Multimodality imaging to guide cardiac interventional procedures

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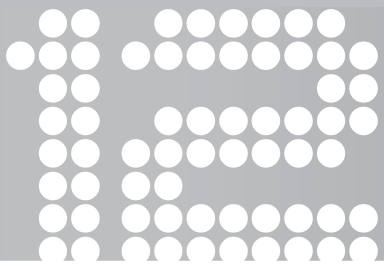

Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation

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ABSTRACT

Background: Atrioventricular (AV) node ablation and subsequent long-term RV pacing is a well-established treatment option in patients with atrial fibrillation (AF).

Objectives: To assess the effects of long-term right ventricular (RV) pacing on left ventricular (LV) dyssynchrony, LV function and heart failure symptoms.

Methods: In 55 patients with drug-refractory AF, AV node ablation and implantation of a pacemaker was performed. At baseline and after a mean of 3.8 ± 1.7 years, LV dyssynchrony (by M-mode echocardiography and tissue Doppler imaging), LV function and volumes and functional status were assessed.

Results: After long-term RV pacing, 27 patients (49%) had developed LV dyssynchrony. Concomitantly, these patients worsened in heart failure symptoms (NYHA class increased from 1.8 ± 0.6 to 2.2 ± 0.7, $p<0.05$), with a decrease in LV ejection fraction (from 48 ± 7% to 43 ± 7%, $p<0.05$) and an increase in LV end-diastolic volume (from 116 ± 39 ml to 130 ± 52 ml, $p<0.05$). Conversely, patients without LV dyssynchrony did not deteriorate in heart failure symptoms, LV function or LV volumes.

Conclusions: Long-term RV pacing can induce LV dyssynchrony in almost 50% of patients treated with AV node ablation for chronic AF. The development of LV dyssynchrony was associated with deterioration in heart failure symptoms, systolic LV function and LV dilatation.

INTRODUCTION

Chronic atrial fibrillation (AF) represents the most commonly encountered cardiac arrhythmia, and contributes substantially to cardiac morbidity and mortality (1). Although pharmacological therapy still is considered first-line therapy (2), anti-arrhythmic drugs are frequently ineffective and may have serious side-effects. Therefore, several non-pharmacological therapies have been introduced (3).

Atrioventricular (AV) node ablation and subsequent permanent pacing is a well-established treatment option in patients with chronic, drug-refractory AF (4). AV node ablation and permanent pacing may improve quality of life and exercise capacity (5), and may be superior to pharmacological therapy in controlling symptoms of AF (4,6).

However, recent studies have shown detrimental effects of long-term right ventricular (RV) pacing (7,8). Left ventricular (LV) dilatation (remodeling) (7) with a decrease in LV ejection fraction (8) after long-term RV pacing have been reported.

The underlying cause of these adverse effects is unknown but may be related to induction of LV dyssynchrony after long-term RV pacing, with subsequent deterioration of LV function. To evaluate this hypothesis, the effects of long-term RV pacing on LV function and dyssynchrony were evaluated in patients with chronic AF with normal LV function and without valvular disease undergoing AV node ablation and RV pacing.

METHODS

Study population

We retrospectively studied 55 patients who suffered from permanent AF, despite optimal pharmacological therapy. Accordingly, all patients were scheduled for AV node ablation and pacemaker implantation. All patients had preserved LV systolic function without significant valvular disease. At baseline and after a minimum period of one year RV pacing, New York Heart Association (NYHA) functional class was assessed and echocardiography was performed.

Ablation and pacemaker implantation

Atrioventricular node ablation was performed with a 4 mm quadripolar mapping / ablation catheter (EPT, Boston Scientific, Natick, Massachusetts, USA), accessed through the femoral vein. A temporary pacing electrode was placed in the RV apex for back-up pacing. Radiofrequency energy was applied at the AV node until complete AV-block was achieved. Thereafter the pacemaker was implanted. Pacemaker leads were inserted through the subclavian vein using standard implantation techniques. The RV leads were positioned in the RV apex in all patients. After implantation, pacemakers were routinely programmed to VVIR mode.

Echocardiography

All patients underwent echocardiography before the ablation procedure and after long-term RV pacing. Images were recorded with patients in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained using a 3.5-MHz transducer at a depth of 16 cm in the parasternal (long- and short-axis) and apical (two-chamber and four-chamber) views. Standard two-dimensional images and color Doppler data triggered to the QRS complex were saved in cine-loop format.

LV end-diastolic and end-systolic volumes and LV ejection fraction were calculated from apical two- and four-chamber images using the biplane Simpson's rule (9). Furthermore, LV end-diastolic diameter was measured from the parasternal long-axis images.

The severity of mitral regurgitation was graded semi-quantitatively using color-flow Doppler in the conventional parasternal long-axis and apical four-chamber images (10). Mitral regurgitation was characterized as: minimal = 1+ (jet area/left atrial area<10%), moderate = 2+ (jet area/left atrial area 10-20%), moderate-severe = 3+ (jet area/left atrial area 20-45%), or severe = 4+ (jet area/left atrial area >45%) (10).

Ventricular dyssynchrony

At baseline and after long-term RV pacing, LV dyssynchrony was assessed. Septal-to-posterior wall motion delay (SPWMD) was assessed using an M-mode recording from the parasternal short-axis view at the papillary muscle level. The interval between the maximal posterior displacement of the septum and the maximal displacement of the LV posterior wall was calculated (11). As reported by Pitzalis et al, SPWMD ≥130 ms was used as the cut-off value for LV dyssynchrony (11,12).

Furthermore, interventricular dyssynchrony was calculated as the difference between LV electromechanical delay (time from QRS onset to aortic systolic flow onset) and RV electromechanical delay (time from QRS onset to pulmonary systolic flow onset) (13). An interventricular delay ≥40 ms was used as a cut-off value for interventricular dyssynchrony, as previously described (13,14).

In addition, LV dyssynchrony was assessed using color-coded tissue Doppler imaging (TDI) after long-term RV pacing in 52 patients. The frame rates ranged from 80 to 115 frames/s, depending on the sector width of the range of interest; pulse repetition frequencies ranged from 0.5 to 1 kHz, resulting in aliasing velocities ranging from 16 to 32 cm/s. TDI parameters were measured from color-coded images of three consecutive heart beats by off-line analysis. Data were analyzed using commercially available software (Echopac 6.1, General Electric-Vingmed). To assess LV dyssynchrony, the sample volume was placed in the basal portions of the septum and lateral wall; the time to peak systolic velocity was obtained in the septum and lateral wall, and the septal-to-lateral delay in peak velocity was calculated as an indicator of LV dyssynchrony. A septal-to-lateral delay ≥65 ms was used as a cut-off value for LV dyssynchrony

assessed with TDI, as previously reported (15). The interventricular dyssynchrony and TDI images were evaluated by two independent observers, blinded to the results of the SPWMD.

Statistical analysis

Results are presented as mean values ± SD, or number (%). Continuous data were compared using paired or unpaired Student *t* test when appropriate. Correlation between SPWMD and TDI was assessed using Pearson's linear correlation. Agreement between SPWMD and TDI was expressed in a 2X2 table using κ statistics. A κ value of <0.4 represents poor agreement, a κ between 0.4 and 0.75 represents fair to good agreement, and a κ value of >0.75 is considered an excellent agreement based on the Fleiss classification (16). A p value <0.05 was considered statistically significant.

RESULTS

Study population

Fifty-five patients were studied. Baseline characteristics of the patients are listed in Table 1. All patients had preserved LV systolic function at baseline. None of the patients had significant mitral regurgitation or LV dysfunction. In all patients AV node ablation with subsequent pacemaker implantation was performed successfully. No complications related to the ablation procedure or pacemaker implantation were observed. Mean follow-up was 3.8 ± 1.7 years (range 1.2 to 8.7 years).

Table 1. Baseline characteristics of the study population

	All patients (n= 55)	Dyssynchrony absent (n = 28)	Dyssynchrony present (n = 27)
Age (yrs)	61 ± 11	60 ± 11	62 ± 12
Gender (M/F)	27/28	15/13	12/15
Duration AF (yrs)	7 ± 5	8 ± 5	7 ± 5
Anti-arrhythmic drugs used per patient	3.3 ± 1.3	3.4 ± 1.5	3.2 ± 1.2
Hypertension	27 (49%)	14 (50%)	13 (48%)
Coronary artery disease	5 (9%)	2 (7%)	3 (11%)
Clinically relevant MR (grade ≥ 2+)	0	0	0
Previous myocardial infarction	3 (6%)	1 (4%)	2 (7%)
NYHA functional class			
I	22 (40%)	13 (46%)	9 (33%)
II	26 (47%)	11 (39%)	15 (56%)
III	7 (13%)	4 (14%)	3 (11%)
IV	0	0	0
QRS duration (ms)	99 ± 12	100 ± 13	98 ± 10
SPWMD (ms)	63 ± 31	60 ± 36	67 ± 22
IVD (ms)	25 ± 13	24 ± 14	25 ± 12

AF = atrial fibrillation; IVD = interventricular delay; MR = mitral regurgitation; NYHA = New York Heart Association; SPWMD = septal-to-posterior wall motion delay.

At baseline, mean interventricular delay was 25 ± 13 ms. None of the patients had an interventricular delay ≥40 ms, representing interventricular dyssynchrony. Mean SPWMD before AV node ablation and pacemaker implantation was 63 ± 31 ms (range 4 to 122 ms). In none of the patients, a SPWMD ≥130 ms was present at baseline, indicating absence of LV dyssynchrony in all patients.

After long-term RV pacing, mean SPWMD was 121 ± 64 ms (range 11 to 240 ms). In 27 patients (49%) a SPWMD ≥130 ms was present, indicating LV dyssynchrony. Accordingly, the study population was divided into two groups: with or without LV dyssynchrony at follow-up, based on a SPWMD delay ≥130 ms after long-term RV pacing. Baseline characteristics of the two groups are listed in Table 1. There were no differences in baseline characteristics between the two groups (Table 1).

Intraventricular dyssynchrony

Intraventricular dyssynchrony as assessed with TDI was available in 52 patients after long-term RV pacing. The patients who did not develop LV dyssynchrony on M-mode echocardiography after long-term RV pacing, did also not exhibit LV dyssynchrony on TDI (mean septal-to-lateral delay 37 ± 45 ms). In contrast, the patients who had developed LV dyssynchrony as assessed by M-mode echocardiography also displayed LV dyssynchrony on TDI (mean septal-to-lateral delay 109 ± 26 ms, $p<0.05$ vs. patients without LV dyssynchrony). Of note, all patients with SPWMD ≥130 ms on M-mode had a septal-to-lateral delay ≥65 ms assessed with TDI (Table 2). In contrast, there were 4 patients without dyssynchrony on M-mode, that had a septal-to-lateral delay ≥65 ms assessed with TDI. A linear relation was found between SPWMD and septal-to-lateral delay ($R = 0.66$, $p<0.01$) (Figure 1). When applying the cut-off values (SPWMD ≥130 ms, septal-to-lateral delay ≥65 ms) for LV dyssynchrony, an excellent agreement ($\kappa = 0.85$) between SPWMD and TDI to detect LV dyssynchrony was observed (Figure 2). Disagreement between SPWMD and TDI was based on 4 (8%) patients, in which LV dyssynchrony could only be detected with TDI (Table 2).

Table 2. Agreement between SPWMD and septal-to-lateral delay

		Septal-to-lateral delay ≥65 ms		Total
		present	absent	
SPWMD ≥130 ms	present	25	0	25
	absent	4	23	27
Total		29	23	52

There is an excellent agreement (92%) between the two methods to assess LV dyssynchrony ($\kappa = 0.85$, $p<0.01$). The disagreement is related to 4 (8%) patients, in which LV dyssynchrony could only be detected with TDI. LV = left ventricle; TDI = tissue Doppler imaging; SPWMD = septal-to-posterior wall motion delay.

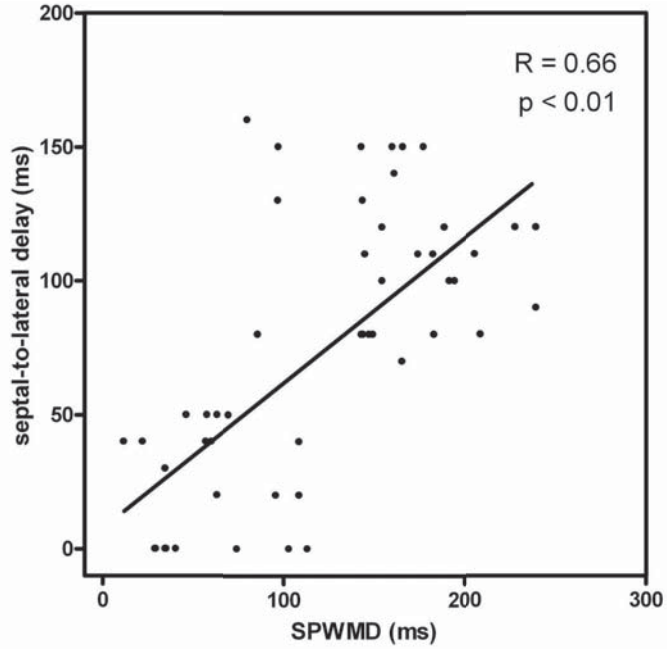

Figure 1. A linear relation was found between SPWMD and septal-to-lateral delay after chronic RV pacing. RV = right ventricle; SPWMD = septal-to-posterior wall motion delay.

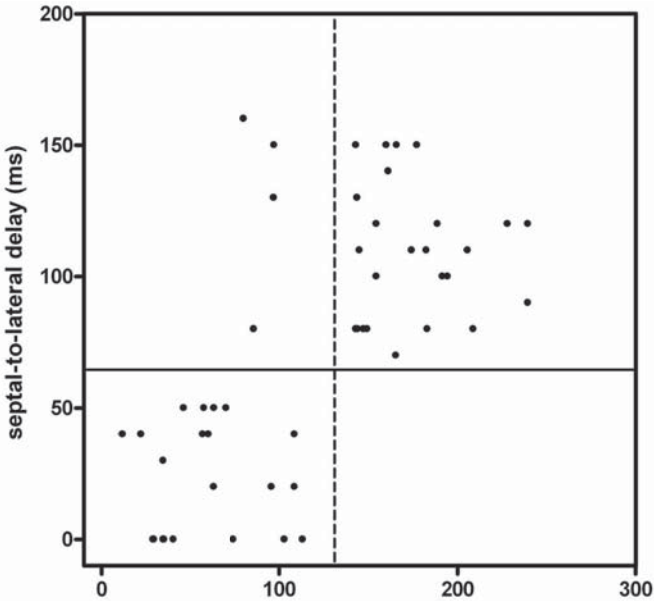

Figure 2. SPWMD and septal-to-lateral delay after chronic RV pacing. For LV dyssynchrony, a cut-off value of SPWMD >130 ms (dashed line), and septal-to-lateral delay >65 ms (solid line) was used. There is a good agreement between SPWMD and septal-to-lateral delay. In only 4 patients, there was a disagreement between SPWMD and septal-to-lateral delay.
LV = left ventricle; RV = right ventricle; SPWMD = septal-to-posterior wall motion delay.

Interventricular dyssynchrony

At baseline, none of the patients exhibited interventricular dyssynchrony (mean interventricular delay 25 ± 13 ms). After long-term RV pacing, mean interventricular delay did not increase significantly in the patients without LV dyssynchrony (24 ± 14 ms vs. 35 ± 25 ms, p=NS). In contrast, interventricular delay revealed a significant increase in the patients with LV dyssynchrony after long-term RV pacing (25 ± 12 ms vs. 49 ± 19 ms, p<0.05). In 19 patients (70%) with LV dyssynchrony, an interventricular delay ≥40 ms was present after long-term RV pacing, indicating the presence of interventricular dyssynchrony. In contrast, in only 5 patients (17%) without LV dyssynchrony, an interventricular delay ≥40 ms was present (p<0.01 vs. patients with LV dyssynchrony).

Clinical and echocardiographic effects of long-term RV pacing

After long-term RV pacing, functional status and LV parameters were re-assessed in all patients. In patients without LV dyssynchrony, NYHA class improved from 1.7 ± 0.7 to 1.4 ± 0.5 (p<0.01), whereas NYHA class deteriorated in patients who had developed LV dyssynchrony (from 1.8 ± 0.6 to 2.2 ± 0.7, p<0.05) (Figure 3). Furthermore, LV ejection fraction decreased significantly in patients with LV dyssynchrony (48 ± 7% vs. 43 ± 7%, p<0.05), whereas LV ejection fraction remained unchanged in patients without LV dyssynchrony (Figure 3).

Also, in patients with LV dyssynchrony, an increase in LV end-diastolic volume (116 ± 39 ml vs. 130 ± 52 ml, p<0.05) and LV end-systolic volume (62 ± 26 ml vs. 75 ± 35 ml, p<0.05) was observed after long-term RV pacing (Table 3). In addition, LV end-diastolic diameter increased significantly in patients with LV dyssynchrony (5.3 ± 0.8 cm vs. 5.6 ± 0.7 cm, p<0.05), whereas no difference in LV diameter was observed in patients without LV dyssynchrony after long-term RV pacing (Table 3).

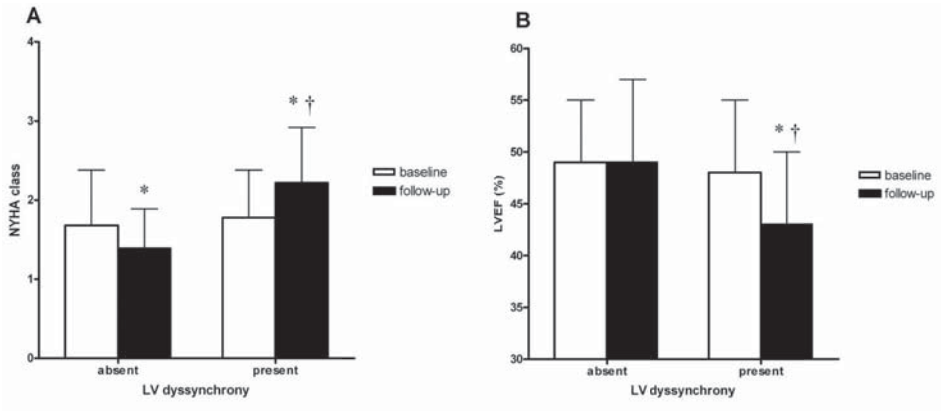

Figure 3. Effects of chronic RV pacing on clinical status and LV ejection fraction. Panel A: In patients with LV dyssynchrony, NYHA functional class deteriorated significantly, whereas NYHA functional class improved significantly in patients without LV dyssynchrony. Panel B: LV ejection fraction decreased significantly in patients with LV dyssynchrony after chronic RV pacing. * p < 0.05 baseline vs follow-up; † p < 0.05 with dyssynchrony vs without dyssynchrony. LV = left ventricle; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RV = right ventricle.

Table 3. LV parameters at baseline and after chronic RV pacing

	Dyssynchrony absent (n = 28)	Dyssynchrony present (n = 27)
LVEF (%)		
Baseline	49 ± 6	48 ± 7
Follow-up	49 ± 8	43 ± 7 * †
LVEDV (ml)		
Baseline	119 ± 46	116 ± 39
Follow-up	121 ± 31	130 ± 52 *
LVESV (ml)		
Baseline	61 ± 25	62 ± 26
Follow-up	62 ± 19	75 ± 35 *
LVEDD (cm)		
Baseline	5.2 ± 0.6	5.3 ± 0.8
Follow-up	5.3 ± 0.4	5.6 ± 0.7 * †
Clinically relevant MR (grade ≥ 2+)		
Baseline	0	0
Follow-up	2 (7%)	5 (18%)

* $p < 0.05$ baseline vs. follow-up; † $p < 0.05$ with dyssynchrony vs. without dyssynchrony. LV = left ventricle; LVEDD = left ventricular end-diastolic diameter, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume, MR = mitral regurgitation, RV = right ventricle.

DISCUSSION

The current observations demonstrate the adverse effects of long-term RV pacing on LV synchrony and LV function. In 49% of the patients treated with AV node ablation and pacemaker implantation, LV dyssynchrony was induced after long-term RV pacing associated with an increase in heart failure symptoms, a decrease in global LV function and LV dilatation.

Effects of long-term RV pacing

In patients with drug-refractory AF, ablation of the AV node and permanent pacing has proven to be effective (4). However, the beneficial effect of the therapy may (partially) be reversed by the non-physiological activation pattern of the interventricular septum. Several studies (7,17-20) have reported negative effects of permanent RV pacing. Regional perfusion defects (17,18), asymmetrical hypertrophy of the ventricular wall (19) and an impairment of LV ejection fraction (20) have been reported after permanent RV pacing.

Furthermore, Thambo et al (7) recently demonstrated the induction of LV dyssynchrony after long-term RV pacing in 23 patients with congenital complete AV-block. Following long-term RV pacing, the mean SPWMD, as a measure of LV dyssynchrony, had significantly increased as compared to baseline (41 ± 16 ms vs. 84 ± 26 ms, $p<0.05$). In addition, the septal-to-lateral delay as measured by TDI was significantly larger in patients with permanent pacing as compared to controls (59 ± 18 ms vs. 19 ± 9 ms, $p<0.01$). Similar results were demonstrated in the current study, showing an increase in SPWMD from 63 ± 31 ms to 121 ± 64 ms ($p<0.05$) after long-term RV pacing, and in 27 (49%) patients the SPWMD exceeded 130 ms, indicating substantial LV dyssynchrony.

The presence of LV dyssynchrony may result in systolic LV dysfunction (21,22). Thambo et al (7) reported a significantly lower cardiac output in patients with LV dyssynchrony after long-term RV pacing, as compared to healthy controls. In addition, LV end-diastolic diameter had significantly increased in these patients as compared to controls (5.5 ± 0.7 cm vs. 4.6 ± 0.6 cm, $p<0.05$). The observations in the present study are in line with these previous results: patients with LV dyssynchrony after long-term RV pacing showed a decrease in LV ejection fraction, with an increase in LV volumes and LV end-diastolic diameter (Table 3) indicating LV dilatation.

Assessment of LV dyssynchrony

In the current study, LV dyssynchrony was measured by M-mode echocardiography. With M-mode echocardiography the SPWMD can be measured as recently introduced by Pitzalis et al (11). The SPWMD indicates the delay between the maximal systolic motion of the septum and the LV free wall, reflecting intraventricular dyssynchrony (11). At baseline, none of the patients in the current study had SPWMD exceeding 130 ms, which is used as the upper limit of normal LV synchrony. After long-term RV pacing however, 27 (49%) patients had developed LV dyssynchrony, as illustrated by a SPWMD ≥130 ms.

In addition to SPWMD, TDI was used to assess the septal-to-lateral delay. TDI is a sophisticated echocardiographic technique that permits measurement and timing of myocardial systolic (and diastolic) velocities. By comparing the differences in time to peak systolic velocities of different LV regions, TDI can identify LV dyssynchrony (23).

Both M-mode using SPWMD and TDI using the septal-to-lateral delay have proven to be effective in the detection of LV dyssynchrony (11,15). In the current study, a good agreement was detected between the SPWMD and septal-to-lateral delay (Figure 2). In particular, all patients with LV dyssynchrony on M-mode also exhibited LV dyssynchrony on TDI, and only 4 patients (8%) without LV dyssynchrony on M-mode had LV dyssynchrony on TDI, indicating minimal underestimation of LV dyssynchrony by SPWMD. Marcus et al (24) have recently demonstrated substantial underestimation of LV dyssynchrony by M-mode echocardiography as compared to TDI in patients with severe LV dysfunction. In particular, in patients with ischemic LV dysfunction and akinesia of the (antero-)septum, assessment of SPWMD may not be feasible and TDI may be preferred for accurate detection of LV dyssynchrony (25). In the current study however, all patients had preserved LV function without significant valvular disease, explaining the better agreement between the two techniques.

Clinical implications

The observations in the current study demonstrate that RV pacing may induce LV dyssynchrony in a substantial percentage of patients with preserved LV function who undergo AV node ablation. In addition, the induction of LV dyssynchrony was associated with a deterioration of LV function and clinical status. Therefore, it needs to be considered whether these patients should have undergone biventricular pacing rather than RV pacing. Recently, several studies

have compared different pacing strategies for patients with AF treated with AV node ablation and permanent pacing. In the PAVE trial (8), 184 patients treated with AV node ablation and pacemaker implantation were randomly assigned to RV pacing or biventricular pacing. After 6 months follow-up, the LV ejection fraction was significantly lower in 81 patients who underwent RV pacing as compared to 103 patients with biventricular pacing (41 ± 13% vs. 46 ± 13%, $p<0.05$). Unfortunately, LV dyssynchrony was not assessed in the PAVE study.

The OPSITE-study (26) compared RV pacing and biventricular pacing in patients with permanent AF undergoing AV node ablation. After 6 months, patients with RV pacing had a significant lower LV ejection fraction as compared to biventricular pacing (43 ± 11% vs. 45 ± 13%, $p<0.05$). In addition, NYHA functional class was significantly lower with RV pacing as compared to biventricular pacing (1.6 ± 0.7 vs. 1.8 ± 0.7, $p<0.05$).

In addition, a positive effect of upgrading long-term RV pacing to biventricular pacing has recently been demonstrated. Leon et al (27) reported an improvement in NYHA functional class and LV function after upgrading to biventricular pacing in 20 heart failure patients with chronic AF, previous AV node ablation and RV pacing.

The aforementioned studies provide evidence for the benefit of biventricular pacing, as compared to RV pacing in patients with chronic AF and AV node ablation (8,26,27). The observations in the present study illustrate that in a substantial part of the patients with preserved LV function who undergo AV node ablation, long-term RV pacing can induce LV dyssynchrony, which appears associated with adverse effects, including an increase in heart failure symptoms, and a decrease in LV function with LV dilatation. Whether LV dyssynchrony results in LV dilatation or vice versa, remains unclear. The abnormal electrical activation pattern induced by RV pacing may result in LV dyssynchrony, with subsequent LV dilatation and regional contraction abnormalities (20,22). Conversely, Yu et al demonstrated that a large LV end-systolic diameter predicted the severity of LV dyssynchrony in patients with heart failure (28). However, in the present study, no differences in baseline LV dimensions or volumes were found between the patients with and without LV dyssynchrony after long-term RV pacing. Therefore, no predictors for the induction of LV dyssynchrony could be identified. It may well be that the patients who develop LV dyssynchrony may benefit from biventricular pacing, whereas the patients who do not develop LV dyssynchrony may not need biventricular pacing. Accordingly, patients should be evaluated after RV pacing for development of LV dyssynchrony, and if LV dyssynchrony is induced, biventricular pacing should be considered. Ideally, patients who are at risk for development of LV dyssynchrony should be identified at baseline (before AV node ablation and pacemaker implantation), but the results of the current study could not demonstrate any difference in baseline variables (Table 1). Clearly, additional studies in large populations are needed to confirm the current findings, and to develop selection criteria for patients with normal LV function who may require biventricular pacing rather than RV pacing after AV node ablation for chronic, drug-refractory AF.

Study limitations

Some limitations of the present study need to be addressed. First, it is a retrospective study, and it has a relatively small study population. Larger, prospective studies on the development (and prediction) of LV dyssynchrony after AV node ablation are needed. Furthermore, relatively soft end-points (NYHA functional class and ventricular remodeling) were used to assess clinical efficacy. However, these parameters are often used as markers for clinical efficacy (8,26,27). Finally, the changes in LV ejection fraction and LV end-diastolic volume in the patients with LV dyssynchrony in the present study are relatively small, but statistically significant.

CONCLUSIONS

In patients treated with AV node ablation, long-term RV pacing induced LV dyssynchrony in 49% of patients. These patients appear to develop heart failure symptoms with a reduction in LV systolic function and LV dilatation. These patients may benefit from biventricular pacing rather than RV pacing.

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