Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2018, Vol. 46(9) 3848–3860

DOI: 10.1177/0300060518781415
journals.sagepub.com/home/imr
SAGE

Effects of right ventricular septum or His-bundle pacing versus right ventricular apical pacing on cardiac function: A systematic review and meta-analysis of randomized controlled trials

Lingfang Zhuang[1,*], Ye Mao[2,*], Liqun Wu[1], Wenquan Niu[3] and Kang Chen[1]

Abstract

Objective: Recent studies have demonstrated that right ventricular apical (RVA) pacing has a deleterious impact on left ventricular function, while right ventricular septum (RVS) or His-bundle pacing (HBP) contribute to improvements in cardiac function. A meta-analysis of randomized controlled trials (RCTs) was conducted to compare the mid- and long-term effects of RVS and HB pacing versus RVA pacing on cardiac function.

Methods: Eligible RCTs were identified by systematically searching the electronic literature databases PubMed®, Cochrane Library, Embase® and Ovid®.

Results: Seventeen articles ($n = 1290$ patients) were included in this meta-analysis, including 14 studies comparing the effects of RVA and RVS pacing on cardiac function and three studies comparing HBP with pacing at other sites. Compared with RVA pacing, RVS or HBP exhibited a higher left ventricular ejection fraction (LVEF) (weighted mean difference 3.28; 95% confidence interval 1.45, 5.12) at the end of follow-up.

Conclusions: RVS pacing exhibited a higher LVEF after long-term follow-up than RVA pacing. RVS pacing could replace the previously used RVA pacing as a better alternative with improved clinical outcomes. However, there remains a need for larger RCTs to compare the safety and efficacy of RVS with RVA pacing.

[1]Department of Cardiology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
[2]Outpatient Department, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[3]Shanghai Institute of Hypertension, Shanghai, China

*These authors contributed equally to this work.

Corresponding author:
Kang Chen, Department of Cardiology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, 197 Ruijin Er Road, Shanghai 200025, China.
Email: chenkang1978@163.com

Keywords
Cardiac pacing, right ventricular apex, septum, ejection fraction

Date received: 12 February 2018; accepted: 14 May 2018

Introduction

Since the advent of cardiac pacing, the right ventricular apical (RVA) area has been regarded as the major pacing site.[1] Recently, some studies have suggested that RVA pacing can change the ventricular activation sequence.[2–4] This can limit left ventricular (LV) apical motion, resulting in LV systolic dyssynchrony and electromechanical delay, which are deleterious to cardiac LV construction and function.[2–4] Chronic RVA pacing may lead to LV systolic and diastolic dysfunction, decreased cardiac output, and consequently can increase the rate of new-onset heart failure and mortality.[4] Therefore, searching for more suitable pacing sites with more synchronous activation patterns remains a challenging and clinically important task. Pacing from the right ventricular septum (RVS) or His-bundle area is considered to provide more physiological LV activation, presumably due to its closer proximity to the specialized conduction system.[5–12] However, there is currently no consensus regarding the effects of RVA and RVS pacing on cardiac function and long-term survival, largely due to the fact that available studies were insufficiently powered to allow for a generalized conclusion.[3,5]

Recently, some meta-analyses have evaluated the effects of different pacing sites besides RVA.[13–15] One meta-analysis found that compared with RVA, right ventricular non-apical pacing (including RVS and right ventricular outflow tract [RVOT]) may be associated with a higher LV ejection fraction (LVEF).[14] However, the heterogeneous results in the articles included in the meta-analysis may be due to various pacing sites (RVS and RVOT) or to the lack of comparison with His-bundle pacing (HBP), which is considered more physiological than RVA pacing.[14] With the accumulation of data from large randomized controlled trials (RCTs), a systematic review and meta-analysis of RCTs was conducted to compare the mid- and long-term effects of RVA with RVS (including RVOT septal pacing) and HBP on LV function and additional outcomes in patients eligible for permanent pacemakers.

Materials and methods

Search strategy

Eligible RCTs comparing the effects of RVS or HBP with RVA pacing published up 1 March 2017 were identified by systematically searching the electronic literature databases PubMed®, Cochrane Library, Embase® and Ovid®. The MeSH search string for the PubMed® search was "Heart Ventricles" [Mesh] AND "Cardiac Pacing, Artificial" [Mesh] AND "humans" [MeSH Terms]. The literature search was limited to studies conducted in humans. To find appropriate RCTs, PubMed® was searched with the following string: (clinical [Title/Abstract] AND trial [Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random* [Title/Abstract] OR random allocation [MeSH Terms] OR therapeutic use [MeSH Subheading]). The search strategy

for the other three databases was similar to that for the PubMed® database, in which the MeSH search string "heart ventricles" and "cardiac pacing" was used in the search process. Reviews and reference lists of retrieved articles were hand searched for potentially relevant publications not previously identified in the database search. All retrieved studies were examined to eliminate potential duplicates or overlapping data. When articles provided unclear additional data in their original publications, the first authors were contacted for clarification.

Trial selection criteria

Articles reporting on RCTs that compared the effects of RVA with RVS or HBP over a mid-or long-term follow-up period with respect to the cardiac function of patients who met the indications for pacing were included in the meta-analysis. The following exclusion criteria were used: (i) the follow-up of the studies was < 6 months; (ii) the outcomes of the studies did not cover cardiac function or LVEF; (iii) the articles compared the RVOT with RVA pacing rather than RVS pacing; and (iv) studies compared the effects of patients who received cardiac resynchronization therapy or implantable cardioverter defibrillator therapy on different pacing sites.

Data extraction

Two review authors (L.Z. and K.C.) independently scrutinized all titles and abstracts, and selected studies based on pre-determined inclusion and exclusion criteria to initially exclude irrelevant articles. Subsequently, the authors reviewed the full texts of the remaining articles. Two authors (L.Z. and K.C.) extracted data from the studies (including the methods, participants, interventions, outcomes and results) independently using a specially-designed data extraction form. The types of treatment and reported treatment quality were rated independently by three authors (L.Z., Y.M. and L.W.). Any disagreements were resolved by discussion, and if necessary, two authors (W.N. and K.C.) were consulted to make the final decision.

Quality assessment

The systematic review and meta-analysis were performed according to the PRISMA statement for reporting systematic reviews and meta-analyses of RCTs.[16] Double-blinding could not be achieved in RCTs involving pacemaker implantation. Therefore, quality was summarized using a modified version of the Jadad scoring system.[17] One point was assigned for an affirmative answer to each of the following five questions: (i) was the study described as randomized?; (ii) was there adequate concealment of allocation?; (iii) were the participant and personnel described as blinded?; (iv) was the outcome assessment described as blinded?; and (v) was there a description of withdrawals/dropouts?

Statistical analyses

The odds ratio (OR) was used to calculate the effect size for dichotomous outcomes and the mean difference between control and intervention groups was calculated for continuous outcomes. Weighted mean difference (WMD) was used if outcomes were measured in the same way across different trials, and on the contrary, standardized mean difference was applied; 95% confidence interval (CI) was presented for all outcomes and comparisons.

For heterogeneous tests, the I^2 ($I^2 < 25\%$ indicated without significant heterogeneity between different articles) and Q statistics (P-value < 0.1 represents statistical heterogeneity) were used to measure heterogeneity among the trials in each analysis. Subgroup and sensitivity analyses were used to look for the possible causes when significant

heterogeneity existed in the review. The study planned to use a funnel plot to explore the possibility of publication bias and small-study effects; and Egger' test to estimate the degree of publication bias. A lack of publication bias was defined as $P > 0.1$.[18] All statistical analyses were conducted using STATA® software version 13 (Stata Corp, College Station, TX, USA). A $P < 0.05$ was considered as statistically significant unless otherwise indicated.

This meta-analysis was carried out in three parts: the first part referred to pacing safety and validation; the second part compared the different pacing sites on cardiac function (including LVEF, 6-min walking test); and the third part compared the effect of different pacing sites on ventricular remodelling after long-term follow-up. Three subgroup analyses were displayed when the effects of LVEF in RVA versus RVS or HBP were compared. The relationship between length of follow-up ($\leq$12 months and $>$12 months) and the effects of His-bundle or para-HBP on LVEF were evaluated.

Results

Literature search

A total of 1795 potentially relevant articles (with duplicates deleted) were identified and screened (Figure 1). First, 1649 articles were

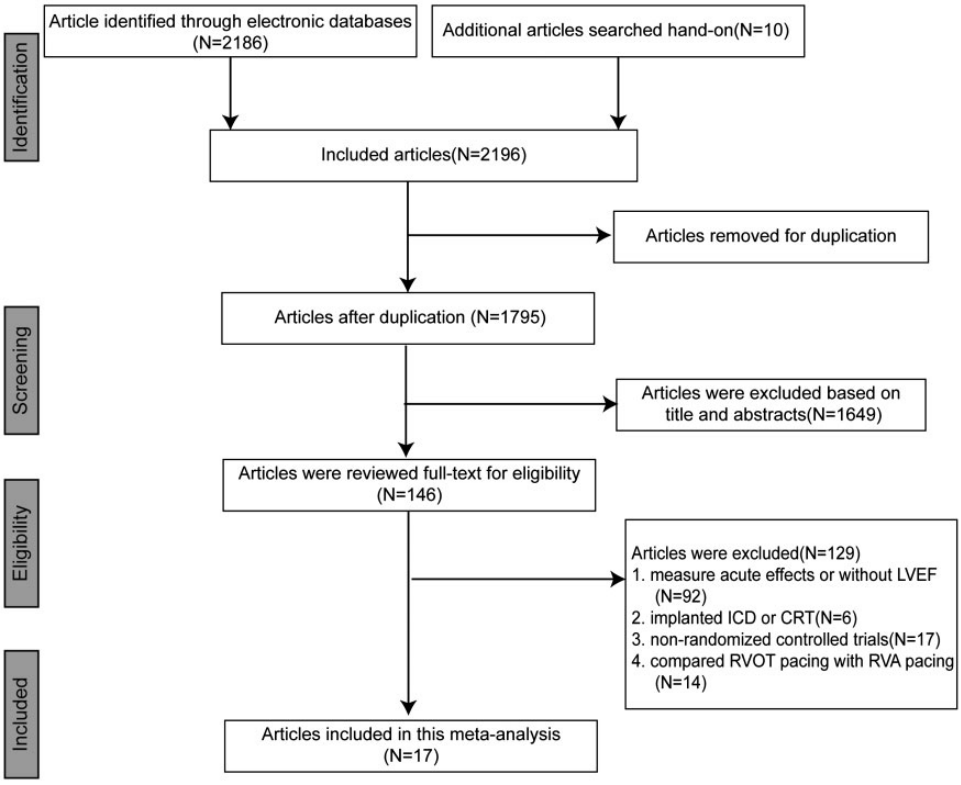

Figure 1. Flow diagram of the study selection process in a meta-analysis undertaken to compare the mid- and long-term effects of right ventricular septum and His-bundle pacing versus right ventricular apical pacing on cardiac function.

excluded based on titles and abstracts, then 146 articles were retrieved for a more detailed evaluation. After cautiously eliminating irrelevant studies, 17 articles were included in this meta-analysis. Fourteen of 17 qualified studies[5–9,19–27] compared the effects of RVA pacing with RVS (including RVOT septal) pacing on cardiac function, and three studies[11,12,28] compared HBP with other pacing sites.

Included articles

Seventeen studies were summarized in the analysis, which evaluated the effects of cardiac function after implantation of cardiac pacemakers.[5–9,11,12,19–28] The main characteristics of the included studies are summarized in Table 1. All studies were designed as randomized, blind, controlled clinical trials, and there were 14 studies[5–9,19–27] conducted by parallel design and three studies[11,12,28] by cross-over design. The characteristics of the participants were described in each article; patient indications for pacemaker implantation included management of atrioventricular block or sick sinus syndrome, and all of the patients had normal heart function prior to pacemaker implantation. All trials reported a baseline comparability of the characteristics of participants between treatment groups, and most of the characteristics of patients at baseline were similar. This meta-analysis included 1290 participants: 665 received RVA pacing and 712 received RVS or HBP; three studies[11,12,28] conducted their trials using a cross-over design so all of the study participants underwent two treatments during the research period.

Eleven studies[5–8,19–22,24,26,27] compared RVA pacing versus RVS pacing with a 12–48 month follow-up period; three studies[9,23,25] compared RVOT septal pacing with RVA pacing; and the remaining three articles described the effects of HBP with other pacing sites.[11,12,28] With respect to the latter, Kronborg et al.[12] compared the different effects of HBP with RVS pacing; and Pastore et al.[11] and Zanon et al.[28] compared HBP versus RVA pacing with a 3-month follow-up period.

Primary outcomes

Pacing parameters. Five studies[7,8,19,22,24] compared pacing capture threshold while pacing with RVA or RVS. These studies included 201 treated and 185 control participants and resulted in a significant WMD of 0.386 (95% CI 0.246, 0.525), with substantial heterogeneity ($I^2 = 83\%$). Another meta-analysis of 234 treatments resulted in a non-significant WMD of 0.07 (95% CI 0.00, 0.15), which failed to describe the effectiveness.[14]

Pacing QRS duration was assessed in six studies,[8,9,20,22,24,26] including 228 treated and 192 control participants. QRS duration in RVS pacing was shorter than RVA pacing (WMD –24.115; 95% CI –34.422, –13.808) with substantial heterogeneity ($I^2 = 86.6\%$).

All included studies evaluated the discrepancy of cardiac function after pacemaker implantation on account of the fact that RVA pacing changes the ventricular activation sequence, which may show deleterious effects on cardiac LV construction over long-term follow-up. Of these, 16 studies measured LVEF to assess cardiac function.[5–7,9,11,12,19–28] This meta-analysis subsequently pooled 16 trials that showed RVS or HBP had a higher LVEF than RVA pacing (WMD 3.28; 95% CI 1.45, 5.12; Figure 2) with substantial heterogeneity ($I^2 = 66.2\%$) between trials. To explore the heterogeneity, a subgroup analysis per comparison group was conducted and showed relevant differences per comparison group (RVS or HBP versus RVA pacing).

Subgroup analysis

Length of follow-up. The subgroup analysis investigated the influence of length of follow-up on LVEF after implantation of

Table 1. Characteristics of 17 articles included in a meta-analysis undertaken to compare the mid- and long-term effects of right ventricular septum and His-bundle pacing versus right ventricular apical pacing on cardiac function.

First author, year	*n*	RVNA pacing sites	Follow-up, months	Evaluated parameters
Bai et al., 2016[19]	96	Mid-RV septum	12	LVEF; LVEDD; LVESD; LVESV; LVEDV; SPWMD; NT-ProBNP
Saito et al., 2015[5]	145	Mid-RV septum	24	LVEF; 6WMT
Kaye et al., 2015[6]	240	High-RV septum	24	LVEF; NT-ProBNP; 6WMT; readmission and mortality rate
Molina et al., 2014[7]	71	Mid-RV septum	12	LVEF; pacing threshold; QRS duration; 6MWT; LVESD; LVEDD; LVEDV; LVESV
Chen et al., 2014[8]	90	Mid-RV septum	18	LVEF; NT-ProBNP; NYHA; 6MWT; QRS; pacing threshold; impedance
Zhang et al., 2012[9]	65	Septal RVOT	28	LVEF; QRS duration; LVESD; LVEDD; NT-ProBNP; NYHA; LAD
Domenchini et al., 2012[21]	59	RVS	48	LVEF; QRS duration; RVEF; NYHA
Leong et al., 2010[25]	58	Septal RVOT	29	LVEF; QRS duration; LVEDV; LVESV; LAV; GLS
Cano et al., 2010[20]	81	Mid-RV septum	12	LVEF; NYHA; QRS duration; 6MWT; BNP; LVEDV; LVESV; quality of life
Tse et al., 2009[27]	24	RVS	24	LVEF; 6MWT
Gong et al., 2009[23]	90	Septal RVOT	12	LVEF; QRS duration; LVEDV; LVESV; Em; Sm; Ts-SD; Te-SD
Takemoto et al., 2009[26]	55	RVS	24	LVEF; LVESD; LVEDD; IVMD; T(sys); QRS duration
Flevari et al., 2009[22]	31	RVS	12	LVEF; pacing threshold; impedance; QRS duration; LVEDV; LVESV
Kypta et al., 2008[24]	98	RVS	18	LVEF; impedance; pacing threshold; QRS duration; NT-ProBNP; exercise capacity
Pastore et al., 2014[11]	37	HBP/PHBP	3	LVEF; QRS duration; LVEDV; LVESV
Kronborg et al., 2014[12]	38	HBP/PHBP	24	LVEF; QRS duration; LVEDV; LVESV
Zanon et al., 2008[28]	12	HBP	3	LVEF; pacing threshold; QRS duration; LVEDV; LVESV

RVNA, right ventricular non-apical; RV, right ventricular; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; SPWMD, septal-to-posterior wall motion delay; NT-ProBNP, N-terminal prohormone of brain natriuretic peptide; 6WMT, 6-min walking test; RVOT, right ventricular outflow tract; NYHA, New York Heart Association Functional Classification; LAD, left atrial dimension; RVS, right ventricular septum; RVEF, right ventricular ejection fraction; LAV, left atrial volume; GLS, global longitudinal strain; BNP, brain natriuretic peptide; Em, early myocardial diastolic velocities; Sm, mean myocardial systolic velocities; Ts-SD, standard deviation of Ts; Te-SD, standard deviation of Te; IVMD, inter-ventricular electromechanical delay; T(sys), time-to-peak systolic velocity; HBP, His-bundle pacing; PHBP, para-His-bundle pacing.

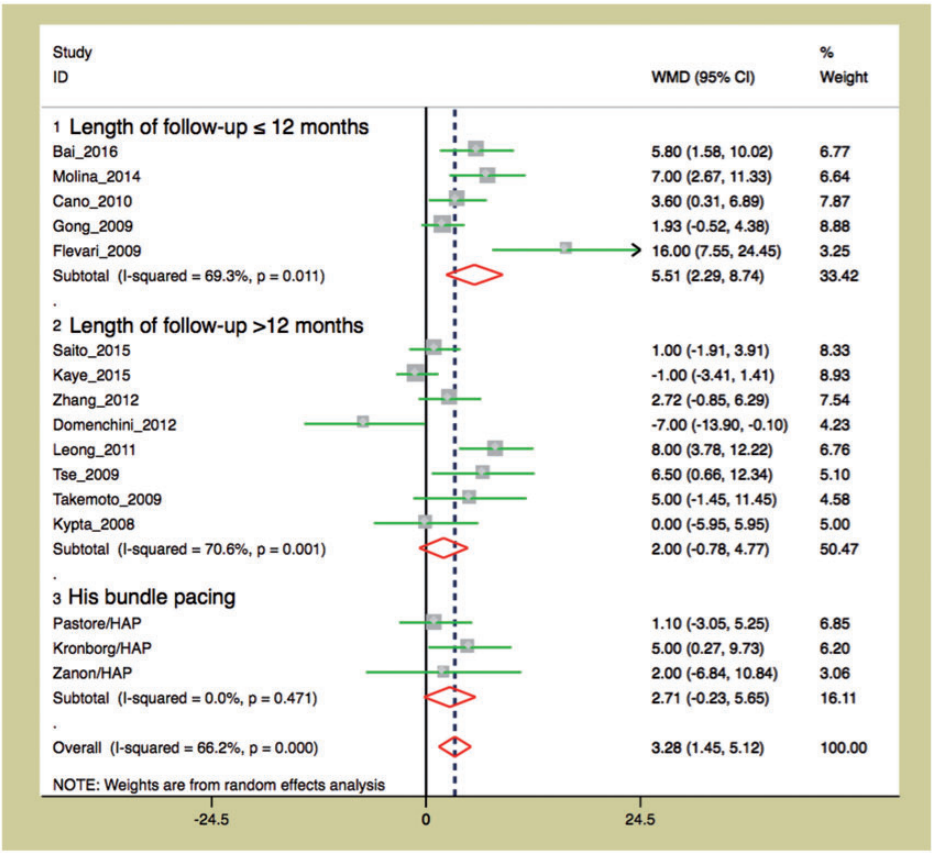

Figure 2. Forest plot of the subgroup analysis that investigated the influence of the length of follow-up on left ventricular ejection fraction after implantation of pacemakers. The colour version of this figure is available at: http://imr.sagepub.com.
WMD, weighted mean difference; CI, confidence interval.

pacemakers. Five studies had ≤12-months follow-up.[7,19,20,22,23] When stratified by length of follow-up, RVS pacing led to a higher LVEF at the end of follow-up than RVA pacing (WMD 5.51; 95% CI 2.29, 8.74; Figure 2) with substantial heterogeneity ($I^2 = 69.3\%$) between trials. In another subgroup with > 12-months follow-up, RVS pacing did not reach a statistically significant difference in LVEF compared with RVA pacing (WMD 2.00; 95% CI –0.78, 4.77) with substantial heterogeneity ($I^2 = 70.6\%$). These findings were in contrast to another meta-analysis, which demonstrated that right ventricular non-apical (RVNA) pacing resulted in a significantly higher LVEF than RVA pacing in six RCTs with ≥12-months follow-up (WMD of LVEF: 7.53%; 95% CI 2.79, 12.27), but there was appreciable evidence of heterogeneity ($I^2 = 93.8\%$).[15] By visual inspection of the Forest plot (Figure 2), there were two RCTs showing extreme effects for RVS or RVA pacing: one RCT demonstrated extremely beneficial effects of RVS compared with RVA,[22] while a second suggested that RVS had more detrimental effects than RVA.[21] However, these two

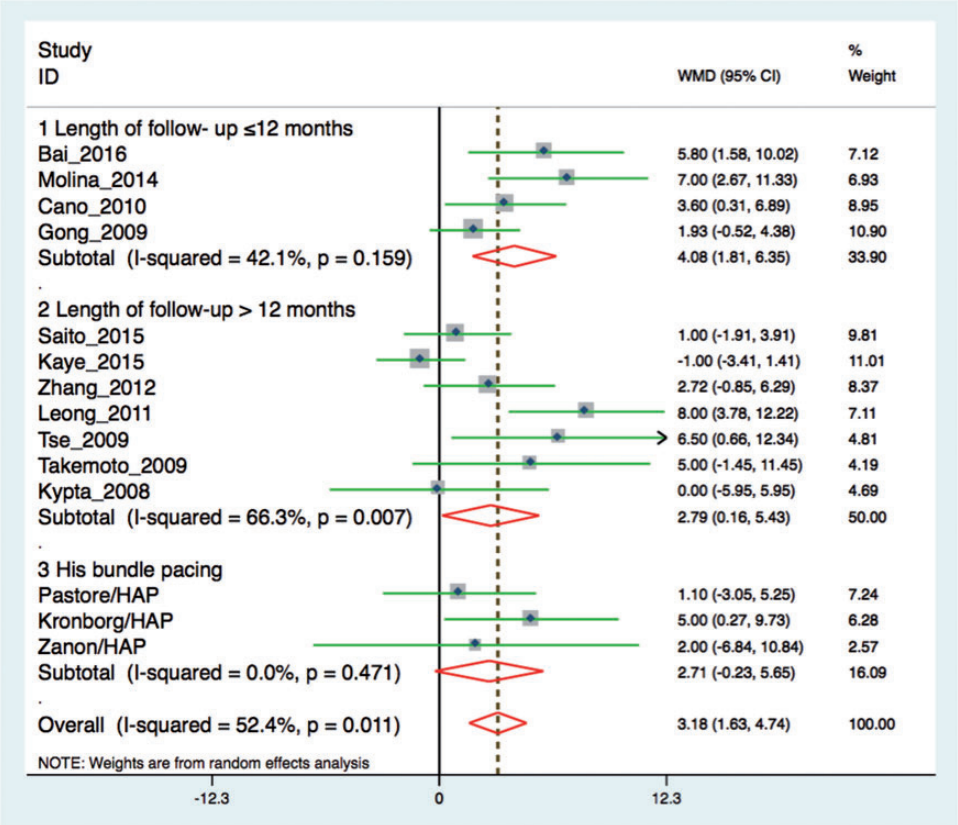

Figure 3. Forest plot of the subgroup analysis that investigated the influence of the length of follow-up on left ventricular ejection fraction after implantation of pacemakers with two trials removed from the analysis. The colour version of this figure is available at: http://imr.sagepub.com.
WMD, weighted mean difference; CI, confidence interval.

studies were limited by their relatively small sample sizes.[21,22] Furthermore, these two studies scored relatively low when evaluated by the Jadad scoring system, and therefore these two RCTs were removed to reassess the influence of the length of follow-up on LVEF (Figure 3).

After excluding the two aforementioned RCTs,[21,22] total effect size was not altered compared with the former analysis (WMD 3.18; 95% CI 1.63, 4.74; WMD 3.28; 95% CI 1.45, 5.12; respectively), but the heterogeneity was reduced to 52.4%. With respect to the subgroup analysis with length of follow-up $\leq$12 months, RVS pacing showed a higher LVEF than RVA pacing with moderate heterogeneity (WMD 4.08; 95% CI 1.81, 6.35; $I^2 = 42.1\%$). Subgroup analysis with length of follow-up $>$ 12 months revealed that RVS pacing had a significantly higher LVEF than RVA pacing (WMD 2.79; 95% CI 0.16, 5.43), but there was significant heterogeneity ($I^2 = 66.3\%$).

HBP compared with other pacing sites. His-bundle pacing is considered more physiological than RVA and RVS pacing. Therefore, the meta-analysis compared LVEF in HBP with other pacing sites. Three RCTs were included: one study

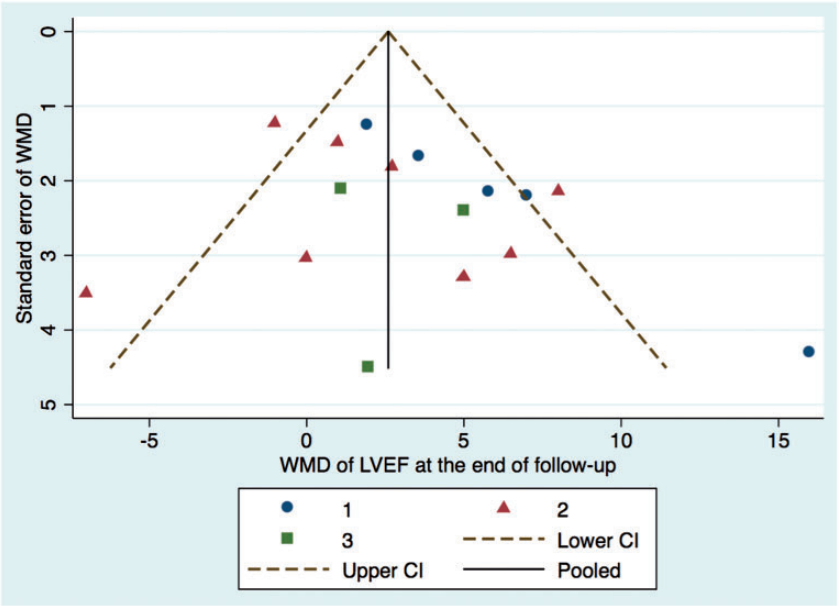

Figure 4. Funnel plot for the effect of different right ventricular pacing sites including data from 16 randomized controlled trials on left ventricular ejection fraction (LVEF) at the end of follow-up. The colour version of this figure is available at: http://imr.sagepub.com.
WMD, weighted mean difference; CI, confidence interval.

compared the different effects of HBP with RVS pacing;[12] while the other two studies compared HBP with RVA pacing.[11,28] The pooled effect size suggested that HBP had a higher LVEF (WMD 2.71) with low heterogeneity ($I^2 = 0.0\%$), but the results did not reach statistical significance (95% CI −0.23, 5.65).

Publication bias

A funnel plot was drawn (Figure 4) and this showed limited asymmetry for LVEF results (based on 16 RCTs).[5–7,9,11,12,19–28] Egger's test also indicated that there was no proof of the existence of publication bias.

Sensitivity analysis

As mentioned above, two RCTs with exaggerated effects for RVS or RVA pacing were excluded, resulting in a change in the pooled effect sizes and heterogeneity. The difference in effects may be explained by the following reasons: (i) relatively small sample size of the two RCTs. This was mainly due to a relatively high dropout and mortality rate (as the patient population was elderly and the duration of follow-up was long). One study[22] included 31 participants and the other one[21] included 59 participants; (ii) accurate location of the pacing sites. Most trials compared apical pacing with septal pacing, but anatomical implantation of the leads may not always be accurate, due to various reasons including technical difficulty of the procedure. Some trials reported that systolic function was significantly reduced when the lead was inadvertently placed in an anterior position instead of a mid-septal position.[2,29] A worse ventricular dyssynchrony and LVEF were reported when the RV lead was placed in an anteroseptal position (confirmed by echocardiography) than at the apex.[29] Thus, the inconsistent results of studies on septal

pacing may be due to variable positioning of the RV lead, which was not properly evaluated in most studies. For example, one study reported that septal lead positioning could not be achieved in 5/31 (16%) patients by echographic validation.[21]

Secondary outcomes

Comparison of the effect of cardiac ventricular remodelling after long-term follow-up. Left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) reflect cardiac ventricular remodelling with long-term cardiac decompensation. This meta-analysis calculated the effect sizes of LVESV and LVEDV to evaluate the effects of different pacing sites on ventricular remodelling. The analysis found that compared with RVA pacing, RVS pacing neither improved LVESV nor LVEDV after implanted pacemaker during long-term follow-up (WMD –9.268; 95% CI –22.088, 3.553; WMD –7.361; 95% CI –16.246, 1.524; respectively) with substantial heterogeneity (I^2= 97.8% and I^2= 75.7%, respectively). These results are inconsistent with those of other meta-analyses.[14,15] For example, one meta-analysis reported that RVA pacing was associated with higher LVESV than RVNA pacing (WMD –5.05, 95% CI –9.26, –0.84).[14] However, there was no distinct inconsistency in LVEDV at the end of follow-up (WMD –3.72, 95% CI –8.82, –1.38).[14]

Discussion

This current meta-analysis compared the mid- and long-term effects of RVS or HBP with RVA pacing in patients suitable for pacemaker implantation. Compared with RVA pacing, RVS pacing was associated with a higher LVEF after long-term follow-up. HBP did not show a significant difference in LVEF compared with other pacing sites. The QRS duration was shorter in RVS or HBP after long-term follow-up. In contrast, the pacing capture threshold was higher compared with RVA pacing. LVESV and LVEDV did not show significant differences among the different pacing sites with substantial heterogeneity between trials.

The right ventricular apex has been used as the major pacing site for patients with sick sinus syndrome and atrioventricular block. However, recently, evidence from small experimental and clinical studies has suggested that RV apical pacing deteriorates LV function, for that RVA pacing causes LV mechanical dyssynchrony because of altered ventricular excitation.[8,20,26] Some trials have found that RVOT, RVS or His-bundle might provide a more physiological LV activation sequence presumably due to the closer proximity to the specialized conduction system.[12,21,30] However, these trials had inconsistent results likely due to their small sample sizes, differences in techniques used or participant baseline characteristics.[12,21,30] Therefore, this current meta-analysis was undertaken to compare the effect of RVS or HBP with RVA pacing on long-term survival.

Compared with RVA pacing, the pacing capture threshold is higher in patients with RVS or HBP.[7,8,19,22,24] Pacemaker electrodes consist of active fixation leads and passive fixation leads; in general, the passive fixation lead is anchored to the right ventricular apex while the active fixation lead is implanted in the septal or His-bundle area. It is thought that local myocardial oedema, inflammation and fibrosis post-operatively may lead to a higher pacing capture threshold of the active leads, which is then gradually reduced due to the release of steroids surrounding the spiral leads; and a similar threshold level to the passive leads is eventually achieved.[31,32] The findings of this current meta-analysis suggested a tendency toward a higher pacing capture threshold in RVS pacing with statistical significance.

Most RCTs suggested QRS duration as a parameter of inter-ventricular dyssynchrony,

which may be related to the long-term differences in LVEF.[8,9,20,22,24,26] In this current meta-analysis, QRS duration was lower in the RVS pacing group than in the RVA pacing group. This finding suggests that RVS or HBP induce more synchronous LV contraction than RVA pacing and result in better electromechanical synchrony than RVA pacing. Nevertheless, QRS duration is not the only variable affecting ventricular synchrony, as it has been previously demonstrated that inter-ventricular dyssynchrony is present even in patients with narrow QRS complexes.[21,33] In order to further elucidate these inconsistencies, more advanced techniques such as 2D echocardiography, tissue doppler imaging and speckle-tracking imaging should be used to evaluate ventricular synchrony and cardiac function.

Compared with the RVS pacing group, patients in the RVA group tended to have a lower LVEF at mid- and long-term follow-up. Subgroup analysis also confirmed the beneficial effects of right ventricular non-apical pacing on LVEF. RVS pacing resulted in a higher LVEF with moderate heterogeneity between trials when the length of follow-up was $\leq$12 months. However, LVEF declined as the length of follow-up increased. These results were contrary to those of a previous meta-analysis,[14] which found that the benefits of RVNA pacing compared with RVA with respect to improved LVEF began to emerge in the 6-month and $\leq$12-month follow-up subgroups; and were increased as the pacing duration increased. These differing results may have been influenced by the age of participants included in the respective studies. Unlike RVS pacing, HBP did not show statistically significant results compared with other pacing sites. This finding may be due to the cross-over design of this meta-analysis, which included three trials examining HBP, and which resulted in a residual effect between groups. The results may also have been influenced by differences in length of follow-up. In two of the trials,[11,28] the duration of follow-up was limited to 3 months. This time frame may have been insufficient to capture significant effects, as it has been suggested that compared with RVS pacing, HBP improves LVEF after a 24-month follow-up period.[12] Thus, larger RCTs are required to verify the relationship between HBP and other pacing sites.

Right ventricular apical pacing could result in LV systolic dyssynchrony and electromechanical delay, which may be deleterious to cardiac LV construction and function.[2–4] However, this current meta-analysis found no significant difference in LVESV or LVEDV between RVA and RVS pacing sites at the end of follow- up. A longer follow-up period may help identify any significant differences in LVEDV or LVESV associated with different pacing sites.

This current meta-analysis had several limitations. First, there was substantial heterogeneity at the end of the follow-up period. This may be attributed to the RCTs' varied populations, different pacing sites, trial design and methodological quality. Three subgroups analyses were conducted to identify the causes of the heterogeneity and two subgroups pooled the effect size with no heterogeneity. 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 have resulted in the loss of the benefits of randomization, leading to confounding and allocation bias.

In conclusion, compared with RVA pacing, RVS pacing was associated with a higher LVEF, a shorter QRS duration pacing and higher capture threshold after long-term follow-up. RVS pacing could replace previously used methods of RV apical pacing as a more preferable method for chronic stimulation. In view of the clinical significance of pacing, there is an urgent

need for continuing research to facilitate our understanding of the safety and efficacy of new pacing sites.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was supported by grants from the National Natural Science Foundation of China (no. 30900604 and no. 81270004).

ORCID iD

Kang Chen http://orcid.org/0000-0001-8615-4577

References

1. Furman S and Schwedel JB. An intracardiac pacemaker for Stokes-Adams seizures. *Pacing Clin Electrophysiol* 2006; 29: 453–458.
2. Mills RW, Cornelussen RN, Mulligan LJ, et al. Left ventricular septal and left ventricular apical pacing chronically maintain cardiac contractile coordination, pump function and efficiency. *Circ Arrhythm Electrophysiol* 2009; 2: 571–579.
3. Thambo JB, Bordachar P, Garrigue S, et al. Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. *Circulation* 2004; 110: 3766–3772.
4. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002; 288: 3115–3123.
5. Saito M, Kaye G, Negishi K, et al. Dyssynchrony, contraction efficiency and regional function with apical and non-apical RV pacing. *Heart* 2015; 101: 600–608.
6. Kaye GC, Linker NJ, Marwick TH, et al. Effect of right ventricular pacing lead site on left ventricular function in patients with high-grade atrioventricular block: results of the Protect-Pace study. *Eur Heart J* 2015; 36: 856–862.
7. Molina L, Sutton R, Gandoy W, et al. Medium-term effects of septal and apical pacing in pacemaker-dependent patients: a double-blind prospective randomized study. *Pacing Clin Electrophysiol* 2014; 37: 207–214.
8. Chen K, Mao Y, Liu SH, et al. Is right ventricular mid-septal pacing superior to apical pacing in patients with high degree atrioventricular block and moderately depressed left ventricular function? *J Zhejiang Univ Sci B* 2014; 15: 507–514.
9. Zhang HX, Qian J, Hou FQ, et al. Comparison of right ventricular apex and right ventricular outflow tract septum pacing in the elderly with normal left ventricular ejection fraction: long-term follow-up. *Kardiol Pol* 2012; 70: 1130–1139.
10. Sharma PS, Dandamudi G, Naperkowski A, et al. Permanent His-bundle pacing is feasible, safe, and superior to right ventricular pacing in routine clinical practice. *Heart Rhythm* 2015; 12: 305–312.
11. Pastore G, Aggio S, Baracca E, et al. Hisian area and right ventricular apical pacing differently affect left atrial function: an intra-patients evaluation. *Europace* 2014; 16: 1033–1039.
12. Kronborg MB, Mortensen PT, Poulsen SH, et al. His or para-His pacing preserves left ventricular function in atrioventricular block: a double-blind, randomized, cross-over study. *Europace* 2014; 16: 1189–1196.
13. Kaye G, Hussain M, Furuya-Kanamori L, et al. A meta-analysis of randomised controlled trials on the effect of right ventricular apical and non-apical pacing on left ventricular ejection fraction. *Heart Lung Circ* 2015; 24: S234.
14. Weizong W, Zhongsu W, Yujiao Z, et al. Effects of right ventricular nonapical pacing on cardiac function: a meta-analysis of randomized controlled trials. *Pacing Clin Electrophysiol* 2013; 36: 1032–1051.
15. Shimony A, Eisenberg MJ, Filion KB, et al. Beneficial effects of right ventricular

non-apical vs. apical pacing: a systematic review and meta-analysis of randomized-controlled trials. *Europace* 2012; 14: 81–91.
16. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; 8: 336–341.
17. Panic N, Leoncini E, de Belvis G, et al. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. *PLoS One* 2013; 8: e83138.
18. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
19. Bai M, Li Q, Jiang G, et al. Comparison of effectiveness of right ventricular mid-septal pacing vs. apical pacing: a randomized-controlled trials. *Eur Heart J Suppl* 2016; 18(Suppl F): F12–F18.
20. Cano O, Osca J, Sancho-Tello MJ, et al. Comparison of effectiveness of right ventricular septal pacing versus right ventricular apical pacing. *Am J Cardiol* 2010; 105: 1426–1432.
21. Domenichini G, Sunthorn H, Fleury E, et al. Pacing of the interventricular septum versus the right ventricular apex: a prospective, randomized study. *Eur J Intern Med* 2012; 23: 621–627.
22. Flevari P, Leftheriotis D, Fountoulaki K, et al. Long-term nonoutflow septal versus apical right ventricular pacing: relation to left ventricular dyssynchrony. *Pacing Clin Electrophysiol* 2009; 32: 354–362.
23. Gong X, Su Y, Pan W, et al. Is right ventricular outflow tract pacing superior to right ventricular apex pacing in patients with normal cardiac function? *Clin Cardiol* 2009; 32: 695–699.
24. Kypta A, Steinwender C, Kammler J, et al. Long-term outcomes in patients with atrioventricular block undergoing septal ventricular lead implantation compared with standard apical pacing. *Europace* 2008; 10: 574–579.
25. Leong DP, Mitchell AM, Salna I, et al. Long-term mechanical consequences of permanent right ventricular pacing: effect of pacing site. *J Cardiovasc Electrophysiol* 2010; 21: 1120–1126.
26. Takemoto Y, Hasebe H, Osaka T, et al. Right ventricular septal pacing preserves long-term left ventricular function via minimizing pacing-induced left ventricular dyssynchrony in patients with normal baseline QRS duration. *Circ J* 2009; 73: 1829–1835.
27. Tse HF, Wong KK, Siu CW, et al. Impacts of ventricular rate regularization pacing at right ventricular apical vs. septal sites on left ventricular function and exercise capacity in patients with permanent atrial fibrillation. *Europace* 2009; 11: 594–600.
28. Zanon F, Bacchiega E, Rampin L, et al. Direct His bundle pacing preserves coronary perfusion compared with right ventricular apical pacing: a prospective, cross-over mid-term study. *Europace* 2008; 10: 580–587.
29. Ng AC, Allman C, Vidaic J, et al. Long-term impact of right ventricular septal versus apical pacing on left ventricular synchrony and function in patients with second- or third-degree heart block. *Am J Cardiol* 2009; 103: 1096–1101.
30. Deshmukh P, Casavant DA, Romanyshyn M, et al. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. *Circulation* 2000; 101: 869–877.
31. de Cock CC, Van Campen CM, In't Veld JA, et al. Utility and safety of prolonged temporary transvenous pacing using an active-fixation lead: Comparison with a conventional lead. *Pacing Clin Electrophysiol* 2003; 26: 1245–1248.
32. Kistler PM, Kalman JM, Fynn SP, et al. Rapid decline in acute stimulation thresholds with steroid-eluting active-fixation pacing leads. *Pacing Clin Electrophysiol* 2005; 28: 903–909.
33. Emkanjoo Z, Esmaeilzadeh M, Mohammad Hadi N, et al. Frequency of inter- and intraventricular dyssynchrony in patients with heart failure according to QRS width. *Europace* 2007; 9: 1171–1176.