volumes in three consecutive cardiac cycles. Analysis was undertaken during post-processing with the software EchoPAC (© General Electric) by two operators.

Responder and super-responder definition

Patients were classified as responders if NYHA class was reduced by at least one level and EF increased ≥10%, and as super-responders if with NYHA class I and EF ≥ 50%.

Statistical analysis

For parametric variables the paired samples *T* test was used. For non-parametric variables the Wilcoxon test was used. Responder, super responder, survival rates, and freedom from heart failure hospitalization rates were calculated.

Ethical considerations

This paper conforms with the Ethical Principles for Medical Research Involving Human Subject Helsinki Declaration, was approved by our local Ethics Committee, and signed informed consent was obtained from all patients.

Results

Forty patients (baseline characteristics in *Table 1*) were included. The acute-phase results have been previously published and showed that the overall mean cardiac output was higher with Tri-V pacing (4.81 ± 0.97 L/min) vs. Bi-V pacing (4.68 ± 0.94 L/min with RVOT septal pacing and 4.66 ± 0.91 L/min with RV apical pacing, $P < 0.001$ for both approaches vs. Tri-V pacing).[4] On an individual patient basis, Tri-V produced a superior cardiac output in 33 (82.5%) patients, and the final pacing mode was chosen accordingly. In the vast majority of patients, the RVOT lead was connected to the atrial channel. Postero-lateral placement of the LV lead was achieved in all cases.

Six patients (all in the Tri-V group) underwent AV node ablation due to low percentages of pacing, five shortly after device implantation, and another at 4 months. Triple site pacing percentage at 6 months was 94 ± 3% and at 12 months 96 ± 2%. All patients had a pacing percentage >90% at these time points. This value was determined by interrogating the device and assessing for the percentage of time during which the device was performing sequential atrial and ventricular pacing, which meant it was in fact performing triple-site

Table 1 Patient baseline characteristics

Group	Global	Tri-V
N	40	33
Age (years, mean ± SD)	73 ± 11	72 ± 10
Male sex (*N*, %)	37 (97.5)	28 (85)
Ischemic cardiomyopathy (*N*, %)	10 (25)	7 (21)
NYHA I (*N*, %)	3 (7.5)	2 (6)
NYHA II (*N*, %)	14 (34)	12 (36)
NYHA III (*N*, %)	24 (58.5)	19 (58)
NYHA IV (*N*, %)	0 (0)	0 (0)
Angiotensin conversion enzyme inhibitor (*N*,%)	34 (85)	28 (85)
Aldosterone receptor blocker (*N*,%)	3 (7.5)	3 (9)
Mineralocorticoid receptor antagonist (*N*,%)	23 (57.5)	19 (57.5)
Beta-blocker (*N*,%)	34 (85)	27 (82)
Diuretic (*N*,%)	36 (90)	29 (88)
Digoxin (*N*,%)	11 (27.5)	8 (245)
Amiodarone (*N*,%)	7 (17.5)	6 (18)
Antithrombotics (*N*,%)	6 (15)	4 (12)
Vitamin K antagonist (*N*,%)	24 (60)	21 (64)
Novel oral anticoagulant (*N*,%)	11 (27.5)	9 (27.5)
Pre-implantation QRS (ms)	170 ± 25	169 ± 27
Left bundle branch block pattern (*N*, %)	34 (85)	29 (87.9)
Pre-implantation ejection fraction (%,mean ± SD)	25 ± 8	26 ± 7
CRT-D (*N*, %)	26 (65)	26 (58)
CRT-P (*N*, %)	14 (35)	14 (42)
AV node ablation (*N*, %)	6 (17.5)	6 (18.2)

ventricular pacing. We did not record the number of fusion or pseudo-fusion beats, as these were uncommon.

There was no difference in follow-up ejection fraction, 6MWT distance, MLHFQ score, and mean NYHA class between these six patients and the remainder Tri-V patients.

Tri-V population results

Outcomes: death and heart-failure hospitalization

During the 12 month follow-up period, four patients died (at 26, 119, 178, and 241 days). There was one hospitalization due to heart failure (at 241 days, culminating in death). One year freedom from heart failure hospitalization is depicted in *Figure 1*.

NYHA Class

NYHA Class distribution at each time point is depicted in *Figure 2* and *Table 2*. At 6 months post-implantation, no patients were in NYHA III or IV. At 12 months, an additional clinical benefit was observed, as the majority of patients were in NYHA class I.

Echocardiographic results

Venticular volumes and ejection fraction results are depicted in *Figures 3* and *4*, and *Table 2*. Both end-diastolic (EDV) and end-systolic (ESV) were significantly reduced over time. There was a statistically significant increase in ejection fraction at 6 and 12 months, but the difference between 6 months and 12 months was not significant.

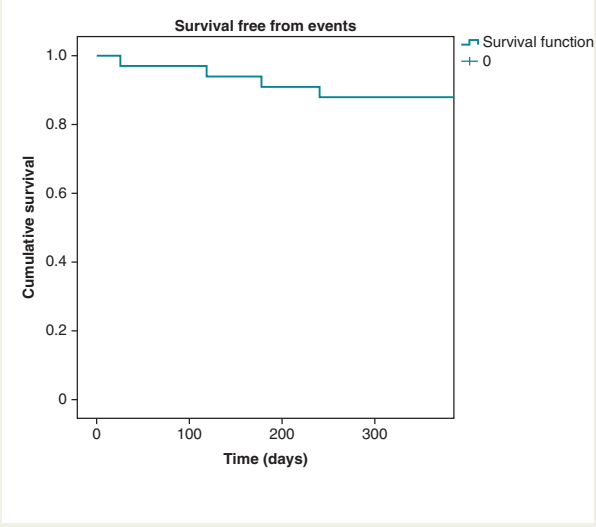

Figure 1 Survival free from heart failure hospitalization at 1 year.

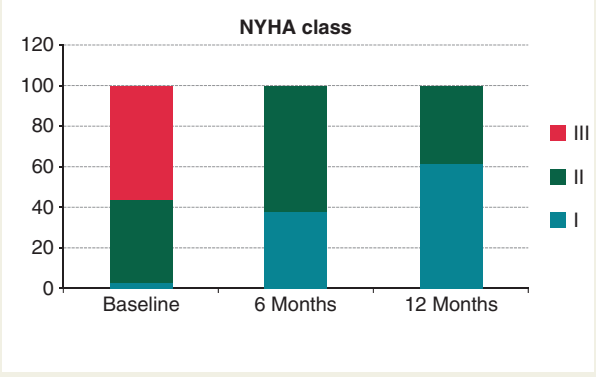

Figure 2 NYHA class distribution (%) at the various time points among all Tri-V patients.

Responders and super-responders

The responder rate was 59% at 6 months and 79% at 12 months. The super-responder rate was 9% at 6 months and 16% at 12 months.

Other clinical data

Functional capacity assessed by the 6-minute walk test

There was a statistically significant improvement in mean walking distance from baseline to 12 months. The difference was not significant between baseline and 6 months, and between 6 and 12 months. Results are depicted in *Figure 5* and *Table 2*.

Minnesota Living with Heart Failure Questionnaire

There was statistically significant improvement in the quality of life scores across time. Results are depicted in *Figure 6* and *Table 2*.

Table 2 Baseline to 6 month follow-up data (mean ± standard deviation values)

	Baseline	6 months	12 months
NYHA class (%)	2.5 ± 0.6	1.6 ± 0.5	1.4 ± 0.5
I	6	37	62
II	36	63	38
III	58	0	0
IV	0	0	0
End-diastolic volume (mL)	239 ± 112	174 ± 76	173 ± 102
End-systolic volume (mL)	184 ± 105	111 ± 70	111 ± 84
Ejection fraction (%)	26 ± 8	39 ± 10	41 ± 10
6MWT distance (m)	384 ± 120	461 ± 114	462 ± 87
MLHFQ score	36 ± 23	17 ± 15	8 ± 6

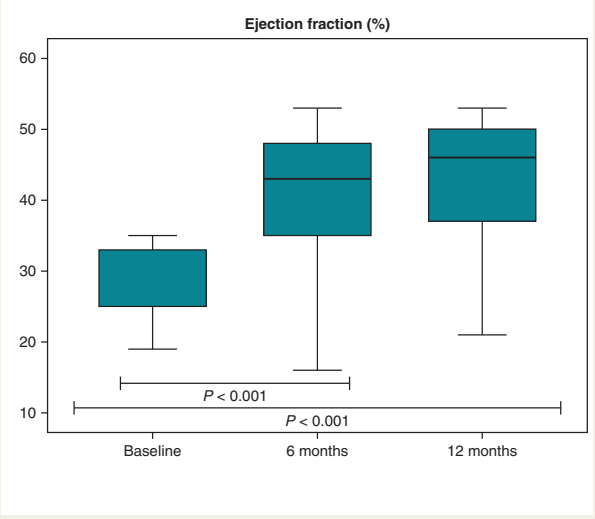

Figure 3 Mean ejection fraction during follow-up.

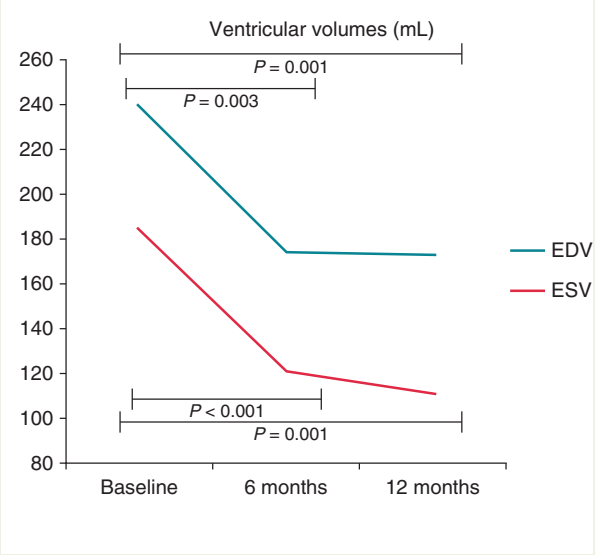

Figure 4 Ventricular volumes over time.

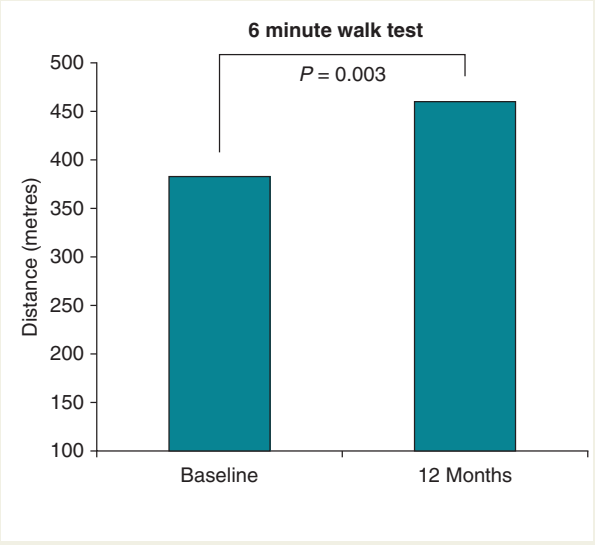

Figure 5 Six-minute walking test distance.

Pacing percentage and safety results

Pacing percentages were 97 ± 5% and 97± 6% at 6 and 12 month, respectively. There were no safety concerns during follow-up.

Bi-V population results

Given the very small number of patients in this group and the fact that this study was not designed for comparing the medium and long-term results of Bi-V vs. Tri-V, no statistical analysis was performed. Responder rate was 60% at 6 months, unchanged at 12 months. There were no super-responders. No heart failure or death events occurred in this group.

Discussion

Overall clinical impact and LV remodeling

In this study, Tri-V CRT produced a very significant symptomatic benefit, as a result of reduced NYHA class (and absence of severely symptomatic patients after CRT), improved quality of life, and increased functional capacity assessed by the 6MWT. There was significant ventricular remodeling, as evidenced by increased ejection fraction.

Other studies with triple-site pacing CRT

Triple-site pacing studies by means of an additional lead are scarce. Three studies have focused on acute-phase results. Two used an additional RV lead[6,7] and another an additional LV lead.[8] Both obtained superior results with triple-site pacing. Our own experience[4] confirmed that Tri-V pacing can produce superior hemodynamic

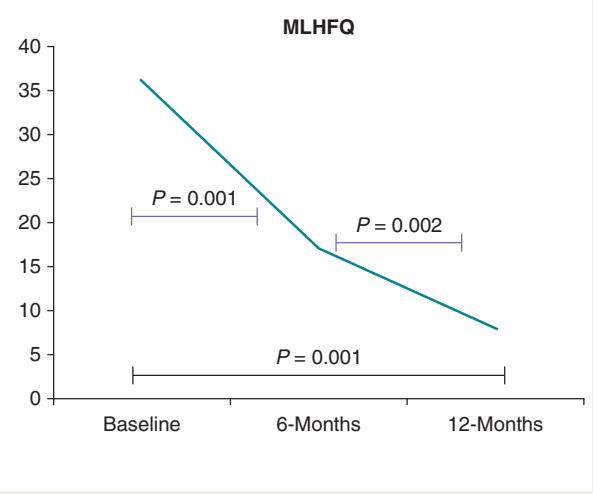

Figure 6 MLHFQ Score across time points.

results in the acute setting. We previously published a detailed analysis of acute-phase proceedings.

Studies focusing on clinical results of triple-site pacing are also scarce. Two studies attempted triple-site pacing by adding a second LV lead.[9,10] Lenarczyk *et al.*[9] randomized 54 patients to whether conventional CRT or Tri-V CRT. The latter produced a superior symptomatic improvement (NYHA class), longer 6MWT distance, higher VO_2 max and ejection fraction, alongside a much higher rate of responders to CRT (96.3 vs. 62.9%). The V3 trial used NYHA class, a clinical composite score, death, heart failure episodes and ejection fraction to assess the benefit of CRT but found no benefit in adding a second LV lead. Thus, studies using only 2 LV leads produced conflicting results.

Only two studies have tested CRT by means of adding a second RV lead.[11,12] Rogers *et al.*[11] compared Tri-V pacing with both 2 RV leads and 2 LV leads as well as RV septal pacing only. Half the study population had an additional RV lead and the other half an additional LV lead. Clinical assessment consisted of NYHA class, 6MWT distance, MLHFQ and EF. Their results demonstrated statistical superiority of Tri-V vs. Bi-V in the group that received 2 LV leads. The group that received 2 RV leads had only a trend towards superiority to Bi-V. However, the study had a cross-over design with switching among groups after just 3 months, which might have hampered the potential benefit of a given pacing mode given the short time period in each configuration. Anselme *et al.*[12] compared right sided Tri-V with conventional Bi-V during a 12-month follow-up period. Patients in Tri-V had a better 6MWT performance and a greater extent of left ventricular remodeling (as evidenced by increased EF and reduced volumes) than patients in Bi-V, even among responders.

All of the above mentioned studies were carried out in patients in sinus rhythm. Leclercq *et al.*[3] published the only study regarding triple-site pacing in patients in AF so far, by means of adding a second LV lead. The study also had a cross-over design in 3-month intervals (between conventional Bi-V and Tri-V), and follow-up was undertaken at 6 and 9 months. Tri-V was only superior with respect to ventricular remodeling assessed by EF and ventricular volumes. It is worth noting, once more, that given the short period of follow-up and the cross-over design, the potential additional benefit of Tri-V might have been hampered.

In summary, Tri-V CRT studies focusing on clinical results are scarce, small, heterogeneous and with significant limitations, but mostly suggest some form of benefit from Tri-V pacing. Only one clinical study was carried out exclusively with 2 RV leads, and only one other study in patients with atrial fibrillation. These facts clearly emphasize that further trials on CRT by means of triple-site pacing are needed.

Our study adds further weight to the hypothesis that Tri-V pacing can be a useful modality in CRT. Our approach is pioneering in the sense that it is the first study to test triple-site pacing by means of 2 RV leads in the most difficult subset of patients for CRT, those with permanent AF.

The benefit of Tri-V CRT over time

In our study, the benefits of Tri-V CRT were clearly established just 6 months after implantation, with relevant further improvement at 12 months, especially regarding NYHA class. Thus, CRT therapy produces a significant and rapid improvement, but it takes a longer time to achieve a larger long term benefit. This might explain why Tri-V studies with a fixed pacing modality and 12-month follow-up have demonstrated a clearer benefit[12] than those who have used cross-over design or shorter follow-up.[3,11] Classic CRT studies also support this concept, even in patients with atrial fibrillation.[13]

The choice of 2 RV leads vs. 2 LV leads

As previously mentioned, there is considerable heterogeneity in trials, and one cannot clearly state that one method is superior to the other. Nonetheless, we believe the addition of a second RV lead is preferable to 2 LV leads, as there had been previous evidence that dual RV pacing could be beneficial on its own and that both acute-phase[6,7] and clinical studies[12] demonstrate the potential benefit of this approach. One possible explanation to this is that the additional stimulation of the septum and anterior wall may provide incremental systolic performance. It is also worth noting that implanting an additional LV lead may result in more complicated procedures with longer duration and greater fluoroscopy exposure.[14]

Safety

Despite heterogeneity, no studies have raised safety concerns. Thus, whatever doubts may linger with respect to the benefits of Tri-V, adding a second RV pacing site is easy and appears to be safe.

Tri-V CRT: a new option for patients with atrial fibrillation?

It is well recognized that patients with atrial fibrillation fare less favourably with CRT than patients with sinus rhythm.[2] The results of Tri-V pacing in our study produced overall superior results than usually reported for conventional CRT in this subset of patients.

Regarding NYHA class 12 months after CRT therapy, the reported reductions in NYHA class among studies and meta-analysis are between 0.8 and 0.9.[15] In addition, Gasparini *et al.*[16] reported a 29% number of patients still in NYHA class III-IV after CRT. Despite the

fact that the latter consisted of a more severely symptomatic population than ours, the reduction we observed with Tri-V is much more significant, with a mean reduction in NYHA class at 12 months of 1, 2, and 0 patients in NYHA class III–IV. The same was true for 6MWT distance (we observed an increase of 65 m vs. a reported increase of 55 m in another study[17]) and the LWHFQ (our population had a mean decrease of 16 points, compared to a mean reduction of 9.7 in a meta-analysis[15]).

Regarding reverse remodeling, reported increases in ejection fraction range from 6 to 10%.[2,13,17,15] This improvement is generally established at 6 months, with minor improvements at 12 months. Remodeling in our study showed a similar evolution over time, yet with a greater degree of improvement, as shown with an increase in EF by 12% at 6 months and 13% at 12 months.

With respect to response rate, the reported rate for patients in atrial fibrillation is 60%.[17] As previously mentioned, even in sinus rhythm, the non-response rate to CRT is often cited as 30%.[1] Also, a significant problem in CRT studies is that the definition of responder is very heterogeneous. Studies using clinical criteria alone yielded non-response rates of 26–40% and those using remodeling criteria alone have sometimes resulted in non-response rates beyond 40%.[18] Our criteria are demanding in the sense that in order to be a responder, a patient had to meet a clinical and remodeling criteria. Indeed, the response rate at 12 months in this study was 79% with a super-responder rate of 16%, suggesting that Tri-V pacing may be more effective than Bi-V pacing in patients with atrial fibrillation.

Twelve-month mortality rates in CRT patients with AF range from 7 to 15%.[13,17,15] The mortality in our Tri-V patients was 12%, in accordance with conventional CRT studies results. Thus, our results do not suggest that Tri-V pacing has an impact on mortality. Nonetheless, this is not a randomized study, and was not powered nor designed to detect the impact of Tri-V pacing in such outcomes.

The issue of AV node ablation deserves a final note. It is well recognized that AV node ablation is a useful strategy in AF patients who undergo CRT and cannot keep high levels of pacing.[15,13] Current ESC guidelines recommend performing AV node ablation when pharmacologic treatment does not enable very high pacing percentages.[19] We complied with these guidelines in this study, and as such only performed AV node ablation in selected patients in order to ensure very high pacing percentages. While follow-up ejection fraction, 6MWT distance, MLHFQ score and mean NYHA class did not differ between patients who underwent AV node ablation and those who did not, the small number of patients in our study does not allow to draw clear conclusions on the effect that ablation might have had in the results. However, the reported rate of AV node ablation in studies varies between 22 and 100%.[15] This study's rate was 18% in the Tri-V population. This may be a consequence of the fact that some patients received a device due to bradycardia to begin with. Yet, one cannot rule out that the clinical and remodeling effect of Tri-V pacing might also have reduced the need for AV node ablation.

Limitations

The patients in this study had a long mean QRS, a high percentage of left bundle branch block pattern, an optimal anatomical lead placement and a high percentage of pacing during follow-up. All of these might have had a positive effect on the response rate, and we cannot be sure how they relate to the effect of triple site pacing. We chose a minimum QRS of 120 ms in the selection criteria in compliance with current European guidelines.[19] While we generally follow these, the level of evidence and strength of recommendation in these guidelines for patients with a mildly enlarged QRS or a non-left bundle branch block pattern is quite lower. As a result, we usually select mostly cases with a strong indication for CRT. In addition, recruiting investigators often felt that because this is an exploratory approach for CRT, it was important to favour those patients with a stronger baseline indication for CRT and therefore a significant expectation of benefit from this therapy.

This study was not a randomized trial and there was no control group. Thus, one cannot draw definitive conclusions regarding the clinical and remodeling effect of triple-site pacing CRT on patients with atrial fibrillation vs. conventional CRT.

The study population is small and as such the observed effects, especially on mortality, may be under or over-represented in this population.

Finally, the fact that a dedicated device was not available at the time of the study led to some heterogeneity in the atrial channel connections and the inability to program an AV interval of 0 ms. These factors might have influenced our results.

Conclusions

Triple-site pacing cardiac resynchronization in patients with permanent AF by means of an additional right ventricle lead was safe and effective. There was a clear symptomatic benefit as evidenced by reduced NYHA class, improved quality of life and functional capacity, and reverse ventricular remodeling demonstrated by increased ejection fraction. The responder and super-responder rates were both high. All these results were superior to those usually reported for conventional cardiac resynchronization therapy. The mortality rate was similar to previously reported results in patients with atrial fibrillation who undergo conventional CRT.

Despite the fact that further, randomized studies are needed, these results warrant considering triple-site pacing as an alternative to conventional CRT, either as first-line therapy in AF patients, or as bailout in non-responders.

Conflict of interest: none declared.

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