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Comparison of effectiveness of right ventricular mid-septal pacing vs. apical pacing: a randomized-controlled trials

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KEYWORDS
Mid-septal pacing;
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Heart function;
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The aim of the present study was to compare conventional right ventricular apical pacing (RVAP) with right ventricular mid-septal pacing (RVMSP) in terms of echocardiographic and clinical/biologic features. Ninety-six patients with high-degree atrioventricular block were randomly allocated to RVMSP ($n = 50$) and RVAP ($n = 46$). Threshold and impedance, echocardiographic left ventricular ejection fraction, ventricular dyssynchrony features, and distance during a 6-min walk test and Minnesota Living with Heart Failure Questionnaire were determined at 6 and 12 months after pacemaker implantation. Serum levels of N-terminal pro-brain natriuretic peptide were measured. At 6 months of follow-up, echocardiographic and clinical/biologic features showed no significant differences between two groups. The RVAP group had more intraventricular dyssynchrony and a trend towards a worse left ventricular ejection fraction compared with the RVMSP at 12 months of follow-up. However, no overt clinical benefits from RVMSP were found. Right ventricular mid-septal pacing was associated with decreased dyssynchrony and better left ventricular ejection fraction compared with the RVAP. Right ventricular mid-septal pacing could represent an alternative pacing site in selected patients to reduce the harmful effects of traditional RVAP.

Background

Chronic right ventricular apical pacing (RVAP) has been associated with negative haemodynamic and clinical effects.[1,2] The strategies that have been adopted to avoid the negative consequences of apical pacing include avoidance of RV pacing and/or implantation of RV leads in non-apical sites. Right ventricular mid-septal pacing has been argued to stimulate a more efficient ventricular contraction.[3] A meta-analysis of 14 randomized studies[4] found that right ventricular mid-septal pacing (RVMSP) is associated with a better left ventricular ejection fraction (LVEF) during follow-up, compared with RVAP. The aim of the present study was to compare RVAP with RVMSP in terms of echocardiographic and clinical/biologic features.

Materials and methods

Study population

People with symptomatic III degree atrioventricular (AV) block requiring elective permanent pacemaker implantation according to current guidelines (Class I) from August 2011 to August 2014 were screened. Patients were excluded before randomization if they met any of the following criteria: age <18 years, the presence of heart failure or any significant structural heart disease, chronic pulmonary heart disease, and any musculoskeletal disease hampering the realization of a 6-min walking test. Once the patient was eligible to enter the study, patients were randomized to receive a mid-septal or apical ventricular lead by a coin toss. All patients provided informed consent, and the study was performed according to the Institutional Guidelines of the First Hospital of Lanzhou University.

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Pacemaker implantation

All patients underwent their first pacemaker implant, using active fixation ventricular leads in the mid-septum and passive fixation in the apex. All procedures were performed by the same two implanters (M.B. and Z.Z.) using direct subclavian puncture in sinus rhythm. Standard passive leads were used for atrial implantation to locate the right atrial appendage. Under fluoroscopic guidance, an active fixation pacing lead was introduced with a stylet and directed to the RVA or RVMS, depending on randomization. To achieve the mid-septal position, first, the RV lead was advanced through the tricuspid valve and then the tip was positioned directly against the interventricular septum with a manually shaped stylet, as verified by frontal and lateral fluoroscopic views. Next, the tip was screwed on the interventricular septum. The procedure has been described by Rosso *et al.*[5] and by our previous study.[6] However, in case of mid-septal lead positioning, fluoroscopic validation of accurate location may prove challenging due to the crescent-like shape of the RV chamber. The electrocardiographic features[7] (positive QRS in lead V6, positive QRS in any of the inferior leads, and a QR pattern in lead aVL, *Figure 1*) and echocardiography were used to confirm the mid-septal position, as previously described by our study (*Figures 2* and *3*).[8] There were no technical problems during or after the procedure.

Ventricular leads from two different manufacturers (CapSureFix 5076, Medtronic, Minneapolis, MN; Tendril DX Model 1388T and Tendril SDX Model 1688T, St. Jude Medical, Secaucus, NJ) were used, depending on the implanter's preference, and were equally distributed between the two groups.

Pacemaker programming

The pacemaker was programmed to DDD mode (60 beats/min) initially. The AV interval was programmed at nominal values: 120 ms for sensed P waves and 150 ms for paced atrial activation. For measuring the paced QRS duration, a standard 12-lead surface electrocardiograph (ECG) at 25 mm/s speed and 50 mm/s speed were recorded with a digital ECG writer (Marquette MAC-5000, GE, USA).The QRS duration was automatically measured with the

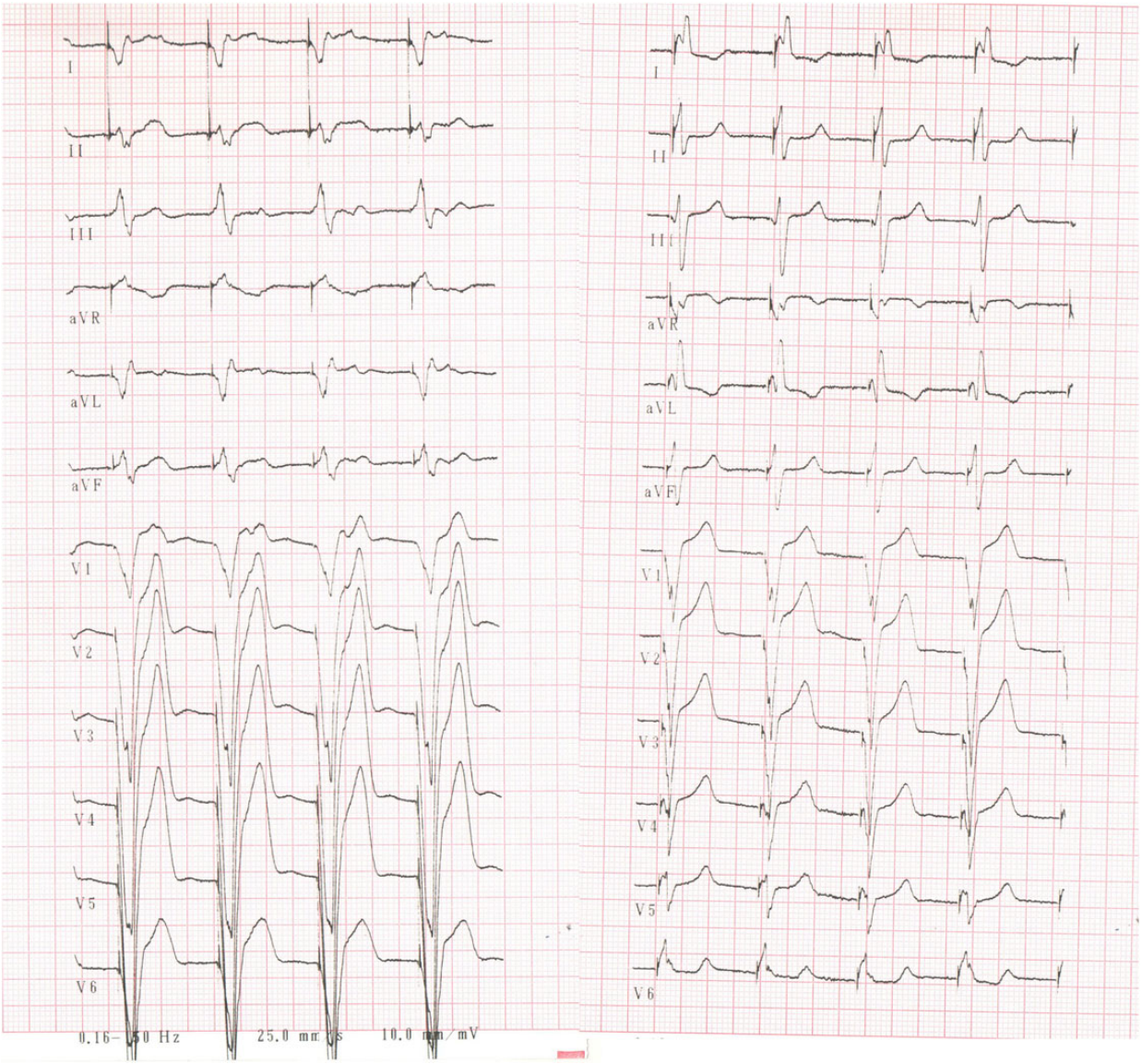

Figure 1 Electrocardiographs of RV lead positioning in RVA and mid-septal pacing. Left part is right ventricular apical pacing, and right part is right ventricular mid-septal pacing.

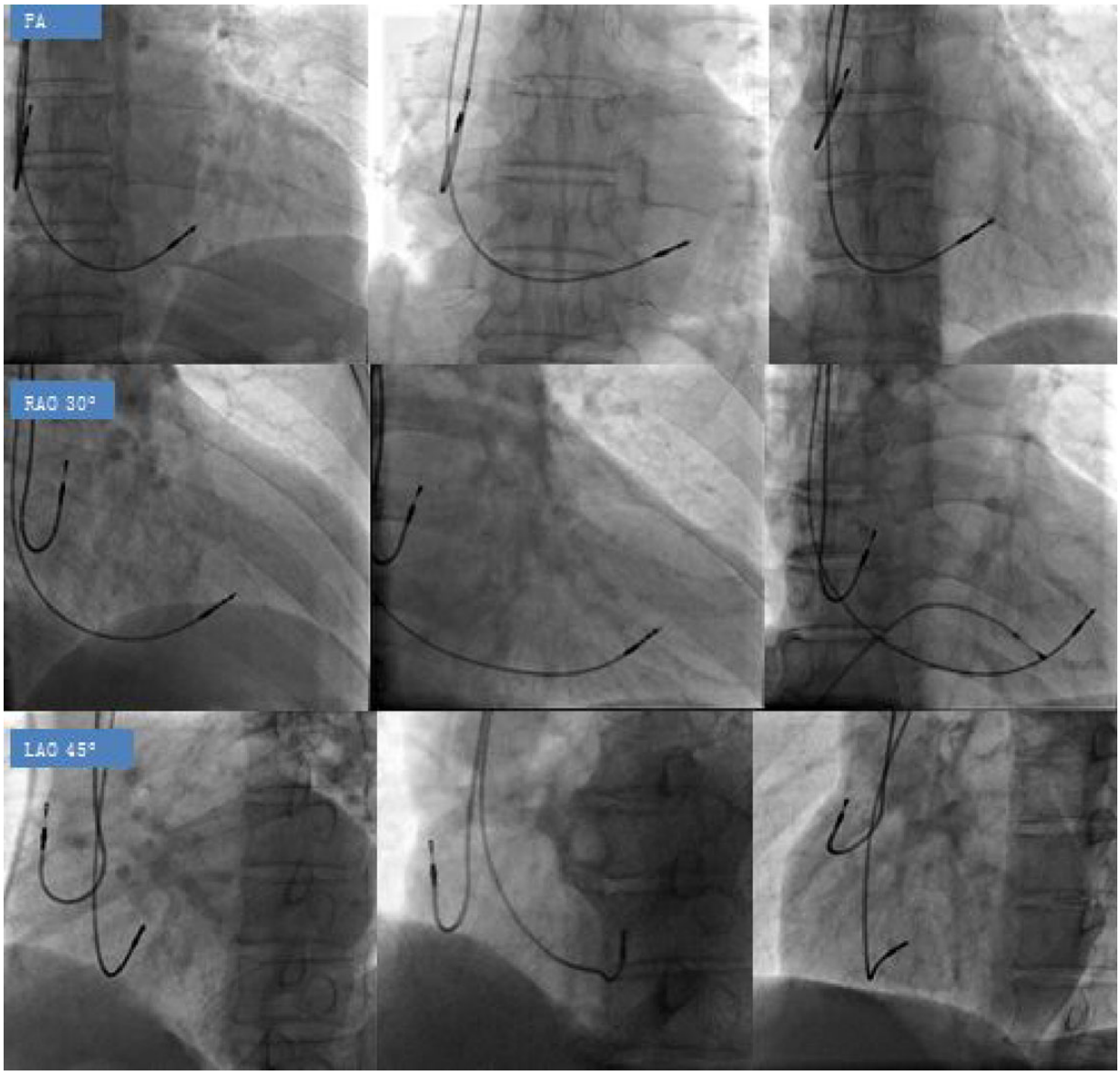

Figure 2 Fluoroscopic images of three patients demonstrating the right ventricular mid-septal pacing. Posteroanterior (PA), 30° right anterior oblique (RAO 30°), and 45°left anterior oblique (LAO 45°)

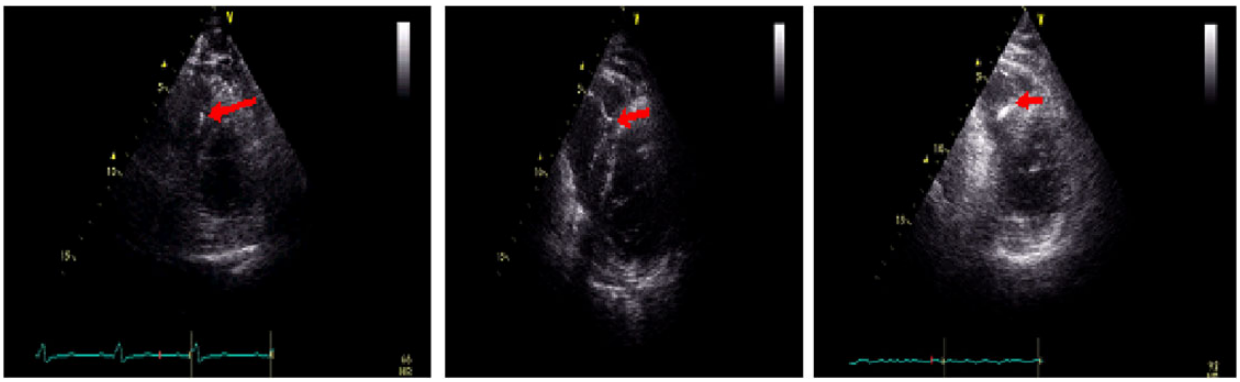

Figure 3 Validation of RV septal lead position by transthoracic echocardiography. Right ventricular lead at mid-septal level in the parasternal short axis view and in the apical four chamber view. The last is RV lead in the groove between the septum and the anterior wall in the parasternal short axis view.

mean duration of all 12 leads. Capture threshold and lead impedance were measured immediately after pacemaker implantation and at each follow-up visit.

Echocardiographic features

We measured and compared cardiac function and cardiac motion synchronization indicators for both RVAP and RVMSP groups, 1 week post-operatively, and both 6 and 12 months post-operatively. Indicators reflecting left ventricular function were the following: left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV), LVEF, and the velocity time integral of the aortic valve orifice. Indicators reflecting synchronization of cardiac motion were the following: APEI (pulmonary artery pre-ejection interval)–PPEI (pulmonary artery pre-ejection interval) and SPWMD (pulmonary artery pre-ejection interval). To ascertain the pre-ejection time of the right ventricle, the time interval from the beginning of the QRS wave group to the initial pulmonary artery blood flow is measured over three continuous cardiac cycles and averaged. The same method is used to measure pre-ejection time of the left ventricle, using the initiation of blood flow through the aortic valve. Subtracting pulmonary artery pre-ejection interval (PPEI) and aortic pre-ejection interval (APEI) gives the value of the difference in pre-ejection time between the left and right ventricles. If APEI–PPEI$>$ 40 ms, it means desynchronization of systolic activity in left and right ventricles.[9] For SPWMD, measuring left ventricular dyssynchrony, parasternal long-axis M-mode echocardiography, and the moving curve of the left ventricular back wall is utilized. The time duration is measured from the peak of ventricular septum contraction to the peak of left ventricular posterior wall contraction. All tissue Doppler imaging echocardiographic measurements were taken as averages of three or more representative cycles. All the echocardiographic evaluations were performed during spontaneous paced rhythm.

Follow-up

The patients were initially evaluated before implantation (baseline evaluation) and after 6 and 12 months of follow-up. All scheduled visits included a complete clinical interview, physical examination, 12-lead electrocardiogram, Minnesota Living with Heart Failure Questionnaire (mlHFQ), transthoracic echocardiography, 6-min walking test, pacemaker interrogation (lead impedance and pacing threshold), and measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP).

Statistical analysis

The continuous data are expressed as the mean $\pm$ SD or range, as appropriate. Comparisons between groups (mid-septal pacing or apical pacing) were performed using analysis of variance for repeated measurement design data for continuous variables and χ^2 test for categorical variables. Data were analysed on an intention-to-treat basis. $P < 0.05$ was considered statistically significant.

Results

A total of 96 patients had a pacemaker successfully implanted, and all patients were confirmed in correct location by the echo. There were no dislodgements occurred. No major complications were observed during implant.

Baseline characteristics

Mean age of RVMSP group was 65.2 $\pm$ 9.4, similar to the RVAP group, 66.7 $\pm$ 10.7 (P = ns). Likewise, 60% of patients in RVMSP group and 60.9% in RVAP group (P = ns) were males. Patients in RVMSP and RVAP groups did not differ significantly with respect to concomitant disease and baseline LVEF. The baseline characteristics of the population are listed in *Table 1*.

Pacing measurements

Right ventricular mid-septal pacing was associated with significantly shorter QRS and lower lead impedance than RVAP during implant (mean paced QRS duration during implant 131 $\pm$ 11 ms for RVMSP vs. 156 $\pm$ 15 ms for the RVAP group, $P < 0.05$). The capture threshold and lead impendence remained stable and comparable between the two locations during at the 6- and 12-month follow-up visits. The lead impedance for the ventricular lead was significantly reduced in both groups. No clinical changes were observed (*Table 2*).

Follow-up outcome

Results showed that prior to pacemaker implantation, no statistically significant difference was found between the RVAP and RVMSP groups for echocardiographic parameters. There were no differences between two groups after 6 months of follow-up. After 12 months of follow-up, the patients allocated to the RVMSP group tended to have more higher LVEF levels, but the difference was not statistically significant [(61.1 $\pm$ 10) vs. (55.3 $\pm$ 11)%, $P > 0.05$]. The LVEDD, LVESD, LVEDV, and LVESV of the RVA pacing group were larger than that of the RVMSP pacing group ($P < 0.05$). These findings indicate that compared with

Table 1 Baseline characteristics

	RVMSP (n = 50)	RVAP (n = 46)	P
Men (%)	33 (66)	27 (59)	0.76
Age (years)	65.2 $\pm$ 9.4	66.7 $\pm$ 10.7	0.38
Hypertension	30 (60)	28 (60.9)	0.93
Diabetes mellitus	11 (22)	8 (17.4)	0.57
Atrial fibrillation	1 (2)	1 (2.1)	0.95
Coronary artery disease	6 (12)	4 (8.7)	0.60

Data are shown as a number (%) or mean $\pm$ SD.

Table 2 Pacing measurements at baseline and after 6 and 12 months

	QRS duration (ms)	Capture threshold (mV)			Lead impendence (Ω)		
		During implant	6 months follow-up	12 months follow-up	During implant	6 months follow-up	12 months follow-up
RVMSP ($n = 50$)	131 ± 11	0.69 ± 0.25	0.60 ± 0.16	0.59 ± 0.15	570 ± 136	435 ± 91	407 ± 94
RVAP ($n = 46$)	156 ± 15	0.62 ± 0.23	0.67 ± 0.20	0.66 ± 0.14	672 ± 190	422 ± 98	418 ± 135
P	0.02*	0.19	0.14	0.12	0.03*	0.56	0.77

Data are expressed as mean ± SD.
*$P < 0.05$ for comparison between RVAP and RVMSP groups.

RVMSP, RVA pacing was more likely to impair left ventricular function.

The RVAP group has more interventricular dyssynchrony than the RVSP group, and the difference was statistically significant at 12 months of follow-up (APEI–PPEI were 15.6 ± 13.6 ms for RVMSP and 39.7 ± 15.3 ms for RVAP, $P < 0.05$); but for SPWMD, the difference was not statistically significant at 6 and 12 months of follow-up (*Table 3*).

The baseline clinical parameters and NT-proBNP values were comparable among the two groups. During 6 and 12 months of follow-up, serum BNP levels, mlHFQ, and distance during the 6-min walk test were not significantly changed between RVMSP and RVAP groups (*Table 4*).

Discussion

True RV mid-septal pacing has until recently been difficult to consistently achieve, because of the lack of suitable lead technology and no standardized nomenclature; furthermore, it is difficult to consistently and accurately position the pacing leads onto the septum because of its posterior orientation within the RV chamber. By the fluoroscopic appearances and electrocardiographic patterns, we have a much clearer understanding of the relationship between the anatomy of the RV chambers, and then it is easier to made the direct active fixation leads onto the true RV mid-septum. Our study found that, compared with conventional RVAP, RVMSP used in this study was shown to involve no clinically relevant changes in pacing threshold or lead impedance, and these pacemaker indices did not change at 1 year post-implantation, and consistent with prior studies.[6,10] More important, RVMSP was more physiologic than RVAP, as determined by the significant reduction in the paced QRS duration and the improvement achieved in dyssynchrony parameters. A positive and statistically significant correlation was found between the paced QRS duration. And then, patients in the RVAP tended to have a lower LVEF than patients in the RVSP and control groups at the 12 months of follow-up. However, these beneficial features did not seem to correlate with a positive effect on clinical outcomes, at least during the first year after implantation.

Right ventricular apical pacing has traditionally been used because of the ease of implanted electrode fixation, a low rate of dislocation, and a steady threshold value. Previous studies have found that acute and long-term RVA pacing may result in ventricular dyssynchrony and deterioration of LV function, and LV dyssynchrony by RVA pacing is associated with worse long-term mortality and increased HF hospitalization rates.[11] In order to minimize the negative effects of RVA pacing, multiple small studies have analysed the benefit of pacing closer to the intrinsic conduction system. Victor *et al.*[12] confirmed the feasibility and safety of permanent RV septal pacing as a routine procedure associated with electrical resynchronization, manifested by a shorter QRS and normalized QRS axis; in contrast to RVAP, RVMSP preserved LVEF in patients with a baseline value of ≤45%, but did not improve LVEF in patients with baseline LVEF >45%. Yusu *et al.*[13] found that RVMSP was associated with comparable operation time, no lead dislodgement,

Table 3 Evolution of echocardiographic parameters during follow-up

	RVMSP ($n = 50$)			RVAP ($n = 46$)		
	Baseline	6 months follow-up	12 months follow-up	Baseline	6 months follow-up	12 months follow-up
LVEF (%)	60.2 ± 9.6	55.1 ± 10	61.1 ± 10	59.5 ± 7.0	56.2 ± 8	55.3 ± 11
LAD (cm)	3.3 ± 1.0	3.4 ± 0.5	3.3 ± 0.5	3.1 ± 1.1	3.4 ± 0.7	3.7 ± 0.6
LVEDD (cm)	4.5 ± 1.4	5.1 ± 0.9	4.7 ± 0.4	4.4 ± 1.6	5.0 ± 0.6	5.4 ± 1.2*
LVESD (cm)	3.0 ± 1.0	3.6 ± 0.9	3.2 ± 0.3	3.1 ± 1.1	3.3 ± 1.1	3.9 ± 1.1*
LVEDV (ml)	104.8 ± 47.4	129 ± 57	104.9 ± 19	102.2 ± 51.3	154 ± 33	152.6 ± 72*
LVESV (mL)	40.1 ± 23.3	59.5 ± 37	40.2 ± 8.6	39.0 ± 24.6	46.1 ± 22	72.3 ± 4.7*
Aortic VTI	20.8 ± 8.6	24.8 ± 6.4	25.0 ± 7.2	20.6 ± 9.6	23.3 ± 6.4	22.2 ± 4.1
APEI–PPEI	22.7 ± 19.7	30.2 ± 23.2	15.6 ± 13.6	18.4 ± 16.6	25.0 ± 13.0	39.7 ± 15.3*
SPWMD	66.0 ± 49.1	78.7 ± 40	82.1 ± 51	58.4 ± 56.8	73.3 ± 45	57.8 ± 42

LA, left atrium; LAD, Left atrial diameter; LVEF, left ventricular ejection fraction; LVEDD/V, left ventricular end-diastolic diameter/volume; LVESD/V, left ventricular end-systolic diameter/volume; Aortic VTI, the velocity time integral of the aortic valve orifice; APEI, pulmonary artery pre-ejection interval; PPEI, pulmonary artery pre-ejection interval; SPWMD, pulmonary artery pre-ejection interval. *$P < 0.05$ for comparison between RVAP and RVMSP groups.

Table 4 Evolution of clinical and biologic parameters during follow-up

	RVMSP group ($n = 50$)			RVAP group ($n = 46$)		
	Baseline	6 months follow-up	12 months follow-up	Baseline	6 months follow-up	12 months follow-up
NT-proBNP (pg/mL)	601 ± 1827	632 ± 1659	511 ± 1257	512 ± 1054	612 ± 1556	578 ± 1087
6MWT (m)	246.5 ± 185	424.5 ± 76	417.8 ± 121	235.7 ± 183	424.4 ± 95	426.1 ± 100
mlHFQ	29.9 ± 25	22.1 ± 21	20.3 ± 14	35.7 ± 26	18.1 ± 20	22.2 ± 11

6MWT, 6-min walking test; mlHFQ, Minnesota Living with Heart Failure Questionnaire.

and no change in the pacing threshold or lead impedance, as well as RVAP; they said that RVMSP might reflect a more physiological and synchronous form of ventricular activation. Our results are in concordance with the findings from that small series. Cano *et al.* [14] conducted a randomized, single-centre, single-blind, prospective study in which patients were randomly assigned to receive an active fixation lead either in the right ventricular apex or in the right ventricular mid-septum. They found that RVAP was associated with increased dyssynchrony compared with the RVMSP and control patients. In the present study, Doppler ultrasonic cardiography was repeatedly utilized, both before and after surgery, to measure the difference in pre-ejection time of both left and right ventricles, as well as SPWMD, in order to evaluate the de-synchronization of both left ventricular and interventricular movements. The results showed that RVMSP can reduce de-synchronization of interventricular and left ventricular movements.

Brain natriuretic peptide was chosen as a 100% investigator independent laboratory method recognized as a valid method to follow heart failure patients,[15] and 6-min walking test is a commonly accepted method to examine cardiac capacity and accurately reflects the work load a cardiac patient can endure. However, no significant differences in terms of NT-proBNP and 6WMT were found in our population sample, and no statistically significant difference in clinical outcomes was observed. This could be probably be explained by the clinical profile of our population sample, which included patients with structurally normal hearts and without any significant comorbidities. Probably, longer follow-up would increase the possibilities of finding clinical benefits.

The limitations of our study are as follows: the present study represents a single-centre experience, the sample size was relatively small, and follow-up was limited to 1 year. Only patients with normal LVEF and without structural heart diseases were included; therefore, it remains unclear whether the findings of this study are applicable to patients with underlying heart disease, LV dysfunction, or both. For these reasons our study was underpowered to show an advantage of mid-septal over apical pacing, but it is unlikely that increasing the sample size would have changed the results.

Conclusions

This study confirmed the reliability and safety of long-term RVMSP. Compared with RVAP, RVMSP was associated with decreased dyssynchrony and better LVEF. Right ventricular mid-septal pacing could represent an alternative pacing site in selected patients to reduce the harmful effects of traditional RVAP.

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Conflict of interest: None declared.

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