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Septal versus apical pacing sites in permanent right ventricular pacing: The multicentre prospective SEPTAL-PM study

Abbreviated title: RV apical versus septal pacing sites for atrioventricular block

Tweet: Apical pacing does not provide deleterious outcomes compared to septal pacing in AV block patients

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Summary

Background. – The optimal right ventricular pacing site for patients requiring pacemaker implantation for permanent atrioventricular block is a matter of debate. Long-term right ventricular apical pacing has been associated with left ventricular ejection fraction impairment and heart failure. Right ventricular septal pacing has been proposed as an alternative.

Aims. – The aim of this randomized prospective multicentre trial was to compare left ventricular remodelling and outcomes between right ventricular apical and septal pacing after mid-term follow-up.

Methods. – Patients requiring pacemaker implantation for high-degree atrioventricular block were enrolled and randomized in a 1:1 fashion to receive a right ventricular apical or septal lead.

Results. – A total of 141 patients were included, 69 in the septal group and 72 in the apical group. Both groups exhibited similar left ventricular ejection fractions after 18 months of follow-up (septal $57.1 \pm 11.9\%$ vs apical $57.4 \pm 13.4\%$), and left ventricular ejection fraction variation was similar in the two groups at the end of follow-up (septal $-1.5 \pm 13.2\%$ vs apical $0.3 \pm 13.3\%$). Additionally, left ventricular volume, quality of life and 6-minute walk distance were similar in the two groups. However, patients in the septal group were more likely to be asymptomatic, with a significantly lower concentration of N-terminal prohormone of brain natriuretic peptide. Lastly, lead position did not impact 18-month survival.

Conclusion. – Pacing from the right ventricular apex does not have any detrimental effect on left ventricular systolic function compared with septal pacing over an 18-month period.

KEYWORDS

High-degree atrioventricular block;

Long-term right ventricular pacing;

Right ventricular apical pacing;

Right ventricular septal pacing

Left ventricular ejection fraction

Abbreviations: LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA: New York Heart Association; RV, right ventricular; RVA, right ventricular apical; RVS, right ventricular septal.

Background

The rate of implantation of permanent pacemakers is increasing significantly each year, exceeding 1 million devices implanted in 2016 [1]. Because of the aging population, atrioventricular block is a common indication for permanent pacemaker implantation in current clinical practice [2]. Traditionally, the pacing lead is implanted in the right ventricular (RV) apex. However, studies have demonstrated that chronic RV apical (RVA) stimulation can deeply alter the physiological activation, contraction and relaxation of both ventricles [3, 4]. Additionally, RVA pacing may lead to left ventricular (LV) dysfunction, especially in patients with reduced LV ejection fraction (LVEF) at baseline [5-7]. Consequently, these data encourage the search for alternative pacing sites with less deleterious long-term RV consequences. Chronic RV septal (RVS) stimulation has been described as a potentially more physiological alternative, associated with better outcomes than RVA pacing [7-9]. However, only a single randomized study comparing RVA and RVS stimulation has been published thus far.

The aim of this prospective randomized multicentre study was to compare LV remodelling and outcomes between RVS and RVA pacing in patients requiring RV stimulation for high-degree atrioventricular block, over a follow-up time of 18 months.

Methods

Study design

The Comparison of SEPTal and Apical Pacing Sites in PerManent Right Ventricular Pacing (SEPTAL-PM; ClinicalTrial.gov identifier NCT00925691) study was a parallel randomized prospective multicentre study (including Angers, Brest, Nantes, Poitiers and Rennes University Hospitals). All patients aged > 18 years requiring pacemaker implantation for high-degree atrioventricular conduction disorders according to current European guidelines were enrolled [2]. Of note, patients in sinus rhythm or atrial fibrillation were included. Exclusion criteria were: patients requiring cardiac resynchronization therapy or implantable cardioverter defibrillator implantation or previously implanted with a pacemaker or implantable cardioverter defibrillator; those requiring atrioventricular node ablation for atrial fibrillation; history of myocardial infarction within the previous month or cardiac surgery/coronary revascularization planned/within the last 3 months; history of surgically treated valvulopathy or tricuspid valve prosthesis; life expectancy < 18 months; pregnancy; and the inability to give informed consent. The study was approved by the regional ethic committees, the French Advisory Committee

on the Treatment of Research Information in the Field of Health and the French National Commission of Informatics and Civil Liberties. All patients provided written informed consent.

Device implantation procedure and follow-up

In the apical group, the lead was implanted as far as possible into the RV apex. Conversely, in the septal group, the lead was inserted into the mid RV septum, delimited by two horizontal lines going through the floors of the pulmonary valve and the tricuspid valve, respectively. Leads assigned to the RV septum were considered optimally implanted when they were oriented frontally and towards the left in a 40–45° left anterior oblique fluoroscopic projection [10]. The pacemaker manufacturer was left to the physician's discretion.

After pacemaker implantation and before hospital discharge, an echocardiogram using contrast enhanced ultrasonography (Sonovue®; Bracco Imaging, Milan, Italy) was performed to accurately evaluate LVEF, LV end-diastolic volume and LV end-systolic volume. Additionally, N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) concentration was measured after pacemaker implantation. After hospital discharge, patients returned for regular clinical visits at 1, 6, 12 and 18 months. At each visit, New York Heart Association (NYHA) functional class, 6-minute walk distance, 12-lead electrocardiogram and device interrogation were assessed. Additionally, the SF-36 quality of life score was completed at 1 and 18 months. Lastly, at 18 months, a repeat echocardiogram using contrast enhanced ultrasonography was performed and NT-proBNP concentration was measured to assess the impact of RVA or RVS stimulation on LV function.

Study endpoints

The primary endpoint was the change in LVEF assessed by echocardiography from baseline (performed in the 2 days after pacemaker implantation) to 18-month follow-up in the apical and septal intention-to-treat groups. The secondary endpoints evaluated the long-term impact of RVA and RVS pacing on quality of life, heart failure clinical status and electrical/LV remodelling, using the SF-36 quality of life score, NYHA class, the 6-minute walk test, QRS duration, LV end-systolic volume, LV end-diastolic volume and NT-proBNP concentration. Results were analysed in the intention-to-treat population.

Statistical analysis

The number of patients was based on a 10% reduction in LVEF at 18-month follow-up in the apical group (with 90% power and 5% alpha risk), and a 5-point improvement in the SF-36 score at 18-month follow-up in the septal group (with 90% power and 5% alpha-risk). Data were analysed in the intention-to-treat population according to the randomized group. Descriptive statistics are expressed as mean \pm standard deviation or median (interquartile range) for continuous variables, and as frequency and percentage for nominal variables. Categorical variables were compared using the χ^2 test; continuous variables were compared using the *t* test or the Wilcoxon rank-sum test. Survival rates were summarized using Kaplan-Meier estimates, and log-rank tests were used to compare groups. A two-tailed *P* value of < 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS, version 22 (IBM, Armonk, NY, USA)

Results

Baseline characteristics

Among the 141 patients enrolled, 69 were included in the septal group and 72 in the apical group. Baseline clinical characteristics of the two groups are described in [Table 1](#). Notably, patients enrolled in the apical group were significantly older than those in the septal group, but no difference was observed regarding other clinical characteristics and cardiovascular risk factors. Regarding electrocardiography variables, most patients were in sinus rhythm at the time of implantation (septal 77.9% vs apical 75.7%) with similar QRS durations. However, although insignificant, a numerically higher rate of patients receiving an apical lead exhibited complete atrioventricular block compared with those enrolled in the septal group. Both groups were discharged from hospital with similar LVEFs (septal $57.8 \pm 10.5\%$ vs apical $57.4 \pm 12.3\%$; $P = 0.87$) and LV dimensions. Of note, some patients had altered LVEF at baseline, as 15 and 20 patients presented LVEF $< 50\%$ in the septal and apical groups, respectively. Lastly, a total of eight patients did not receive an adequate final lead position according to randomization: in the septal group, two patients received an apical lead, whereas in the apical group, the lead was implanted in a septal site in six patients as a result of suboptimal sensing and/or pacing threshold.

Follow-up and endpoints

Among the 141 patients enrolled in this study, a total of 57 and 60 recipients reached the 18-month follow-up in the septal and apical groups, respectively (Fig. 1). As illustrated in Fig. 2, both groups exhibited a similar RV pacing burden during the 18 months of follow-up (82% vs 92% in the septal and apical groups, respectively; $P = 0.07$).

Regarding the primary endpoint, the two groups exhibited similar LVEFs after 18 months of follow-up (septal $57.1 \pm 11.9\%$ vs apical $57.4 \pm 13.4\%$) and LVEF variation was similar in the two groups at the end of follow-up (septal $-1.5 \pm 13.2\%$ vs apical $0.3 \pm 13.3\%$). Importantly, LVEF was also evaluated according to the final lead position, and no difference was observed between patients with real septal and apical leads in the per-protocol analysis ($56.7 \pm 12.5\%$ vs $57.7 \pm 12.9\%$, respectively; $P = 0.65$). Additionally, as described in Table 2, LV end-systolic and end-diastolic dimensions were similar in the two groups. Notably, there was a trend toward shorter paced QRS duration in the septal group compared with the apical group (152 vs 163 ms; $P = 0.08$). Lastly, the 6-minute walk test distance, SF-36 quality of life and NYHA functional class were similar in the two groups, although a trend towards a higher proportion of asymptomatic patients was observed in the septal group. Indeed, 72% of patients in the septal group and 54% in the apical group were in NYHA class I. These data are supported by the significant lower NT-proBNP concentration among patients enrolled in the septal group compared with those in the apical group: 252 (113–699) pg/mL vs 554 (211–1802) pg/mL, respectively ($P = 0.032$). Importantly, both groups experienced similar survival (Fig. 3). During the study follow-up, 18 patients, (7 [10.1%] in the septal group and 11 [15.3%] in the apical group) required a total of 22 hospitalizations for heart failure during follow-up ($P = 0.51$), and a few patients required an upgrading procedure for LVEF impairment as a result of RV pacing (three and two in the septal and apical groups, respectively).

Discussion

Main results

Our study aimed to compare the mid-term impact of RVA and RVS pacing on LV function. The main results are as follows: (1) RVA stimulation did not have a deleterious effect on LVEF compared with RVS pacing after 18 months of follow-up, and LVEF did not change over time in either group; (2) quality of life and clinical status were similar in the two groups, despite that fact that patients who

received RVS lead implantation had a significantly lower NT-proBNP concentration after 18 months of follow-up.

Deleterious effects of RVA pacing

The potential deleterious effect of chronic RVA pacing was hypothesized in several studies published many years ago. Indeed, in a cohort of 12 pacemaker recipients with normal LV function, Nahlawi et al. observed that LVEF decreased from 60% to 53% after 1 week of RVA pacing [5]. Similarly, in a population of 43 patients with complete heart atrioventricular block receiving a permanent pacemaker, the authors showed that long-term RV apical pacing was associated with a high incidence of myocardial perfusion, leading to LVEF impairment [11]. Additionally, the deleterious impact of apical stimulation has been especially well established in patients with reduced LVEF at baseline. Indeed, in a randomized study enrolling 28 patients for permanent RVA or RVS stimulation after atrioventricular node ablation, apical stimulation was associated with a decrease in LV function among those with impaired LVEF at baseline (i.e. $\leq 45\%$), whereas septal pacing preserved LVEF after 3 months of follow-up. This result is supported by a recent meta-analysis demonstrating that in patients with reduced LVEF at baseline (i.e. $< 40\%$) and requiring chronic RV pacing, apical stimulation is associated with a higher deterioration in LV function compared with non-apical stimulation after 12 months of follow-up [12].

In our study, among a population of patients with preserved LVEF, we did not observe any change in LVEF between those receiving an apical or septal lead after 18 months of follow-up. Our work is supported by a recent study comparing the effect of long-term RV stimulation from the apex and the high septum in a cohort of 240 patients [13]. Among this population, a total of 168 patients reached 2-year follow-up, and had RV pacing percentages of 98% and 93% in the apical and septal groups, respectively. At 2 years of follow-up, LVEF decreased in both by 2% (from 57% to 55% and 56% to 54%), in the apical and septal group, respectively ($P < 0.05$) |Although the difference in both groups was statistically significant, we may have questions about the clinical relevance of the 2% decrease, especially with the limitation of the assessment of LVEF in this study, using conventional echocardiography without contrast. Similarly, in a smaller study with longer follow-up, Domenichini et al. noted that RV septal pacing did not confer any advantage in terms of LV function compared with the apex after 4 years of follow-up [14]. However, the authors highlighted that inadvertent implantation

of the RV lead in an anterior position instead of the septum results in a significant reduction of LV function.

Furthermore, we evaluated the impact of the lead position on clinical functional status, and observed a numerically higher (although not significant) proportion of asymptomatic patients in the septal group compared with the apical group (72% vs 54%; $P = 0.06$). These data are supported by the significantly lower concentration of NT-proBNP in the septal group at 18-month follow-up. Nonetheless, the higher NT-proBNP concentration in the apical group may be explained by advanced age, worse renal function and potentially more heart failure with preserved LVEF. Additionally, prescription of diuretics was not collected – a factor known to influence NT-proBNP concentration. Nonetheless, the lead position did not influence quality of life or effort capacities, as no difference was observed regarding the SF-36 score and the 6-minute walk test distance between the two groups. Similar results were found in the PROTECT-PACE study, with no statistical difference in the 6-minute walk distance [13].

Lastly, we observed that patients with an apical lead had a trend towards a larger paced QRS duration compared with those receiving a septal lead (163 vs 152 ms, respectively). Despite being non-significant, our result is consistent with a previous study that demonstrated a significant shortened QRS duration with mid-septal pacing compared with apical pacing (147 vs 154 ms, respectively) [15]. Additionally, authors observed that in comparison with septal stimulation, intra- and interventricular dyssynchrony were higher with apical pacing, leading to a decrease in LVEF. Similarly, another work confirmed these results in a larger population of 55 patients, and showed that after 4 years of follow-up, RVA pacing induced higher LV dyssynchrony, which was positively correlated to the percentage decrease in LVEF [16]. Lastly, septal RV pacing was evaluated in patients scheduled for cardiac resynchronization therapy implantation in the SEPTAL CRT study. Similar to the results we have reported, RVS pacing was not inferior to RVA pacing at 6-month follow-up, with no difference in clinical outcomes [10].

Study limitations

Despite the prospective and randomized design of our study, it has several limitations. The randomization was inhomogeneous between the two groups – in particular, a higher proportion of patients with third-degree atrioventricular block received an apical lead. This difference can probably

explain the disparity in the RV pacing rate at 18 months. Additionally, we did not show any deleterious impact of RVA stimulation, and it is possible that the 18-month study period was insufficient to show a significant change in LVEF. Indeed, previous works have suggested that a change in LVEF might occur after 12–18 months of apical stimulation [17, 18]. Another explanation is the lower number of patients included in both groups, preventing significant results from being reached. Additionally, we used echocardiography with contrast to assess LVEF and LV volumes, to minimize the variability of the echocardiogram, but other echocardiography variables that evaluate LV function (i.e. LV strain or ventricular filling pressures) would have been of interest in this study. Indeed, it is now well accepted that LVEF is not an optimal variable for assessing LV function and the impact of treatments. Global longitudinal strain could have been used, but this tool was not largely available when the first patients were included in the study, and we know that experience in using a tool can affect its relevance.

Conclusions

Pacing from the RV apex does not have any detrimental effect on LV systolic function compared with septal pacing over an 18-month period. However, the impact of RV lead position on LVEF needs to be further evaluated in younger patients requiring a permanent pacemaker and several decades of RV stimulation.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Figure legends

Figure 1. Study flow chart. AV: atrioventricular; LVEF: left ventricular ejection fraction.

Figure 2. Right ventricular pacing rate recorded at each clinical visit in the apical and septal group.

Figure 3. Survival curves for the apical and septal groups.

Table 1 Baseline characteristics for the septal and apical groups.

	Septal group (<i>n</i> = 69)	Apical group (<i>n</i> = 72)	<i>P</i>
Age (years)	75.9 ± 8.5	79.1 ± 8.9	0.033
Male sex	49 (76.0)	46 (63.9)	0.37
Body mass index (kg/m ²)	27.0 ± 3.7	27.2 ± 4.4	0.76
Hypertension	45 (66.2)	56 (77.8)	0.14
Diabetes mellitus	54 (78.3)	53 (73.6)	0.10
Dyslipidaemia	37 (55.2)	34 (47.9)	0.39
Renal dysfunction (eGFR < 60 mL/min)	3 (4.2)	9 (13.6)	0.05
History of cancer	9 (12.6)	16 (25.4)	0.05
Electrocardiogram			
Sinus rhythm	53 (77.9)	53 (75.7)	0.76
Atrioventricular block			0.08
Second degree, type 2	19 (27.5)	9 (12.5)	
Third degree	50 (72.5)	63 (87.5)	
Bundle branch block			
None	14 (22.2)	16 (26.7)	0.96
Right	30 (47.6)	29 (49.3)	0.90
Left	17 (27.0)	14 (23.3)	
Other	2 (3.2)	1 (1.7)	
Heart failure at diagnosis	20 (29.0)	20 (28.2)	0.99
Biology variables			
Serum potassium (mmol/L)	4.2 ± 0.4	4.2 ± 0.5	0.71
Serum creatinine (µmol/L)	105 ± 50	118 ± 49	0.11
NT-proBNP (pg/mL) (day 0 + 2)	416 (222–987)	1384 (532–2990)	0.15
Dual-chamber pacemaker implantation	65 (94.2)	66 (91.7)	0.80
Final RV lead position			
Non-septal position	2 (2.9)	–	NA

Non-apical position	–	6 (8.3)	
LVEF before hospital discharge (%)	57.8 ± 10.5	57.4 ± 12.3	0.87
LVEF ≤ 50% before hospital discharge	15 (21.7)	20 (27.8)	0.18
LVEDV before hospital discharge (mL)	91 ± 42	96 ± 34	0.48
LVEDS before hospital discharge (mL)	39 ± 22	44 ± 23	0.23
Mitral regurgitation	19 (28.8)	29 (43.3)	0.16

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range).

eGFR: estimated glomerular filtration rate; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NA: not applicable; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; RV: right ventricular.

Table 2 Secondary endpoints at 18-month follow-up.

	Septal group (<i>n</i> = 69)	Apical group (<i>n</i> = 72)	<i>P</i>
Quality of life (SF-36)			
Physical health score	40.85 ± 12.07	39.26 ± 10.38	0.45
Mental health score	48.95 ± 10.38	50.31 ± 10.74	0.44
NYHA functional class I/II/III (%)	72/25/3	54/32/14	0.05
6-minute walk test distance (m)	398 (340–630)	377 (291–452)	0.23
QRS duration (ms)	152 ± 28	163 ± 40	0.08
LVESV (mL)	45 ± 28	50 ± 33	0.38
LVEDV (mL)	103 ± 41	107 ± 44	0.57
NT-proBNP (pg/mL)	252 (113–699)	554 (211–1802)	0.032

Data are expressed as mean ± standard deviation or median (interquartile range), unless otherwise indicated. LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; NYHA: New York Heart Association.

Figure 1

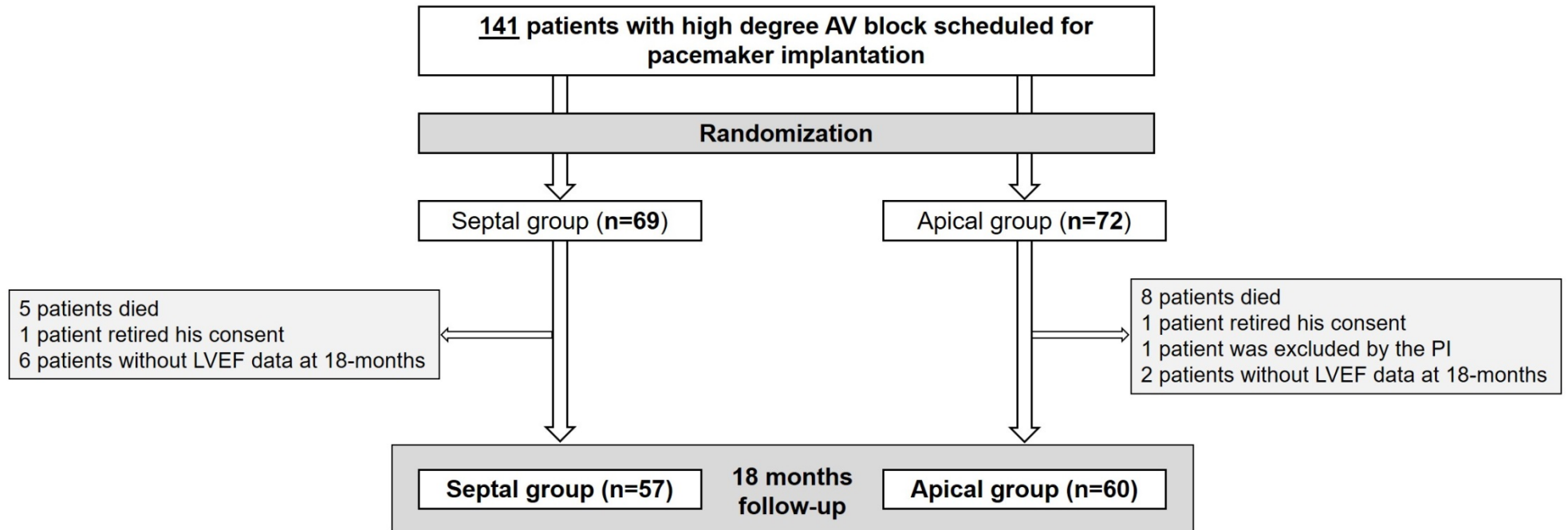


Figure 2

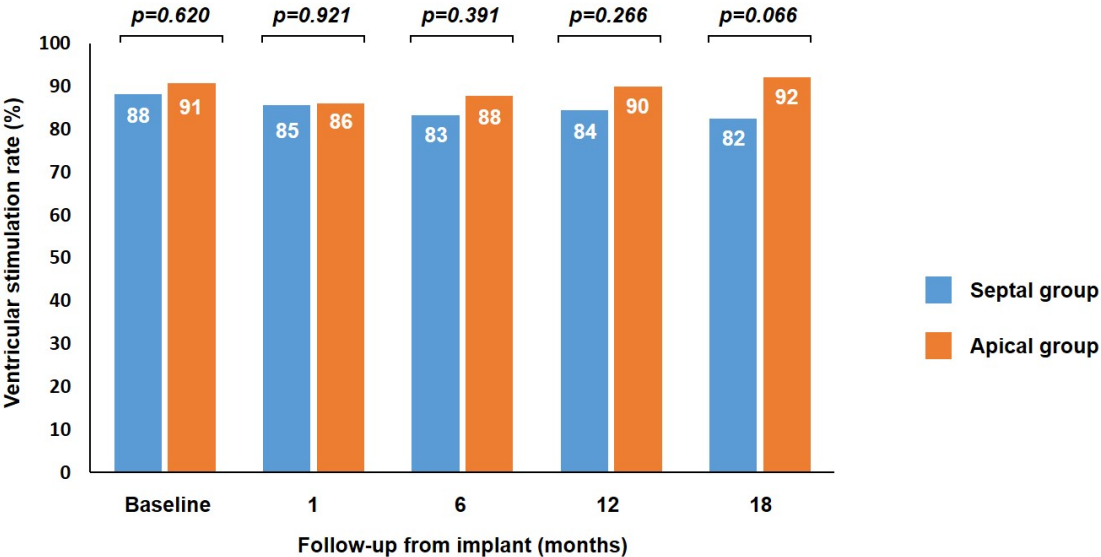
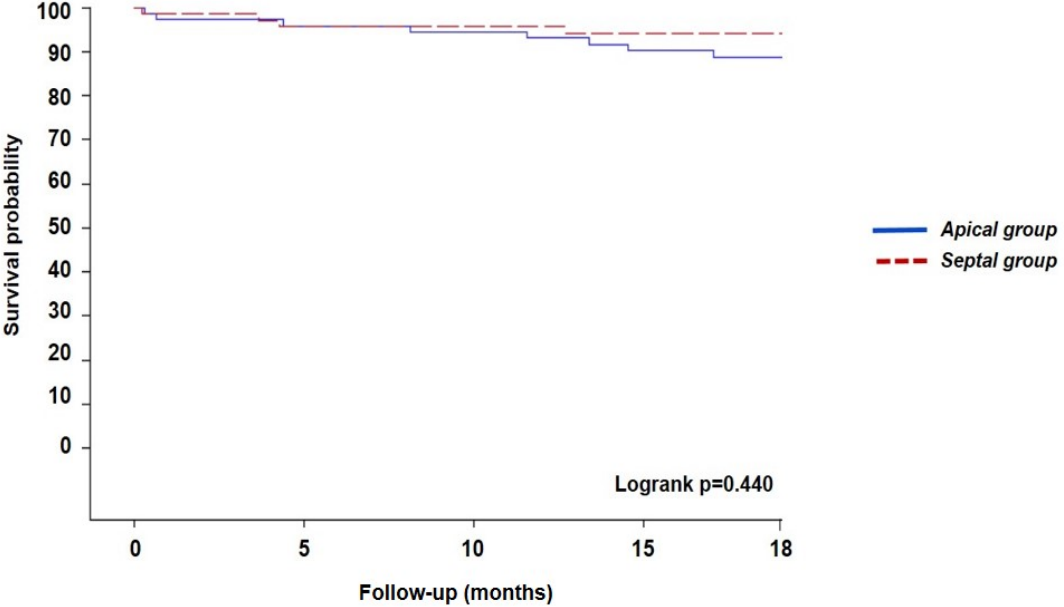


Figure 3



Number at risk					
	0	5	10	15	18
Apical group	72	69	68	63	60
Septal group	69	65	65	64	57