

ORIGINAL ARTICLE

The Effect of Cardiac Resynchronization Therapy in Patients with Atrial Fibrillation and Non-Left Bundle Branch Block Morphology: The Role of Atrioventricular Node Ablation

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Abstract

Background: The clinical and mortality benefit of cardiac resynchronization therapy (CRT) in patients with atrial fibrillation (AF) has been reported previously. However, no clear data is present regarding this benefit in AF patients with non-left bundle branch block (LBBB) pattern.

Objective: The aim of the present study was two-fold: first, to assess the clinical and echocardiographic benefit of CRT in AF patients with non-LBBB pattern compared to patients with LBBB pattern; second, to investigate the role of atrioventricular node (AVN) ablation in patients with AF and non-LBBB pattern undergoing CRT.

Methods: A total of 41 HF patients either with LBBB (n=19) or intraventricular conduction delay (IVCD) (n=22) requiring CRT were included in the study. After 2 months of implantation, patients with ineffective biventricular pacing (n=10 in LBBB group, n=11 in IVCD group) underwent AVN ablation. Clinical (NYHA functional class) and echocardiographic (left ventricular ejection fraction and mitral regurgitation grade) parameters were followed-up for a mean follow-up period of 32.9 ± 8.9 months.

Results: At the end of the follow-up period, both LBBB and IVCD patients with or without AVN ablation showed an improvement in the NYHA functional class, mitral regurgitation grade and left ventricular ejection fraction. The improvement in LVEF was significantly better in IVCD patients compared to LBBB patients without ablation ($6.8\% \pm 7.2$ vs. $12.5\% \pm 3.0$, $p=0.027$). However, at the end, there were no significant differences among 4 groups regarding the changes of clinical and echocardiographic parameters from the baseline except for the above (all $p>0.05$).

Conclusion: The benefit obtained by CRT in non-LBBB patients with or without ablation has demonstrated that these patients should be evaluated for this important treatment modality of heart failure.

Keywords: ablation; biventricular pacing; intraventricular conduction delay

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The prevalence of atrial fibrillation (AF) increases in heart failure and with increasing New York Heart Association (NYHA) functional class.¹ Therefore, the prevalence of heart failure patients with AF needing cardiac resynchronization therapy (CRT) increases. The benefit of CRT in heart failure patients with AF has been similar to that in patients with sinus rhythm.² The role of atrioventricular node (AVN) ablation in patients with AF undergoing CRT has been shown.³⁻⁵ AVN ablation has been used to assure rate control.^{2,6} However, patients included in these studies have had a native left bundle branch block (LBBB) pattern on electrocardiogram (ECG). The mortality benefit of CRT in patients with non-LBBB morphologies has been also demonstrated.⁷ However, less clear data exists regarding to AVN ablation in these patients.

The aim of the present study was two-fold: first, to assess the clinical and echocardiographic benefit of CRT in AF patients with non-LBBB pattern compared to patients with LBBB pattern; second, to investigate the role of AVN ablation in patients with AF and non-LBBB pattern undergoing CRT.

Methods

We prospectively implanted biventricular pacing devices to 41 heart failure patients with AF. Patients were either ischemic or nonischemic with functional NYHA class III/IV. Standard 12-lead ECG fulfilled the criteria of QRS duration >120 ms with either LBBB ($n = 19$) or non-specific intraventricular conduction delay (IVCD) ($n = 22$) pattern. LBBB was defined as QRS duration ≥ 120 ms; QS or rS in lead V1; broad notched or slurred R wave in leads I, aVL, V5, and V6; and an occasional RS pattern in leads V5 and V6. RBBB was defined as QRS duration ≥ 120 ms; rsR', rSR', or qR in leads V1 or V2; and a wide and notched R wave and wide S wave in leads I, V5, and V6. Nonspecific IVCD was defined as QRS ≥ 120 ms without typical features of LBBB or RBBB.⁸ Patients with left ventricular ejection fraction of $\leq 35\%$, and resistant to optimal pharmacotherapy (beta-blocker, ACE-inhibitor, angiotensin II receptor blocker, aldosterone antagonist, and diuretic) requiring CRT were possible candidates of our study. Biventricular pacers with defibrillator capacity were implanted to all patients (Lumax HF-T, Biotronik). Subclavian vein puncture was used for venous access. Right ventricular leads with passive fixation were implanted in the RV apex. After cannulation of coronary sinus with guiding catheters, over the wire left ventricular bipolar passive fixation pacing leads were introduced to the targeted branch. Pacers were programmed in VVI-R. Minimum heart rate was usually set at 70/min (≥ 80 /min for 2 weeks after ablation). Immediately after CRT implantation, patients received optimal negative chronotropic drugs, and the rate adaptive mode with pacing features including ventricular rate regularization and/or trigger function were programmed to maximize biventricular pacing. The maximum rate was set at 85% of the theoretical maximum heart rate. Because of ineffective rate control (not achieving to obtain a percentage of biventricular pacing $>85\%$ at the second month control) with optimal medical therapy, radiofrequency AVN ablation (10 patients in LBBB

group, 11 patients in IVCD group) was performed by standard electrophysiological techniques from either the right or left side after 2 months of implantation. Clinical (NYHA functional class) and echocardiographic (left ventricular ejection fraction and mitral regurgitation grade) parameters were followed-up at 6 and 12 months after implantation, and every 6 months thereafter. In our analysis, only values at the time of implantation, 6th and 12th months, and last visit were used. A written consent was obtained from all patients and our local ethical committee approved the study.

Statistical analysis

Data were analyzed with the SPSS software version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean \pm SD and categorical variables as frequency and percentage. The Kolmogorov–Smirnov test was used to assess the distribution of continuous variables. Student's t-test was used to compare normally distributed continuous variables and the Mann–Whitney U test for variables without normal distribution. The χ^2 test or the Fisher exact test was used to compare categorical variables. Changes in NYHA functional class, left ventricular ejection fraction, and mitral regurgitation grade during the follow-up period were analyzed using analysis of variance followed by Bonferroni's post hoc test for repeated measurements. A two-tailed p-value of <0.05 was considered statistically significant.

Results

The study population comprised a total of 41 patients, 34 male and 7 female, with a mean age of 65.0 ± 9.0 years (age range, 39–77 years). The mean follow-up period was 32.9 ± 8.9 months. The underlying disease was ischemic cardiomyopathy in 51.2% of patients. The NYHA functional class was III in 75.6% of patients. The duration of AF was 32.2 ± 15.9 months and the mean left ventricular ejection fraction was $24.7 \pm 5.2\%$.

The baseline clinical, electrocardiographic and echocardiographic characteristics of 4 groups (LBBB, LBBB with ablation, IVCD, and IVCD with ablation) were presented in table 1. There was no statistically significant difference among 4 groups regarding the baseline characteristics.

Table 1. Baseline characteristics of 4 groups.

Characteristics	LBBB (n=9)	LBBB with ablation (n=10)	IVCD (n=11)	IVCD with ablation (n=11)
Age (years)	66.3 ± 7.4	68.3 ± 6.5	63.4 ± 9.2	62.5 ± 11.8
Male sex	7 (77.8%)	8 (80.0%)	9 (81.8%)	10 (90.9%)
Ischemic cardiomyopathy	5 (55.6%)	6 (60.0%)	5 (45.5%)	5 (45.5%)
NYHA class	3.2 ± 0.4	3.2 ± 0.4	3.3 ± 0.5	3.3 ± 0.5
III	7 (77.8%)	8 (80.0%)	8 (72.7%)	8 (72.7%)
IV	2 (22.2%)	2 (20.0%)	3 (27.3%)	3 (27.3%)
Duration of AF (months)	26.3 ± 13.6	37.9 ± 17.1	34.3 ± 16.3	29.9 ± 16.0
ACE-I use	8 (88.9%)	10 (100.0%)	9 (81.8%)	8 (72.7%)
BB use	6 (66.7%)	8 (80.0%)	10 (90.9%)	9 (81.8%)
Diuretic use	9 (100.0%)	10 (100.0%)	9 (81.8%)	10 (90.9%)
Aldosterone antagonist use	7 (77.8%)	4 (40.0%)	6 (54.5%)	8 (72.7%)
Digoxin use	6 (66.7%)	4 (40.0%)	7 (63.6%)	8 (72.7%)
Amiodarone use	2 (22.2%)	3 (30.0%)	4 (36.4%)	2 (18.2%)
QRS duration (ms)	179.4 ± 18.4	164.8 ± 16.8	168.6 ± 27.8	189.0 ± 30.8
LVEF (%)	25.6 ± 4.5	24.6 ± 5.3	24.5 ± 5.7	24.4 ± 5.6
MR grade	3.1 ± 0.6	3.1 ± 0.6	3.1 ± 0.5	3.1 ± 0.5
LA diameter (mm)	52.9 ± 7.3	52.0 ± 6.9	50.6 ± 6.1	48.8 ± 5.7
Ablation site (right)	-	9 (90.0%)	-	9(81.8%)
Follow-up period (months)	29.7 ± 9.8	32.1 ± 9.7	34.1 ± 8.1	34.9 ± 8.6

ACE-I, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; BB, beta-blocker; IVCD, intraventricular conduction delay; LA, left atrium; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association

At 6 months follow-up, both LBBB and IVCD patients with or without AVN ablation showed an improvement in the NYHA functional class, mitral regurgitation grade and left ventricular ejection fraction. Moreover, these improvements continued throughout the follow-up period (Figure 1).

The changes in NYHA class, mitral regurgitation grade, and the left ventricular ejection fraction occurred within the first 6 months and continued for up to 3 years in 4 groups (Figure 1, Table 2).

At the end of the follow-up period, 1-) there were no significant differences between LBBB patients with and without ablation regarding to the NYHA class ($p=0.257$), mitral regurgitation grade ($p=0.438$), the left ventricular ejection fraction ($p=0.058$), and QRS duration ($p=0.193$), 2-) there were no significant differences between IVCD patients with and without ablation regarding to the NYHA class ($p=0.183$), mitral regurgitation grade ($p=0.202$), the left ventricular ejection fraction ($p=0.140$), and QRS duration ($p=0.290$), 3-) there were no significant differences between LBBB and IVCD patients without ablation regarding

to the NYHA class ($p=0.165$), mitral regurgitation grade ($p=0.276$), and QRS duration ($p=0.410$) except for the left ventricular ejection fraction ($p=0.027$), 4-) there were no significant differences between LBBB and IVCD patients with ablation regarding to the NYHA class ($p=0.325$), mitral regurgitation grade ($p=0.360$), the left ventricular ejection fraction ($p=0.229$), and QRS duration ($p=0.142$), 5-) there were no significant differences between LBBB patients without ablation and IVCD patients with ablation regarding to the NYHA class ($p=0.637$), mitral regurgitation grade ($p=0.972$), the left ventricular ejection fraction ($p=0.352$), and QRS duration ($p=0.795$), and lastly 6-) there were no significant differences between LBBB patients with ablation and IVCD patients without ablation regarding to the NYHA class ($p=0.841$), mitral regurgitation grade ($p=0.710$), the left ventricular ejection fraction ($p=0.933$), and QRS duration ($p=0.754$) (Table 3).

Table 3. Change in clinical, echocardiographic and electrocardiographic parameters at the end of follow-up.

Characteristics	LBBB (n=9)	LBBB with ablation (n=10)	IVCD (n=11)	IVCD with ablation (n=11)
Change in NYHA class	-0.9 ± 1.2 (p=0.052)	-1.4 ± 0.7 (p<0.001)	-1.5 ± 0.5 (p<0.001)	-1.1 ± 0.7 (p<0.001)
Change in MR grade	-0.4 ± 0.7 (p=0.104)	-0.7 ± 0.7 (p=0.010)	-0.8 ± 0.8 (p=0.005)	-0.5 ± 0.5 (p=0.016)
Change in LVEF (%)	6.8 ± 7.2 (p=0.023)	12.4 ± 4.7 (p<0.001)	12.5 ± 3.0 (p<0.001)	9.5 ± 5.7 (p<0.001)
Change in QRS duration (ms)	-36.1 ± 18.5 (p<0.001)	-26.2 ± 13.2 (p<0.001)	-28.6 ± 20.6 (p=0.001)	-38.5 ± 22.1 (p<0.001)

IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association

p values for changes of each variable from the baseline.

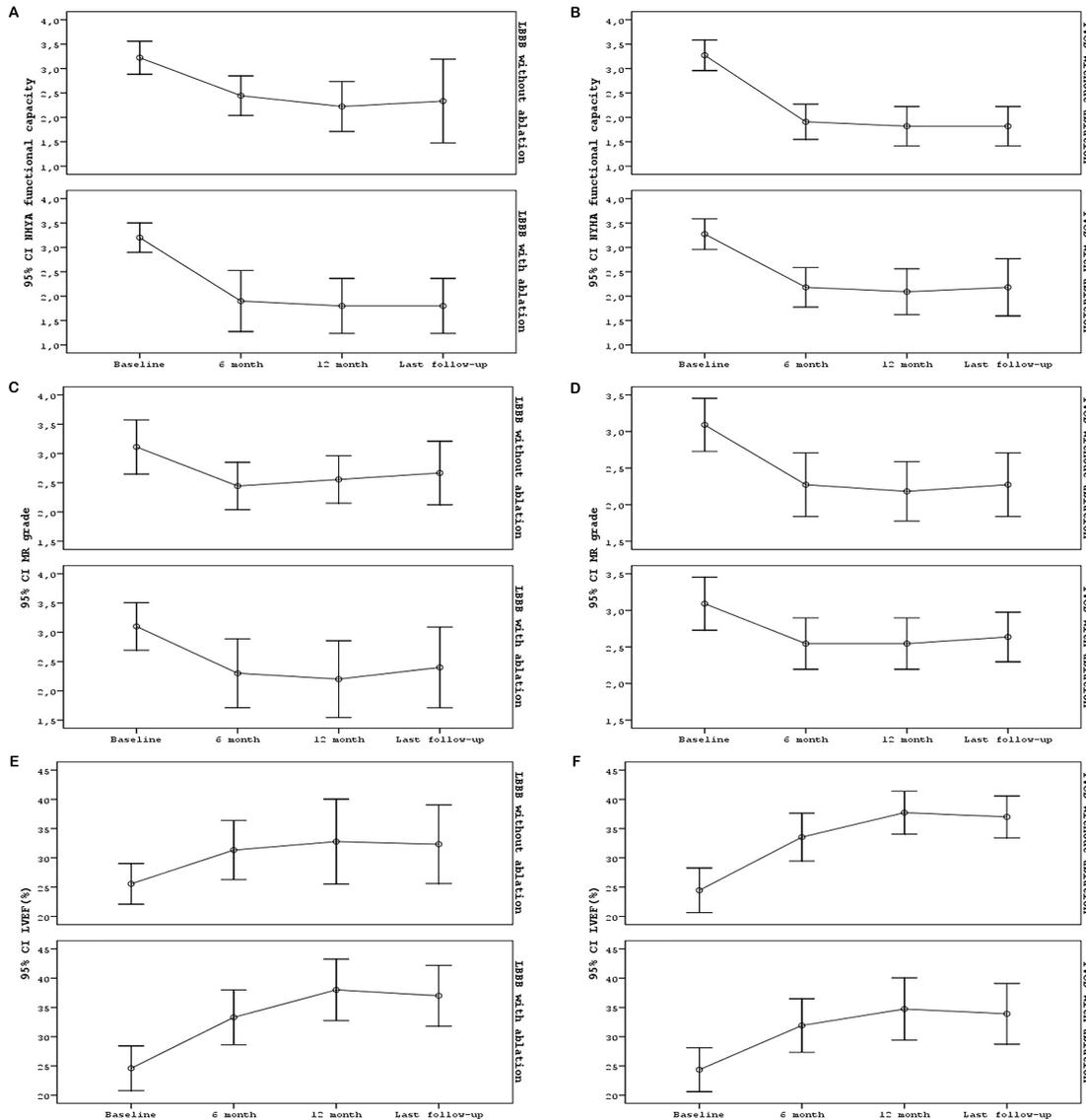


Figure 1. Changes in NYHA functional class (A, B), MR grade (C, D) and LVEF (E, F) of patients with LBBB and IVCD patterns. LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association.

Discussion

This is the first log-term, prospectively designed study demonstrating the clinical benefit of AVN ablation in patients with AF and non-LBBB pattern undergoing CRT. The magnitude of benefit with CRT with and without AVN ablation was similar between LBBB and IVCD patterns.

In LBBB patients, the right ventricle is firstly innervated followed by right-to-left septal activation and last depolarization of the left ventricular free wall.⁹ On the other hand, variable depolarization of the either ventricle or both of them is seen in IVCD patients.

CRT is related to significant increase in left ventricular ejection fraction and mortality in heart failure patients.¹⁰⁻¹¹ No significant difference in ventricular function and mortality has been detected between AF and sinus rhythm patients.⁵ A continuous increment in left ventricular ejection fraction over a 4-year period has been observed in AF patients.⁴ The improvement in NYHA functional class and left ventricular ejection fraction has been found to be similar in both ablated and non-ablated patients.¹² These benefits have been also showed in AF patients treated with the combined CRT and AVN ablation suggesting a strong recommendation of AVN ablation to achieve effective pacing in AF patients.⁴⁻⁵ In these studies, among patients with AF, just those patients ablated demonstrated a significant improvement in left ventricular ejection fraction and mortality. The mechanism for better results of ablated patients might be full regularization of rhythm by optimizing the alternation of systolic and diastolic phases of the cardiac cycle.¹³ Obtaining a regular rhythm with AVN ablation has been related with improved cardiac functions.¹³ In contrary to these data, AF patients with a LBBB pattern and AVN ablation showed similar improvement compared to AF patients with a LBBB pattern but not ablated. This result might be due to the small sample size of our study population although the difference in left ventricular ejection fraction was nearly significant ($p=0.058$). In daily clinical practice, most patients with systolic heart failure requiring CRT have non-LBBB pattern in their ECGs. In IVCD patients, less clear data is present compared to LBBB and RBBB patients. NYHA functional class has not been found to improve in IVCD patients undergoing CRT compared to controls in retrospective analysis of the MIRACLE

study.¹⁴ The marginal difference seen in LBBB patients, however, was not observed in AF patients with an IVCD pattern. Without AVN ablation, a significant improvement was observed in ejection fraction in LBBB patients compared to IVCD patients as shown in a previous study.⁷ However, this significant increase in ejection fraction was not seen between LBBB and IVCD patients undergoing AVN ablation. Moreover, no mortality difference has been detected. It has been demonstrated that CRT improves symptoms, left ventricular function and survival in heart failure patients.¹¹ Significant functional and ventricular improvements were observed in HF patients undergoing CRT.¹⁵ The reason for AVN ablation was not fast ventricular rate refractory to anti-arrhythmic drugs (beta-blockers, digoxin, and amiodarone), but rather insufficient percentage of biventricular pacing in our study. Amiodarone and digoxin were stopped in ablated patients, while beta-blockers were continued.

The significant improvement in NYHA functional class of patients with IVCD without ablation compared to patients with LBBB without ablation at 6 months was disappeared at 12 months. However, the improvement in LVEF continued. As in previous studies, the improvement in LVEF of patients with LBBB with ablation compared to patients without ablation was also observed after 12 months. Interestingly, the improvement in LVEF was significantly higher in IVCD patients without ablation compared to LBBB patients without ablation.

Limitations

This is a non-randomized observational study. A lack of proper control group and small sample sizes of each group are major important limitations of our study. Our study patients were recruited from a single center and therefore may not be representative of patients admitted to other centers. Probable overestimation of percentage of biventricular pacing due to fusions and pseudofusions is another limitation. As AVN ablation was not randomly performed, different results between groups may reflect selection bias.

Conclusion

Improved clinical variables seen in patients with non-LBBB pattern with or without AVN ablation

have demonstrated that these patients should not be undervalued when evaluating for CRT. Prospective randomized studies should be conducted to further confirm our findings.

Conflict of Interests

None

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