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Beneficial effects of right ventricular non-apical vs. apical pacing: a systematic review and meta-analysis of randomized-controlled trials

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Aims Previous studies have suggested that right ventricular apical (RVA) pacing may have deleterious effects on left ventricular function. Whether right ventricular non-apical (RVNA) pacing offers a better alternative to RVA pacing is unclear. We aimed to conduct a systematic review and meta-analysis of randomized-controlled trials (RCTs) in order to compare the mid- and long-term effects of RVA and RVNA pacing.

Methods and results We systematically searched the Cochrane library, EMBASE, and MEDLINE databases for RCTs comparing RVA with RVNA pacing over >2 months follow-up. Data were pooled using random-effects models. Fourteen RCTs met our inclusion criteria involving 754 patients. Compared with subjects randomized to RVA pacing, those randomized to RVNA pacing had greater left ventricular ejection fractions (LVEF) at the end of follow-up [13 RCTs: weighted mean difference (WMD) 4.27%, 95% confidence interval (CI) 1.15%, 7.40%]. RVNA had a better LVEF at the end of follow-up in RCTs with follow-up ≥12 months (WMD 7.53%, 95% CI 2.79%, 12.27%), those with <12 months of follow-up (WMD 1.95%, 95% CI 0.17%, 3.72%), and those conducted in patients with baseline LVEF ≤40–45% (WMD 3.71%, 95% CI 0.72%, 6.70%); no significant difference was observed in RCTs of patients whose baseline LVEF was preserved. Randomized-controlled trials provided inconclusive results with respect to exercise capacity, functional class, quality of life, and survival.

Conclusions While RCTs suggest that LVEF is higher with RVNA than with RVA pacing, there remains a need for large RCTs to compare the safety and efficacy of RVNA and RVA pacing.

Keywords Pacemaker • Right ventricular apex • Septum • Ejection fraction

Introduction

Permanent cardiac pacing is the most efficient treatment for patients with chronic high-degree atrio-ventricular (AV) block and symptomatic sick sinus syndrome (SSS).[1] The traditional site for right ventricular (RV) pacing lead placement has been the right ventricular apex (RVA). However, numerous studies have suggested that the dyssynchronous contraction associated with RVA pacing can have deleterious effects on left ventricular (LV) function, resulting in myocardial perfusion defects, and heart failure.[2–8] These observations have led to an increased interest in identifying alternative pacing sites with more beneficial effects on LV contraction.[9–12] Of these right ventricular non-apical (RVNA) pacing sites, the right ventricular outflow tract (RVOT) has been the most comprehensively studied. Other RVNA pacing sites that have been proposed include the mid-septum, upper-septum, and septal his-bundle.

A previous meta-analysis of nine prospective studies found that RVOT pacing may have superior haemodynamic effects compared with RVA pacing. However, only two of the nine included studies assessed mid- to long-term haemodynamic outcomes.[13] In addition, several randomized-controlled trials (RCTs) comparing the mid- and long-term effects of RVA and RVNA pacing have since been published. These RCTs are difficult to interpret due

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to their small sample sizes and conflicting results. We therefore conducted a systematic review and meta-analysis of RCTs to compare the mid- and long-term effects of RVA and RVNA pacing on LV function and additional outcomes in patients eligible for permanent pacemakers.

Methods

Search strategy

We systematically searched the Cochrane library, EMBASE, and MEDLINE databases from inception to March 2011 to identify all RCTs comparing the effects of RVNA pacing to those of RVA pacing. The MeSH search string for this literature search was (right [All Fields] and ('heart ventricles' [MeSH Terms] or ('heart' [All Fields] and 'ventricles' [All Fields]) or 'heart ventricles' [All Fields] or 'ventricular' [All Fields]) and pacing [All Fields] and site [All Fields]) and ('humans' [MeSH Terms] and English [Lang]). We limited our literature search to studies conducted in humans and published in peer-review journals in English. Reviews and reference lists of retrieved articles were hand searched for potentially relevant publication not previously identified in the database search. The retrieved studies were examined to eliminate potential duplicates or overlapping data.

Inclusion criteria

We included a study in our systematic review if: (i) it was a trial in which the subjects were randomly assigned to RVA or RVNA pacing in a parallel-group or cross-over design; (ii) it was conducted in subjects aged $\geq$18 years eligible for permanent pacemaker implantation; (iii) it reported cardiovascular outcomes and/or assessed quality of life; and (iv) its duration of follow-up was at least 2 months. We excluded conference abstracts as their results may not be final.

Data extraction

Two reviewers (A.S. and G.A.) independently extracted data from each trial. Results were compared and any disagreements were resolved by consensus. Data extracted for each RCT included first author, year of publication, study location, study design, length of follow-up, number of participants and their characteristics, and pacemaker technical aspects. Outcomes extracted included brain natriuretic peptide (BNP) levels, echocardiographic synchrony parameters, exercise capacity, functional class, mortality, pulse width threshold, quality of life, and valves function. In addition, we extracted data concerning baseline and final left ventricular ejection fraction (LVEF), imaging tool, and whether baseline LVEF served as an inclusion criteria. If the investigators reported outcomes at two different follow-up times, outcomes for the longest available duration of follow-up were used.

Quality assessment

The systematic review and meta-analysis were performed according to the PRISMA statement for reporting systematic reviews and meta-analyses of RCTs.[14] Each study was evaluated using a modified version of the Jadad scale.[15] Double-blinding is not possible in RCTs of pacemaker implantation. Therefore, quality was summarized using a modified version of the Jadad scoring system. One point was assigned for an affirmative answer to each of the following five questions: (i) Was the study described as randomized?; (ii) Was the method of randomization adequate?; (iii) Was there adequate concealment of allocation?; (iv) Was the outcome assessment described as blinded?; and (v) Was there a description of withdrawals/dropouts?

Statistical analysis

We used DerSimonian and Laird random-effect models[16] to compare the effects of RVA and RVNA pacing on LVEF at the end of follow-up across studies. These pooled effects are presented as weighted mean differences (WMD) with corresponding 95% confidence intervals (CI). Statistical heterogeneity was assessed using the Q statistic, (with $P < 0.1$ considered significant), and I^2 statistics were calculated to estimate the proportion of variance due to between-study heterogeneity. Randomized-controlled trials that stratified results by baseline LVEF were treated as separate trials.

In secondary analyses, we stratified analyses by duration of follow-up ($<$12 months vs. $\geq$12 months) and baseline LVEF (preserved vs. $<$40–45%). In addition, the relationship between length of follow-up and the WMD in LVEF was explored using meta-regression. For RCTs that reported a range of follow-up periods, we used the mid-point of the range in the meta-regression analysis. The presence of publication bias was assessed by visual inspection of a funnel plot (plots of effect estimates against sample size). Funnel plots are usually skewed in the presence of publication bias, typically with over-representation of significant or 'positive' studies. Our primary and secondary analyses included both parallel-group and cross-over RCTs. Using sensitivity analyses, we stratified the data by trial design (parallel-group vs. cross-over) to ensure that the results did not differ substantially by trial and, in additional sensitivity analyses, we excluded RCTs responsible for increasing the between-study heterogeneity. All analyses were conducted using STATA 9.0 (Stata-Corp, College Station, TX, USA).

Results

In total, 985 studies (excluding duplicates) were identified by our literature search (*Figure 1*). After the exclusion of non-relevant studies, case reports, and reviews by title and abstracts, 29 studies were retrieved for further consideration. Seven additional studies were included at this stage from a manual search of references of retrieved articles. We then excluded observational studies and RCTs that only examined the acute affects of different pacing sites. Finally, 14 RCTs were included in our systematic review.[17–30]

Description of randomized-controlled trials

Table 1 summarizes the characteristics of the included RCTs. These trials involved a total of 754 patients (385 and 369 paced at RVNA and RVA sites, respectively) with the number of subjects in each RCT ranging from 20 to 122. In two RCTs, results were stratified by baseline LVEF (low vs. preserved).[23,28] Length of follow-up ranged from 2 to 120 months. In nearly all RCTs, analyses were restricted to subjects who completed follow-up. The mean or median age of participants ranged from 60 to 77 years. Participants were predominantly male in all but for one RCT[26] (range 45–88% males). Indications for pacemaker implantation included chronic high-degree AV block, symptomatic SSS, and post-AV node ablation therapy for chronic atrial fibrillation. Right ventricular non-apical sites examined were the septal his-bundle, mid- or high septum (or septum as a general rule), or the RVOT. Data obtained from the pacemaker data showed no difference in the percentage of ventricular pacing between the groups

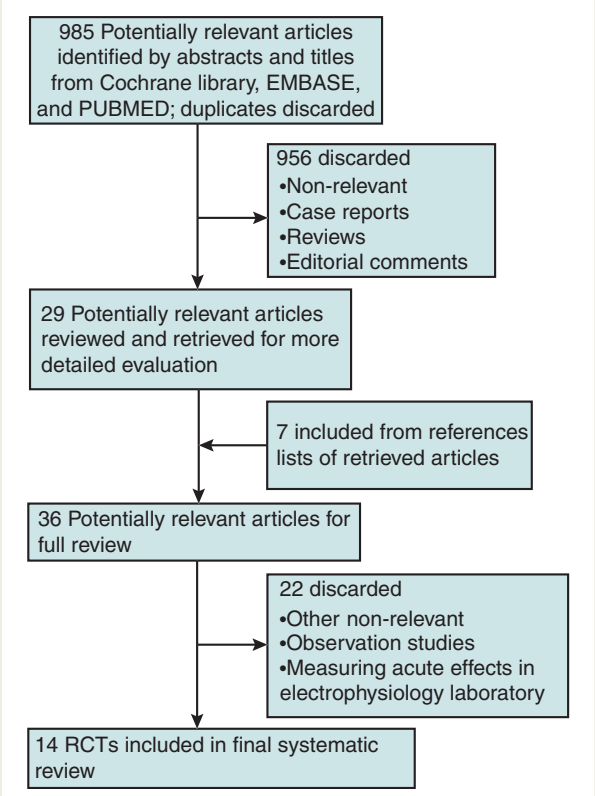

Figure 1 Flowchart describing systematic literature search and study selection process.

with >90% of ventricular pacing in most studies at the end of follow-up.

Eight of the 14 RCTs achieved a score of ≥3 for quality in our modified Jadad score.[17,18,20–22,25,27,30] Methodological shortcomings included: method of randomization not described (9 studies scored 'unclear'), unclear concealment of allocation (13 studies scored 'unclear'), and failure to blind the outcome assessment (9 studies scored 'unclear').

Left ventricular ejection fractions meta-analysis and examination of heterogeneity

Left ventricular ejection fractions was reported in 13 RCTs; baseline and follow-up LVEF data are summarized in *Table 2*. When data were pooled across RCTs, the pooled LVEF at the end of follow-up was higher with RVNA pacing than with RVA pacing (WMD of LVEF: 4.27%, 95% CI 1.15%, 7.40%) (*Figure 2*). The heterogeneity between studies in this primary analysis was high (I^2 = 89.3%, $P < 0.001$). To ensure that differences in final LVEF were not the result of differences in baseline LVEF, we pooled baseline LVEF data across studies. No apparent differences were observed in baseline LVEF (WMD of LVEF: 0.14%, 95% CI −1.06%, 1.34%) and there was no evidence of heterogeneity (I^2= 0.0%, $P = 0.92$).

A stratified analysis was performed to investigate for potential sources of heterogeneity. Visual inspection of our forest plot identified two RCTs with extremely 'positive' benefit for RVNA over RVA pacing with little within-study variance.[19,26] A repeated analysis without these two trials continued to show that RVNA resulted in significantly higher LVEF than RVA pacing, though the difference was attenuated (WMD of LVEF: 2.84%, 95% CI 1.27%, 4.40%). There was only mild heterogeneity between RCTs in this analysis ($I^2 = 26.3\%$, $P = 0.18$). When data were pooled across studies with high-quality score ≥3 in our modified Jadad score, RVNA still resulted in a greater LVEF at the end of follow-up than RVA pacing (WMD of LVEF: 2.70%, 95% CI 0.51%, 4.88%). There was mild heterogeneity between RCTs in this analysis ($I^2 = 42.0\%$, $P = 0.11$). Visual inspection of our funnel plot revealed that publication bias may be present suggesting that 'positive' studies for RVNA pacing were more likely to get published (*Figure 3*).

Subgroup analysis for LVEF

When stratified by length of follow-up, RVNA pacing resulted in greater LVEF at the end of follow-up than RVA pacing in the six RCTs with ≥12 months follow-up (WMD of LVEF: 7.53%, 95% CI 2.79%, 12.27%) (*Figure 2*). There was appreciable evidence of heterogeneity ($I^2 = 93.8\%$, $P < 001$) between studies. The exclusion of the two previously identified outlying RCTs[19,26] resulted in attenuated effects (WMD of LVEF: 4.39%, 95% CI 1.47%, 7.30%) and mild heterogeneity ($I^2 = 54.0\%$, $P = 0.09$). In RCTs with <12 months of follow-up, RVNA pacing resulted in a modest but significant increase in LVEF at the end of follow-up (WMD of LVEF: 1.95%, 95% CI 0.17%, 3.72%) with no heterogeneity ($I^2 = 0.0\%$, $P = 0.44$). There was no evidence of an association between duration of follow-up and the effect of RVNA pacing on LVEF at the end of follow-up (regression coefficient for 1 month of follow-up: 0.06, 95% CI −0.08%, 0.2%, $P = 0.38$).

When data were pooled across the three studies that reported upon patients with baseline LVEF ≤ 40–45%,[23,25,28] RVNA pacing resulted in a greater LVEF at the end of follow-up than RVA pacing (WMD of LVEF: 3.71%, 95% CI 0.72, 6.70; $I^2 = 0.0\%$, $P = 0.39$). In five RCTs in which baseline LVEF ≥ 40–50% was an inclusion criteria , no significant difference was observed in the pooled LVEF at the end of follow-up (WMD of LVEF: 3.38%, 95% CI − 0.62%, 7.38%). Heterogeneity between studies conducted in patients with preserved baseline LVEF was high ($I^2 = 87.4\%$, $P < 0.001$). We repeated the analysis without one RCT that was shown to have extremely 'positive' results with little within-study variance.[26] This analysis showed superiority for RVNA pacing (WMD LVEF: 1.91%, 95% CI 0.14%, 3.69%) ith no heterogeneity between RCTs ($I^2 = 0.0\%$, $P = 0.71$).

Qualitative review of other outcomes

Table 3 summarizes other outcomes for which formal meta-analyses were not possible or appropriate. The paced QRS duration was significantly longer in patients in the RVA group in most studies. Only one study compared the long-term (120 months) survival with RVOT and RVA pacing sites.[20] Right ventricular outflow tract provided no additional benefit for survival over RVA pacing. Five RCTs compared the effects of RVNA and RVA pacing sites on New-York Heart Association (NYHA) heart failure class.[17,22,23,25,28] No significant differences were observed

Table 1 Study-level characteristic of randomized-controlled trials comparing the mid- and long-term effects of right ventricular apical pacing and right ventricular non-apical pacing in patients eligible for permanent pacemaker implantation

Author	Country	Trial design	Analysed data in trials	RVA (*n*)	RVNA (*n*)	RVNA pacing site	Follow-up (months)	Participants characteristics	Technical aspects	Outcomes
Leong *et al.* 2010	Australia	Parallel	Analyses were conducted in patients who completed follow-up	26	32	RVOT	11–53	SSS in 26; symptomatic AV block in 32; none with indication to cardiac resynchronization therapy	DDD in all patients; At 6-month follow-up, 30 patients were paced 100% and 37 were paced >50% of the time in the ventricle	LVEF, LV volumes, LV dyssynchrony parameters, left atrium structure and function
Cano *et al.* 2010	Spain	Parallel	Analyses were conducted in patients who completed follow-up	28	32	Mid-septum	12	SSS in 3; symptomatic AV block in 57; without structural heart disease; all with LVEF ≥ 50%	VVI in 7 and DDD in 53; active fixation bi-polar steroid eluting lead for all; one reposition in each group; mean percentages of ventricular pacing at 12-months follow-up were 88 and 81% for RVA and RVNA subjects, respectively	LVEF, LV volumes, LV dyssynchrony parameters, quality-of-life score, BNP levels, 6-min-walk test
Gong *et al.* 2009	China	Parallel	Analyses were conducted in patients who completed follow-up	44	46	RVOT	12	Symptomatic AV block in all; all with LVEF ≥ 50%; none with heart failure	DDD in all patients; RVA patients with passive fixed leads; RVNA patients with helix-fixation leads; no reposition reported; mean percentages of ventricular pacing at 12-months follow-up were 97% and 98% for RVA and RVNA subjects, respectively	LVEF, LV volumes, LV dyssynchrony parameters
Flevari *et al.* 2009	Greece	Parallel	Analyses were conducted in patients who completed follow-up	15	16	Lower-mid-septum	12	Symptomatic AV block; none with angina or LV hypertrophy	DDD in all patients; all patients with active fixation leads; no reposition reported; mean percentages of ventricular pacing at 12-month follow-up were 97 and 95% for RVA and RVNA subjects, respectively	LVEF, LV volumes, LV dyssynchrony, degree of mitral and tricuspid regurgitation
Dabrow-ska *et al.* 2009	Poland	Parallel	Analyses were done on the intention-to-treat basis	66	56	RVOT	120	SSS in 17; symptomatic AV block in 80; atrial fibrillation in 24; all with LVEF ≥ 40%	VVI-R, VDD or DDD. All patients with passive fixation leads; one pneumathorax in each group; no reposition reported; mean percentages of ventricular pacing at 120-months of follow-up were 95 and 94% for RVA and RVNA subjects, respectively	Survival analysis
Kypta *et al.* 2007	Austria	Parallel	Analyses were conducted in patients who completed follow-up	45	53	Mid-septum or RVOT	3	Symptomatic AV block in all; 14 patients with LVEF ≤ 40%; none with heart failure, recent myocardial infarction or history of atrial fibrillation, significant co-morbidity, or inability to perform stress test	DDD in all; passive fixation leads for RVA group and active fixation bi-polar steroid eluting lead for RVNA group; one reposition and one pocket haematoma, both in RVA group; mean percentages of ventricular pacing at the end of follow-up were 95 and 91% for RVA and RVNA subjects, respectively	LVEF, BNP levels, exercise capacity, survival and safety analysis

Occhetta *et al.* 2006	Italy	Cross-over	Analyses were conducted in patients who completed follow-up	16	16	His-bundle	2 Periods of 6 months	Chronic atrial fibrillation patients who underwent AV node ablation	Bipolar (active or passive) lead for RVA and active fixation lead for RVNA; both leads in each patient. Lead to RVNA connected to 'atrial' port with AAIR mode. Lead to RVA connected to 'ventricular' port with VVIR mode; one dislodgement in RVS after 1 month; consistent ventricular capture since patients underwent AV node ablation	LVEF, LV volumes, exercise capacity, degree of mitral and tricuspid regurgitation
Victor *et al.*[a] 2006	France	Cross-over	Analyses were conducted in patients who completed follow-up	16	16	Septum	2 Periods of 3 months	LVEF $\geq$ 45%; Chronic atrial fibrillation patients who underwent AV node ablation	Bipolar lead for RVA and active fixation lead for RVNA; both leads in each patient. Lead to RVNA connected to 'atrial' port with AAIR mode. Lead to RVA connected to 'ventricular' port with VVIR mode; consistent ventricular capture since patients underwent AV node ablation	LVEF, exercise capacity, peak VO^2
Victor *et al.*[a] 2006	France	Cross-over	Analyses were conducted in patients who completed follow-up	12	12	Septum	2 Periods of 3 months	LVEF $\leq$ 45%; Chronic atrial fibrillation patients who underwent atrioventricular node ablation	Bipolar lead for RVA and active fixation lead for RVNA; both leads in each patient. Lead to RVNA connected to 'atrial' port with DDDR mode. Lead to RVA connected to 'ventricular' port with VVIR mode; consistent ventricular capture since patients underwent AV node ablation	LVEF, exercise capacity, peak VO^2
Lewicka-Nowak *et al.* 2006	Poland	Parallel	Analyses were conducted in patients who completed follow-up	14	13	RVOT	89–93	SSS in 2; symptomatic AV block in 23; chronic atrial fibrillation with bradycardia in 2	Pacing modes were VVI-R, VDD or DDD; Passive fixation leads for both groups; mean percentages of ventricular pacing at the end of follow-up were 94 and 99% for RVA and RVNA subjects, respectively	LVEF, LV volumes, diastolic assessment , degree of valve regurgitation, BNP levels
Stambler *et al.* 2003	USA	Parallel[c]	Analyses were conducted in patients who completed follow-up	37	43	RVOT	3	Patients with heart failure and LVEF $\leq$ 40%; eligible for VVIR; 64% post AV node ablation	Active fixation leads for RVA and RVNA. Both leads in each patient; Lead to RVNA connected to 'atrial' port with AAI mode. Lead to RVA connected to 'ventricular' port with VVI mode; all with $>$90% V pacing	LVEF, LV volumes, quality of life, heart failure assessment, degree of valve regurgitation
Tse *et al.* 2002	China	Parallel	Analyses were conducted in patients who completed follow-up	12	12	RVOT	18	All patients with complete AV block and LVEF $\geq$ 50%; none with coronary artery disease, significant valvular disease, hypertension	Active fixation leads for RVA and RVNA; mean percentages of ventricular pacing at the end of follow-up were 95 and 97% for RVA and RVNA subjects, respectively	LVEF, perfusion defects

Continued

Table 1 *Continued*

Author	Country	Trial design	Analysed data in trials	RVA (*n*)	RVNA (*n*)	RVNA pacing site	Follow-up (months)	Participants characteristics	Technical aspects	Outcomes
Bourke *et al.* 2002	England	Parallel	Analyses were conducted in patients who completed follow-up	10	10	RVOT	3–12	Chronic atrial fibrillation patients who underwent AV node ablation.	DDDR in 13, VVIR in 7; Passive fixation leads for RVA group; leads features for RVNA group not stated; consistent ventricular capture since patients underwent AV node ablation	LVEF, systolic and diastolic function, right ventricle area
Victor *et al.*[b] 1999	France	Cross-over	Analyses were conducted in patients who completed follow-up	10	10	RVOT	2 Periods of 3 months	LVEF $\geq$ 40%; chronic atrial fibrillation; complete AV block either spontaneous or by ablation	Passive fixation leads for RVA group and active fixation leads for RVNA; both leads in each patient. Lead to RVNA connected to 'atrial' port with AAIR mode. Lead to RVA connected to 'ventricular' port with VVIR mode; consistent ventricular capture since patients underwent AV node ablation	LVEF, cardiac output, peak VO^2
Victor *et al.*[b] 1999	France	Cross-over	Analyses were conducted in patients who completed follow-up	6	6	RVOT	2 Periods of 3 months	LVEF $<$ 40%; chronic atrial fibrillation; complete AV block either spontaneous or by ablation	Passive fixation leads for RVA group and Active fixation leads for RVNA; both leads in each patient. Lead to RVNA connected to 'atrial' port with AAIR mode. Lead to RVA connected to 'ventricular' port with VVIR mode; consistent ventricular capture since patients underwent AV node ablation	LVEF, cardiac output, peak VO^2
Mera *et al.* 1999	USA	Cross-over	Analyses were conducted in patients who completed follow-up	12	12	High septum	2 Periods of 2 months	Chronic atrial fibrillation patients who underwent AV node ablation	Passive fixation leads for RVA group and active fixation leads for RVNA; both leads in each patient. Lead to RVNA connected to 'atrial' port with AAIR mode. Lead to RVA connected to 'ventricular' port with VVIR mode; consistent ventricular capture since patients underwent AV node ablation	LVEF, LV diameters.

AV, atrio-ventricular; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LV, left ventricular; RVA, right ventricular apex; RVNA, right ventricular non-apex; RVOT, right ventricular outflow tract; SSS, sick sinus syndrome.
[a,b]RCTs in which results were presented and analysed separately for subjects with low or preserved LVEF.
[c]Original study design was cross-over. For the purpose of analysis only the first period could be extracted, and therefore a 'parallel' design is presented.

Table 2 Randomized-controlled trials that compared the effects of right ventricular apical pacing ($n = 277$) and right ventricular non-apical pacing ($n = 297$) on left ventricular ejection fraction

Author	LVEF as an inclusion criterion	Mode of LVEF assessment	Follow-up (months)	Baseline LVEF (%) (mean ± SD)		Final LVEF (%) (mean ± SD)	
				RVA	RVNA	RVA	RVNA
Leong *et al.* 2010	No	Echocardiography	11–53[c]	60.0 ± 6.0	61.0 ± 9.0	52.0 ± 9.0	60.0 ± 7.0
Cano *et al.* 2010	Yes; ≥50	Echocardiography	12	62.9 ± 6.3	64.2 ± 8.0	62.9 ± 7.9	66.5 ± 7.2
Gong *et al.* 2009	Yes; ≥50	Echocardiography	12	67.9 ± 6.4	68.3 ± 6.4	65.7 ± 6.6	67.6 ± 5.2
Flevari *et al.* 2009	No	Echocardiography	12	49.0 ± 4.3	50.0 ± 4.9	43.0 ± 3.1	59.0 ± 3.0
Kypta *et al.* 2008	No	Echocardiography	3[b]	59.0 ± 11.0	55.0 ± 11.0	57.0 ± 10.0	57.0 ± 10.0
Occhetta *et al.* 2006	No	Echocardiography	6	51.9 ± 8.8	51.9 ± 8.8	50.0 ± 7.9	53.4 ± 7.9
Victor *et al.* 2006	Yes; ≥45	Nuclear imaging	3	52.0 ± 6.0	52.0 ± 6.0	51.0 ± 7.0	52.0 ± 6.0
Victor *et al.* 2006	Yes; <45	Nuclear imaging	3	38.0 ± 5.0	38.0 ± 5.0	37.0 ± 4.0	42.0 ± 5.0
Lewicka-Nowak *et al.* 2006	No	Echocardiography	89–93	56.0 ± 11.0	54.0 ± 7.0	47.0 ± 8.0	53.0 ± 9.0
Stambler *et al.* 2003	Yes; <40	Echocardiography	3	Stated as 'similar'		41.0 ± 13.4	43.8 ± 14.4
Tse *et al.* 2002	Yes; ≥50	Nuclear imaging[a]	18	57.0 ± 12.0	59.0 ± 14.0	47.0 ± 3.0	56.0 ± 1.0
Bourke *et al.* 2002	No	Nuclear imaging	3–12	51.0 ± 9.0	49.0 ± 6.0	48.0 ± 10.0	45.0 ± 9.0
Victor *et al.* 1999	Yes; ≥40	Nuclear imaging	3	51.0 ± 5.0	51.0 ± 5.0	48.0 ± 7.0	48.0 ± 5.0
Victor *et al.* 1999	Yes; <40	Nuclear imaging	3	27.0 ± 9.0	27.0 ± 9.0	30.0 ± 10.0	28.0 ± 9.0
Mera *et al.* 1999	No	Nuclear imaging	2	Not measured		43.0 ± 10.0	51.0 ± 14.0

LVEF, left ventricular ejection fraction; RVA, right ventricular apex; RVNA, right ventricular non-apex; SD, standard deviation.
[a]Baseline LVEF was measured by echocardiography and final LVEF was measured by nuclear imaging.
[b]Original study had two periods of follow-up (3, 18 months). The results of the longer follow-up could not be used due to insufficient data.
[c]Since follow-up period ranged from 11 to 53 months, the data from Leong *et al.* were pooled together with those studies with a long-term follow-up, i.e. ≥12 months.

in four RCTs.[17,23,25,28] One RCT[22] showed that RVNA but not RVA pacing significantly improved NYHA heart failure class. Various echocardiographic parameters of LV synchronous contraction were measured in four RCTs/[17–19,30] RVNA pacing induced a more synchronized pattern of LV contraction in three RCTs,[17,18,30] while there were no significant differences between groups at 12 months in the fourth RCT.[19] Exercise capacity was assessed in four RCTs by 6-min-walk test[22,25] or treadmill exercise test.[23,28] No significant differences were observed between pacing sites in all but for one RCT,[22] which showed greater exercise capacity with RNVA. Quality of life was evaluated in two RCTs with different questionnaires.[22,25] There were no differences in most of the quality-of-life scores between the groups in one RCT.[25] In the other RCT,[22] there was a significant improvement with para-hisian pacing only.

Discussion

Our systematic review and meta-analysis were designed to compare the mid- and long-term effects of RVNA and RVA pacing in patients eligible for permanent pacemakers. We found that RVNA pacing resulted in a better LVEF compared with RVA pacing at the end of follow-up. Larger differences were found when the LVEF was reduced at baseline or when the study duration was >1 year. We also found that data regarding exercise capacity, functional class, quality of life, and survival were limited and inconclusive, highlighting the need for additional RCTs examining this issue.

The RVA is the traditional site for ventricular pacing mainly due to technical aspects such as the electrode design and the ease of the apical approach. However, it became apparent from a large body of evidence that pacing via the RVA may have a harmful effect on LV function.[2–8] This observation led to the first RCT by Barin *et al.*[31] that compared RVA to RVOT pacing, which showed that RVOT pacing is feasible, and that the pacing and sensing parameters at the RVOT were indistinguishable from those at the RVA. Randomized-controlled trials examining acute, mid-, and long-term effects have since been conducted assessing several alternative RV pacing sites to achieve a more 'physiological' pacing pattern, and thus to avoid LV function deterioration. The majority of RCTs with mid- and long-term follow-up measured LVEF as a surrogate marker of cardiovascular morbidity and mortality. However, these individual studies were inconclusive due to their small sample sizes. Our systematic review and meta-analysis has helped to reduce this limitation, lessening the amount of uncertainty surrounding treatment effects.

Our subgroup analyses found that RVNA pacing resulted in higher LVEF at the end of follow-up than RVA pacing in RCTs that examined mid- and long-term LVEF, although benefits were attenuated in mid-term RCTs. Physiologically, it is plausible to think that the longer the follow-up period is, the greater the benefit of RVNA or reduction in harm associated with RVA pacing should be. Although our meta-regression analysis found

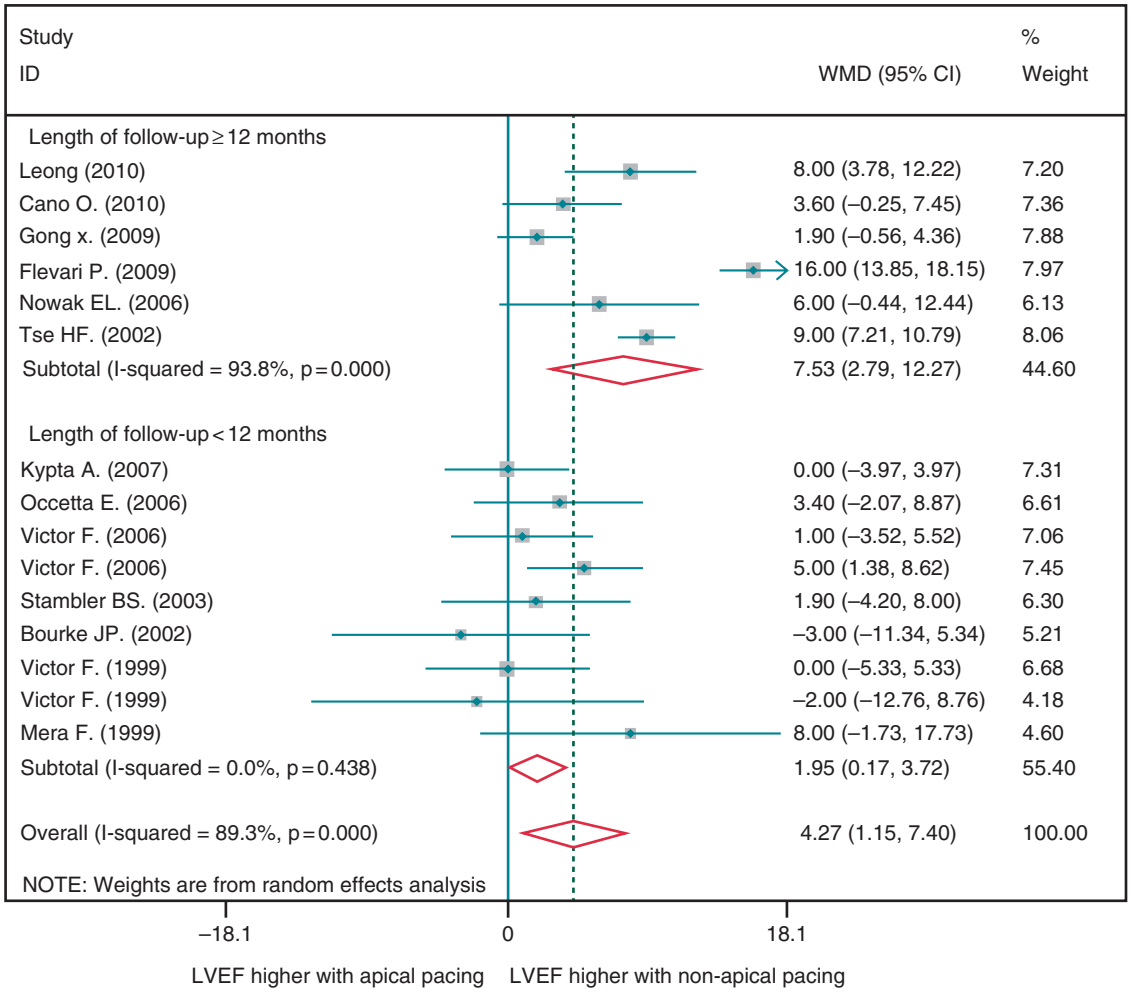

Figure 2 Forest plot comparing the effect of right ventricular apical vs. non-apical pacing on left ventricular ejection fraction (LVEF) at the end of follow-up in randomized-controlled trials with mid- and long-term follow-up. Weighted mean differences (WMDs) are presented for each trial and were pooled using a random-effects model to obtain summary estimates with corresponding 95% confidence intervals. Data are stratified by duration of follow-up and an overall summary estimate is presented at the bottom of the figure.

that the magnitude of benefit of RVNA pacing remained modest and similar irrespective of duration of follow-up, we were limited by the time periods of the individual studies. Thus, we cannot completely rule out an association between time of pacing and the degree of LVEF deterioration.

Our meta-analysis identified baseline LV function as an important predictor of the effect of RVNA pacing on LVEF. Right ventricular non-apical pacing led to a greater LVEF at the end of follow-up compared with RVA pacing in patients with baseline LVEF $< 40-45\%$ but there was no clear observable difference in final LVEF among patients with preserved baseline LVEF. One explanation for this finding is that there is an interaction between the deleterious effect of RVA pacing and certain myocardial substrate as was recently suggested.[32] There may also be a correlation between the longer-paced QRS duration by RVA pacing observed in most of the RCTs in our systematic review and the final LVEF. Prolonged electrical conduction causes mechanical delay within the LV that can result in reduced systolic function and LV cavity dilatation. This may deleteriously affect mainly patients with low LVEF at baseline. On a similar note, cardiac resynchronization therapy is recommended as a proven therapy for patients with severe LVEF and wide QRS. Its use in a population with preserved or even milder degrees of LV dysfunction is controversial and not recommended at present. Then again, we might be lacking a long-enough follow-up time to observe beneficial changes in the normal LVEF at-baseline group.

While differences in final LVEF were detected between pacing sites, our findings should be interpreted with caution given the observed effect size. The small pooled differences fall within the inter-observer and intra-observer variability for LVEF measurement.[33] In addition, the higher LVEF achieved by RVNA pacing may not correlate with improved clinical outcomes. In particular, the RVOT did not appear to provide a benefit in terms of long-term survival over RVA pacing,[20] although survival data were

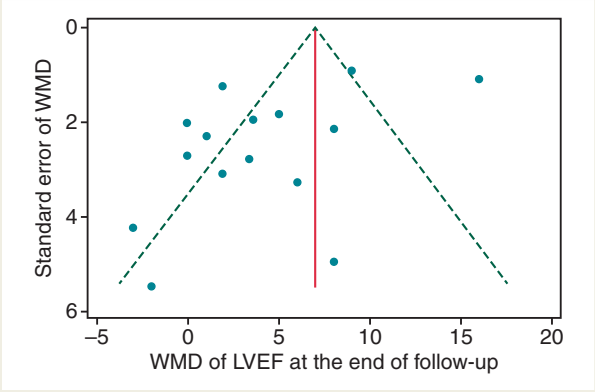

Figure 3 Funnel plot with pseudo (doted lines) 95% confidence limits of the effect of right ventricular pacing site (right apical vs. right non-apical) on left-ventricular ejection fraction at the end of follow-up. Evidence of publication bias exists. WMD, weighted mean difference; LVEF, left ventricular ejection fraction.

limited and inconclusive and no published study was powered to look at survival. Likewise, no significant differences were observed in NYHA heart failure class in four out of five RCTs examining this endpoint.[17,22,23,25,28] There are two large ongoing RCTs comparing the medium to long-term effects of RVNA and RVA pacing while a third trial was abandoned.[34] One ongoing trial uses high-septum pacing whereas the second uses the mid-septum inflow tract as the alternative pacing sites. A potential limitation to these RCTs is their choice of primary endpoint, which is the change in LVEF after 2–3 years of pacing. Evidence from the present study qualitative review suggests that the clinical significance of the small differences in final LVEF between the pacing sites is unclear. Consequently, clinical utility of the results of these ongoing RCTs may be modest. It is important to note that another alternative to RVA pacing is also currently explored in the form of bi-ventricular pacing (cardiac resynchronization therapy), and has showed some success.[35,36]

Our study has several potential limitations. First, there was a marked heterogeneity for our main meta-analysis of LVEF at the

Table 3 Summary of randomized-controlled trials comparing the effects of right ventricular apical pacing and right ventricular non-apical pacing on exercise capacity, functional class, quality of life, and survival

Author	Results
Leong *et al.* 2010	The paced QRS duration was significantly longer in patients in the RVA group; the RVA group had more intra-ventricular dyssynchrony than the RVNA group; left atrium volume was significantly lower among RVNA- than RVA-paced subjects
Cano *et al.* 2010	The paced QRS duration was significantly longer in patients in the RVA group; the RVA group had more intra-ventricular dyssynchrony than the RVNA group; BNP levels, NYHA functional class and quality of life were similar
Gong *et al.* 2009	The RVA group had more intra-ventricular systolic dyssynchrony than the RVNA group; LV end-diastolic and systolic volumes were similar
Flevari *et al.* 2009	The paced QRS duration was significantly longer in patients in the RVA group; at 12 months, there were no significant differences between groups in LV dyssynchrony; similar degree of mitral and tricuspid regurgitation
Dabrowska *et al.* 2009	The RVNA pacing provided no additional benefit in terms of long-term survival over RVA pacing
Kypta *et al.* 2008	The paced QRS duration was significantly longer in patients in the RVA group; changes of BNP level, and exercise capacity (bicycle exercise stress test) from baseline to 18 months were statistically not different between groups
Occhetta *et al.* 2006	The paced QRS duration was significantly longer in patients in the RVA group; the RVNA group allowed a significant improvement in NYHA functional class, quality of life and exercise capacity (6 -min-walk test); mitral and tricuspid regurgitation improved from baseline with RVNA pacing, with a slight worsening during apical pacing
Victor *et al.* 2006	The paced QRS duration was significantly longer in patients in the RVA group; no significant difference was observed in mean NYHA functional class, peak VO_2
Lewicka-Nowak *et al.* 2006	Progression of tricuspid valve regurgitation was observed in the RVA groups but not in the RVNA group; BNP levels were significantly higher in the RVA group than the RVNA group; no changes in QRS duration at the end of follow-up
Stambler *et al.* 2003	The paced QRS duration was significantly longer in patients in the RVA group; most of the quality-of-life scores were similar between groups; there were no significant differences between groups in the NYHA functional class, exercise capacity (6-min-walk test), or mitral regurgitation degree
Tse *et al.* 2002	The paced QRS duration was significantly longer in patients in the RVA group; the incidence of myocardial perfusion defects and regional wall motion abnormalities were higher in the RVA group than the RVNA group
Bourke *et al.* 2002	No significant differences were identified between the groups in parameters of systolic LV function and right and LV area; some diastolic parameters worsened with RVA pacing
Victor *et al.* 1999	The paced QRS duration was not longer in patients in the RVA group; there were no significant differences between groups in NYHA functional class, exercise capacity, and maximal oxygen uptake in patients with LVEF above and below 40%.
Mera *et al.* 1999	The paced QRS duration was significantly longer in patients in the RVA group; there were no significant differences between groups in exercise capacity.

BNP, brain natriuretic peptide; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New-York heart association; RVA, right ventricular apical; RVNA, right ventricular non-apical.

end of follow-up. This may be attributed to the RCT's varied populations, different pacing site, trial design, and methodological quality. However, after excluding two RCTs with the largest 'positive' effects, our results were attenuated but continued to show that RVNA had positive effects on LVEF with no heterogeneity between RCTs. Secondly, most of the RCTs only analysed data for patients who completed follow-up. The use of this analytical approach, rather than the use of an intention-to-treat approach, may result in the loss of the benefits of randomization, leading to confounding and allocation bias. Although we cannot rule out such bias, no significant differences were observed between the groups in baseline LVEF. Thirdly, data were presented in the original publications as baseline and follow-up LVEF values rather than as changes from baseline. Consequently, we were unable to pool changes in LVEF, and our analysis of LVEF at the end of follow-up therefore assumes no difference in baseline LVEF (an assumption that is supported by our analysis of baseline LVEF data). Fourthly, we carried our meta-analysis with both cross-over and parallel-group RCTs. Cross-over RCTs bear a potential risk of a carryover effect, which occurs when the treatment given in the first period influences the patient's response in the subsequent intervention period.[37] However, we performed a sensitivity analysis in which we restricted the analysis to parallel-group RCTs. The results of this sensitivity analysis continued to show significant benefit with RVNA pacing. Fifth, skewed funnel plot was found in our study, suggesting publication bias of positive results for RVNA pacing. This may be a concern in meta-analytic review of the current literature. However, in the absence of a large conclusive trial, our systematic review and meta-analysis of all available RCTs is the best method for appraising the literature. Finally, we combined all RVNA pacing sites into one group. This approach may limit the interpretation of the meta-analysis results for a specific pacing site.[38] We were unable to examine specific RVNA pacing sites due to the limited available data. However, not only RVNA sites have been poorly defined to date, most use overlapping areas of the interventricular septum. Therefore, we believe that the results of our approach are relevant and important for future research.

In conclusion, the present systematic review and meta-analysis suggest that after chronic pacing, RVNA site is associated with a higher LVEF than RVA. While this finding is encouraging, its clinical significance is uncertain. Available data for endpoints other than LVEF are limited and inconclusive. There remains a need for large RCTs powered to examine clinically relevant endpoints to conclusively compare the safety and efficacy of RVNA and RVA pacing for patients eligible for permanent pacemaker implantation.

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