The effect of right ventricular apical and non-apical pacing on the short- and long-term changes in left ventricular ejection fraction: a systematic review and meta-analysis of randomized-controlled trials

Running title: RV pacing site and LVEF

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Abstract

Background: *The right ventricular apex (RVA) is the traditional lead site for chronic pacing but in some patients may cause impaired left ventricular (LV) systolic function over time. Comparisons with non-apical (RVNA) pacing sites have generated inconsistent results and recent meta-analyses have demonstrated unclear benefit due to heterogeneity across studies.*

Methods and Results: *A systematic search for randomized controlled trials that compared LVEF outcomes between RVNA and RVA pacing was performed up to October 2014. Twenty four studies (n=1,628 patients) met the inclusion criteria. To avoid between study heterogeneity two homogenous groups were created; group one where studies reported a difference (in favor of RVNA pacing) and group two where studies reported no difference between pacing sites. For group one weighted mean difference (WMD) between RVNA and RVA pacing in terms of LVEF at follow-up was 5.40% (95% CI: 3.94 to 6.87), related in part to group one's RVA arm demonstrating a significant reduction (mean loss -3.31%; 95% CI: -6.19 to -0.43) in LVEF between study baseline and end of follow-up. Neither of these findings were seen in group two. Weighted regression modeling demonstrated that inclusion of poor baseline LVEF (<40%) in combination with greater than 12 months follow-up was three times more common in group one compared to group two (weighted RR 2.82; 95% CI 1.03 – 7.72; P=0.043).*

Conclusions: *In patients requiring chronic right ventricular pacing where there is inclusion of impaired baseline LVEF (<40%), RVA pacing is associated with deterioration in LV function relative to RVNA pacing.*

Key Words: *Right ventricular apical pacing, right ventricular non-apical pacing, septal, LVEF, pacing site, randomized trial*

Introduction

The right ventricular apex (RVA) has been the traditional site of choice for permanent pacing lead placement worldwide.^{1, 2} The technology has proven stable and safe over long periods of time. Accumulating experimental and clinical data suggest, however, that RVA pacing can potentially result in long-term deleterious effects on left ventricular (LV) systolic function in some patients, increasing the risk of heart failure and death.³⁻⁵ Concern about RVA pacing has driven an examination of non-apical sites and have included the right ventricular septum, outflow tract area and the His bundle.^{4, 6} Accurate septal lead placement has, until recently proven unreliable and so a general term, right ventricular non-apical pacing sites (RVNA) has been adopted to cover all sites deemed not to be apical. Septal pacing, being theoretically closer to the His-Purkinje system has been felt more likely to avoid LV dysfunction.⁴ In the late 1990s two small randomized controlled trials (n<35 participants) comparing RVNA to conventional RVA pacing showed a non-statistically significant difference in left ventricular ejection fraction (LVEF) favoring RVNA pacing.^{7, 8} Although there have since been a number of clinical studies comparing RVA to RVNA sites, overall results have been inconsistent and no clear pacing position superiority has emerged.

There have been three meta-analyses comparing RVA to RVNA pacing that pooled data incrementally as trials accrued.⁹⁻¹¹ The first meta-analysis by De Cock *et al.* pooled data from nine studies, and reported a significant difference in hemodynamic effect in favor of RVNA pacing.⁹ However, these results could not be extrapolated to long-term pacemaker implants as only two of the nine studies included in their analysis examined mid to long-term outcomes. More recently, two meta-analyses^{10, 11} specifically considered study duration but the combined trials were markedly heterogeneous in terms of inclusion criteria. The heterogeneity resulted in wide confidence intervals even with longer term follow-up

[Weighted mean difference (WMD) 4.27; 95% CI 1.15 – 7.40 and 3.58; 95%CI: 1.80 – 5.35]. These intervals may still be too narrow given that the statistical model these studies utilized potentially underestimated the statistical error.^{12, 13} However, both meta-analyses concluded that RVNA pacing in general was better than RVA pacing in terms of protection of LV function and that a greater than 12 months follow-up was required to document the superiority of RVNA pacing.^{10, 11} No adverse outcome from RVNA was also noted.¹⁰

Since the last meta-analysis there have been a number of further publications including a large randomized trial¹⁴ and a number of smaller trials.¹⁵⁻²² As a result we have undertaken this review to address the issues discussed above by providing further analyses that we feel deals specifically with the heterogeneity across studies.

Methods

Search strategy and selection criteria

A systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.²³ Four medical and life sciences databases (PubMed, Embase, Cochrane Central Register of Controlled Trials [CENTRAL] and Cochrane Database of Systematic Reviews) were searched from inception to October 2014 for randomized controlled trials that compared LVEF at baseline and after pacing lead placement in RVNA or RVA. The search strategy included the terms “Cardiac Pacing, Artificial”, or “Pacing(s)”, together with “Heart Ventricles” or “Ventricle(s)” or “Ventricular”, and “select-site pacing ” together with either “randomised study”, “randomised trial”, or “controlled clinical trial” and was modified to ensure the use of the correct database-specific syntax. The complete search strategy for PubMed is available in Appendix 1. In order to achieve a comprehensive evaluation of the published evidence, the systematic search was combined with the first 20 related citations of each included paper for qualifying publications that were not identified in the initial systematic search.²⁴

Inclusion was restricted to human studies, full-text articles, and randomized controlled trials comparing LVEF in RVA pacing with RVNA pacing irrespective of whether this was the primary endpoint. Non-apical leads were mostly, but not definitely, placed in the septum. We did not attempt to distinguish septal from non-septal locations because fluoroscopy, used widely to adjudicate final lead position, either alone or in conjunction with ECG criteria do not allow clinicians adequate discrimination between mid-septal, free wall and RVOT sites.^{25, 26} Data for LVEF measurements at baseline and at follow-up had to be available in an extractable format. Trials that included bi-ventricular pacing were excluded from the meta-analysis. Exclusions were also made for conference presentations and abstracts, or studies that presented data in a non-extractable format (i.e. graphical representation). There were no language restrictions on trial eligibility. Corresponding authors were contacted for further information regarding the mean LVEF and standard deviations if this was missing in the report.

Study selection and data extraction

Two authors (MH and LFK) independently confirmed the eligibility of studies and collated the data from the qualifying studies. MH extracted the data which were double checked by LFK and discrepancies were resolved through discussion and consensus following independent evaluation by another author (SARD). Data from the included studies were extracted and summarized in a spreadsheet. The recorded fields included study identifiers (authors, publication year, country); trial characteristics (design, randomization method, blinding, sample size, pacing parameters, location of RVNA pacing site, duration of follow-up); study population characteristics (age, gender proportion); and outcome (mode of LVEF assessment, LVEF baseline and post pacing placement).

Quality assessment

The quality of each study was assessed using expanded bias criteria as recommended in the Cochrane Handbook.²⁷ The quality scale assessed 5 different types of bias (design, selection, information, confounding, and analytical bias) through 17 questions

as outlined in Appendix 2. A univariate quality score was also computed to rank each study by summing item scores and the maximum possible sum was 25 points. The study rank was determined as each study score divided by the maximum score in the list thus creating a quality rank that starts at 1 for the best study and has a minimum value of zero.

Statistical analysis

The primary endpoint was the percentage difference in LVEF at end of follow-up between RVNA and RVA pacing sites. In order to avoid between study heterogeneity, the studies were grouped into two homogenous sub-groups based on the effect magnitude and defined by visual and statistical homogeneity of the effects within each group. The subgroups were group one where the weighted mean difference (WMD) was in favor of RVNA pacing; and group 2 where WMD was not different between RVNA and RVA pacing. The weighted mean differences (WMD) in LVEF across studies were pooled using three different meta-analytic models, given that the random effects (RE) model²⁸ is known, among other problems, to underestimate the statistical error and lead to overconfident results.¹² The two other statistical approaches used were the bias adjusted quality effects (QE) model²⁹ and its bias unadjusted variant called the inverse variance heterogeneity (IVhet) model³⁰. Both, the QE and the IVhet models use a quasi-likelihood based variance structure without distributional assumptions and thus have coverage probabilities for the CI well within the 95% nominal level and have been documented to have a better performance when compared to the RE method.³¹ Cochran's Q test and the I^2 were used to assess heterogeneity amongst studies. $I^2 > 50\%$ was considered to indicate practically significant heterogeneity.

An inverse variance weighted generalized linear model was used to gain additional insight into differences between positive and negative studies by supplementing the meta-analysis with investigation of important clinical differences between trials. The differences studied were defined *a priori* as 1) studies with a mean age of 70 years or more in both groups, 2) studies not solely recruiting AV node ablation/AV block indications for pacing, 3) studies which included subjects whose LVEF was poor (less than 40% ³²) and 4) studies

whose duration of follow-up was at least 12 months. Such studies were coded 1 and the remainders under each criterion were coded 0. Year of study publication was also considered as a variable but later dropped as it correlated with duration of follow-up. The generalized linear model was fit on the dichotomized outcome group (one versus two) of each study (coded 1 and 0 respectively) using a Poisson regression with a log-link and robust error variance in order to generate weighted rate ratios based on the study level predictors.³³ This regression used the inverse of the variance of each study as weights to allow the observations with the least variance to provide the most information to the model. Finally, we ran a pre-post mean gain meta-analysis for each arm (RVNA and RVA) by subgroup. The mean gain and its standard error were computed as follows:

$$ES_{\mu_g} = \bar{X}_{T2} - \bar{X}_{T1}$$

$$SE_{\mu_g} = \sqrt{\frac{2s_p^2(1-r)}{n}}$$

$$s_p^2 = (s_{T1}^2 + s_{T2}^2) / 2$$

where T1 and T2 denote the baseline and end of follow-up respectively and s_p^2 is the pooled variance across both time-points and r is fixed at 0.5. Publication bias was assessed through visual inspection of Funnel and *Doi* plots.³⁴ All tests were two-tailed and a p-value of less than 0.05 was deemed statistically significant. All the meta-analyses were conducted using MetaXL version 2.0 (EpiGear Int Pty Ltd; Brisbane, Australia; <http://www.epigear.com>). The generalized linear model was run in Stata version 12, StataCorp LP, College Station, TX, USA.

Results

Yield of search strategy

The search strategy identified 662 unique publications, the titles and abstracts of which were screened for inclusion. The full text of 105 articles was retrieved, of which 21 studies met the inclusion criteria plus three studies that were identified through related

citations. The 24 studies contributed 26 datasets (two studies contributed two datasets each) of which 14 datasets examined the effects of right ventricular pacing site on LVEF at one year or more and the remaining 12 datasets looked at shorter term effects. Reasons for exclusion of the remaining articles are indicated in *Figure 1*.

Characteristics of the included studies

The included studies recruited 1628 participants. The proportion of male subjects ranged from 20% to 100% in different studies. The mean or median age reported across studies ranged between 58 to 79 years. Thirteen studies included mainly caucasian populations^{7, 8, 14, 21, 22, 35-42}, eight were conducted exclusively in Asian individuals^{15, 19, 20, 43-47} and one each in Mexico¹⁶, Iran¹⁸ and Argentina.¹⁷ Inclusion criteria included chronic high degree AV Block, post AV node ablation,^{7, 8, 14-19, 21, 35-43, 45-47} symptomatic sick sinus syndrome^{18, 35, 38, 39}, and chronic atrial tachyarrhythmia⁷ and bradyarrhythmias.^{22, 44, 45} Fifteen studies (seventeen datasets) documented LVEF as an inclusion criterion (Table 1).^{7, 14, 15, 17, 19, 21, 35, 37, 41-47} Six studies (six datasets) had an inclusion criterion specifically for patients with ejection fraction less than 40%.^{7, 19, 21, 37, 41, 42} The LVEF was reported at baseline in both groups in 19 studies (21 datasets),^{7, 14-17, 20-22, 35-40, 42, 43, 45-47} and omitted in five studies (five datasets).^{8, 18, 19, 41, 44} Of those who reported LVEF at baseline, the mean level was less than 35% in two studies (2 datasets),^{7, 21} 35–45% in one study (1 dataset)⁴² and >45% in 18 studies (18 datasets).^{7, 14-17, 20, 22, 35-40, 42, 43, 45-47} In four studies LVEF was measured with nuclear imaging^{7, 8, 42, 46} and in one using quantitative gated SPECT¹⁵. The rest were measured with standard trans-thoracic echocardiography. Most trials used a mid/lower or high right ventricular septum (RVS) site for RVNA pacing,^{8, 14-17, 19, 21, 22, 35-37, 42, 44, 45}, nine^{7, 18, 20, 38, 39, 41, 43, 46, 47} used the RVOT and in one study the RVNA lead was placed at the His bundle.⁴⁰ Five studies incorporated crossover designs^{7, 8, 40-42} whereas the others were all parallel group studies^{15-22, 35-39, 43-47} (Table 1 and Appendix 4).

The quality score ranged (Appendix 3) from 10 to 23 out of 25 possible points. Three studies were double-blinded,^{14, 16, 22} and eight studies were single blind.^{8, 18, 21, 35, 38, 40, 41, 47} In

12 studies blinding was not described.^{7, 15, 17, 19, 20, 36, 37, 39, 42-46} A rigorous method of randomization was explicitly described in only one study,¹⁴ and in four studies, though randomization was described, concealment was unclear;^{19, 37, 45, 46} . In the remainder, this information was absent or unclear. Three studies^{43, 44, 47} did not provide details of participants who withdrew or were lost to follow-up. Participant completion rates ranged from 69 to 100% for RVA group and 70 to 100% in RVNA group. Length of follow-up was at least 2 months in those followed up for less than 12 months and at most 120 months in those who had more than 12 months follow up. Out of 24 studies included in meta-analysis only one study followed intention-to-treat analysis¹⁴ (Appendix 3).

Quantitative synthesis

There were two homogenous subgroups created based on visual inspection of the forest plot and statistical assessment of heterogeneity (Table 2). In terms of LVEF difference at the end of follow-up, fourteen datasets were in group 2 where no difference between RVNA and RVA pacing was evident (bias adjusted WMD -0.07; 95% CI: -1.14 to 1.01) and 12 datasets were in the group 1 where a benefit for RVNA compared to RVA pacing was seen (bias adjusted WMD 5.40; 95% CI: 3.94 to 6.87). Group 2 had studies that all individually reported a mean difference in LVEF at the end of follow-up of less than 2%. The results using the other statistical models concurred (Table 2). The Chen et al study had the largest weight because the standard deviations reported were the smallest among the group of studies and not consistent with study size.¹⁹ When this study was excluded from the analysis, results remained similar (Table 2).

The mean gain in LVEF was negligible across arms in group 2 (*Figure 2, bottom panel*) while in group 1, there was a net loss in systolic function over time for the RVA arm but not for the RVNA arm (*Figure 2, top panel*). When we looked at study level predictors of group 1 membership, there was an interaction between inclusion of poor LVEF and longer duration of follow-up, such that the trials with this combination were more common within

group one (weighted RR 2.82; Table 3). Older age also was more common within group one (weighted RR 3.49; Table 3).

On visual inspection of the *Doi* and funnel plots (all studies), there was symmetry (intercept -0.49, $P=0.446$) when assessed using Egger's regression. Both plots (*Figure 3*) looked visually symmetrical.

Discussion

Accumulating evidence has suggested that RVA pacing may adversely affect LV function and results from the DAVID trial focused clinical attention on the adverse clinical effects of RV pacing.⁴⁸ This trial demonstrated that RV pacing increased the risk of heart failure and death in a group of patients with poor baseline LV function compared with a cohort in whom ventricular pacing was minimized. Other studies have subsequently also shown a lower risk of heart failure hospitalization where baseline LV function was preserved and where there were associated co-morbidities such as pre-existing ventricular conduction delay, previous myocardial infarction or heart failure.^{49, 50} One of these, the MOST study, reported a <2% hospitalization for heart failure linked to pacing over 2 years where baseline LV function prior to pacing was normal and in the absence of pre-existing cardiac pathology.⁵¹ Where there was pre-existing pathology, there was a marked increase in the risk of heart failure hospitalization, by up to 50%.^{48, 49} The largest randomized trial to date, the Protect-Pace study published recently, recruited only subjects with exclusively good baseline LV function and did not find a difference in LVEF between RV apical and high septal pacing sites after two years of follow up.¹⁴ This outcome was also noted in the Danpace sub-study where RV lead position did not appear to influence the rate of heart failure in patients without significant co-morbidity and with good baseline LVEF.⁵⁰

Our meta-analysis agrees with these results and confirms that an important factor linked to pacing-induced LV dysfunction is indeed impaired LV function prior to pacing.⁵² We have pooled previous and new studies using a rigorous statistical approach in order to address differing enrolment criteria and different study durations. This approach uses

subgroups where study effects were homogenous to identify possible effects of poor LVEF. We then used a weighted regression approach to elucidate the impact of poor LVEF and related factors and our results provide compelling evidence supporting the superiority of RVNA pacing over RVA pacing in terms of left ventricular systolic function preservation.

In summary, protection was seen predominantly where studies belonged to group one (three times more likely to includes studies with subjects who had poor baseline LVEF), and we report a weighted mean LVEF at end of follow-up to be between 4-7% higher in the RVNA as opposed to RVA arms while no significant difference was seen in group two. Additional analysis suggests that where studies belonged to group one (three times more likely to includes studies with subjects who had poor baseline LVEF), a deterioration also occurs over time (pre-post follow-up) with RVA pacing, which was not seen in group 2. The outcome of our analysis therefore suggests that where baseline LV function is preserved, studies report the same effect of chronic RVA and RVNA pacing in terms of LVEF changes over time. However, where baseline LV function is impaired (inclusion of LVEF<40%) studies are more likely to report a significant reduction in LVEF with RVA compared to RVNA pacing. This was especially so when study follow-up was in excess of twelve months though a trend for lesser follow-up could not be excluded. Another factor that seems to play a role that we could identify was the inclusion of more elderly subjects.

Our study confirms the results of the two previous meta-analyses and emphasizes the importance of baseline LV function at the time of pacemaker implant in relation to lead placement. Traditionally right ventricular pacing has been the mainstay of delivery of anti-bradycardia support, the technology proving stable and highly reliable. Clinical studies have emphasized the need to minimize right ventricular pacing suggesting that perhaps RV pacing itself, irrespective of site, may be deleterious.⁵³ As a result of concerns over chronic RVA pacing, other sites, in particular the RV septum or outflow-tract have been extensively studied. Despite compelling experimental data supporting a septal pacing site,⁶ individual

clinical studies have provided inconsistent results when comparing the latter to the apical pacing site and the reasons for this are now becoming clearer.

Other modalities which can be used in lieu of RVNA/RVA pacing include cardiac resynchronization therapy (CRT), His bundle pacing, and dual site right ventricular pacing. Guidelines recommend CRT where there is LBBB and impaired LV function and so will also be applicable where there is RV pacing induced LBBB type morphology. Of three clinical studies comparing CRT to RV pacing, two showed a favorable outcome for CRT^{54, 55} whereas one was inconclusive.⁵⁶ In the Block-HF study, the QRS width was not particularly broad at study inclusion. However widespread use of CRT will be constrained by cost, expertise and the small but consistent problems with reliable LV lead placement which in some studies has been as high as 10 percent.⁵⁷ In pacing dependency, LV lead failure then reverts the patient to RV pacing. His bundle pacing is also attractive as it utilizes the HPS for ventricular depolarization. Although there has been a recent upsurge in interest there remain technical issues which may prevent widespread dissemination, particularly high pacing thresholds and the difficulties with reliable His bundle capture. However, newer approaches have provided more reliable outcomes and future large scale studies will determine whether His bundle has a more widespread future. In small scale studies dual site RV pacing has also shown promise but there are no large scale data and further trials are required.^{58, 59}

In summary, the body of experimental evidence evaluated through this meta-analysis strongly suggests that RVA pacing causes deleterious effects on LV systolic function in selected patients, and that non-apical pacing prevents this from occurring. In our analysis, group one appears to benefit most from RVNA pacing. This group has a greater probability of containing those with impaired baseline LV function, more elderly subjects and those with longer (greater than a year's) follow-up, supporting an ongoing deleterious effect from pacing in those patients with already impaired LV function. Where baseline LV function is preserved it does not appear that either RVA or RVNA pacing produces a significant and clinically important difference in LV function accepting that the longest follow-up period was two

years. From this meta-analysis, we therefore cannot exclude the possibility that RVNA pacing results in a more gradual deterioration in LVEF when baseline LV function is preserved rather than no deterioration at all. However, 1-2 years is sufficient to discern differences in LV function, suggesting that the impact is related to the already compromised nature of the ventricle. A clinical trial into the effect of RVA versus RVNA pacing in patients with impaired LV function would be ethically difficult to justify. A study comparing RVNA to cardiac resynchronization therapy (CRT) might be more acceptable and provide a clear answer but will be difficult to perform clinically due to the observed beneficial outcomes of studies with CRT in patients with heart block.^{55, 60} However from observational studies, most patients do not have a deleterious outcome to RV pacing and perhaps, as implanters, we need to be better at identifying those patients where LV function is likely to deteriorate with RV pacing. This meta-analysis therefore provides support for a change in clinical approach: we suggest that where LV function is preserved then pacing either at the RVA or RVNA is acceptable. Where LV function is significantly impaired (LVEF <35%) a RVNA position together with optimal medical treatment is also valid, although CRT may be a better initial pacing mode. Where CRT is unavailable or not achievable then RVNA should be the site of choice. If baseline LV function is mild to moderately impaired (LVEF 35-50%) there is support for a RVNA lead and regular monitoring of LVEF will identify those patients where LV function continues to deteriorate.

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Tables

Table 1.- Left ventricular ejection fraction characteristics of studies included in the meta-analysis

Auth or, year of publi catio n	LV EF as an inc lus ion crit eri a	Method of assess ment	Baseline		Final		Mean		Qua lity Sco res (out of 25)	Outcome/ Remarks
			LVEF (±SD)	(% RV A	LVEF (±SD)	(% RV A	percenta ge of ventricul ar pacing at the end of the follow up (RVA RVNA)			
Can o et al, 2010	Ye s; ≥5 0%	Echocar diograp hy	62. 9±6 .3	64.2 ±8.0	62.9 ±7.9	66.5 ±7.2	RVA= 88% and RVNA= 81%	20	No differences in LVEF, NT-pro BNP, 6-minute walk, NYHA functional class	
Che n et al, 2014	Ye s; 35 to 40 %	Echocar diograp hy	NSD		36.7 ±0.7	41.8 ±2.2	RVA=94 % AND RVNA=93 %	14	RVNA provides a better clinical utility, compared with RVA, in patients with high-degree AV block and moderately depressed LV function whose LVEF	

									levels ranged from 35% to 40%.
Domenicini et al, 2012	No	Echocardiography	54.0 ± 8.0	52.0 ± 13.0	55.0 ± 8.0	46.0 ± 15.0	99% in all patients	20	No differences in LVEF between groups
Flevari et al, 2009	No	Echocardiography	47.0 ± 13.2 ^{\$}	52.0 ± 13.2 ^{\$}	43.0 ± 12.0 ^{\$}	59.0 ± 12.0 ^{\$}	RVA= 97% and RVNA=95%	17	Increase in LVEF with septal pacing
Gong et al, 2009	Yes; >50%	Echocardiography	67.9 ± 6.4	68.3 ± 6.4	65.7 ± 6.6	67.6 ± 5.2	RVA= 97% and RVNA=98%	16	RVNA had no benefit over RVA pacing in aspect of preventing cardiac remodelling and preserving LV systolic function after 12 months of pacing in patients with normal cardiac function
Hemayat et al, 2014	No	Echocardiography	NSD		58.1 ± 6.1	59.3 ± 3.8	RVA=55.61% and RVNA=62.49%	12	LVEF did not vary significantly between RVA and RVNA pacing

Inoue et al, 2011	Yes; ≥ 4 0%	Echocardiography	NSD	65.0 ± 6.0	68.0 ± 6.0	RVA=92.7% and RVNA=94.3%	10	No added advantage with RVNA on LVEF	
Kaye et al, 2014	Yes; ≥ 4 0%	Echocardiography	57.0 ± 9.0	56.0 ± 10.0	55.0 ± 9.0	54.0 ± 10.0	RVA=98% and RVNA=93%	23	RVNA pacing does not provide a protective effect on left ventricular function over RVA pacing in the first 2 years
Kristiansen et al, 2012	Yes; ≤ 3 5%	Echocardiography	25.0 ± 4.0	24.0 ± 4.0	31.0 ± 6.0	31.0 ± 8.0	Not reported	20	No improvement in LVEF
Kypta et al, 2008	Yes; ≤ 4 0%	Echocardiography	59.0 ± 1.0	55.0 ± 11.0	57.0 ± 10.0	57.0 ± 10.0	RVA=95% and RVNA=91%	18	No differences in LVEF, NT-proBNP or exercise
Lang et al, 2014	Yes; ≥ 4 5%	Echocardiography	58 ± 7.1	57.8 ± 9.3	62.3 ± 7.8	59.2 ± 8.8	98% in all patients	16	LVEF did not vary significantly between RVA and RVNA pacing

Leon g et al, 2010	No	Echocar diograp hy	60. 0±6 .0	61.0 ±9.0	52.0 ± 9.0	60.0 ± 7.0	RVA=95 % and RVNA=97 %	21	Better remodelling RVNA septal pacing	LVEF	and with
Lewi cka- Now ak et al, 2006	No	Echocar diograp hy	56. 0±1 1.0	54.0 ±7.0	47.0 ± 8.0	53.0 ± 9.0	RVA=99 % and RVNA= 94%	15	Better diastolic function with RVNA	LVEF	and
Mera et al, 1999	No	Nuclear Imaging	Not mentioned		43.0 ±10. 0	51.0 ±14. 0	Permane nt ventricula r capture since patient underwen t AV node ablation	15	RVS produces shorter QRS duration and better chronic LV function than RVA pacing in patients with mild to moderate LV dysfunction and chronic AF after His bundle ablation. Resting LVEF better with RVNA.		pacing
Moli na et al,	No	Echocar diograp hy	52. 0±1 0.0*	57.0 ±10. 0*	54.0 (11. 0) ^a	61.0 (7.0) ^a	98% ventricula r pacing were	14	Patients with septal ventricular leads have better clinical and functional		

2014		included							(LVEF) outcome	
Ocheta et al, 2006	No	Echocardiography	51.9 ± 8.8	51.9 ± 8.8	50.0 ± 7.9	53.4 ± 7.9	Consistent ventricular capture as patients undergo AV node ablation	20	Compared with conventional apical pacing, it allows improvement in functional and hemodynamic parameters over long-term follow-up.	with right it an in and
Stamler et al, 2003	Yes; ≤40%	Echocardiography	NSD	41.0 ± 13.4	43.8 ± 14.4	>90% in both RVA and RVNA groups	in 15	No differences in LVEF, NYHA, 6-minute walk	in 6-	
Tse et al, 2002	Yes; ≥50%	Nuclear Imaging	57.0 ± 2.0	59.0 ± 14.0	47.0 ± 10.3	56.0 ± 3.4 ^{\$}	RVA=95% and RVNA=97%	18	Better LVEF and diastolic function with RVNA	and
Tse et al, 2009	Yes; >50%	Echocardiography	58.0 ± 4.0	59.0 ± 5.0	59.6 ± 6.5 ^{\$}	59.5 ± 8.31 ^{\$}	Permanent ventricular capture as	19	In patients with permanent AF, RVNA, but not at RVA, preserves LVEF and provides	with AF, not at preserves provides

								patients		incremental	benefit
								undergone		for exercise capacity	
								e AV			
								node			
								ablation			
Vict	Ye	Nuclear	51.	49.0	48.0	45.0	Permane	19	No	differences	in
or et	s;	Imaging	0 ± ±	±	±10.	±	nt			LVEF, VO2 max and	
al,	<4		9.0	6.0	0	9.0	ventricula			CO	
1999	0%						r capture				
							as				
							patients				
							undergone				
							e AV				
							node				
							ablation				
Vict	Ye	Nuclear	27.	27.0	30.0	28.0	Permane	19	No	differences	in
or et	s;	Imaging	0±9	±	±10.	±	nt			LVEF, VO2 max and	
al,	≥4		.0	9.0	0	9.0	ventricula			CO	
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							patients				
							undergone				
							e AV				
							node				
							ablation				

Victor et al, 2006	Yes; ≥ 4 5%	Nuclear Imaging	52.0 ± 6.0	52.0 ± 6.0	51.0 ± 7.0	52.0 ± 6.0	Permanent ventricular capture as patients underwent AV node ablation	19	Better septal pacing with ECG baseline LVEF < 45%
Victor et al, 2006	Yes; < 4 5%	Nuclear Imaging	38.0 ± 5.0	38.0 ± 5.0	37.0 ± 4.0	42.0 ± 5.0	Permanent ventricular capture as patients underwent AV node ablation	19	
Wang et al, 2011	Yes; ≥ 5 5%	Echocardiography	63.7 ± 6.5	65.2 ± 4.5	63.2 ± 5.0	63.4 ± 4.3	>95% in both groups	18	The RVNA pacing in AV block patients over 1 year may be superior to RVA pacing in terms of regional LV

										performance, LV global electromechanical delay, and IVMD, although intraventricular dyssynchrony and LV volumes do not differ.
Zhang et al, 2012	No	Echocardiography	59.5±6.21	57.8±6.06	54.2±8.7	56.9±5.54	RVA=82.91% and RVNA=82.79%	19	LVEF did not markedly vary in the RVNA group compared to RVA, compared to RVA pacing, RVNA (RVOTS) pacing had no remarkable benefit in terms of preventing cardiac remodelling	
Zhang et al, 2014	Yes; ≥4 5% e measur	Echocardiography (Baseline	64.0±07.0	63.0±04.0	59.0±13.0	59.0±11.0	>95% in all patients	17	There were no significant changes in LVEF, LV end-systolic volume, and LV end-diastolic volume from	

ement);	the 1-week follow-up
Quantit	to the 6-month
ative	follow-up in the
Gated	RVNA and RVA
SPECT(	groups.
end line	
measur	
ement)	

*Measured at 1st week after implantation; ^a Median (IQR); \$- standard deviation was estimated from reported Standard error; RVA-Right Ventricular Apical; RVNA-Right Ventricular Non-Apical; NSD- Non significant difference; NYHA-New York Heart Association; NT Pro BNP- N-terminal prohormone of brain natriuretic peptide.

Table 2. Meta-analysis results

Subgroup	Statistical model	%LVEF difference* (95% CI)	Cochran's Q	P (Cochran's Q)	Number of study datasets
Group 1	<i>Bias adjusted (QE)</i>	5.40 (3.94 – 6.87)	16.40	0.23	12
	<i>IVhet</i>	4.97 (3.31 – 6.62)			
	<i>Random effects</i>	5.13 (3.80 – 6.47)			
Group 1	<i>Bias adjusted (QE)</i>	5.30 (3.51 – 7.09)	16.27	0.18	11
Excluding	<i>IVhet</i>	4.79 (2.93 – 6.66)			
Chen et al	<i>Random effects</i>	5.34 (3.58 – 7.11)			
Group 2	<i>Bias adjusted (QE)</i>	-0.07 (-1.14 – 1.01)	14.23	0.36	14
	<i>IVhet</i>	0.42 (-0.61 – 1.44)			
	<i>Random effects</i>	0.30 (-0.71 – 1.31)			

* Weighted mean difference (RVNA – RVA)

Table 3: Rate ratios for group 1 membership according to study selection criteria* (Poisson regression using a log-link and binomial outcome with robust error variance and study inverse variance weighted)

Selection criterion	Rate ratio	P	[95% Conf. Interval]
Other indications	2.04	0.173	(0.73, 5.66)
Older subjects	3.49	0.055	(0.98, 12.45)
Long duration (good LVEF)	1.08	0.906	(0.32, 3.64)
<i>Interaction</i>			
<i>Poor LVEF</i>			
of long duration	2.82	0.043	(1.03, 7.72)
of short duration	3.16	0.120	(0.74, 13.48)

*Results were in a similar direction after exclusion of Chen et al.¹⁹

Figures

Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the literature search conducted in August 2014 for the systematic review and meta-analysis.

Figure 2: Mean gain in LVEF from baseline to end of follow-up in group 1(top panel) and group 2(bottom panel). (a) RVNA arms of included studies; (b) RVA arm of included studies. Studies not reporting LVEF at baseline were excluded.

Figure 3: Funnel (a) and Doi (b) plots of all studies