

# Right ventricular septal or apical? which is optimal positioning in pacemaker implantation: A systematic review and meta-analysis

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## Abstract

**Aims:** Right ventricular (RV) apical pacing (RVAP) has been the preferred pacing site for decades but recent evidence suggests chronic RVAP can deteriorate cardiac function. RV septal pacing (RVSP) has emerged as an alternative site but its benefits over RVAP remain unclear. This meta-analysis aims to compare the effect of RVSP and RVAP on cardiac function.

**Methods:** PubMed, EMBASE, and Cochrane were systematically searched for studies examining RVSP and RVAP. The inclusion criteria was randomized clinical trials comparing the effect of RVAP and RVSP on cardiac function and structure at follow-up. Data was pooled using random effects model.

**Results:** Twenty-five studies (N=2,315 patients) randomized into RVAP (n=1,028) and RVSP (n=1,287) were included in this meta-analysis. Pooled data across the studies showed RVSP patients achieved significantly higher mean gain in LVEF at the end of follow-up (standardized mean difference: SMD, 0.394, 95% CI: 0.715-0.073), a narrower QRS duration (SMD, -1.172, 95% CI: 0.672-1.672) and lower levels of serum B-type natriuretic peptide (BNP) (SMD, 0.328, 95% CI: 0.039-0.617, p=0.02). Although RVSP showed a positive trend towards protecting against both LV dyssynchrony and remodelling as well as having better lead performance (R-wave, pacing threshold and impedance), the difference was not significant (p>0.01).

**Conclusion:** In patients with significantly impaired LV systolic function who are eligible for RV pacing, RVSP may improve their LV function and lower serum BNP levels but may not protect them against ventricular dyssynchrony and remodeling.

## Introduction

Pacemaker or artificial endocardial pacing is a well-established treatment for multiple symptomatic bradyarrhythmias arising from an impairment in the heart's electrical conduction system usually secondary to chronic atrioventricular block or sinus node dysfunction [1]. For close to five decades, the right ventricular apical pacing (RVAP) has remained the mainstay of pacemaker implantation due to technical ease of transvenous lead placement, electrode stability and treatment efficacy [2-4]. Clinical data in the past five decades also suggest chronic RVAP improves quality of life and life expectancy [5,6]. However, in some patients, chronic RVAP has been associated with intra- and inter-ventricular dyssynchrony [6] resulting in negative hemodynamic changes such as decreased cardiac output, increased myocardial workload and oxygen consumption, and altered neuro-hormonal and electrophysiological activities [3,5]. These hemodynamic changes can lead to the development of LV dysfunction, atrial fibrillation and heart failure [6].

Several non-apical positions have already been investigated including RV outflow tract (RVOT) in the septal region, septum, HIS-bundle and pulmonary infundibulum [3,4]. Of these, RVOT and RV septum are the most attractive options because of the relative technical ease of transvenous lead placement and electrode stability [6]. Experimental data supports RVSP but individual clinical trials provide inconsistent findings, and consequently, RVSP superiority to RVAP with regard to clinical outcomes, cardiac function and hemodynamic stability remains unclear [6-9]. Findings from previous four meta-

analyses have also not firmly established beneficial outcomes of RVSP over RVAP [10-13]. They suggest that RVSP has a favourable effect on hemodynamic and on preserving LV systolic function for acute period (short-term) [10-12] or up to two years [13] but some of the studies reported wide confidence interval (CI) levels because of a large heterogeneity in the criteria of patient selection in individual studies [10-12]. Since then, additional clinical trials [3,4,6,7,14,15] examining other clinically relevant end-points with longer follow-up have accrued. The present meta-analysis seeks to extend the four previous meta-analysis by comparing their effect of RVAP and RVSP on LV systolic function (LVEF) and remodelling (LV volumes), LV systolic synchrony (Ts-SD) and long-term lead performance (R-wave sensing, stimulation threshold, and impedance).

## Methods

### Search strategy

We systematically searched PubMed, EMBASE, and Cochrane Central Register of Controlled Trials) from inception to October 2018

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for RCTs comparing the effect of RVSP and RVAP on cardiac function and on lead performance after pacing. The search strategy included the following search terms: “cardiac pacing” OR “endocardial pacing” OR “pacing site” OR “pacemaker implantation” AND “heart ventricles” OR “ventricular” AND “controlled trials” OR “clinical trials”. We identified additional studies through a manual search of references of the included studies and review of included articles.

### Inclusion criteria

The criteria for inclusion was as follows: the study (a) randomized subjects to either RVSP or RVAP; (b) compared RVSP and RVAP at baseline and after pacing; (c) reported cardiac functional outcomes, dyssynchrony and lead performance for both RVSP and RVAP; (c) provided data in an extractable form; and (d) followed patients for a period at least two months. Studies were excluded if they examined animal models, were conference papers, and were available only in abstract form. Finally, there was no restriction on publication language or publication period.

### Data extraction

Two reviewers sequentially and independently screened each study against the inclusion criteria and subsequently collated data from all the included studies. Results from the two independent reviewers were then compared and any discrepancy resolved through discussion and consensus. Extracted data from each study was then summarized in a Microsoft Excel spreadsheet. The extracted data included first author, publication year, number of patients in RVSP and RVAP, follow-up period, common clinical or functional outcomes assessed and remarks on the optimal pacing site between RVSP or RVAP. If a study assessed more than one outcomes, each of the outcome was analysed independently.

### Quality assessment

A modified version of the Oxford quality scoring system (Jadad scale) [16] was used to assess the quality of the included studies. The scoring system controls bias in three main research aspects: study design, subject recruitment or withdrawal and statistical analysis. Scoring involved responding 11 questions. The scoring system assigns two points first two questions and one point each for the remaining eight questions for a total score of 13 points. The 11 questions are as follows. (i) Was the study described as randomized? (ii) Was there concealment of randomisation? (iii) Was there a description of withdrawals and dropouts? (iv) Were study objective defined? (v) Were outcomes measured and define clearly? (vi) Was there a clear description of inclusion and exclusion criteria? (vii) Was the patient sample justified? (viii) Was there a clear description of interventions used? (ix) Was there a control group? (x) Were methods assessing adverse effects clearly described? (xi) Were statistical methods clearly described and justified?

### Statistical analysis

Continuous data was expressed as mean and standard deviation (SD) while categorical data was expressed as frequencies and percentages. Comprehensive meta-analysis software was used to pool dichotomous data across studies and outcomes were treated as standardized mean difference (SMD) with corresponding 95% confidence interval (CI). The degree of heterogeneity across studies was calculated using the  $I^2$  statistic and a random model effect was used when  $I^2 > 50\%$  and a fixed model when  $I^2 < 50\%$ . P-value  $< 0.01$  was considered statistically significant.

## Results

### Search results

The search strategy yielded 749 unique citations. Of these, title and abstract screening excluded 709 articles while 40 were included for full text screening. A further 15 studies were excluded based on non-extractable data (6), no comparison between RVSP and RVAP (3), and having outcomes unrelated to LV function or structure (6). The remaining 29 studies met the eligibility criteria and were included for analysis [1,2,4,5,7,8,15,17-38]. Figure 1 provides a summary of the search process. However, additional four studies [20-23] were excluded from the final dataset due to difficulty in extracting data or lacked numerical data of interest this study.

### Study characteristics

Summaries of study and patient characteristics are provided in Table 1. Three studies [17,34,36] adopted a crossover design while the remaining adopted a parallel design [1,2,4,5,7,8,15,18,19,24-33,36]. Twenty-one studies [1,2,4,5,8,15,17-19,26-34,36-38] provided LVEF values at baseline and after pacing, eight [2,4,8,15,31,32,37,38] of them reported echocardiographic measures of changes in LV volumes (LVEDV and LVESV) (Table 2). Seventeen studies examined the effect of RVSP and RVAP on QRS [2,4,8,15,19,24-27,30-36,38]. Seven [4,8,15,24,35,38] of the 17 QRS studies also evaluated the effect on R-wave stimulation, pacing threshold and/or impedance (Table 3). Four studies examined tissue Doppler imaging (TDI)-defined LV synchrony [15,31,32,37] (Table 4). Three studies [7,17,25] assessed neuro-hormonal changes (B-type Natriuretic Peptide [BNP]) (Table 5). The 25 studies making the final dataset had a total of 2,315 patients randomized into RVAP (n=1,028) and RVSP (n=1,287) with a mean enrolled follow-up period of 14.04 months.

### Results of analyses

LV function: Left ventricular systolic function (LVEF values) were reported in 21 RCTs at follow-up for both RVAP and RVSP groups. Pooled data at the end of follow-up showed RVSP patients achieved a

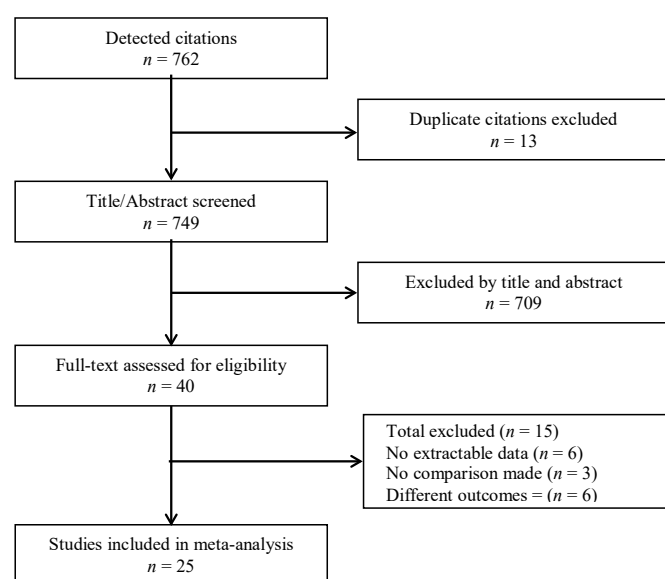


Figure 1. Flow chart of the search process

**Table 1.** Summary of study characteristics

First Author [Reference No.]	Year	No. of Patients		Follow-up (Months)	Is Septal better	Outcomes/Remarks
		Apical	Septal			
Alhous, MH. et al. [15]	2015	8	14	2	±	RVSP improves LVEF and LV synchrony CRT candidates
Arnold, CT. et al. [18]	2009	17	17	36	-	RVSP is inferior to RVAP. Has poorer LEVF and dyssynchrony
Atteia, I. et al. [38]	2012	20	20	6	+	RVSP has less adverse effects on LV function/dyssynchrony than RVAP
Bai, M. et al. [28]	2016	46	50	12	+	RVSP reduces deleterious effects of RVAP in selected patients
Cano, O. et al. [29]	2010	46	47	12	+	RVSP reduces RVAP-induced LV dyssynchrony
Chen, K. et al. [30]	2014	47	45	18	+	RVSP has better clinical utility in AV-block and LVEF:35-40%
Cho, GY et al. [31]	2011	45	34	1	±	RVSP has a smaller increase in QRS than RVAP. Additional studies required
Domenichini, G. et al. [27]	2012	28	31	48	-	RVSP confers no clinical benefits over RVAP.
Fat-Hung, TSE. et al. [26]	2009	12	12	18	+	Upgraded RVSP reverses deleterious effects of RVAP in chronic RV pacing
Gong, X. et al. [32]	2009	48	48	12	±	RVSP has no benefits over RVAP in preventing cardiac remodeling
Kikuchi, M. et al. [24]	2012	70	79	24	+	RVSP is safer and has favorable clinical benefits than RVAP
Leclercq C. et al. [8]	2015	132	131	12	±	RVSP is non-inferior to RVAP for LV reverse modelling at 6 months.
Lewicka-Nowak et al. [33]	2006	14	13	9	+	In normal LV function RVSP reduces unfavorable effects of chronic RVAP
Mera, F. et al. [34]	1999	--	12	2	+	RVSP has better LV function in LV dysfunction and chronic AF patients
Mizukami, A. et al. [5]	2016	223	223	25	±	RVSP did not show superior medium-term advantages over RVAP
Molina, L. et al. [2]	2014	34	37	12	+	RVSP has better clinical and LV function at 12 months
Nikoo, MH et al. [7]	2011	39	35	2	±	No significant differences between RVSP and RVAP
Occhetta, et al. [4]	2015	33	244	21	+	RVSP is safe and effective and reverses deleterious effect of chronic RVAP
Ren, X. et al. [35]	2009	39	36	12	+	RVOT has stable lead performance and no serious complication.
Victor, F. et al. [19]	1999	10	6	3	±	At 3 months RVOT has no symptomatic/hemodynamic benefit than RVAP
Victor, F. et al. [36]	2006	--	28	3	+	RVSP preserves LV function in LVEF≤45% than RVAP.
Wada, T. et al. [25]	2011	46	44	36	±	RVSP has no clear clinical benefits compared to RVAP.
Wang, F. et al. [37]	2011	29	31	12	±	RVSP is non-inferior to RVAP in intraventricular dyssynchrony/LV volumes
Zanon, F. et al. [17]	2008	--	12	3	+	RVSP is superior to RVAP in LV dyssynchrony and mitral regurgitation
Zou, C. et al. [1]	2015	42	38	24	+	RVSP has fewer adverse effects on patients with normal cardiac function.

**Table 2.** Summary of studies examining left ventricular function

First Author [Reference No.]	LVEF				LVEDV				LVESV			
	Apical		Septal		Apical		Septal		Apical		Septal	
	Baseline	Pacing	Baseline	Pacing	Baseline	Pacing	Baseline	Pacing	Baseline	Pacing	Baseline	Pacing
Alhous, MH. et al. [15]	29±7	28±7	29±7	32±6	205±52	207±47	205±52	207±68	146±41	150±40	146±41	132±53
Arnold, CT. et al. [18]	52±1	47±2	54±8	53±1								
Atteia, I. et al. [38]	67±7	61±7	68±7	68±8		49±6		47±6		62±7		69±8
Bai, M. et al. [28]	59±6	54±8	57±6	57±5								
Cano, O. et al. [29]	62±6	63±8	64±8	67±7								
Chen, K. et al. [30]		38±7		42±2								
Cho, GY et al. [31]	60±8	56±9	62±8	63±8	85±28	89±33	107±37	100±28	38±16	38±21	44±21	40±16
Domenichini, G. et al. [27]	54±8	53±1	52±1	47±2								
Fat-Hung, TSE. et al. [26]	58±4	59±6	55±3	60±30								
Gong, X. et al. [32]	68±6	66±7	68±6	68±5	84±32	78±18	83±25	79±16	27±10	27±10	27±11	26±7
Leclercq C. et al. [8]	30±8	38±11	29±8	36±10	215±84	178±81	221±94	188±99	154±72	115±68	158±83	126±87
Lewicka-Nowak et al. [33]	56±11	47±8	54±7	53±9								
Mera, F. et al. [34]		55±16	43±10	51±14								
Mizukami, A. et al. [5]	69±13	70±8	70±13	71±8								
Molina, L. et al. [2]	52±10	54±10	57±10	61±10	71±34	62±22	66±32	68±30	36±27	32±21	34±26	33±25
Occhetta, et al. [4]		43±9	49±11	53±11	98±22	139±31	100±37	104±40	47±14	79±22	49±27	55±31
Victor, F. et al. [19]	51±9	48±1	49±6	45±9								
Victor, F. et al. [36]	38±5	37±4	38±5	42±5								
Wang, F. et al. [37]	64±7	63±5	65±5	63±4	95±36	83±19	96±21	81±18	36±22	31±10	34±9.8	30±8
Zanon, F. et al. [17]	59±7	61±10	59±7	63±12								
Zou, C. et al. [1]	66±12	51±10	65±14	62±14								

\*LVEF: Left ventricular ejection fraction; +=Yes; -=No; ± = No difference; Missing apical patients = cross-over study

**Table 3.** Summary of studies examining lead performance (QRS, R-wave, Threshold and Impedance)

First Author [Reference No.]	QRS		R-wave		Pacing Threshold		Impedance	
	Apical	Septal	Apical	Septal	Apical	Septal	Apical	Septal
Alhous, MH. et al. [15]	196±26	179±20			0.9±0.3	1.0±0.5	497±105	539±64
Atteia, I. et al. [38]	162±5.9	148±6.9	11.9±1.7	11.7±1.6	0.53±0.17	0.52±0.19	625±89	633±94
Chen, K. et al. [30]	175±20	153±18						
Cho, GY et al. [31]	163±18	152±26						
Domenichini, G. et al. [27]	158±17	150±15						
Fat-Hung, TSE. et al. [26]	171±4	160±4						
Gong, X. et al. [32]	177±23	161±22						
Kikuchi, M. et al. [24]	176±25	149±24	15.3±9.1	12.4±6.6	0.62±0.3	0.92±0.3	800±397	581±334
Leclercq C. et al. [8]	140±26	136±26	14.2±6.9	13.8±6.8	0.8±0.3	0.7±0.3	676±146	762±172
Lewicka-Nowak et al. [33]	178±19	177±21						
Mera, F. et al. [34]	170±11	158±10						
Molina, L. et al. [2]	158±30	146±46	11.3±3.7	12.3±5.4	0.7±0.4	0.7±0.2	711±175	610±120
Occhetta, et al. [4]	165±10	122±9				0.8±0.5		540±116
Ren, X. et al. [35]	177±21	138±23	10.7±4.4	11.4±5.1	0.91±0.2	0.92±0.2	568±198	592±201
Victor et al. [19]	163±22	164±19						
Victor, F. et al. [36]	170±40	145±40						
Wada, T. et al. [25]	162±14	147±17						

\*HF: Heart failure; AF: Atrial fibrillation

**Table 4.** Summary of studies examining LV systolic dyssynchrony

First Author [Reference No.]	Ts-SD (ms)			
	Apical		Septal	
	Baseline	Pacing	Baseline	Pacing
Alhous, MH. et al. [15]	50±19*	43±14	50±19	37±17
Cho, GY et al. [31]	33.3±11.9**	36.5±16.1	33.3±11.9**	38.6±14.6
Gong, X. et al. [32]	26.4±14.4	35.3±15.3	24.8±15.5	28.3±15.1
Wang, F. et al. [37]	33.0±18.4	32.5±21.0	34.5±29.3	33.4±25.4

\*Mean of all patients; \*\*No baseline values, Ts-SD obtained from controls; **Ts**: time to the peak systolic velocity with reference to the QRS complex; **SD**: standard deviation of the time difference in 12 basal and mid segments

**Table 5.** Summary of studies examining changes in B-type natriuretic peptide

First Author [Reference No.]	Year	No. of Patients		Follow-up (Months)	BPN	
		Apical	Septal		Apical	Septal
Nikoo, MH et al. [7]	2011	39	35	2	494±292	310±292
Wada, T. et al. [25]	2011	46	44	36	141±141	119±139
Zanon, F. et al. [17]	2008	NR	12	3	74.1±62	69±57

\*BNP: B-type natriuretic peptide; NR: Not Reported

significant increase in mean gain in LVEF compared to RVAP (SMD, 0.394, 95% CI: 0.715-0.073, p=0.01). Heterogeneity between the studies was also high (I<sup>2</sup>=89.7%, p<0.01) (Figure 2). To ensure the changes in LVEF were not attributed to differences in baseline LVEF values, we pooled LVEF baseline data across studies. There was no significant differences between RVSP and RVAP (SMD, 0.15, 95% CI: 0.05-0.25) and there was no evidence of heterogeneity across the 21 studies (I<sup>2</sup>=0.00%, p<0.974).

**Cardiac remodelling:** In eight studies [2,4,8,15,31,32,37,38], cardiac remodelling was assessed by changes in LV diastolic and systolic volumes measured using LVEDV and LVESV. When the data was pooled across the eight studies, there was a trend towards reduced LV volumes in the RVSP group but the difference was not statistically supported: LVEDV: (SMD, 0.14, 95% CI: -0.16-0.44, p=0.03, I<sup>2</sup>=77.8%) and LVESV: (SMD, 0.02, 95% CI: 0.33-0.38, p=0.90, I<sup>2</sup>=78.6%). Three studies [8,33,34] examined the effect of RVSP and RVAP on LV end-diastolic (LVEDD) and end-systolic diameter (LVESD) and all reported no significant differences at the end-of follow-up.

**LV Systolic synchrony:** Four studies [15,31,32,37] examined the effect of RVAP and RVSP on LV systolic synchrony. While different

parameters were used, the common measure was LV systolic dyssynchrony index, Ts-SD, defined as the standard deviation of the time to peak myocardial systolic velocity of all 12 left ventricular segments. Pooled data at follow-up showed no statistically significant differences in mean Ts-SD between RVAP and RVSP but there was a trend towards increased LV systolic dyssynchrony in RVAP (SMD, 0.151, 95% CI: -0.097-0.398, p=0.233) (Figure 3). There was also mild heterogeneity between studies in this sub-analysis (I<sup>2</sup>=35.02%, p=0.20).

**Lead performance:** Lead performance was assessed using QRS duration, R-wave, pacing threshold and impedance. Pooled data from 17 RCTs [2,4,8,15,19,24-27,30-36,38] that provided data on baseline and paced QRS duration revealed at the end of follow-up, the RVAP group had significantly prolonged mean QRS duration compared to the RVSP group (SMD, 1.172, 95% CI: 0.672-1.672, p=0.00) with a high heterogeneity (I<sup>2</sup>=94.34%, p=0.00) (Figure 4). Pooled data from seven studies [4,8,15,24,35,38] reveal the RVSP group had slightly higher mean R-wave (SMD, 0.029, 95% CI: 0.274-0.216), pacing threshold (SMD, 0.149, 95% CI: 0.645-0.348) and impedance (SMD, 0.106, 95% CI: 0.592-0.380) but the difference was not statistically significant (p>0.01).

Natriuretic peptides: B-type natriuretic peptides (BNP) is an important biomarker of the severity of heart failure and its levels are useful in reflecting hemodynamic changes resulting from different pacing modes. Three studies [7,17,25] assessed BNP levels after RVAP

and RVSP. When pacing BNP levels were pooled, RVAP had higher mean values but the difference with RVSP lacked statistically significant support (SMD, 0.328, 95% CI: 0.039-0.617,  $p=0.026$ ) (Figure 5). There was low heterogeneity between the studies ( $I^2=23.55\%$ ,  $p=0.27$ ).

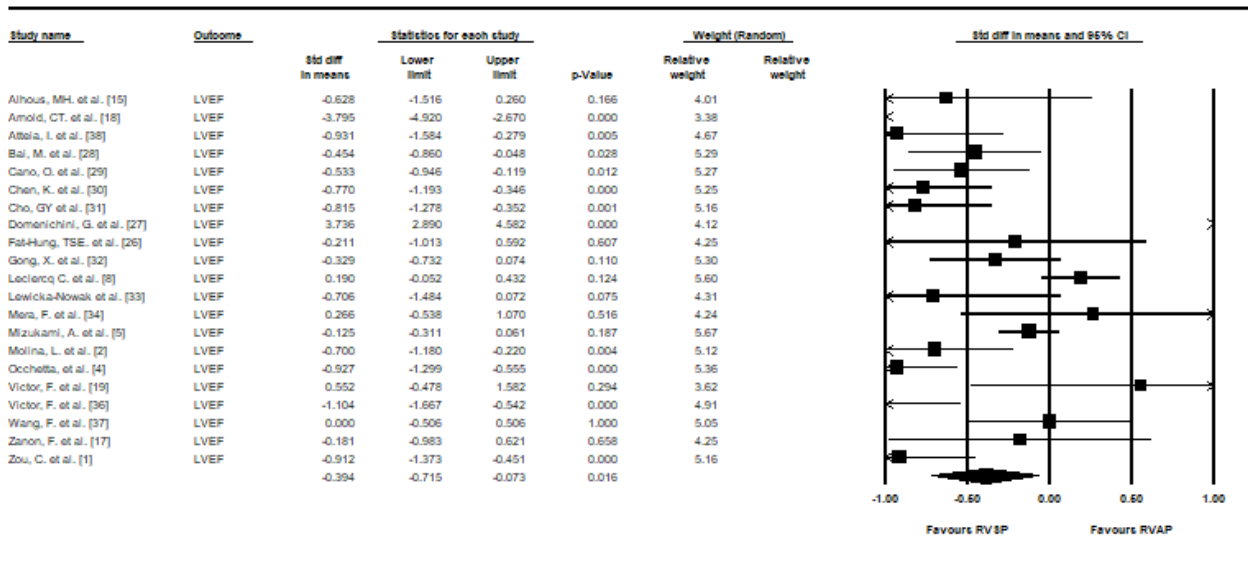


Figure 2. Standard mean differences in LVEF between RVSP and RVAP

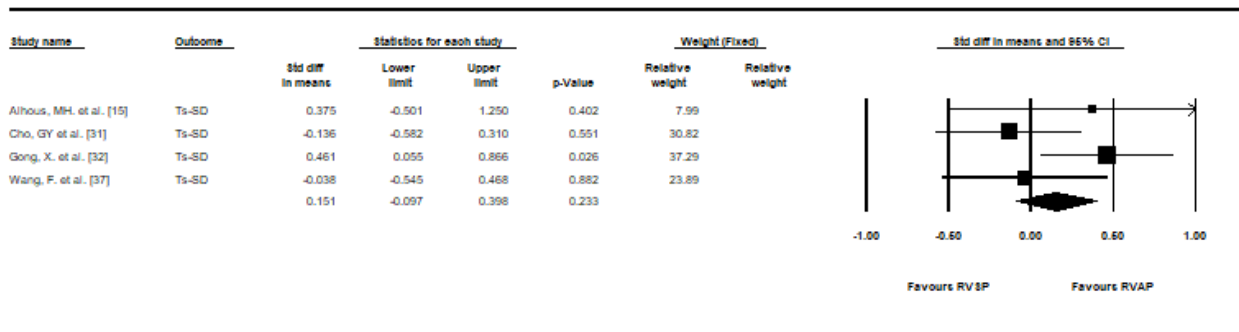


Figure 3. Standard mean differences in Ts-SD between RVSP and RVAP

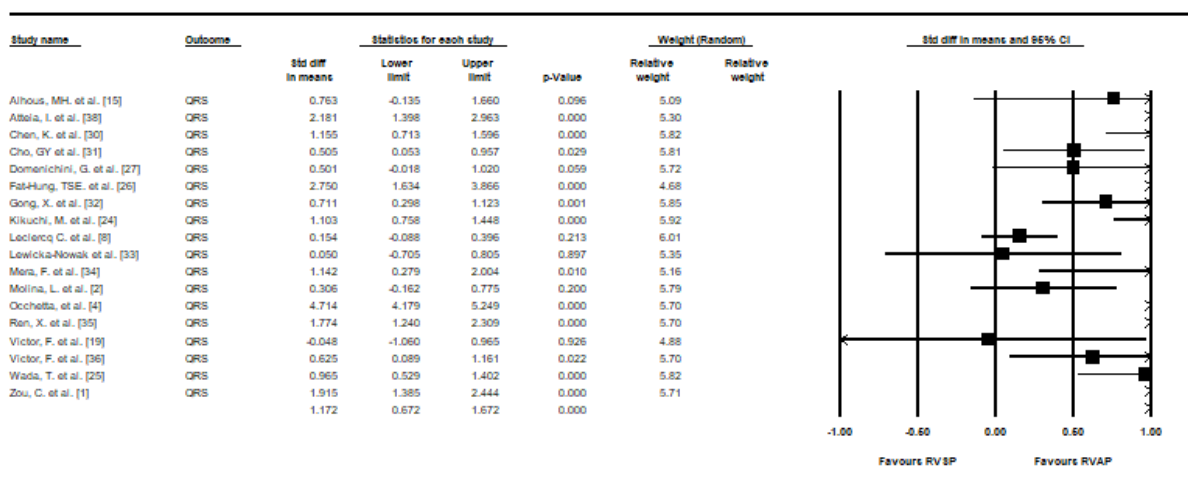


Figure 4. Standard mean differences in QRS Duration between RVSP and RVAP

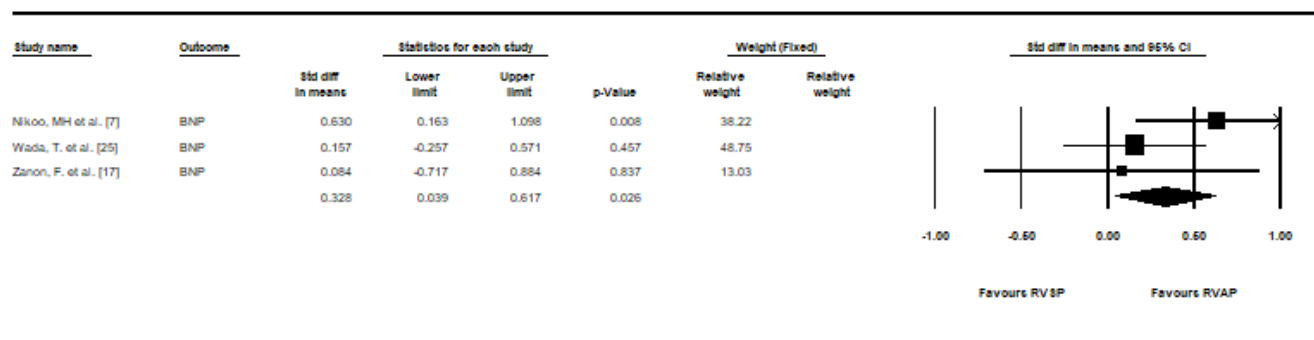


Figure 5. Standard mean differences in plasma BNP Levels between RVSP and RVAP

## Discussion

The present meta-analysis compared the effects of RVAP and RVSP on ventricular function, remodelling and dyssynchrony on patients who are eligible for cardiac pacing. The effect of RVAP and RVSP on lead performance and plasma BNP levels after pacing was also compared. The results indicate RVSP is superior in preserving LV function (LVEF) and on narrowing QRS duration compared to RVAP. The findings also suggest a positive trend of RVSP providing better protection against cardiac remodelling (reducing LVESV and LVEDV) and LV systolic dyssynchrony but the difference is not significant. There was also a non-significant difference between RVAP and RVSP on R-wave, pacing threshold and impedance. Finally, while RVSP showed a positive trend in preserving serum BNP levels, when compared to RVAP, but the difference was not significant. In overall, the findings suggest modest benefits of RVSP over RVAP but not significant to conclude which of the two pacing sites produce superior clinical outcomes.

The present findings are consistent with those of two previous meta-analyses, which reported RVSP achieved significantly higher mean LVEF values compared to RVAP as well as offered better protection for interventricular synchrony and cardiac function [11-12]. While the present analysis did not examine the relationship between baseline LVEF and RVSP-associated LVEF improvement, previous meta-analyses suggest that patients with significantly impaired baseline LV function (LVEF<35%), elderly or with longer follow-up period (> 12 months) can achieve the greatest benefits when using RVSP [10,12]. On the other, hand, for patients eligible for pacing with preserved baseline LVEF, there is no evidence of either RVSP or RVAP producing significant and clinically important difference in preserving LVEF [12].

The effect of RVAP-associated deleterious effect on LV function has been attributed to ventricular dyssynchrony and remodelling [2,4,20]. However, in the present findings, although RVAP induces greater LV systolic dyssynchrony and ventricular remodelling (changes in LV systolic volumes – LVESV and changes in LV diastolic volumes (LVEDV), the difference with RVSP are minimal. These findings support three previous RCTs that reported in patients with normal LV function, there is insignificant differences in the effect of RVAP and RVSP on LV structure (LVEDD and LVESD) [8,32-34]. These findings suggest that RVSP does not provide superior protection against LV systolic dyssynchrony and cardiac remodelling after 12 months of pacing in patients with normal cardiac function, although it causes more synchronous LV contraction. Individual studies also show pacing may have different outcomes in different patient groups. RVSP reduces atrial fibrillation in patients with sick sinus syndrome [21] while RVAP may have detrimental ventricular remodelling in patients with congenital heart block [21-23].

The present findings also find RVSP achieves a greater narrowing of QRS duration after pacing compared to RVAP. The difference may be explained by reports that RVSP initiates ventricular depolarization in the septal wall across the mitral septal papillary muscle, where pacing activation starts. As a result, RVSP has a narrower QRS duration than RVAP leading into the LV contractions that are more efficient. On the other hand, longer QRS duration in RVAP means a more desynchronization effect on LV than on RVSP [2]. In addition, while RVSP shows a trend on higher pacing threshold, R-wave sensitivity and lead impedance, the difference was not significant. Ren [35] reported stable lead performance and no serious complications for RVSP relative to RVAP. These findings suggest RVSP may be considered as a first choice pacing-site because of long-term stable lead performance and reduced complications but additional RCTs are warranted to confirm these benefits.

Finally, serum BNP levels is an important biomarker for cardiac dysfunction [7]. In the present study, we used BNP levels to determine hemodynamic changes associated with different pacing modes. We associated RVSP with significantly lower levels of BNP compared to RVAP. In addition, lower BNP levels in RVSP patients has been shown to be independent of sex, age and LVEF [7]. Since BNP are neuro-hormones secreted by the heart in relation to changes in pressure [7,25,26], higher levels may suggest the degree of cardiac dysfunction. Further, two of the included studies [24,25] suggested non-significant lower rate of hospitalization and death between RVSP and RVAP patients (event free RVSP: 2 years, 98%; RVAP: 81%,  $p<0.05$ ) [24] and hospitalization (RVSP: 4.4% vs. RVAP 6.8%,  $p>0.01$ ) [25]. The findings suggest RVSP may provide better protection against cardiac dysfunction compared to RVAP but long-term studies are warranted to confirm this benefit.

In conclusion, in selected patients, RVAP may deteriorate LV systolic function, and these patients may benefit from RVSP. The most important benefit after at least 12 months follow-up include improved LV systolic function (LVEF), narrow QRS duration and lower levels of serum BNP. RVSP also shows a positive trend towards protection against LV systolic dyssynchrony and ventricular remodeling, and stable lead performance but these benefits are not significant. In patients eligible for cardiac pacing with significantly depressed LV systolic function, RVSP may improve cardiac function. It is important to determine baseline LV systolic function to identify patients who may potentially benefit from RVSP. However, additional studies examining the contribution of pacing duration, sex, age and baseline LVEF are warranted to confirm the benefits of RVSP over RVAP in protecting against cardiac dysfunction.

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