Comparison of right ventricular septal pacing and right ventricular apical pacing in patients receiving cardiac resynchronization therapy defibrillators: the SEPTAL CRT Study

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Aims	Cardiac resynchronization therapy (CRT) is a recommended treatment of heart failure (HF) patients with depressed left ventricular ejection fraction and wide QRS. The optimal right ventricular (RV) lead position being a matter of debate, we sought to examine whether RV septal (RVS) pacing was not inferior to RV apical (RVA) pacing on left ventricular reverse remodelling in patients receiving a CRT-defibrillator.
Methods and results	Patients ($n = 263$, age = 63.4 ± 9.5 years) were randomly assigned in a 1:1 ratio to RVS ($n = 131$) vs. RVA ($n = 132$) pacing. Left ventricular end-systolic volume (LVESV) reduction between baseline and 6 months was not different between the two groups (-25.3 ± 39.4 mL in RVS group vs. -29.3 ± 44.5 mL in RVA group, $P = 0.79$). Right ventricular septal pacing was not non-inferior (primary endpoint) to RVA pacing with regard to LVESV reduction (average difference = -4.06 mL; $P = 0.006$ with a -20 mL non-inferiority margin). The percentage of 'echo-responders' defined by LVESV reduction >15% between baseline and 6 months was similar in both groups (50%) with no difference in the time to first HF hospitalization or death ($P = 0.532$). Procedural or device-related serious adverse events occurred in 68 patients (RVS = 37) with no difference between the two groups ($P = 0.401$).
Conclusion	This study demonstrates that septal RV pacing in CRT is non-inferior to apical RV pacing for LV reverse remodelling at 6 months with no difference in the clinical outcome. No recommendation for optimal RV lead position can hence be drawn from this study.
ClinicalTrials. gov number	NCT 00833352.
Keywords	Cardiac resynchronization therapy • Right ventricular lead position • Right ventricular defibrillation lead • Left ventricular end-systolic volume

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Introduction

Cardiac resynchronization therapy (CRT) is a recommended therapeutic strategy in the treatment of patients with symptomatic heart failure (HF) and depressed left ventricular ejection fraction (LVEF) and wide QRS.[1] Cardiac resynchronization therapy is obtained by simultaneous or sequential pacing of the right and left ventricles. Despite such implantation is technically successful in >90% of patients;[2–4] clinical improvement or left ventricular (LV) reverse remodelling is achieved in no more than 2/3 of the patients. Several reasons may explain such incomplete response: sub-optimal patients selection,[1,4–8] inadequate LV lead position,[9–12] and sub-optimal programming.[13]

Whether the right ventricular (RV) lead position may improve the response to CRT is a matter of debate. Apical position is conventional, especially in patients receiving a CRT-defibrillator (CRT-D) but long-term RV apical pacing may adversely affect cardiac function in intracardiac cardioverter defibrillator (ICD) recipients.[14–16] Alternative RV pacing sites, mainly RV septal, have been recently proposed in CRT recipients. No significant benefit of these alternative RV pacing sites was demonstrated with the limitations of either retrospective analysis of large prospective trials,[11,12] prospective non-randomized trials,[10,17–21] or single-centre randomized study.[22] We hence conducted a prospective randomized European multicentre trial to examine the effects of the RV lead positions, i.e. apical or septal, on the LV reverse remodelling in patients receiving a CRT-D.

Study design and objectives

SEPTAL CRT is a randomized, controlled, single-blind, multicentre trial, including two parallel patient groups receiving a CRT-D randomly assigned to implantation of the ICD lead at the RV mid-septum (RVS) or at the RV apex (RVA). This study was approved by the Ethics Committee of Rennes University Hospital, France. All patients signed written, informed consent prior enrolment in the study. The study complied with the Declaration of Helsinki.

The primary objective was to demonstrate that RVS pacing was not inferior to RVA pacing in terms of changes in the left ventricular end-systolic volume (LVESV) between baseline and 6 months.

The main secondary objectives were:

(1) to assess the percentage of 'echo-responders' defined by a reduction in LVESV >15% at 6 months;
(2) to assess the implant success rate of the ICD lead using pre-specified electrical criteria;
(3) to compare the clinical outcome between the two groups using the 6 minutes' walk test (6 MWT) and the Milton Packer score;[23] and
(4) to assess the total mortality and HF hospitalizations at 12 months.

Patient selection

The patients included in this trial were ≥18 years of age and had indications for CRT-D implantation according to the 2008 European Society of Cardiology (ESC) guidelines,[24] i.e. patients with a documented LVEF (assessed by the implanting centre) ≤35% in the last 3 months, a New York Heart Association (NYHA) class III or ambulatory class IV stable for the last month prior enrolment receiving optimal medical therapy for at least 1 month, a QRS ≥120 ms with a stable sinus rhythm. The inclusion criteria were modified after the release of the ESC updated Guidelines 2010[25] with extension of the inclusion to NYHA class II patients with a QRS ≥150 ms.

Implantable cardioverter-defibrillator lead implantation

All patients received an ENDOTAK RELIANCE® G (Guidant/Boston Scientific, Natick, MA, USA) active fixation, single- or dual-coil ICD lead, implanted in the RVS vs. the RVA. Leads assigned to the RVS were considered optimally implanted when they were oriented frontally and towards the left in a 40–45° left anterior oblique fluoroscopic projection (*Figure 1A*). Leads assigned to the RVA group were advanced as far as possible towards the RV apex (*Figure 1B*).[26] After implantation, the location of RV leads was reviewed by two physicians, in a blinded manner.

Lead implantation was considered successful when the four following electrical endpoints were obtained: (i) R wave amplitude >5 mV, (ii) RV capture threshold <1.5 V/0.5 ms, (iii) pacing lead impedance between 450 and 1800 Ω at a 5 V, all measured with a pacing system analyser, and (iv) a 10 J safety margin for defibrillation threshold. If all these criteria were not obtained, a second attempt in an adjacent assigned position was performed. In case of subsequent failure, the lead was repositioned at the alternative site.

Left ventricular lead implant

Left ventricular lead was inserted in the coronary sinus. The lateral position was targeted first, then the posterolateral position, and finally the posterior position. In case of coronary sinus lead implant failure, an epicardial lead was surgically implanted (n = 6).

Echocardiographic methods

In each centre, echocardiographic recordings were performed by cardiologists certified for this study. The main following parameters were assessed:

– Left ventricular end-systolic and end-diastolic diameters (LVESD and LVEDD),
– Left ventricular end-systolic volume and LVEDVs,
– Left ventricular ejection fraction calculated by the Simpson method, and
– Left ventricular filling time.

Right and left pre-ejection delays and interventricular mechanical delay.

Left ventricular volumes were measured in the apical two and four chambers views and averaged. Left ventricular ejection fraction, left atrial area, and LV diameters were measured using standard methods. Echocardiograms were sent on digital storage media to an independent echocardiographic core laboratory (Genevieve

Figure 1 Right ventricular lead apical and septal locations.
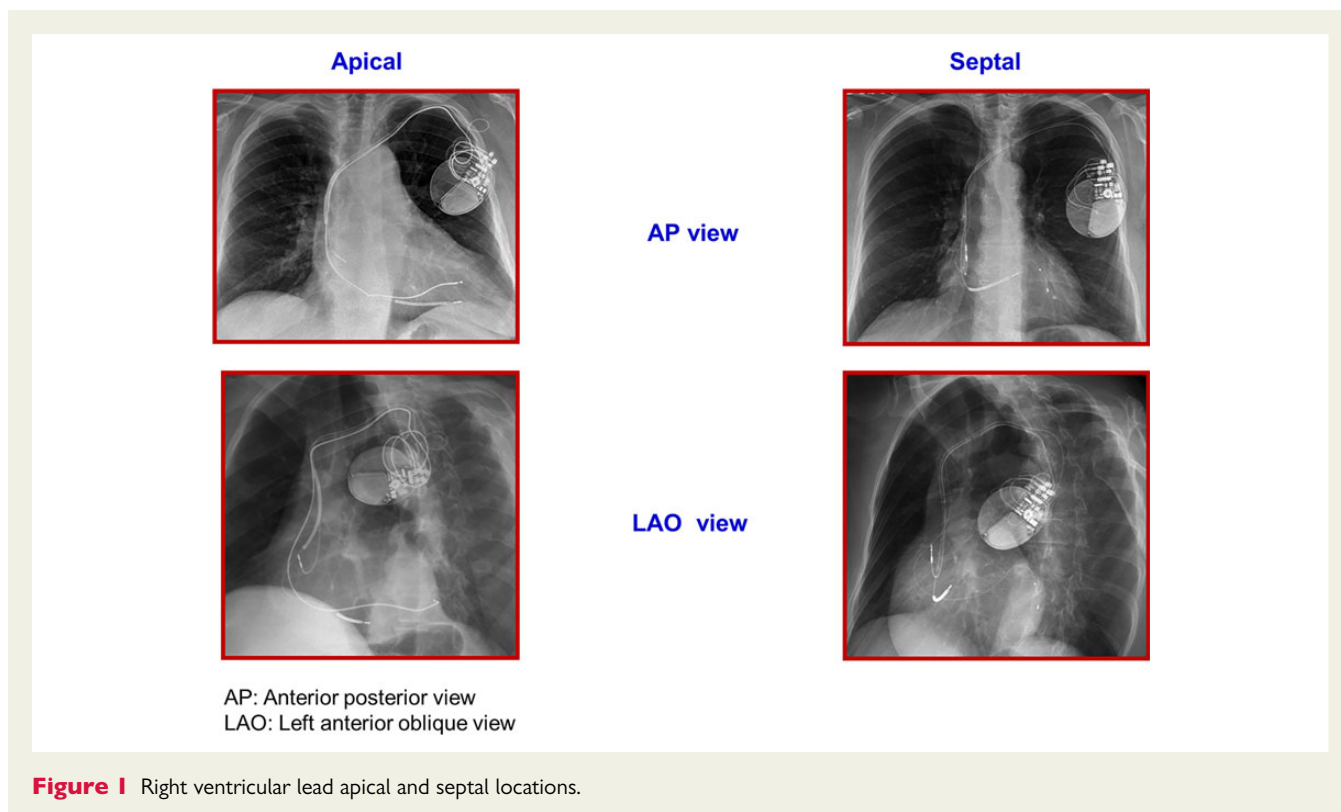
Derumeaux, University Hospital, Créteil, France), where they were screened for quality. All measurements were made at baseline and in patients with echocardiograms available at 6 and 12 months. Core laboratory intra- and inter-observer variabilities of echocardiographic parameters measurements have been reported earlier and were, respectively, 12 and 16% for LVESV.[27]

Baseline data, follow-up, and data collection

Device interrogation was performed at pre-discharge, at 1, 6, and 12 months. Following tachycardia parameters were recommended for ICD programming: ventricular fibrillation (VF) zone ≥220 b.p.m. and in case of a ventricular tachycardia (VT) zone, a minimum of six anti-tachycardia pacing attempts before shock delivery. Electrical lead characteristics as well as arrhythmic events were collected at each interrogation. AV delay optimization was performed before discharge using the iterative mitral flow method under echocardiography. New York Heart Association class was assessed at each follow-up by a physician blinded to the lead position. The 6 MWT and the Milton Packer test were performed at baseline, 6, and 12 months and assessed by a blinded observer.

Statistical analysis

The study planned to include 240 patients to prove the non-inferiority of RVS pacing in terms of LVESV reduction at 6 months with a 90% power at 2.5% unilateral significance level, and a rate of 33% of non-available assessments at 6 months. The intention to

treat (ITT) population included all randomized patients. Patients without at least one major deviation and with LVESV measurable at baseline represented the per protocol (PP) population.

The ITT population was analysed according to the randomized group while the PP population was analysed according to the implanted site. For both the ITT and PP populations, non-inferiority was analysed by examining the lower limit of the confidence interval of the difference in LVESV reduction between groups. If the lower limit was greater than the non-inferiority margin of −20 mL, the null hypothesis was rejected and the septal group was considered non-inferior with regard to the apical group. Superiority analysis was conducted if non-inferiority was achieved using bilateral t-test and analysis of variance adjusted on baseline value. The global alpha risk level was kept at 5%, according to the a priori ordered hypotheses theory. In addition, sensitivity analysis was performed by variance analysis, with the baseline LVESV value as adjustment factor.

Patients with a 6 months reduction >15% in LVESV were compared between groups using the χ^2 test. Other criteria were analysed in the ITT population by the use of descriptive statistics and univariate tests (χ^2 test or Fisher's exact test according to expected number in crossings for categorical variables, Kruskal−Wallis test for ordinal variables, and analyses of variance on ranked transformed variables for quantitative variables). Changes from baseline were tested by the use of the Wilcoxon sign-rank test. Time to appearance of adverse events was analysed by Kaplan−Meier estimates and comparison between groups was made using the log-rank test. As a conservative approach, the last observation carry forward method was used for echocardiographic data and 6 MWT.

All statistical analyses were performed using the SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 263 patients (72.6% male) were randomized to RVA ($n = 132$) or to RVS ($n = 131$) pacing in 25 centres, 16 in France and 9 in Spain (Appendix) and represent the ITT population. Crossover due to failure of fulfilling the RV implantation criteria in the randomized location was evenly distributed in both arms with two patients crossing over in each group. Two hundred and thirty-one patients reached the end of follow-up (death: $n = 9$, lost to follow-up:

$n = 10$, and premature exit: $n = 13$). The mean follow-up was 11.04 ± 3.3 months.

The PP analysis included 182 patients (RVA: $n = 92$) (*Figure 2*).

Patient's characteristics of ITT and PP populations are reported in *Tables 1* and *2* with no statistical difference between the the groups. Briefly, 72.6% were male, with approximately three of four of non-ischaemic cardiomyopathy and 88.5% were in NYHA class III. The mean age was 63.4 ± 9.5 years and the mean LVEF was $30 \pm 8\%$.

The targeted lateral or posterolateral LV lead positions were obtained in 89% of RVS randomized patients and in 91.3% of RVA randomized patients. In total, there was no statistical difference in LV position ($P = 0.147$) within the two groups. The number of
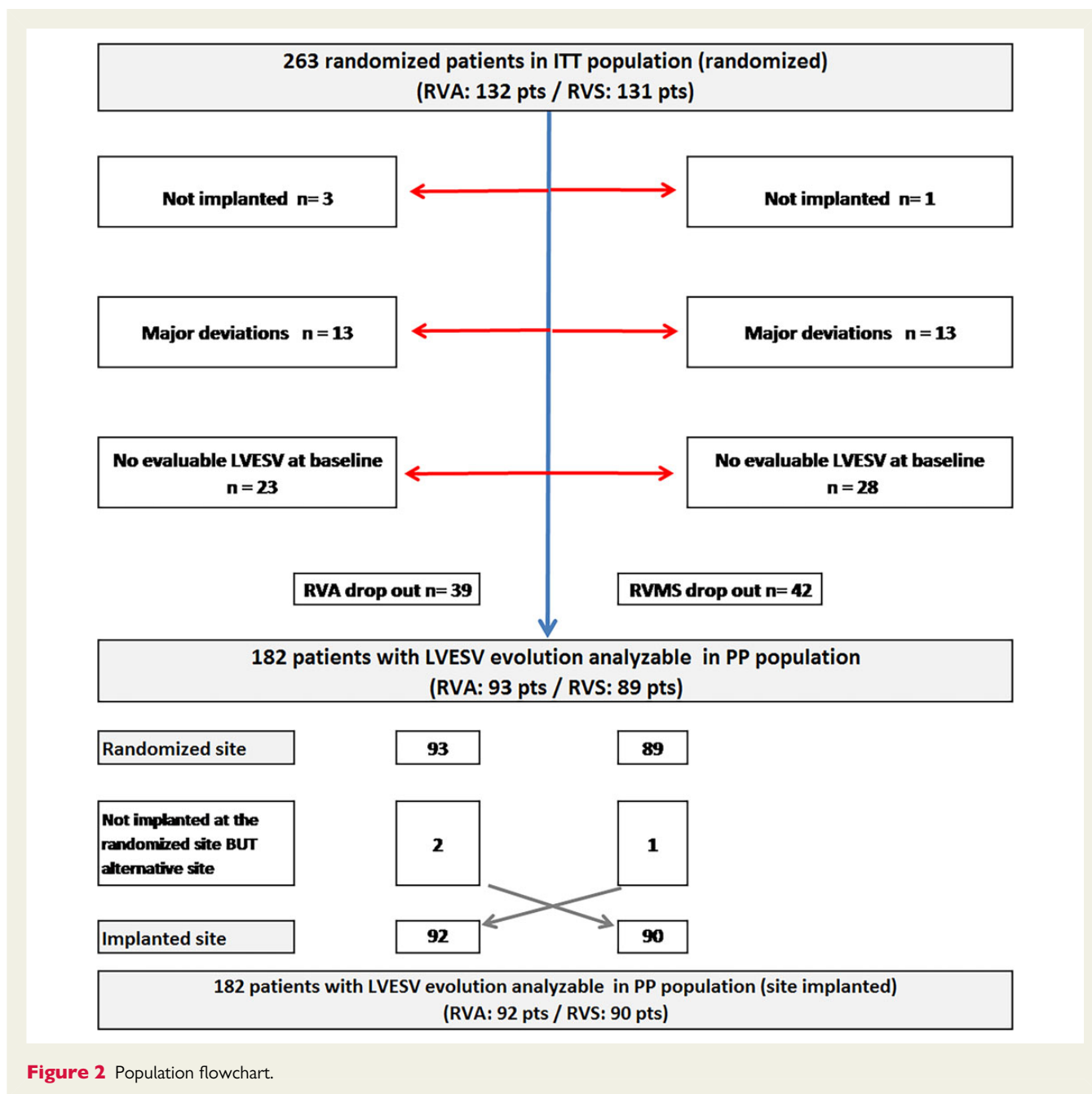

Figure 2 Population flowchart.

Table 1   **Baseline characteristics of the intention to treat population**

	RVA (132)	RVS (131)	*P*-value	Total (263)
Men (%)	74.2	71.0	0.582	72.6
Age (years)	63.8 ± 9.5	63.1 ± 9.4	0.583	63.4 ± 9.5
NYHA class II (%)	6.9	7.8	0.707	7.3
NYHA class III (%)	88.5	88.4		88.5
NYHA class IV ambulatory (%)	4.6	3.9		4.2
Ischaemic cardiomyopathy (%)	27.3	26.0	0.889	26.6
LVEF (%)	30.0 ± 7.7	29.6 ± 8.1	0.858	30 ± 8
LVESV (mL)	154 ± 72	157 ± 80	0.794	155 ± 76
Baseline medication (%)				
Diuretics (%)	83.3	86.3	0.607	84.8
ACE inhibitor or ARB (%)	93.4	95.6	0.591	94.5
Aldosterone antagonist (%)	33.3	37.4	0.521	35.4
Beta-blocker (%)	88.6	90.1	0.842	89.4
ICD indication for primary prevention (%)	98.5	97.7	0.684	98.1
QRS duration (ms)	161.2 ± 21.4	161.0 ± 22.9	0.703	161.1 ± 22.1
>150 ms (%)	70.1	65.4	0.502	67.7
LBBB (%)	81.6	80.2	0.856	80.9
Intrinsic QRS axis (°)	−11 ± 51	−12 ± 45	0.295	−12 ± 48
RV lead procedural data				
R wave (mV)	14.2 ± 6.9	13.8 ± 6.8	0.581	14.0 ± 6.8
RV pacing threshold (V/0.5 ms)	0.8 ± 0.3	0.7 ± 0.3	0.12	0.8 ± 0.3
RV lead impedance (Ω)	676.3 ± 146	761.5 ± 171.5	<0.001	718.1 ± 164.6
Paced QRS duration (ms)	140.0 ± 26.0	136.6 ± 25.7	0.201	132 ± 53
Paced QRS axis (°)	31 ± 136	62 ± 103	0.06	47 ± 121

Values are means ± SD, or % unless otherwise indicated. All between-groups differences are statistically non-significant except for RV lead impedance.
NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LBBB, left bundle block branch.

epicardial lead was evenly distributed in both groups (three in each group). Implant duration time was 118 ± 55 min in the septal group and 112 ± 47 min in the apex group (*P* = 0.464), and the fluoroscopic time was 24 ± 18 vs. 22 ± 19 min, respectively (*P* = 0.175).

Primary endpoint

There was no difference in the LVESV at baseline between the two groups in the PP population (157.8 ± 82.5 mL in the RVS group and 153.5 ± 72.3 mL in the RVA group, *P* = 0.73). The mean LVESV decreased to 132.5 ± 85.9 mL (*P* < 0.001) in the RVS group and to 124.2 ± 66.9 mL (*P* < 0.001) in the RVA group (*P* = 0.61 between the two groups) at 6 months. The reduction in LVESV was not different between the two groups (−25.3 ± 39.4 mL in the RVS group and −29.3 ± 44.5 mL in the RVA group, *P* = 0.79) (*Table 3*) with no further significant changes at 12 months (*Table 4*). The primary endpoint, i.e. non-inferiority of RVS vs. RVA pacing in the LVESV change between baseline and 6-month follow-up, was reached with the lower limit of the unilateral 97.5% confidence interval equal to − 16.36 mL within the −20 mL non-inferiority margin with a mean difference = −4.06 mL (*P* = 0.006 for non-inferiority). When adjusted on baseline LVESV value, the lower limit of 97.5% confidence

interval was −16.54 mL (the mean difference −4.72 mL, *P* = 0.006 for non-inferiority). In the ITT population, the reduction in LVESV between baseline and 6 months was not different between the two groups (−22.4 ± 37.3 mL in the RVS group and −29.1 ± 45.4 mL in the RVA group, *P* = 0.57). The lower bound of the confidence interval is −18.36 (*P* for non-inferiority = 0.013). The non-inferiority is also reached (−18.37 mL) after adjustment on the LVESV baseline value (*P* for non-inferiority = 0.013).

Secondary endpoints

The percentage of 'echo-responders' defined by a reduction in LVESV >15% at 6 months was not different (50% in both groups) (*P* = 1.000) in the PP population. Subgroup analysis revealed that none of the following parameters [i.e. age, sex, NYHA class, cardiomyopathy aetiology, intrinsic or paced QRS width or pattern (left bundle block branch (LBBB) or non-LBBB), LVEF, LV volumes] were associated with a further LVESV reduction. None of the studied parameters could predict whether one RV lead position was superior to the other. The implant success rate based on pre-specified RV lead electrical criteria was not inferior in the RVS group when compared with the RVA group (90.0% in RVS vs. 86.8% in RVA;

Table 2 Baseline characteristics of the per protocol population (site implanted)

	RVA (92)	RVS (90)	*P*-value	Total (182)
Men (%)	73.9	71.1	0.741	72.5
Age (years)	64.1 ± 9.7	62.5 ± 9.8	0.300	63.3 ± 9.8
NYHA class II (%)	5.4	10.1	0.376	7.7
NYHA class III (%)	90.2	85.4		87.8
NYHA class IV ambulatory (%)	4.3	4.5		4.4
Ischaemic cardiomyopathy (%)	27.2	25.6	0.867	26.4
LVEF (%)	29.9 ± 7.7	29.7 ± 8.2	0.940	30 ± 8
LVESV (mL)	154 ± 72	158 ± 83	0.734	156 ± 77
Baseline medication				
Diuretics (%)	83.7	86.7	0.678	85.2
ACE inhibitor or ARB (%)	93.7	95.7	0.747	94.7
Aldosterone antagonist (%)	38.0	40.0	0.879	39.0
Beta-blocker (%)	90.2	91.1	1.000	90.7
ICD indication for primary prevention (%)	98.9	97.8	0.619	98.4
QRS duration (ms)	160.1 ± 21.4	159.2 ± 23.0	0.730	159.6 ± 22.1
>150 ms (%)	70.8	62.5	0.267	66.7
LBBB (%)	85.7	81.8	0.643	83.8
Intrinsic QRS axis (°)	−12 ± 53	−12 ± 46	0.8	−12 ± 49
RV lead procedural data				
R wave (mV)	14.1 ± 6.9	12.9 ± 6.5	0.256	13.5 ± 6.7
RV pacing threshold (V/0.5 ms)	0.8 ± 0.3	0.7 ± 0.3	0.035	0.8 ± 0.3
RV lead impedance (Ω)	761 ± 175	682.4 ± 165	<0.001	721.7 ± 174
Paced QRS duration (ms)	140.0 ± 26.0	136.6 ± 25.7	0.201	138.3 ± 25.9
Paced QRS axis (°)	31 ± 136	56 ± 108	0.16	44 ± 123

Values are means ± SD, or % unless otherwise indicated. All between-groups differences are statistically non-significant except for RV lead impedance.
NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LBBB, left bundle block branch.

lower limit of 97.5% confidence interval = −3.36% > −9% threshold). This relative low percentage of fulfilled electrical criteria requirement was mainly due to the non-completion of the defibrillation test (DFT) (*n* = 27) that was mandatory in the study, but not performed by the investigator due to poor haemodynamic status in most cases. Excluding DFT non-completion, the total implant success rate was 99%, with no difference in the two groups. The RV lead procedural data are displayed in *Tables 1* and *2*. There was no significant change in RV lead characteristics (R wave amplitude, RV pacing threshold and impedance) throughout the follow-up. Procedural or device-related serious adverse events (SAEs) occurred in 68 patients (RVS, *n* = 37) with no difference between the two groups (*P* = 0.401). These SAEs were mainly related to the LV lead (*n* = 30, septal: *n* = 15). The most common LV lead-related SAE was the loss of LV capture (*n* = 16, septal = 9) requiring seven LV lead replacements, septal = 5), eight LV lead repositioning (septal = 4), and one reprogramming (apex). Right ventricular lead SAE occurred in seven patients, three in the septal group and in four in the apical group (*P* = 1.000).

At baseline, 6 MWT was similar between the two groups (356 ± 113 vs. 352 ± 115 m, RVS vs. RVA, *P* = 0.750) with a significant increase between baseline and 6 months in both groups (+28 ± 85 m, *P* < 0.0001) with no difference between the two groups (*P* = 0.648).

Although not significant (*P* = 0.056), there was a trend towards a higher percentage of improved patients according to the Milton Packer score in the RVS group (85%) vs. the RVA group (76%).[24]

Nine patients died during the study, five in the RVS group and four in the RVA group (*P* = 0.749) (*Table 5*). The time to first HF hospitalization or death was not different between the two groups (*P* = 0.532) (*Figure 3*).

Discussion

This study demonstrates that RVS pacing in CRT is not inferior to RVA pacing for LV reverse remodelling with a similar reduction in the LVESV at 6 months. There was also no difference in the clinical outcome with an identical benefit in terms of 6 MWT and Milton Packer composite score. Finally, the composite endpoint including the time to first hospitalization for HF and total mortality was similar

Table 3 Echocardiographic measures—changes from baseline to 6 months—per protocol population

	RVA (n = 92)			RVS (n = 90)			P-value
	Baseline	6 Months	Change	Baseline	6 Months	Change	
LVESV (mL)							
Mean ± SD	153.5 ± 72.3	124.2 ± 66.9	−29.3 ± 44.5	157.8 ± 82.5	132.5 ± 85.9	−25.3 ± 39.4	0.788
Median	134.0	115.0	−20.0	141.5	110.0	−19.5	
Q1; Q3	105.5; 182.5	78.0; 154.0	−47.5; 0.0	106.0; 191.0	84.0; 163.0	−50.0; 0.0	
LVESD (mm)							
Mean ± SD	62.0 ± 11	58.6 ± 13.4	−3.4 ± 7.6	64.8 ± 11.8	61.4 ± 13	−3.5 ± 7.2	0.681
Median	60.0	56.5	0.0	63.5	61.0	−1.0	
Q1; Q3	55.0; 70.0	50.0; 70.0	−6.0; 0.0	56.5; 71.0	52.0; 69.0	−6.0; 0.0	
LVEDV (mL)							
Mean ± SD	215.2 ± 84	189.7 ± 77.1	−25.5 ± 47	220.6 ± 93.8	195.3 ± 95.8	−25.3 ± 47.7	0.959
Median	198.5	178.0	−19.5	209.0	177.5	−18.0	
Q1; Q3	159.5; 247.0	134.0; 229.0	−46.5; 0.0	156.0; 262.0	139.0; 227.0	−48.0; 0.0	
LVEDD (mm)							
Mean ± SD	72.2 ± 11.3	69.3 ± 12.8	−2.9 ± 6.9	74.1 ± 11.4	71.6 ± 11.9	−2.5 ± 7.4	0.925
Median	71.0	68.0	0.00	74.0	70.0	0.0	
Q1; Q3	66.0; 77.0	61.0; 77.0	−8.0; 0.0	65.5; 81.0	64.0; 78.0	−5.0; 0.0	
LVEF (%)							
Mean ± SD	30.0 ± 7.7	35.9 ± 10.2	6.0 ± 8.7	29.7 ± 8.2	35.5 ± 9.9	5.8 ± 9.1	0.770
Median	30.0	36.0	3.0	30.0	36.0	4.0	
Q1; Q3	26.0; 34.0	29.0; 42.0	0.0; 10.0	25.0; 35.0	28.0; 41.0	0.0; 10.0	
LV filling time (ms)							
Mean ± SD	383.9 ± 122.6	431.8 ± 127	48 ± 120	377.5 ± 155.4	431.2 ± 143.8	53.8 ± 133.7	0.353
Median	381.0	435.0	29.0	365.5	414.0	50.0	
Q1; Q3	284.0; 452.0	341.0; 525.0	0.0; 97.0	275.5; 440.0	324.0; 512.0	0.0; 125.5	

LVESV, left ventricular end-systolic volume; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

in both groups. Implantation success and complication rates were similar for both positions.

Cardiac resynchronization therapy is a widely accepted therapy for patients with LV systolic dysfunction and wide QRS complex.[1] Clinical success and/or reverse LV remodelling can however only be achieved in 50–65% of patients. Among the potential solutions to increase this response rate, the optimal location of the RV lead remains a matter of debate. Apical RV lead position is conventional especially in patients receiving a CRT-D but there are convincing data on the harmful effects of long-term RV apical pacing.[14,16]

Several studies assessed the potential benefit of RVS pacing in patients with conventional PM indications, irrespective of LV function.[1] The results of these studies are not uniform but there is a trend towards a beneficial effect of septal pacing. For example, de Cock et al.[28] reported the haemodynamic effects of RV outflow tract pacing (septal pacing) in 217 patients included in 9 studies and found a significantly better haemodynamic effect (odds ratio 0.34, confidence interval 0.15, 0.53) of septal pacing compared with conventional RV pacing.

The feasibility and safety of septal ICD lead positioning have only been recently demonstrated in non-CRT patients. In a prospective study including 215 patients with ICD lead randomized to septal position or to apical position, Mabo et al.[26] reported an identical implant success rate, based on strict electrical predefined criteria, in both groups (89.7% in the RVS group vs. 91.7% in the RVA group, P = 0.65) with no difference in the defibrillation success rate. In a similar non-CRT population, Kolb et al.,[29] however, reported a tendency towards a higher defibrillation threshold in the mid-septal group. Our study confirms the feasibility of septal ICD RV lead implantation in a CRT population. Although non-significant, there was, however, a trend towards a prolongation in the total implant duration and fluoroscopic time in the septal group.

In CRT recipients, the results of alternative RV pacing sites, mainly septal, have recently been reported but the potential effects of the RV lead position are derived from *post hoc* analysis of large trials.[12,30] Thebault et al.[12] analysed the influence of RV and LV lead positions. A more favourable CRT outcome with regard to LV reverse remodelling and the composite of time to death or first HF hospitalization

Table 4 Echocardiographic measures—change from baseline to 12 months—per protocol population

	RVA (n = 92)			RVS (n = 90)			P-value
	Baseline	12 Months	Change	Baseline	12 Months	Change	
LVESV (mL)							
Mean ± SD	153.5 ± 72.3	114.98 ± 67.79	−38.55 ± 50.92	157.8 ± 82.5	125.77 ± 88.63	−32.0 ± 43.21	0.472
Median	134.0	104.0	−32.0	141.5	105.5	−24.5	
Q1; Q3	105.5; 182.5	68.0; 139.5	−60.5; −2.0	106.0; 191.0	76.0; 144.0	−58.0; 0.0	
LVESD (mm)							
Mean ± SD	62.0 ± 11	56.70 ± 14.16	−5.26 ± 8.33	64.8 ± 11.8	58.72 ± 12.91	−6.11 ± 8.36	0.645
Median	60.0	55.5	−2.5	63.5	57.0	−4.0	
Q1; Q3	55.0; 70.0	48.0; 67.0	−10.0; 0.0	56.5; 71.0	50.0; 67.5	−11.0; 0.0	
LVEDV (mL)							
Mean ± SD	215.2 ± 84	178.08 ± 80.6	−37.16 ± 55.87	220.6 ± 93.8	188.01 ± 99.03	−32.63 ± 53.68	0.419
Median	198.5	168.0	−34.0	209.0	166.0	−21.0	
Q1; Q3	159.5; 247.0	123.0; 211.0	−62.0; 0.0	156.0; 262.0	129.0; 215.0	−64.0; 4.0	
LVEDD (mm)							
Mean ± SD	72.2 ± 11.3	68.93 ± 13.27	−3.28 ± 6.59	74.1 ± 11.4	69.56 ± 12.34	−4.55 ± 7.39	0.515
Median	71.0	67.0	−1.0	74.0	68.0	−3.0	
Q1; Q3	66.0; 77.0	60.0; 76.0	−9.0; 0.0	65.5; 81.0	60.0; 76.0	−9.0; 0.0	
LVEF (%)							
Mean ± SD	30.0 ± 7.7	38.15 ± 11.44	8.21 ± 10.04	29.7 ± 8.2	36.49 ± 10.32	6.78 ± 9.67	0.722
Median	30.0	39.0	7.0	30.0	36.5	7.5	
Q1; Q3	26.0; 34.0	30.0; 44.0	0.0; 13.5	25.0; 35.0	30.0; 42.0	0.0; 14.0	
LV filling time (ms)							
Mean ± SD	383.9 ± 122.6	442.38 ± 130.47	58.52 ± 110.94	377.5 ± 155.4	418.61 ± 124.37	41.16 ± 152.75	0.966
Median	381.0	433.0	39.0	365.50	416.00	55.0	
Q1; Q3	284.0; 452.0	358.0; 536.0	−10.0; 122.0	275.5; 440.0	338.0; 492.0	−11.5; 129.0	

LVESV, left ventricular end-systolic volume; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

was observed when the LV lead was implanted in the lateral wall, away from the LV apex while no difference was observed between RV apical (n = 237) and RV non-apical (n = 108) lead position. Kutyifa et al.[30] retrospectively analysed the influence of the RV lead position on the clinical outcome in 742 of the 1089 CRT patients (68%) included in the MADIT-CRT trial. Right ventricular lead position was classified as apical (n = 656) or non-apical (n = 86). There was no difference in the primary endpoint (HF or death) in patients with non-apical vs. patients with apical RV lead location (P = 0.983). However, a higher risk of VT/VF death (HR 2.45, P = 0.003) and VT/VF alone (HR 2.52, P = 0.002) predominantly in the first year after device implantation was reported with the non-apical lead position. Similar results with no difference between the two RV lead positions were also reported in small prospective non-randomized trials.[10,17–21] Kristiansen et al.[22] compared two RV lead locations in a prospective single-centre study. They included 85 consecutive CRT patients randomized to RV apex (n = 43) or high posterior septal (n = 42). They found no difference in terms of LV reverse remodelling at 6 months with a similar proportion of patients with a >15% reduction in LVESV in the RV high posterior septal group

(n = 25, 64%) and in the RV apex group (n = 26, 65%) (P = 0.93). The results of the SEPTAL CRT study which included a larger population in a multicentre trial confirm these preliminary results. In other terms, from this study, it appears that in a general population, RV lead position does not appear to be of major importance. The implanting physician should thus implant the lead in the RV position he is the most familiar with. However, rather than an empiric predetermined (septal or apical) RV location, it could be hypothesized that the optimal RV lead location may also be tailored according to the LV position. Indeed, Merchant et al.[31] found a significant correlation between LV–RV interlead distance and LV lead electrical delay with both parameters acting synergistically in predicting LV anatomic reverse remodelling. Miranda et al.[32] prospectively assessed the influence of the RV lead in 50 patients randomized to apical or septal position, on the maximal electrical separation (MES) between the LV and RV leads. Interestingly, MES, commonly associated with a better clinical outcome, was significantly greater in the mid-septum (161 ± 23 ms) when compared with the apex (146 ± 26 ms) (P < 0.001), suggesting the potential favourable effects of chronic septal pacing in CRT recipients. Efforts to optimize
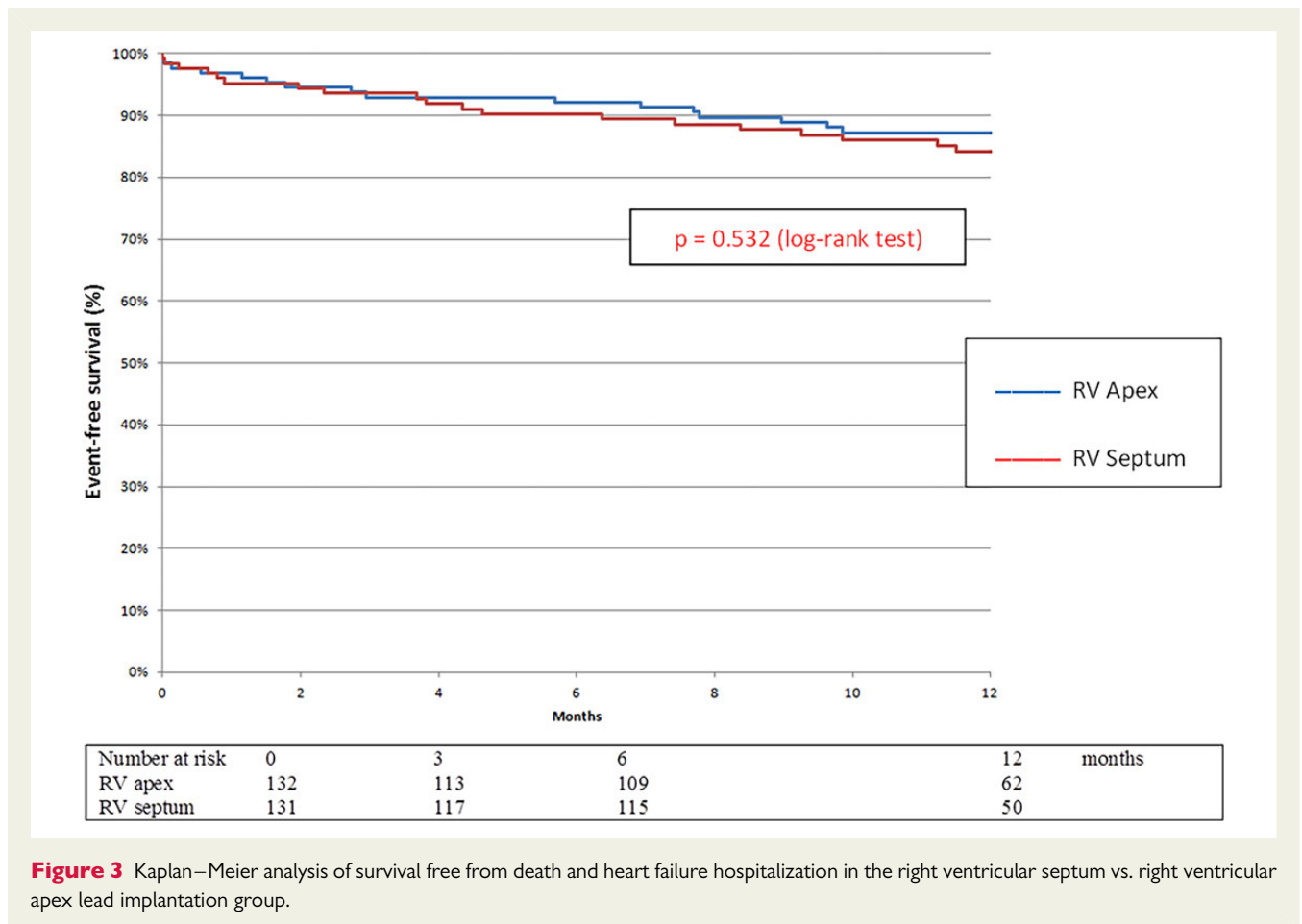
Figure 3 Kaplan−Meier analysis of survival free from death and heart failure hospitalization in the right ventricular septum vs. right ventricular apex lead implantation group.

both interlead distance and electrical delay may improve CRT outcomes.

Limitations

The SEPTAL CRT study has some limitations:

− There is a substantial amount of echocardiographic missing data, leading to incomplete results, especially for the primary endpoint. This underlines the difficulties of echo recordings and the feasibility of echo in CRT trials due to technical limitations. On the other hand, the results are strengthened by a core laboratory analysis, and a conservative method was used for the analysis with the Last Carry Forward Value method.
− The determination of the anatomical distance and electrical delay between the LV and the RV leads and their potential influences on the change in the LVESV were not prospectively assessed in the present study.

Conclusion

This study demonstrates that septal RV pacing in CRT is non-inferior to apical RV pacing for LV reverse remodelling at 6 months, with no difference in the clinical outcome. No recommendation for optimal RV lead position can hence be drawn from this study. Further prospective information about the anatomical and electrical

relationships between RV and LV lead positions may be one of the next steps in the CRT research agenda.

Appendix

The following institutions and investigators participated in the SEPTAL trial

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