

ORIGINAL ARTICLE

Comparison of triple-site ventricular pacing versus conventional cardiac resynchronization therapy in patients with systolic heart failure: A meta-analysis of randomized and observational studies

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Abstract

Background: Conventional cardiac resynchronization therapy (CRT, Bi-V) is associated with no response in about 40% patients due to an insufficient resynchronization. Some studies showed triple-site ventricular (Tri-V) pacing had greater benefits compared with Bi-V pacing, but the results of these studies were conflicting. We hypothesized that Tri-V pacing had greater benefits on long-term outcomes compared with Bi-V pacing in patients with heart failure.

Methods: PubMed, EMBASE, and the Cochrane Library were searched for clinical studies with related outcomes. Weighted mean differences (WMD) and 95% confidence intervals (CIs) were calculated to compare the change in left ventricular ejection fraction (LVEF), left ventricular geometry, functional capacity, and quality of life between Tri-V pacing group and control group.

Results: Five trials with 251 patients were included in the analysis. Patients in the Tri-V pacing group had a greater improvement in LVEF (WMD 4.04; 95% CI 2.15-5.92, $P < .001$) and NYHA classes (WMD -0.27 ; 95% CI -0.42 to -0.11 , $P = .001$) compared with control group. However, there were no significant differences in left ventricular geometry, six-min walk distance, or Minnesota Living With Heart Failure Questionnaire score between the two groups. The subgroup analyses showed there might be a greater improvement in LVEF in the Tri-V pacing group in patients with QRS duration ≥ 155 ms (WMD 5.60; 95% CI 3.09-8.10, $P < .001$).

Conclusions: The present analysis suggests that Tri-V pacing has greater benefits in terms of an improvement in LVEF and functional capacity in patients with systolic heart failure, especially in patients with the duration of QRS ≥ 155 ms.

KEYWORDS

cardiac resynchronization therapy, left ventricular ejection fraction, meta-analysis, systolic heart failure, triple-site ventricular pacing

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1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) is an important therapy in patients with drug-refractory heart failure (HF) and shown to have benefits on the improvement in symptoms, quality of life, exercise tolerance, left ventricular (LV) systolic performance, and mortality.¹ Therefore, CRT is recommended as an important device treatment in patients with sinus rhythm, low left ventricular ejection fraction (LVEF), prolonged QRS duration, and left bundle branch block (LBBB) in current guidelines for the management of heart failure.² However, not all patients received CRT could get benefits from the therapy. Up to 40% patients could not get benefits from CRT therapy, which were described as CRT nonresponders.³

An insufficient resynchronization effect from conventional CRT (Bi-V) might mainly contribute to the nonresponder. Therefore, triple-site ventricular (Tri-V) pacing was devised to improve the resynchronization effect in patients treated with CRT.⁴ Previous studies showed greater benefits of Tri-V pacing on hemodynamics and dyssynchrony compared with Bi-V pacing.^{5,6} However, clinical studies comparing the efficacy of Tri-V pacing versus Bi-V pacing on the long-term outcomes in patients with HF had conflicting results. In the study by Lenarczyk et al⁷ and the study by Rogers et al,⁸ Tri-V pacing showed a greater improvement on LV remodeling, NYHA classes, and 6-minute walking distance (6MWD) compared with Bi-V pacing. In the study by Leclercq and colleagues, Tri-V pacing had a greater improvement on LV remodeling, but had similar effects on quality of life and 6MWD compared with Bi-V pacing.⁹ However, other two studies showed that there were no significant differences between Tri-V pacing and Bi-V pacing groups with respect to NYHA classes and LV remodeling at the end of study.^{10,11} Therefore, it is necessary to conduct a meta-analysis and to compare the benefits of Tri-V pacing versus Bi-V pacing on the LV remodeling, quality of life, and exercise capacity in patients with HF.

2 | METHODS

2.1 | Literature search

A literature search was performed on the PubMed, EMBASE, and Cochrane Library to identify all the studies that reported the effects of Tri-V pacing on the clinical outcomes in patients with HF. The following medical subject headings were used: cardiac resynchronization therapy, heart failure, and triple-site ventricular pacing (or triple ventricular pacing or multisite pacing). For all relevant publications, the records retrieved with the “related articles” link in PubMed were reviewed; reference lists were also checked for other relevant studies. The final literature search was finished on January 31, 2017. The major inclusion criteria were as follows: (i) clinical trials published in peer-reviewed journals with full-text available; (ii) clinical trials comparing the efficacy of Tri-V pacing with Bi-V pacing in patients with HF; (iii) follow-up duration ≥ 6 months. The major reasons for exclusion of studies were as follows: (i) duplicates; (ii) data published in the form of abstracts without peer-reviewed publication of

manuscripts; (iii) studies without appropriate outcomes; (iv) studies with no control group or those with an inappropriate control group.

2.2 | Data collection

Two investigators independently reviewed all potentially eligible studies using predefined eligibility criteria and collected data from the included studies. Both randomized controlled trials (RCTs) and nonrandomized observational studies (nROS) comparing the efficacy of Tri-V pacing with Bi-V pacing in patients treated with CRT were included. Any discrepancy was resolved by consensus. Characteristics of the included studies and baseline characteristics of patients, as well as data about intervention and outcomes of each trial, were extracted.

2.3 | Statistical analysis

Statistical analyses were performed using STATA 11.0 (StataCorp LP, College Station, TX, USA). Continuous variables were presented as mean \pm SD, and categorical data were summarized as frequencies or percentages. Weighted mean differences (WMD) and 95% confidence intervals (CIs) were calculated for continuous variables. Heterogeneity was evaluated by Cochran's Q statistic and quantified by I^2 statistic. A value of $P < .05$ for Q test or $I^2 > 50\%$ indicated significant heterogeneity. If there was a significant heterogeneity, random-effects model was used; otherwise, fixed-effects model was used. Publication bias was evaluated by Begg's and Egger's methods. Results were considered statistically significant if $P < .05$. Sensitivity analyses were undertaken by omitting one study at a time to examine the influence of one study on the overall summary estimate, and fixed- or random-effects models described above were used.

We explored possible explanations for heterogeneity according to the prespecified hypothesis, which included mean age, gender, design of study, baseline NYHA classes, duration of QRS complex, etiology of heart failure, left ventricular size, and modality of Tri-V pacing. Recognizing that any cutoff point was arbitrary, we chose cutoff points before analyzing the data using two criteria: Thresholds had to be biologically sensible; and they had to divide the trials into two subgroups with a similar number of trials.

3 | RESULTS

3.1 | Search results

Figure 1 showed the detailed study selection process. A total of 81 potential literature citations were identified through systematic search, with 41 citations being excluded during title and abstract review. The full-text documents of the remaining 40 articles were retrieved. Of these 40 articles, 35 articles were excluded because of review articles, without an appropriate control group or with no relevant outcomes. Finally, five trials (1 RCT, 2 single-blind randomized crossover studies, and 2 nROSs) with 251 patients were included in the analysis. The characteristics of included studies are shown in

Table 1. There were two different pacing modalities proposed using multiple leads: the first using one right ventricular (RV) lead and two left ventricular (LV) leads inserted in the two separate tributaries of the coronary sinus, and the second using two RV leads and one LV lead.

3.2 | Baseline characteristics of patients

The baseline characteristics of patients enrolled were summarized in Table 2. The mean age ranged from 56 to 70 years old. The mean proportion of male patients ranged from 27.8% to 100%. Patients from all studies had impaired systolic LV function (mean LVEF ranging from 23% to 29%) and prolonged QRS duration (mean QRS duration ranging from 138 ms to 174 ms). The proportion of ischemic heart disease ranged from 27% to 62.8%. Most patients in these studies received the optimal pharmacologic therapy with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) (mean proportion ranging from 87.9% to 98%) and β -blockers (mean proportion ranging from 73% to 94%).

3.3 | Comparison of left ventricular remodeling between the two groups

All 5 studies investigated the efficacy of the two pacing strategies on the left ventricular remodeling, which was assessed by left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVDV), and left ventricular end-systolic volume (LVSV). As the

baseline LVEFs were different among the enrolled studies, it seemed more plausible to compare the improvement in LVEF, LVDV, and LVSV between the two groups (change from baseline to follow-up). I^2 statistic and Q test showed that there was no significant heterogeneity of improvement in LVEF among the studies ($I^2 = 32.2\%$, $\chi^2 = 5.9$, $P = .207$), so the fixed-effects model was used to pool the data. The pooled data showed that the improvement in LVEF in the Tri-V pacing group was greater compared with that in the Bi-V pacing group (WMD 4.04; 95% CI 2.15-5.92, $P < .001$, Figure 2). The heterogeneities of changes in LVDV and LVSV among the studies were neither significant ($I^2 = 0.0$, $\chi^2 = 1.29$, $P = .864$ for LVDV; $I^2 = 0$, $\chi^2 = 2.14$, $P = .711$ for LVSV). However, the pooled data showed that the changes in LVDV and LVSV were similar between the two groups (WMD -1.10, 95% CI -17.06-14.87, $P = .89$ for LVDV, Figure 3A; WMD -6.01, 95% CI -20.02-7.99, $P = .4$ for LVSV, Figure 3B).

3.4 | Comparison of functional capacity between the two groups

All 5 studies compared the functional capacity between the two groups by means of NYHA classes or 6-MWD. I^2 statistic and Q test showed that there was no significant heterogeneity of change in NYHA classes among the studies ($I^2 = 0$, $\chi^2 = 2.08$, $P = .556$), so the fixed-effects model was used to pool the data. The pooled data showed a greater improvement in NYHA classes in the Tri-V pacing compared with Bi-V pacing group (WMD -0.27; 95% CI -0.42 to

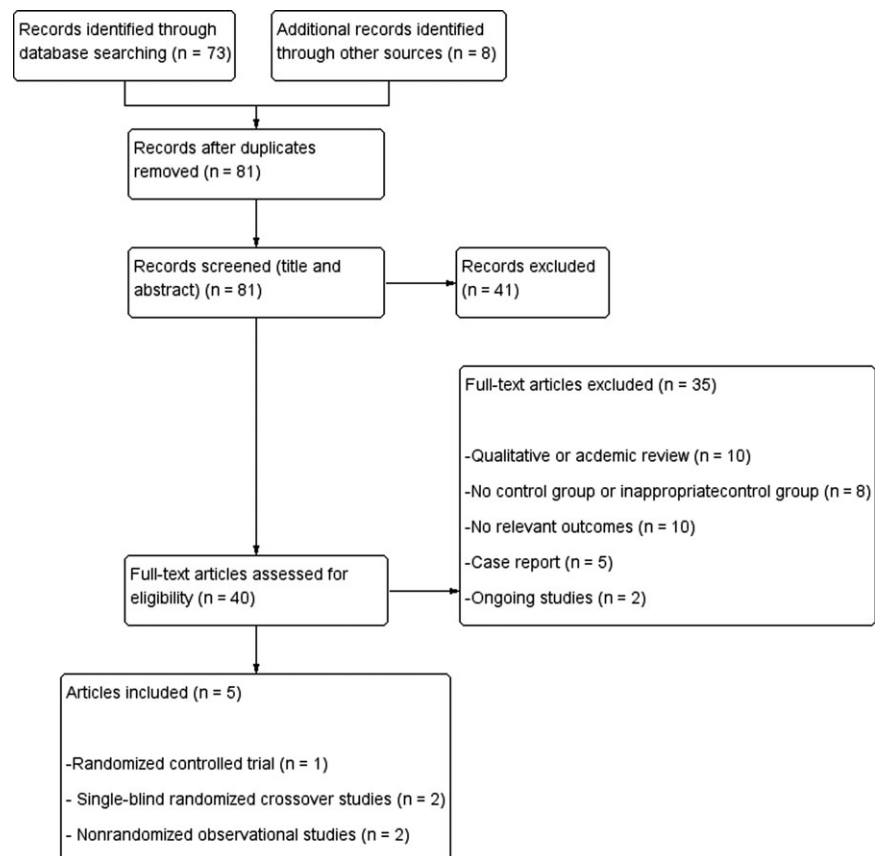


FIGURE 1 Study selection flow diagram

TABLE 1 Description of characteristics from studies included in the meta-analysis

Study	Country	Design	Subjects (n)	Include criteria	Exclude criteria	Tri-V group	Bi-V group
Anselme 2016	France	RCT	76	Patients with sinus rhythm, LVEF<35%, QRS duration>120 ms for NYHAIII-IV, QRS duration>150 ms for NYH II.	Patients with complete AV block were excluded.	Two RV leads and one LV lead.	A bipolar LV lead and a RV lead positioned at RV apex.
Leclercq 2008	France, Germany; Belgium	Single-blind randomized crossover study	26	NYHA III-IV; permanent AF requiring cardiac pacing; LVEF≤35%	ICD implantation; MI, cardiac surgery or PCI within 3 mos; chronic pulmonary disease; thyroid disease; intravenous inotropic therapy; inability to comply with the study; pregnant or <18 years old	Two LV leads and one RV lead.	One LV lead and one RV lead
Lenarczyk 2009	Poland	Retrospective study	54	NYHA III-IV; LVEF≤35%; LBBB and QRS duration≥120 ms	Pregnant; age < 18; MI, cardiac surgery or PCI within 3 mos; intravenous inotropic therapy; inability to comply with the study; chronic AF; previous PM or ICD implantation	Two LV leads and one RV lead	One LV lead and one RV lead
Ogano 2013	Japan	Nonrandomized controlled study	58	NYHA II-IV; LVEF≤35%; LBBB and QRS duration ≥120 ms	Not available	Two LV leads and one RV lead	One LV lead and one RV lead
Rogers 2012	UK	Single-blind randomized crossover study	37	NYHA II-IV; LVEF≤35%; LBBB and QRS duration ≥150 ms (or < 150 ms with evidence of mechanical dyssynchrony)	age < 18; significant right-sided valvular disease; intravenous inotropic drug therapy; inability to comply with the study	Two LV leads and one RV lead or two RV leads and one LV lead	One LV lead and one RV lead

RCT, randomized controlled trial; LVEF, left ventricular ejection; RV, right ventricular; LV, left ventricular; AV block, atrioventricular block; NYHA, New York Heart Association; ICD, implantable cardiac defibrillator; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention; UK, United Kingdom.

−0.11, $P = .001$, Figure 4A). However, the heterogeneity of the improvement in 6MWD was significant among the studies ($I^2 = 63.3\%$, $\chi^2 = 8.18$, $P = .042$), so the random-effects model was used to pool the data. The pooled data showed the improvements in 6MWD were similar between the two groups (WMD 6.09; 95% CI −34.68 - 46.78, $P = .77$, Figure 4B).

3.5 | Impact on quality of life

Three studies compared the effects of Tri-V pacing on the quality of life versus Bi-V pacing in patients with HF, which was evaluated by Minnesota Living With Heart Failure Questionnaire score (MLHFQ

score, higher scores indicating worse symptoms). I^2 statistic and Q test showed that there was no significant heterogeneity of MLHFQ score among the studies ($I^2 = 0$, $\chi^2 = 1.21$, $P = .55$), so the fixed-effects model was used to pool the data. The pooled data showed no significant difference in the improvement in MLHFQ score between the two groups (WMD −4.4; 95% CI −9.88 - 1.08, $P = .12$, Figure 5).

3.6 | Comparison of mechanical dyssynchrony by echocardiography

Two studies compared the improvement in mechanical dyssynchrony between the two groups by different criteria. In the study by

TABLE 2 Baseline characteristics of patients in trials enrolled

Study	Age (yrs)	Male n (%)	IHD n (%)	AF n (%)	LVEF (%)	LVDV (mL)	LVSV (ml)	Duration of QRS (ms)	ICD n (%)	ACEI/ARB n (%)	β -blocker n (%)	Baseline NYHA class
Anselme 2016	69.4 \pm 10.7	54 (71.1)	33 (43.4)	20 (26.3)	28.7 \pm 6.3	202 \pm 70.7	145 \pm 58.9	162 \pm 21	50 (65.8)	NA	NA	2.95 \pm 0.44
Leclercq 2008	70 \pm 8	26 (100)	7 (27)	10 (38.5)	24 \pm 11	197 \pm 68	164 \pm 68	159 \pm 47	NA	25 (96)	19 (73)	3.08 \pm 0.28
Lenarczyk 2009	56.6 \pm 8.8	15 (27.8)	21 (38.9)	NA	24 \pm 6.2	273 \pm 79	211 \pm 72	174 \pm 31	13 (24.1)	49 (91)	51 (94)	3.2 \pm 0.35
Ogano 2013	69 \pm 13	43 (74.3)	24 (41.4)	6 (10.3)	25.5 \pm 10.4	236 \pm 107	183 \pm 102	150.8 \pm 32.9	NA	51 (87.9)	44 (75.9)	2.86 \pm 0.68
Rogers 2012	66 \pm 11	35 (81.4)	27 (62.8)	6 (14)	23.4 \pm 6.7	251 \pm 85	196 \pm 80	138 \pm 33	NA	42 (98)	35 (81)	2.97 \pm 0.37

IHD, ischemic heart disease; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; LVDV, left ventricular end-diastolic volume; LVSV, left ventricular end-systolic volume; ICD, implanted cardiac defibrillator; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; NA, not available.

Anselma and colleagues,¹¹ the two groups had similar effects on left pre-ejection interval, interventricular delay, and LV filling time. In the study by Lenarczyk et al,⁷ there was a greater improvement in septal-to-lateral wall motion delay and anterior-to-inferior wall motion delay in the Tri-V pacing group, but similar effects on interventricular delay between the two groups.

3.7 | Subgroup analyses

The results of subgroup analyses showed there might be a greater improvement in LVEF from Tri-V pacing in patients with wider baseline QRS duration, but the benefits were not significant in patients with the baseline duration of QRS less than 155 ms. In addition, the benefits of Tri-V pacing on the improvement in LVEF were not affected by the design of studies, modality of tri-V pacing, mean age of patients, sex, LVDV, LVSV, etiology of HF, and baseline NYHA class (Table 3).

3.8 | Risk of publication bias

Funnel plot was performed to assess the risk of publication bias for 5 studies with the outcome of change in LVEF (Figure S1). Results showed that the funnel plot was symmetrical. The Egger's and Begg's tests showed no potential publication bias existed among the included trials (Egger's test, $P = .42$; Begg's test, $P = .24$).

3.9 | Sensitivity analyses

Firstly, sensitivity analyses were performed by omitting one study at a time and calculating the pooled WMD for the remaining studies. Secondly, the pooled WMD were estimated using fixed-effects model and random-effects model, respectively. Sensitivity analysis indicated that the results of the meta-analysis were reliable and stable.

4 | DISCUSSION

We performed this meta-analysis of 1 RCT, 2 single-blind randomized crossover studies, and 2 nROS with 251 patients to compare the efficacy of Tri-V pacing versus Bi-V pacing on the improvement on LV remodeling, quality of life, and exercise capacity in patients treated with HF. The results showed that Tri-V pacing had greater benefits on the improvement in LVEF and NYHA classes compared with Bi-V pacing, but similar efficacy on the improvement in left ventricular geometry, δ MWD, and quality of life. For assurance, we performed Egger's and Begg's tests to exclude the influence of publication bias on the analysis.

Restoration of intra-LV synchrony is the most important mechanism underlying the benefits of CRT in patients with heart failure and LBBB. Previous study showed two distinctive patterns of LV propagation, slow propagation without conduction block and propagation with a linear conduction block.¹² The propagation with a

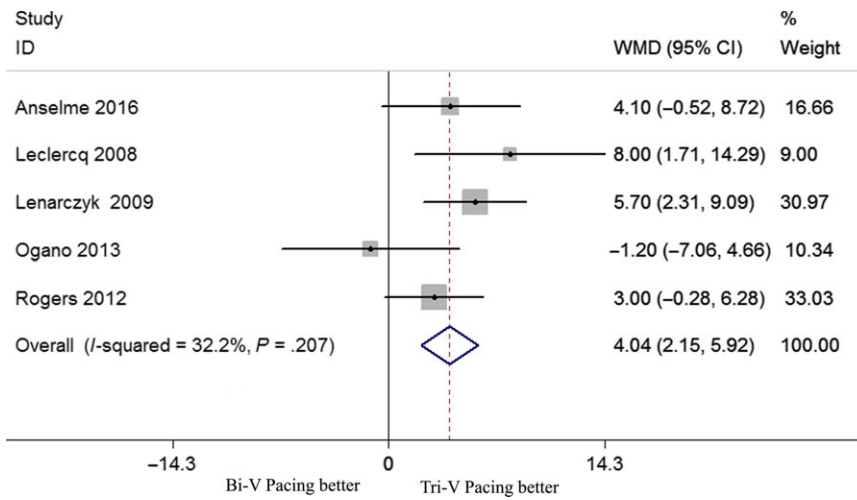


FIGURE 2 Comparison of the change in LVEF between Tri-V pacing group and Bi-V pacing group (absolute increase in %LVEF). The improvement in LVEF in the Tri-V pacing group was greater compared with that in the Bi-V pacing group (WMD 4.04; 95% CI 2.15-5.92, *P* < .001)

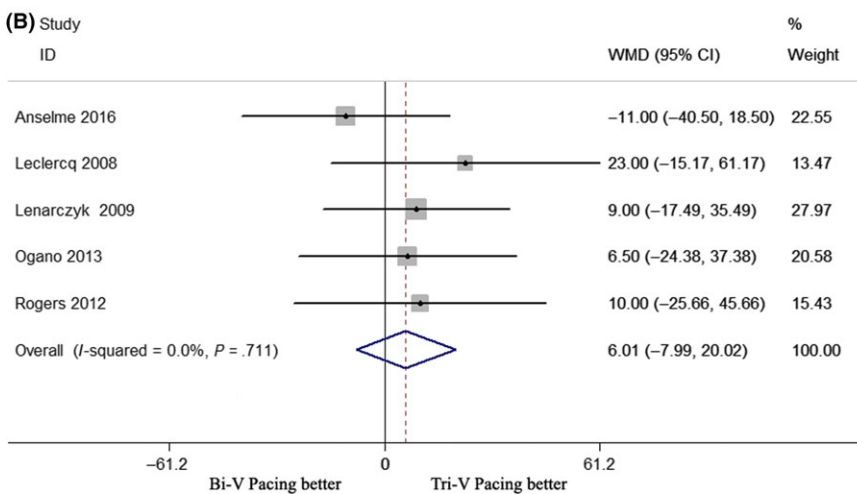
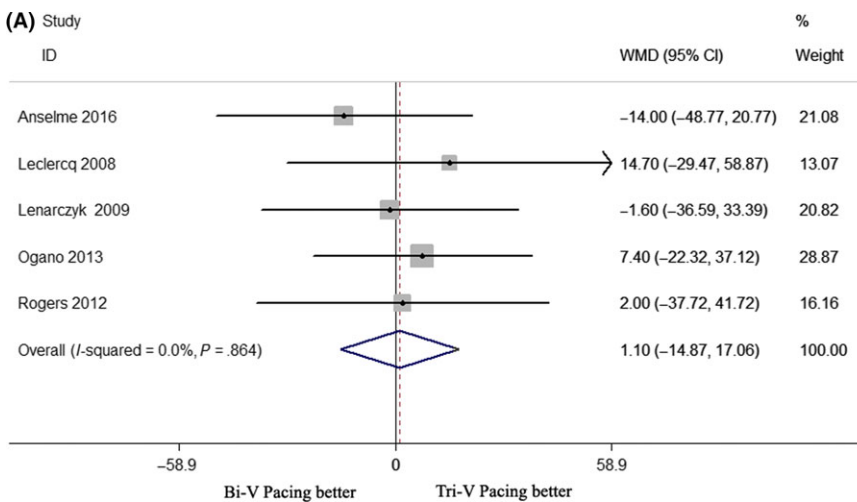


FIGURE 3 Comparison of the change in LVDV (A) and LSVV (B) between Tri-V pacing group and Bi-V pacing group (absolute decrease in ml). The changes in LVDV and LSVV were similar between the two groups (WMD -1.10, 95% CI -17.06-14.87, *P* = .89 for LVDV, A; WMD -6.01, 95% CI -20.02-7.99, *P* = .4 for LSVV, B)

linear conduction block might be amenable to correction by LV pacing, and patients with this type of LV propagation might respond to the traditional CRT. But patients with the first type of LV propagation exhibited lesser response to conventional Bi-V pacing and might contribute to the nonresponders of conventional CRT.¹³ In these patients, Tri-V pacing showed benefits of improvement on the LV synchrony and the acute hemodynamic response compared with

Bi-V pacing.¹⁴ The presence of scar in the ventricular is another important factor associated with the response failure to CRT.¹⁵ The presence of scar in ventricular reduces the amount of myocardium available for contraction in CRT. In addition, myocardial scar is not readily excitable, thereby reducing the volume of excitable myocardium in the vicinity of the LV pacing stimulus and delaying activation of potentially recruitable myocardium. The scar tissue in the pacing

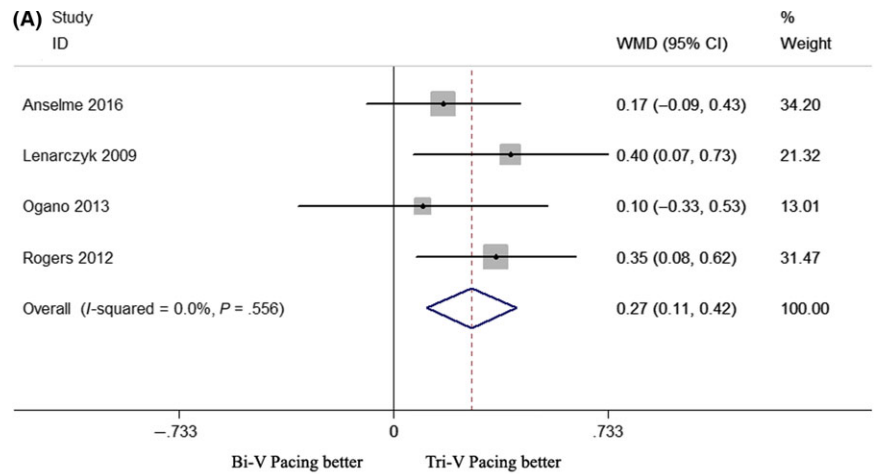


FIGURE 4 Comparison of the changes in NYHA classes (absolute increase in NYHA classes, A) and 6-minute walking distance (B, absolute increase in meter) between the Tri-V pacing group and the Bi-V pacing group. There was a greater improvement in NYHA classes in the Tri-V pacing compared with the Bi-V pacing group (WMD -0.27; 95% CI -0.42 to -0.11, *P* = .001, A). But the improvements in 6MWD were similar between the two groups (WMD 6.09; 95% CI -34.68 -46.78, *P* = .77, B)

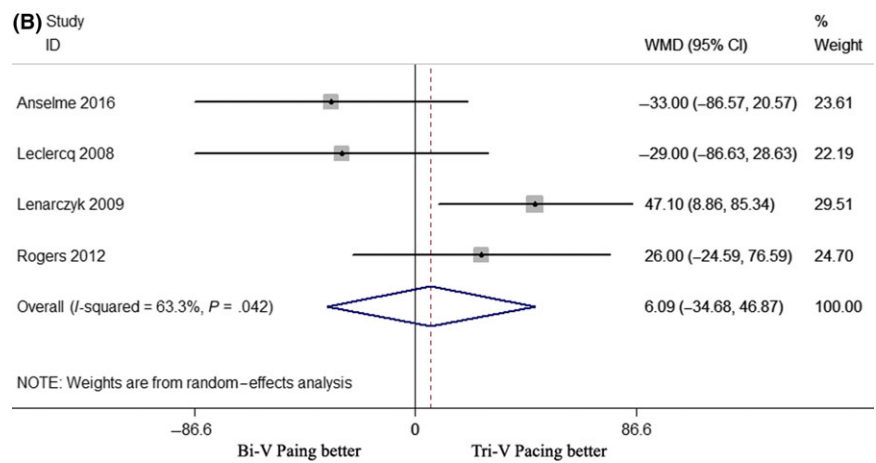
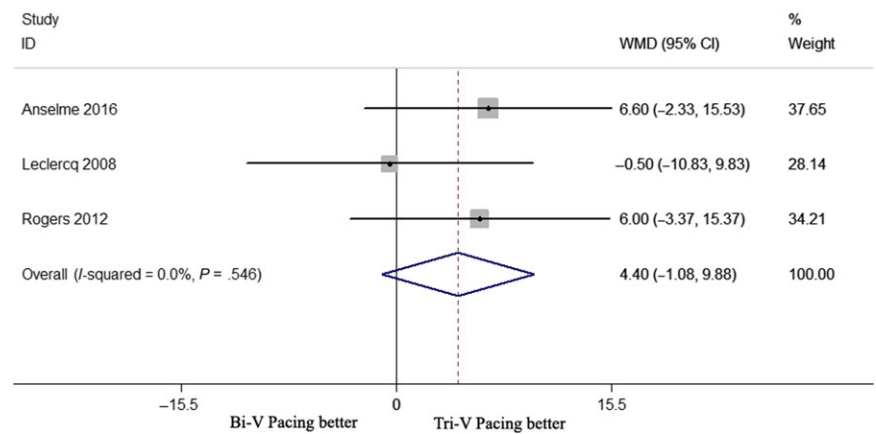


FIGURE 5 Comparison of the change in Minnesota Living With Heart Failure Questionnaire score (MLHFQ score) between the Tri-V pacing group and the Bi-V pacing group. The improvement in MLHFQ score between the two groups was similar (WMD -4.4; 95% CI -9.88 -1.08, *P* = .12)



site may lead to a prolonged and fragmented QRS complex as well as exacerbate the electrical and mechanical dyssynchrony.¹⁶ Therefore, the strategy of Tri-V pacing employing 2 LV leads or 2 RV leads to perform multisite LV pacing might simultaneously recruit a larger volume of myocardium and attenuate the electrical and mechanical dyssynchrony in these patients. Acute hemodynamic studies showed that Tri-V pacing provided greater benefits on improvement in LV function and dyssynchrony than Bi-V pacing in patients with posterolateral scar.¹⁷ Therefore, Tri-V pacing might provide more benefits in these nonresponders to conventional CRT. Our

comprehensive meta-analysis of five clinical studies also showed a greater improvement in LV function and NYHA classes in the Tri-V pacing group.

However, when interpreting the results of the meta-analysis, we should note that several factors might influence the response to CRT and the results of the meta-analysis. First factor is the gender of patients. Clinical study showed that female gender was an independent predictor of the response to CRT. Female patients exhibited a better response to CRT and had a greater improvement in cardiac remodeling compared with males.¹⁸ Therefore, the proportion of

TABLE 3 Subgroup analyses based on the improvement in LVEF

Subgroup	Studies (N)	WMD (95% CI)	P value
Design of studies			
Crossover study	2	4.07 (1.16-6.98)	.006
Control study	3	4.01 (1.53-6.49)	.002
Mean proportion of male patients			
≥80%	2	4.07 (1.16-6.98)	.006
<80%	3	4.01 (1.55-6.49)	.002
Mean age			
≥66 years old	3	3.55 (0.41-6.70)	.027
<66 years old	3	4.31 (1.95-6.66)	<.001
Mean proportion of patients with NYHA class IV			
≥10%	2	3.97 (1.04-6.91)	.008
<10%	3	4.08 (1.62-6.54)	.001
Mean Baseline duration of QRS			
≥155 ms	3	5.60 (3.09-8.10)	<.001
<155 ms	2	2.00 (-0.87-4.86)	.17
Proportion of ischemic heart disease			
≥40%	3	2.58 (0.15-5.02)	.038
<40%	2	6.22 (3.24-9.20)	<.001
Mean LVDV (mL)			
≥212	2	5.47 (1.75-9.19)	.004
<212	3	3.54 (1.35-5.73)	.002
Mean LVSV (mL)			
≥180	3	3.54 (1.35-5.73)	.002
<180	2	5.47 (1.75-9.19)	.004
Modalities of Tri-V pacing			
Two RV leads	2	3.37 (0.69-6.04)	.014
Two LV leads	3	4.69 (2.04-7.35)	.001

LVEF, left ventricular ejection fraction; WMD, weighted mean differences; CI, confidence interval; NYHA, New York Heart Association; LVDV, left ventricular end-diastolic volume; LVSV, left ventricular end-systolic volume; RV, right ventricular; LV, left ventricular.

female patients in the study population might affect the improvement in LVEF. Secondly, the underlying etiology of HF is another predictor of clinical response to CRT. Clinical study showed CRT therapy reversed left ventricular remodeling with a more extensive effect on nonischemic heart disease,¹⁹ and ischemic etiology of HF was showed to be an independent determinant of nonresponse to CRT.³ So the proportion of ischemic heart disease might also affect the improvement in LVEF. Thirdly, the baseline duration of QRS might be another predictor of the response to CRT. Clinical study showed that the benefits of CRT on the improvement on LV remodeling increased progressively with QRS prolongation.²⁰ Therefore, the baseline duration of QRS might also affect the result of our study. In addition, the design of the study, baseline NYHA class, and LVDV were also shown to be the predictors of response to CRT, and these factors might influence the improvement in LVEF.^{21,22} However, the results of our subgroup analyses found the

improvement in LVEF in the Tri-V pacing group was not affected by these factors except for the duration of QRS. The benefits on the improvement in Tri-V pacing were significant in patients with QRS duration ≥155 ms, but not in patients with QRS duration <155 ms.

Although the result of our meta-analysis showed that Tri-V pacing had greater benefits on LV function and functional capacity compared with Bi-V pacing, Tri-V pacing strategy was not used widely in clinical practice. There might be several technical problems to be resolved before Tri-V pacing was popularly accepted. The procedure duration in the Tri-V pacing group was longer than that in the Bi-V pacing group, potentially exposing patients to an increased risk of pocket infection.²³ The available CRT devices at present only have two ventricular ports, and to deliver Tri-V pacing, the two LV leads are connected to the single LV port via a parallel bipolar Y-connector. This might result in a drop in LV pacing dependence with a concomitant increase in current delivery and power consumption, which would reduce the device longevity and require more frequently generator replacement. Moreover, the Y-connector was bulky and might predispose to skin erosion.²⁴ In addition, failure of placing the second LV lead is another technical problem to be resolved. In these experienced medical centers, about 15%-46% patients failed to place the second LV lead owing to no accessible vein, unstable lead position, unacceptable pacing threshold, or phrenic nerve stimulation.⁷⁻¹⁰ The combination of two RV leads and one LV lead was another modality used to deliver Tri-V pacing, which might have similar effects on resynchronization compared with the combination of two LV leads and one RV lead. Provided that the pacing leads are positioned far enough one from each other, the placed areas would be close: A high septal RV lead would be near to a LV lead position in the great cardiac vein, while an apical RV lead would be near to a LV lead positioned in a posterior/posterolateral vein.¹¹ The results of the subgroup analyses also showed that the benefits of Tri-V pacing on the improvement in LVEF were not affected by the combination of two RV leads and one LV lead. In the study by Anselme and colleagues, all patients were successfully received Tri-V pacing using the combination of two RV leads and one LV lead.¹¹ Therefore, the combination of two RV leads and one LV lead might be a safe and effective modality to deliver Tri-V pacing. However, further large studies are needed to assess the efficacy and the safety of this strategy. At last, not all patients would derive benefits from Tri-V pacing. Studies showed that patients with slow propagation without conduction block in the left ventricular, posterolateral scar, and patients not meeting strict criteria of LBBB would get benefits from Tri-V pacing.^{14,17,25} However, there are no criteria to identify patients who would get benefits from Tri-V pacing at present. Further studies are needed to investigate how to identify these patients.

There are limitations in the present study. First, of the 5 studies included, there is only one randomized controlled study. Despite the fact that much effort has been exerted to control bias, residual confounding factors may exist. Therefore, we should interpret the results with caution. Secondly, all studies enrolled had small size and limit period of follow-up. This would influence the value of our

meta-analysis. At last, no study included in our study had power to assess the benefits of Tri-V pacing in terms of mortality, mobility, or other clinical outcomes. This would limit the clinical value of our study. The ongoing TRUST CRT study and V3 trial will give us more information.

5 | CONCLUSION

The present analysis suggests that Tri-V pacing has benefits in terms of an improvement in LVEF and functional capacity in patients with systolic heart failure treated with CRT, especially in patients with the duration of QRS \geq 155 ms.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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