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ORIGINAL ARTICLE

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Cardiac resynchronization therapy in the presence of total atrioventricular block reduces long-lasting atrial fibrillation episodes

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Abstract

Background: There is an ongoing debate on how cardiac resynchronization therapy (CRT) in the presence of total AV block affects atrial fibrillation (AF) episodes and symptoms in patients with AF.

Methods: Seventy-five patients with symptomatic, drug and ablation refractory AF received, irrespective of their left ventricular ejection fraction (EF), either a CRT device and underwent subsequent atrioventricular node (AVN) ablation or already had a total AV block and underwent CRT upgrade. Long-lasting AF episodes (>48 h), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left atrial diameter (LAD), NTproBNP levels, EHRA score, and NYHA class had been monitored on the follow-up.

Results: The number of patients experiencing long-lasting AF episodes (>48 h) and symptoms decreased significantly within 24 months after CRT implantation in the presence of total AV block ($p < .001$) from 57 (76%) to 25 (33.3%). Mean LAD decreased from 52 mm (IQR 48.0–56.0) to 48 mm (IQR 42.0–52.0, $p < .001$) and LVEDD from 54 mm (IQR 49.0–58.0) to 51 mm (IQR 46.5–54.0, $p < .001$).

Conclusion: A combination of total AVN block and biventricular pacing markedly reduces long-lasting AF episodes, symptoms, left atrial diameter, and left ventricular end-diastolic diameter.

KEYWORDS
atrial fibrillation, atrial fibrillation episodes, atrioventricular node ablation, CRT, reverse remodeling

1 | INTRODUCTION

Approximately 8 million people in Europe suffer from atrial fibrillation (AF).[1] Both the 2016 and the 2020 ESC guidelines on the management of atrial fibrillation classify pacemaker implantation with consecutive atrioventricular node (AVN) ablation in patients with AF that cannot be controlled medically or by catheter ablation as a class IIa recommendation (Level B).[2,3] There is, however, still a debate about the type of the preferred pacemaker to implant before AVN ablation and guidelines remain imprecise in this regard.

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Until now several studies addressed differences in outcomes in patients with right ventricular (RV), left ventricular (LV), and biventricular (BiV) pacing.[4–6] BiV pacing led to improvements in echocardiographic parameters[4–6] in heart failure patients but observed changes in functional parameters, like exercise capacity or exertional dyspnoea, were inconclusive. While one study did not find any significant differences between BiV and RV pacing,[4] others showed improvements in NYHA class[5] or 6-min walking distance, respectively,[6] in patients with BiV pacing.

The efficacy of cardiac resynchronization therapy (CRT) in AF patients without AVN ablation is limited due to often inadequate biventricular pacing at fast atrial rhythms.[7–9] In many patients, different QRS morphologies are present. They correspond to fusion beats, as intrinsic conduction falls into a paced beat or pseudo fusion beats reflecting a pacing artifact due to a pacing impulse within the repolarization period of an intrinsic beat. Fusion and pseudo fusion beats, however, are hemodynamically not as effective as a regular BiV-paced beats.[10] AVN ablation ensures pacing if medical rate control is not sufficient to increase percentages of BiV capture adequately.[9,11]

Functional and echocardiographic outcomes after AVN ablation, however, still remain controversial.[12] Some studies suggested significant improvements in left ventricular ejection fraction (LVEF), NYHA class, or exercise capacity and showed reverse remodeling of the left ventricle in heart failure patients with atrial fibrillation after AVN ablation compared with those without AVN ablation.[9,11] The morbidity phase of the APAF-CRT trial showed that AV node ablation and CRT are superior to pharmacological therapy in reducing heart failure and hospitalizations and improving the quality of life in elderly patients affected by permanent AF.[13] The recently published mortality phase of the same trial could even document a significant reduction of mortality during the follow-up of 4 years in patients with permanent AF, narrow QRS, and at least one prior hospitalization due to heart failure after AVN ablation and CRT.[14]

So far, various studies indicated that successful pulmonary vein isolation (PVI) leads to reverse atrial remodeling in patients with AF.[15–17] However, cardiac resynchronization has to our knowledge rarely been investigated in this regard and reverse remodeling of the left atrium has never been objectified. In fact, trials addressing the effect of AVN ablation in patients with cardiac resynchronization therapy did not report any significant differences in echocardiographic[18,19] or functional parameters.[19]

The aim of this retrospective real-life observation study was to analyze the effect of cardiac resynchronization therapy on long-lasting AF episodes of >48 h in patients with symptomatic drug-refractory AF and preexisting or therapeutically induced total AV block.

2 | METHODS

2.1 | Patients

The study population included consecutive patients with highly symptomatic atrial fibrillation and insufficient pharmacological rate or rhythm control after recurrent atrial fibrillation despite at least three complete pulmonary vein isolations, selected for a "pace-and-ablate" strategy who underwent AVN ablation after CRT implantation irrespective of their left ventricular ejection fraction (n = 68). In addition, seven patients with permanent atrial fibrillation and a pacemaker due to AV block were included, who were selected for CRT upgrade because of decreasing left ventricular ejection fraction. Importantly, sinus rhythm maintenance was not actively pursued in the study population, and no patient received attempts of cardioversions during the follow-up. Patients were enrolled between January 2010 and October 2019.

Exclusion criteria were symptomatic coronary and ischemic heart disease, valvular heart disease, or structural heart disease, and age <18 years. Written informed consent of all subjects had been acquired and the trial was approved by the ethics committee of the Canton of Zurich (KEK project ID 2016–00073).

NTpro-BNP levels, LVEF, left ventricular end-diastolic diameter (LVEDD), and left atrial diameter (LAD) had been measured at every routine check-up by echocardiography. To evaluate the number of patients experiencing AF episodes >48 h, CRT recordings had been analyzed every 3 months during the first year after implantation and once a year thereafter. The minimal follow-up was 6 months.

2.2 | Device implantation and programming

As previously described,[20] right ventricular leads were positioned at the distal or mid-right ventricular septum and LV electrodes were implanted through the coronary sinus and placed whenever possible in the basal to mid-lateral or posterolateral LV areas.[21] All patients additionally received an atrial lead. Immediately after AVN ablation, a base rate of 80 bpm was programmed for 4 weeks in all CRT devices. Devices were initially programmed in DDD or DDI mode (the later for patients with permanent AF). Thereafter devices were adjusted to the patient's individual needs at the discretion of the responsible attending physician.

2.3 | Atrioventricular junction ablation

A transfemoral venous approach was used in all patients. 4 or 8 mm tip ablation catheters were positioned at the AV junction on the maximal amplitude of the bipolar HIS-potential, withdrawn until the distal catheter tip recorded an atrial-to-ventricular signal ratio >1, together with a small IS signal. Radiofrequency energy was delivered with a power output of 50 Watts (target temperature 60°) for at least 120 s until a complete AV block became evident.

2.4 | Echocardiography

All patients underwent echocardiography before CRT implantation and at follow-up visits every 3 months during the first year after AVN ablation. Physicians and technicians performing echocardiography

were not members of the study team. Transthoracic echocardiography was performed according to the guidelines of the American Heart Association with either a *Siemens Acuson SC2000*[11] or *Philipps EPIQ 7G*.

Echocardiography included standard short, and long axis views, as well as apical three-, four-, and two-chamber views. Standard examinations also included M-Mode tracings of long axis views. ECG-triggered standard loops (2 cycles) from all examinations were stored digitally. LVEF was assessed using Simpson's biplane analysis, and systolic LAD was assessed on M-Mode analysis tracings from parasternal long axis views.

2.5 | Statistical analysis

Statistical analysis had been performed with IBM SPSS Statistics for Macintosh (Version 26, Armonk NY). RStudio (Version 1.2.5033, Vienna, Austria) was used to create diagrams and to perform the Nominal symmetry test.

Continuous variables are expressed as the median and interquartile range (IQR) and compared using Wilcoxon signed-rank test and Nominal symmetry test. Categorical variables are expressed as total numbers and percentages and compared using McNemar's test. Valid percent was used to show the number of patients experiencing long-lasting AF episodes. A two-sided p value of <.05 was considered statistically significant.

TABLE 1 Patient characteristics ($n = 75$)

Follow-up time (months)	25 (IQR 21–32)
Age (years)	73 (IQR 67–78)
Male	41 (54.7%)
NYHA class	2 (IQR 2–3)
EHRA score	3 (IQR 2–3)
eGFR (mL/min)	60 (IQR 47.5–76)
QRS duration (ms)	94 (IQR 80–121)
Atrioventricular block Grade 3	7 (9.3%)
LVEF (%)	45 (IQR 40%–52%)
HFpEF >50%	22 (29.3%)
HFmrEF 40%–49%	35 (46.7%)
HFrEF <40%	18 (24%)
Mitral valve regurgitation	
Light	37 (49.3%)
Moderate	8 (10.7%)
Severe	3 (4.0%)
Paroxysmal AF	22 (29.3%)
Persistent AF	34 (45.3%)
Permanent AF	19 (25.3%)
AV-node ablation	68 (90.7%)
CRT-P	64 (85.3%)
CRT-D	11 (14.7%)
Biventricular pacing	>99% in all patients

3 | RESULTS

Seventy-five patients with highly symptomatic and treatment-refractory atrial fibrillation who underwent AVN ablation after CRT implantation or had a preexisting AVN block and underwent CRT upgrade/AVN ablation between January 2010 and October 2019 were included in this study. Detailed patient characteristics are shown in Table 1. All patients were medically treated for AF before CRT implantation and/or AVN ablation (Table 2). In addition to medical treatment, 45 patients (60%) underwent several unsuccessful pulmonary vein isolation procedures. Seven patients (9.3%) with pacemakers did not receive AVN ablation as they presented with a preexisting AV block and >99% of biventricular pacing after CRT upgrade.

Complication rates of device implantation and AV nodal ablation were minimal in the cohort. A pocket hematoma requiring surgical revision was observed in 1 and lead dislodgments requiring reinterventions in two patients. There were no device infections, no discontinuations of CRT, and no relevant increases in pacing thresholds.

NYHA class improved from 2 (IQR 2–3) before AVN ablation/CRT upgrade to 1 (IQR 1–2, $p < .001$) after the procedure. Additionally, EHRA scores decreased from 3 (IQR 2–3) to 1 (IQR 1–1; $p < .001$) after the intervention. In parallel, NT-proBNP levels improved from 984 pg/mL (IQR 762–1612) to 712 pg/mL (IQR 496–1005; $p < .001$, Figure 1).

Besides that, a significant improvement of LVEF, increasing from 45.0% (IQR 40.0–52.0) to 54.0% (IQR 48.0–58.0; $p < .001$) was observed. Moreover, LAD declined from 52.0 mm (IQR 48.0–56.0) to 48.0 mm (IQR 42.0–52.0; $p < .001$) and LVEDD decreased from 54.0 mm (IQR 49.0–58.0) to 51.0 mm (IQR 46.5–54.0; $p < .001$, Figure 2).

The number of patients with AF episodes lasting 48 h or longer decreased from 57 (76%) preintervention to 44 (58.7%) 3 months postintervention ($p = .012$). Six months after AVN ablation or CRT upgrade, this number further declined to 39 (52%; $p = .004$). Nine months postintervention only 34 patients still had AF episodes of >48 h (45.3%; $p = 0.001$). Twelve months postintervention, the number further decreased to 30 patients (40%; $p < .001$) and 24 months after intervention, it dropped to 25 (33.3%; $p < .001$); see Figure 3. Importantly, we observed spontaneous conversion to sinus rhythm, and a progressive reduction in AF burden also in our patients with permanent AF.

The number of patients suffering from AF episodes lasting 24 h or longer declined from 68 (90.7%) to 30 patients (40%; $p < .001$), 24 months after the intervention.

TABLE 2 Heart failure, antiarrhythmic, and rate control medications in $n = 75$ patients pre-CRT/AVN ablation

Betablockers	64 (85.3%)
Ca-Antagonists	9 (12.0%)
Amiodarone	18 (24.0%)
Digoxin	14 (18.7%)
ACE/ARB and ARN inhibitors	41 (54.7%)
Aldosterone antagonists	7 (9.3%)
SGLT2 inhibitors	10 (13.3%)

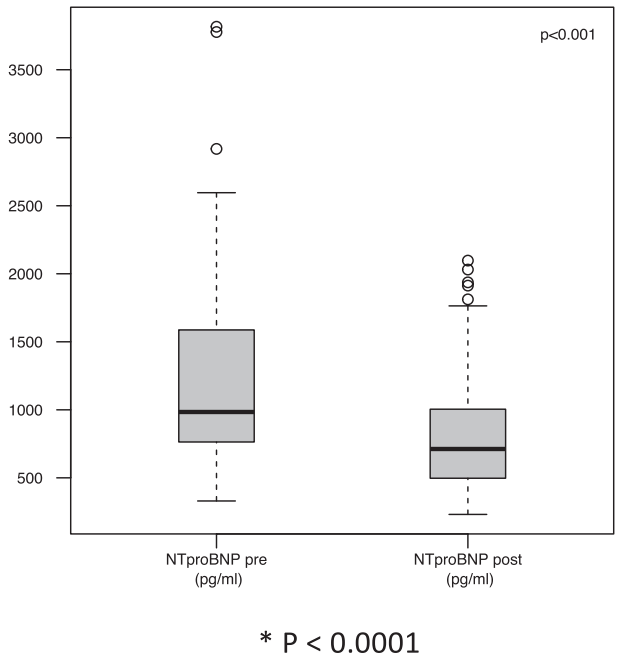


FIGURE 1 NTproBNP levels before cardiac resynchronization therapy implantation/AV-node ablation (pre) and at last follow-up (post).

4 | DISCUSSION

Our retrospective real-life analysis provides evidence that combined AV node block and cardiac resynchronization with biventricular pacing significantly decreases long-lasting AF episodes >48 h, symptoms, LAD, and LVEDD, while increasing left ventricular ejection fraction, in patients with treatment-refractory AF. The reduction of long-lasting AF episodes was already apparent at the first follow-up visit. Twelve months after AVN ablation, the proportion of patients experiencing AF episodes for >48 h further decreased. Moreover, echocardiographic parameters, such as LAD and LVEDD decreased significantly while LVEF markedly increased. In parallel, there were significant and impressive reductions in average NYHA class, EHRA score, and NTproBNP levels.

Our results regarding left ventricular function are in line with similar findings of Gasparini et al.[9,11] as well as Tolosana et al. 2013.[19] Tolosana et al., however, did not demonstrate a significant difference in LVEF increase between patients treated with CRT and AVN ablation and those treated with CRT and pharmacological rate control,[19] while Gasparini found significantly different outcomes between those two groups.[9,11] This discrepancy is most likely due to the fact that patients in Tolosana's trial[19] reached higher percentages of BiV capture than those in Gasparini's trials[9,11] ($94 \pm 5\%$ vs. $87 \pm 14\%/88.2 \pm 3.1\%$). This supports the fact that the extent of BiV capture is an important predictor of LVEF improvement. The importance of high BiV capture in this context was later emphasized by Steinberg et al. (2019).[7]

Several studies reported reverse left atrial remodeling after successful catheter ablation of AF.[15–17] It appears that improved hemodynamics in sinus rhythm also takes the strain off the atrial myocardium. However, the trials of Pump et al. 2013[15] and Tops et al. 2006[17] also showed a decrease in atrial size in patients with AF recurrence, although not to the same extent as in patients who maintained sinus rhythm. Hof et al. 2011[22] suggested that atrial shrinkage could, to some extent, be the result of atrial fibrosis caused by catheter ablation. In our study, we also found a significant reduction of left atrial size, but not only in patients after pulmonary vein ablation. About 60% of our patients underwent unsuccessful pulmonary vein isolation and 40% received AVN ablation only. Thus, it is rather unlikely, that catheter ablation induced atrial fibrosis by itself accounts for the reduction of the atrial size. Our data rather support the idea that rhythm control facilitates structural reverse remodeling of the atrium. In fact, the mechanism of reverse remodeling might be a combination of optimal heart control, rhythmic contraction of chambers optimizing filling, and the effect of continuous biventricular electrical stimulation. From this point of view, it would be interesting to compare AF burden in patients with CRT/AVN ablation to patients with the recently established conduction system/HIS-bundle pacing and AVN ablation.

Reduction of AF burden after CRT implantation had been described in several studies, but patients recruited in these studies had not received AVN ablation.[23,24] In our study, all patients either received AVN ablation or were already presented with a third-degree AV block, therefore, optimal BiV pacing was ensured, and we were able, in contrast to other studies, to address long-lasting AF episodes under optimal BiV pacing conditions. In a trial by Adelstein et al.,[23] AF burden and echocardiographic parameters of patients undergoing CRT implantation (responders and non-responders) were compared with a control group with matched baseline characteristics. Considering that AF patients only benefit significantly from CRT if they undergo AVN ablation ensuring optimal BiV pacing,[9,25] it is not surprising that Adelstein et al.[23] could not observe a significant reduction of AF burden as nonresponders were also included in their evaluation. In another trial,[24] patients with moderate to severe heart failure (HF) underwent CRT implantation and AF burden was determined at follow-up visits after 1, 2, and 3 months. However, patients with and without AF history were included, and AF burden was only recorded for the first 3 months after implantation.[24] Nevertheless, they also

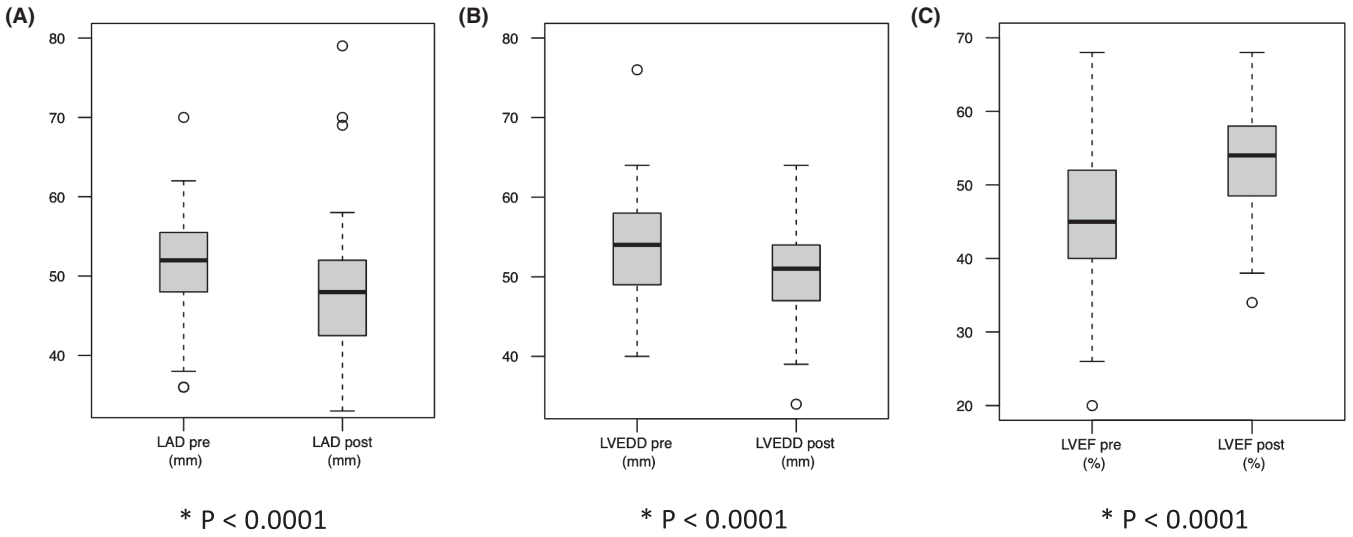
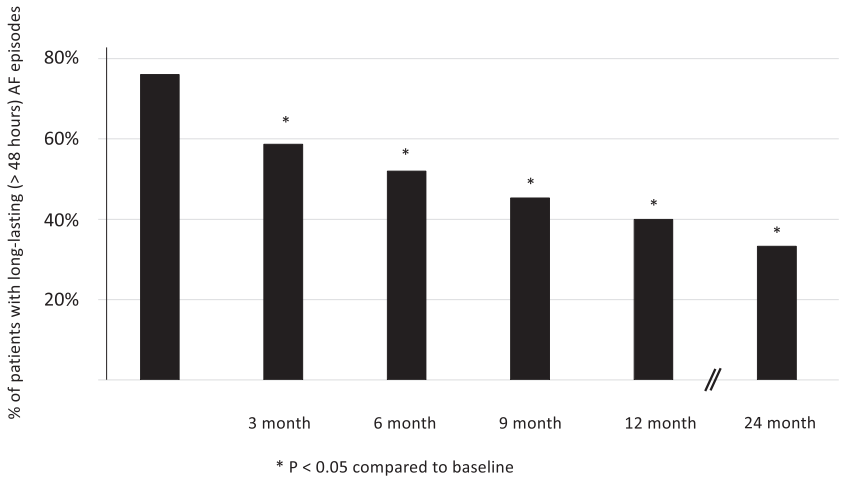


FIGURE 2 (A) LAD, (B) LVEDD, and (C) LVEF before cardiac resynchronization therapy implantation/AV-node ablation (pre) and after 6-month follow-up (post).

FIGURE 3 Percentage of patients experiencing long-lasting AF episodes ≥48 h before cardiac resynchronization therapy implantation/AV-node ablation (pre) and on follow-up.



detected a significant reduction in AF burden from the first to the third month after implantation.[24]

In our retrospective observational study, we found both, reverse atrial and left ventricular remodeling and a significant reduction of long-lasting AF episodes in patients with total AVN block with refractory AF treated with CRT. Obviously, BiV pacing as the most physiological pacing method has beneficial effects on the efficacy of cardiac hemodynamics.[26]

As previously mentioned, many trials reported similar outcomes after successful pulmonary vein isolation. Our findings suggest for the first time a combined pace-and-ablate strategy as an efficient treatment option for refractory atrial fibrillation in terms of both reduced long-lasting AF episodes as well as improved left ventricular and left atrial remodeling and improved left ventricular function. This goes in line and is probably related to the significant decrease in hospitalization and all-cause mortality but also to the significant symptom reduction reported in the morbidity and mortality trials of APAF-CRT.[13,14] Whether these effects and outcomes are due to improved hemodynamics because of the absence of ventricular high-rate episodes or due to not yet clarified effects of permanent electrical stimulation, remains speculative.

There are several limitations of our study. First of all, this is a retrospective analysis of a moderate number of patients without a control group. Furthermore, our population was heterogeneous and not divided into subgroups. Therefore, it is not possible to determine which CRT patient subgroups benefit most from a "pace and ablate" approach. Nevertheless, our findings warrant the initiation of larger prospective registries to analyze the impact of cardiac resynchronization on atrial fibrillation after AVN ablation in patients with refractory symptomatic atrial fibrillation.

Taken together, we demonstrated for the first time a beneficial effect of biventricular pacing in the presence of total AV block on

long-lasting AF episodes in patients with symptomatic AF. We found in this "real-world" patient cohort reverse remodeling of the left ventricle and of the left atrium.

5 | CONCLUSION

This retrospective real-life study showed that biventricular pacing in the presence of total AVN block in patients suffering from medical and PVI refractory AF improves symptoms, promotes reverse remodeling of the left atrium, and significantly reduces long-lasting AF episodes. Further prospective, randomized trials are needed to confirm our findings.

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CONFLICT OF INTEREST

There are no conflicts of interest in the context of this study. U.E. reports research and education support from Biotronik, Medtronic, Boston Scientific, Sorin.

DECLARATIONS

Approval of the research protocol: Approved by the ethics committee of the Canton of Zurich (KEK project ID 2016-00073).

Informed consent: Written informed consent of all subjects had been acquired.

Registry and registration number: N/A.

Animal studies: N/A.

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