Systematic Review and Meta-analysis of Left Ventricular Endocardial Pacing in Advanced Heart Failure: Clinically Efficacious but at what cost?

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Abstract:

Introduction Cardiac resynchronization using a left ventricular (LV) epicardial lead placed in the coronary sinus is now routinely used in management of heart failure patients. LV endocardial pacing is an alternative when this is not feasible, with outcomes data sparse.

Objective To review the available evidence on the efficacy and safety of endocardial LV pacing via meta-analysis.

Methods EMBASE, MEDLINE and COCHRANE databases with the search term "endocardial biventricular pacing" or "endocardial cardiac resynchronization" or "left ventricular endocardial" or "endocardial left ventricular". Comparisons of pre-and post QRS width, LV ejection fraction and NYHA functional classification was performed, and mean differences (and respective 95%CI) applied as a measurement of treatment effect.

Results Fifteen studies, including 362 patients, were selected. During a mean follow-up of 40±24.5 months, death occurred in 72 patients (11 per 100 patient-years). Significant improvements in LV ejection fraction (mean difference 7.9%, 95%CI 5 to 10%, P<0.0001; I^2 = 73%), QRS width (mean difference: -41% 95% -75 to -7%; P< 0.0001; I^2 = 94%), and NYHA class (mean difference: -1.06, 95% -1.2-to -0.9, P< 0.0001; I^2 = 60%), (all p<0.0001). occurred. Stroke rate was 3.3 to 4.2 per 100 patient years, which is higher than equivalent heart failure trial populations & recent meta-analysis that included small case series.

Conclusion LV endocardial lead implantation is a potentially efficacious alternative to CS lead placement, but preliminary data suggest a potentially higher risk of stroke during follow-up when compared to the expected incidence of stroke in similar cohorts of patients.

Key Words: Stroke, LV Lead, Endocardial, Resynchronisation

Introduction

Cardiac resynchronization therapy (CRT), by placement of an epicardial left ventricular (LV) lead in coronary sinus (CS) has now become a routine procedure to improve symptoms and reduce mortality in patients with advanced heart failure, wide QRS and a LV ejection fraction less than 35%(1–3).

Implanting a CRT device may not be possible in approximately 2.5-10% of patients due to inability to access CS, unstable lead position, or unsuitable distal lead position(4,5), phrenic capture. A further problem is non-response to CRT, occurring in up to one third of patients(6).

Patients in whom implantation of an LV lead in the coronary sinus fails can be paced on the LV epicardium using a surgical approach with thoracoscopy or a thoracotomy(7). Insertion of a transvenous left ventricular endocardial lead has recently been employed as an approach for improving response to CRT and addressing the needs of patients with a failed CS lead implant(8).

Knowledge on the effectiveness and safety of this therapy is sparse, with an increased risk of stroke thought likely. We performed a systematic review and meta-analysis to address this matter.

Methods

Study selection

We undertook searches on MEDLINE (via PubMED), EMBASE, clinicaltrials.gov and COCHRANE databases (from inception to 30th September 2017) using the following search string: ("endocardial biventricular pacing" or "endocardial cardiac resynchronisation" or "left ventricular endocardial" or

"endocardial left ventricular")

Reference lists of all accessed articles were further searched for sources of potentially relevant information. Authors of full-text papers and congress abstracts were also contacted by e-mail to retrieve additional information.

Only longitudinal studies performed in humans were considered for inclusion. The population, intervention, comparison and outcome (PICO) approach was used(9). The population of interest included patients with advanced heart failure and the intervention was CRT implantation, with a LV endocardial lead. The patients acted as their own controls, and the comparison was pre-and post-procedure. LV ejection fraction, QRS width and NYHA functional class at last follow-up were the outcomes. Data on procedural complications and long-term follow-up complications including stroke, and infection was also collected.

Additional inclusion criteria were: ≥ 5 patients in the study, method of anticoagulation stated, LV implantation method described, presence of follow-up regarding any of the pre-specified endpoints. Minimum follow-up duration was 2 months.

Studies including a mixture of LV endocardial and epicardial leads without individually reported data for each group (and thus, not allowing assessment of LV endocardial lead outcomes), and cross-sectional studies without follow-up were not considered appropriate for inclusion.

Three independent reviewers (AG, SH and RP) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then evaluated to determine the eligibility of the study for the review and meta-analysis. Agreement of at least two reviewers was required for decisions regarding inclusion or exclusion of studies. Study quality was formally evaluated using the *National Heart, Lung, and Blood Institute*

Quality Assessment Tool for Case Series Studies(10) by three reviewers (AG, SH and RP). An agreement, between the three reviewers was mandatory for the final classification of studies.

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group(11). The following data were extracted for characterizing each patient sample in the selected studies, whenever available: age, follow up duration, anticoagulation regime, gender, % ischaemic cardiomyopathy, QRS width pre and post, LV ejection fraction (LVEF) pre and post, NYHA class pre and post, fluoroscopy time, procedure time, lead composition, transseptal puncture technique, venous access (femoral vein, internal jugular vein, subclavian vein, others), procedural success, complications and death during follow up.

Statistical analysis

Data were pooled using random-effects, as per the Mantel-Haenszel model, through Comprehensive Meta-analysis software (Version 2). The mean difference (MD) and respective 95% confidence intervals (95% CI) were used as a measurement of treatment effect. Comparisons were performed for the endpoints: LV ejection fraction and NYHA class.

Incidence (with 95%CI) of procedural and long-term complications was assessed. Assessed procedural complications were pneumothorax, cardiac tamponade, stroke (<1 week of procedure), lead dislodgement (during index procedure admission), pocket haematoma, major bleeding, and complications occurring during follow-up (following discharge after the index procedure) were infection, transient ischaemic attack (TIA), stroke, and late lead displacement.

As concerns exist regarding an increased risk of post-implant stroke in this population, sensitivity analyses were performed to assess the impact of study design, lead composition (silicone vs. polyurethane), access site for left sided crossing (femoral vs internal jugular vein), and access to LV (inter-atrial septum vs inter-ventricular septum).

Statistical heterogeneity on each outcome of interest was assessed and quantified using the Cochran Q test and the I^2 statistic, respectively. The I^2 statistic describes the percentage of total variation across studies due to heterogeneity rather than chance. Values of less than 25%, 25% to 50% and greater than 50% are by convention classified low, moderate, and high degrees of heterogeneity, respectively.

Funnel plots were obtained using Comprehensive Meta-Analysis software (Version 2) for evaluating the presence of publication bias and traced for comparisons including more than 10 studies (minimum number for assuring the appropriateness of the method)(12).

Results

1. Search results

Figure 1

2. Study Design and Population

Baseline data and the design of selected trials are summarized in Table 1. A total of 362 patients undergoing endocardial LV lead implantation. All studies were observational non-randomized, and had no control groups. Two studies were multi-centre (8,13), the rest were single-centre case series. Quality assessment of the included studies is shown in the Data Supplement. The full text studies met more data quality criteria with the largest study, ALSYNC, being rated the highest(8,13–22).

Most studies utilised the interatrial septum to access the left side of the heart(8,13–19,21,23–25),with the interventricular septum used two in studies(20,26), with the subclavian vein used to access the septum and deliver the lead. 3 studies used an LV apical approach, via a thoracotomy, to deliver the lead to the endocardium(13,22,26).

Equipment used to puncture interatrial septum ranged from standard Mullens sheath and Brockenbrough needle(14,15,18), Mullens sheath and Endrys needle (21), SL-1 sheath with transeptal needle(17), St Jude Agilis(23) to Radiofrequency needle(8,16,25). To puncture the interventricular septum Brockenbrough needle(20) (Betts), Radiofrequency needle(20) or radiofrequency via a guide wire(20,26) were used.

The venous access for puncture was femoral(8,13,14,16–19,21,23,24), internal jugular (14,15) or subclavian/axillary/left pectoral vein(8,25).

Lead delivery was via the Subclavian vein(8,13,16,17,19,21,23,24) in most cases, with one group using the femoral vein for both lead delivery and interatrial septal access(18) and others used the right internal jugular(14,15).

Active leads were used in all but one of the studies that specified lead type. Lead material was either Polyurethane(8,16,19,20,23,25), Silicone(14,15,17,18,21) or a combination of the two(13,22).

Polyurethane leads were thinner (4.1Fr in all reporting studies, except for 10 patients in Rademakers et al. with 5.7Fr polyurethane leads)(8,13,16,19,23). Silicone leads were usually 6-Fr or thicker(14,15,18,21). Information on techniques employed is shown in the supplementary material.

Mean procedure duration was 124 minutes (95%CI 96-151), and use of fluoroscopy was 28 minutes (95%CI 15-42) in average per case. The overall success rate of LV lead delivery was 98.1%

Table 1

3. Safety

There was one peri-procedural death (0.28%), one peri-procedural stroke, (0.28%) one pneumothorax (0.28%) and 2 (0.55%) case of cardiac tamponade/effusion. The most common peri-procedural complication was pocket haematoma, which occurred in thirteen (3.65%).

Stroke occurred during follow up in seventeen patients (4.7%) 2.60 per 100 patient-years (95%CI 1.56-4.07), with the study from Rademakers(13) having a higher proportion of strokes (13.7%) 5.88 per 100 patient years. All patients with ischaemic events in that study had a sub-therapeutic INR at the time.

Device-related infections occurred in thirteen patients (3.6%) with an incidence of 2 per 100 patient years (95%CI 01.1-3.3), and similar numbers were observed for late lead dislodgement (Supplementary material).

4. Outcomes

Mean follow-up was 22.3±19.2 months minimum: 7.6±4.6, maximum: 40±24 months. Three (0.84%) patients were transplanted (0.5 per 100 patient-years, 95%CI 0.1-1.3) with death occurring in 72 (19.9%) (11 per 100 patient-years, 95%CI 13.3-19.5). – ask RUI

The pooling of all study results reveals a reduction in QRS width (mean difference: -41% 95% -75 to -7%; P< 0.0001; I^2 = 94% (Supplementary material)). Improvements were demonstrated in NYHA class (mean difference: -1.06, 95% -1.2-to -0.9, P < 0.0001; I^2 = 60%) left ventricular ejection fraction (mean difference 7.9%, 95%CI 5 to 10%, P <0.0001; I^2 = 73%) following endocardial LV lead implantation (Figure 2).

The funnel-plot on NYHA change following implant (only comparison with more than 10 included studies) shows the presence of a mild degree of publication bias (with >5% of studies being outside the 95%CI limit) (Supplementary material).

Figure 2

5. Sensitivity analyses for Stroke During Follow-up

Analysis of data only from full-text papers and multicentre studies yield values as high as 3.7 per 100 patient-years (Table 2), compared to 2.6 per 100 patient years in the initial pooled data analysis. However, single-centre studies and studies published as abstracts provided more favourable data, with an incidence close to of 1.68 and 0 per 100 patient-years. Therefore, analysis of more rigorously scrutinised data showed that the incidence of stroke during follow-up is higher than suggested in the overall pooling of data.

Interventricular septum access was associated with no strokes. However, a high incidence was observed with the transapical approach.

When pooling studies per the composition of the LV lead, among the 9 studies providing this information, the incidence of stroke was comparable between silicone(14,15,18,21) and polyurethane-coated(8,13,16,19,23) leads.

Table 2

Discussion

LV endocardial pacing reduces QRS duration, and improves LVEF and NYHA, suggesting it can be an alternative for failed CS lead implants. However, its effect on mortality remains to be assessed in randomized controlled studies. Importantly, the safety profile of LV endocardial leads is not entirely reassuring and some questions merit future consideration, namely the long-term risk of stroke.

With no controlled studies using LV endocardial leads available, the quality of the data used in this meta-analysis is low. Studies were typically single centre case series, with only two multi-centre. There was heterogeneity in the implant procedures, in terms of site used to access the left ventricle and techniques employed to do so. Furthermore, baseline characteristics of the population such as QRS width and LV were not clearly defined in some studies(16,19) and there was inter-study variability. Prevalence of atrial fibrillation was not documented in six studies(16,22–25) and CHADSVASC score was not included in any study, although many of them preceded its inception.

LV endocardial pacing has been shown to result in superior haemodynamics, when compared to epicardial pacing(27) and permits LV electrical mapping, aiding selection of the optimal lead placement site, thus reducing risk of phrenic nerve capture(18). This contrasts with coronary sinus implants often being limited by anatomical constraints. Furthermore, it has been shown to be associated with better LV systolic performance and LV filling characteristics(28). Pacing the epicardium may be linked to arrhythmia via QT prolongation caused by the reversal of electrical activation (29). One patient in the Morina-Vasquez(18) study was reported to have had a marked reduction in ventricular arrhythmias with endocardial pacing. A physiologically appealing explanation for this being the restoration of the natural electrical excitation pattern engaging the endocardial Purkinje network(18).

Thromboembolic Risk

Thromboembolic events in up to a third of patients have been reported with inadvertent endocardial placement of LV leads(30). The high rates of stroke observed in some studies (8,13) are particularly concerning, with Rademakers et al. finding 5.88 strokes per 100 patient years. The author postulated this could be due to the higher number of NYHA class 4 patients in the study and sub therapeutic INR values. Without standard biventricular pacing controls these data are difficult to interpret. The overall incidence of stroke in this meta-analysis was 2.6 per 100 patient-years (95%CI 1.56-4.07), with an overall stroke rate of 4.7% during follow up. In the sensitivity analyses it was even higher at 3.29 – 4.2 per 100 patient-years. This is of relevance, as this analysis included larger studies with better quality outcomes data(8,13–21,31). These findings are contrary to those of Gamble(32) in a recent meta-analysis of this subject. They reported a stroke risk of 2.5 per 100 patient years and compared this to the 1.5 per 100 patient years rate quoted in the SAVE trial(33), and 0.84 per 100 patient years in the WARCEF trial(34), concluding that their results were not statistically different from these similar heart failure cohorts. Comparing our results to the SAVE and WARCEF trials shows a significantly increased risk of stroke ($p=<0.05$). This may be due to under-reporting in case reports and small cohorts of patients (<5 patients) without systematic follow-up in the Gamble meta-analysis. Importantly this means that the reassuring message from this paper is misleading. Thus, in comparison to WARCEF data our cohort have 3-4 times higher rate of stroke.

Without accurate baseline characteristics of patient cohorts it is difficult to compare studies and how the techniques or implant sites may have influenced results. ALSYNC excluded CHADSVASC >5, but lower CHADSVASC scores in other cohorts could explain lower stroke. Jais, Pasquie and Rademakers(13–15) have suggested that many strokes have occurred with sub therapeutic INR values. This raises the role of novel anti-coagulation

agents for LV endocardial leads. Theoretically, these agents could reduce the risk of thromboembolic complications by offering a steady state of anticoagulation. Whether a comparison could be made with the RE-ALIGN trial, that was stopped early due to higher stroke rates in patients with metallic valves anticoagulated with Dabigatran vs Warfarin, is open for debate(35). Again, more data is needed on this issue and would need to be evaluated with the use of RCT's.

Mitral valve (MV) prosthesis being more likely to thrombose than an aortic valve (AV) due to low flow state in the left atrium led to the idea that this may apply to pacing leads. It may be that leads placed via the IVS or apex with no atrial component would have a lower stroke risk. This, and a desire to avoid lead interference with the MV, was the driver behind the use of interventricular septum and LV apical punctures to access the LV endocardium. Numbers in this meta-analysis are too small to test this hypothesis, accounting for less than 30% of the sample, but are hypothesis generating. No events were observed in patients whose LV lead was implanted through the ventricular septum. This contrasts with transapical implants which showed a trend for more strokes, although concerns exist regarding INR control in the Kis et al. cohort(22). Of note concerns about MR, with leads that traverse the MV, were not borne out in the included studies(8,13–18,21).

Lead Materials

The types of leads employed were primarily polyurethane or silicone based. Polyurethane leads theoretically offer a reduction in the risk of thrombo-embolism and thin leads may reduce the risk of complications with MV(7). Even though a study in dogs in the 90s suggested that thrombogenicity with polyurethane leads may be lower(36), we have observed a comparable incidence of stroke in patients implanted with polyurethane and silicone leads (3.84 and 4.18 per 100 patient-years). Polyurethane leads are thinner and therefore may also reduce the risk of

complications with the mitral valve(7). The incidence of these complications was so low that we could not observe any differences between the 2 lead compositions.

Infection

Infective Endocarditis is a recognised complication with standard right sided pacing devices, with pulmonary embolism a known sequela. The risks associated with mitral valve infection due to a left sided lead are higher, with cerebrovascular accidents, cerebral abscesses and renal abscess associated with a high mortality and morbidity. This meta-analysis has shown higher infection rates of 2 per 100 patient years, (13 patients 3.6%) when compared to standard cardiac resynchronization therapy (1.0%) (4). Although other studies have shown infection rates as high as 4.8%(37). It is plausible to hypothesise that that this infection risk would be higher. Given the known association between pocket haematomas and infection, with all patients being given intra-operative heparin it is perhaps surprising that the haematoma rate was only 2.7%. This figure is comparable to the 2-4% rate for patients with no anticoagulation or Warfarin therapy(38). With regards to increased infection risk due to repeat procedures, 2.1% of patients had a lead dislodgement during follow up and 1.9% suffered from an acute dislodgement. Cumulatively, this is compares favourably to a 5.8% prevalence quoted for coronary sinus implantation(4).

Another potential problem is the complexity and risk associated with procedures to remove infected LV leads, with current technology poorly adapted for their removal(7). Although all infected devices were extracted without complication in these studies we do not know yet what the impact of percutaneously extracting an endocardial LV lead 10 years after its implant would be.

Limitations of Technology

The lack of equipment specifically designed for implantation of LV endocardial leads represents a challenge to the operator. The studies included have used a variety of techniques and adapted equipment not specifically designed for delivery of a LV lead.

Morbidity and mortality of open surgical techniques for epicardial lead implant limit it's routine use(39,40). Hence most cases treated with LV endocardial pacing have been patients with contraindications to surgery and failed attempts at CRT therapy for reasons previously described. However, there are other alternatives to failed CS lead implants which do not require a surgical approach and still need to be tested against LV endocardial pacing: direct-His bundle pacing and Bifocal RV pacing, future novel endocardial leadless electrodes. Direct His bundle pacing has been shown to reduce heart failure admission in patients with >60% ventricular pacing when compared to standard RV lead placement(41). Thus, offering optimism for its potential use as an alternative to CS lead placement. However, results from Bifocal RV pacing show that this technique may be inferior to standard biventricular pacing(42). Wireless ultrasound powered endocardial pacing(43) or battery powered devices(44,45) offer new alternatives for avoiding leads altogether. These technologies face challenges in terms of additional subcutaneous generator placement for the US powered devices and ensuring an optimal acoustic window with stable capture synchronised to an endocardial RV lead versus non-US leadless electrodes that will require stable wireless communication with right sided standard or leadless systems.

Limitations of Study

This meta-analysis is subject to several limitations. First, high heterogeneity among included studies leading to data interpretation being non-linear. Second, the low quality of studies clearly affects data interpretation, and the positive result of the global analyses should be interpreted very conservatively. Third, as patient-level data were available only for a minority of studies, there is no data on time-to-event for most the assessed

outcomes. Therefore, we used total follow-up, which presents the data on the incidence of complications as “a best-case scenario”. In fact, had we used time-to-event data, we could expect a 10 to 20% relative increase in the incidence rate. Even though this is an issue, we believe that our safety data should raise concern regarding this technique, even in this best-case scenario. Last, a randomized controlled trial is still needed in this area comparing the technique to matched epicardial CRT cohort.

Conclusion

LV endocardial lead implantation offers an efficacious alternative to traditional coronary sinus implantation leading to an improvement in NYHA class, LVEF and QRS duration. However, it is limited by concerns surrounding its safety profile, particularly an increased risk of stroke which we believe has been underestimated in recently published work. Further data with randomized controlled trial or observational case-controls are required before this approach can be recommended to the broad heart failure population.

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References

Figure 1 – Study Selection Diagram

Figure 2 – Forestplot NYHA and LVEF pre vs post endocardial CRT

LVEF = Left Ventricular Ejection Fraction
Note: Kassai et al 2011 is a subgroup of Kis et al 2017 in which NYHA and LVEF data was available(31)