Endocardial left ventricular pacing for cardiac resynchronization: systematic review and meta-analysis

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Aims
Endocardial left ventricular (LV) pacing for Cardiac Resynchronization Therapy has been proposed as an alternative to conventional LV lead placement via the coronary sinus. In order to assess the relative benefits and risks of this technique, we have performed a meta-analysis of published reports.

Methods and results
A systemic search was performed using online databases to identify studies of lead-based endocardial pacing. A random-effects meta-analysis was performed, to assess the rate of complications and clinical response (defined as ≥1 decrease in NYHA class). We selected 23 studies, including 384 patients. The trans-atrial septal technique was used in 20 studies, 1 used the trans-ventricular apical technique, and 2 used the trans-ventricular septal technique. Mean age was 66 years, male 66%, EF 26%, NYHA class 3.0. Procedural success rates were over 95% in all studies. Clinical response was reported by 16 studies for 262 patients, giving a response estimate of 82% (95% CI 71–89%). There was significant heterogeneity, and response in the only large study was 59%. Thromboembolic (TE) complications were reported by all studies, over 22 ±32 months follow up. The rate of stroke was 2.5 events per 100 patient years (95% CI 1.5–4.3), and TIA 2.6 (1.1–6.1). The mortality rate was 4.5 (1.5–13.6) per 100 patient years.

Conclusion
LV endocardial pacing appears to be a viable technique when conventional lead placement is not possible. Response rates were heterogeneous but comparable with conventional CRT. There is likely to be a small increase over expected rates of stroke, although included patients were high risk.

Keywords
Cardiac resynchronization therapy • Left ventricular lead • Endocardial pacing • Meta-analysis

Introduction
Despite the well-established efficacy of Cardiac Resynchronization Therapy (CRT) placing a left ventricular (LV) lead can still be challenging. We have shown in another meta-analysis that in contemporary trials the rate of failure to place a LV lead is 2.4%, with a 95% Confidence Interval (CI) of 1.9–3.1%, and that this has steadily improved over time since the introduction of CRT.¹ This improvement is multifactorial, but reasons include operator experience, better, and more specialized delivery equipment, and the impact of multipolar leads.² As the use of CRT expands the need for LV lead replacement and extraction has increased, however, it is not feasible to replace the lead via the coronary sinus (CS) in up to 20% of cases.³

These factors have stimulated the development of alternatives to pacing via the coronary sinus. Surgical epicardial LV lead placement remains a well-established alternative, despite a small but significant peri-procedural risk.⁴ A problem with surgical lead placement is that access to the optimal posterolateral basal aspect of the LV is relatively difficult and may not always be achieved in clinical practice.⁵ Patients who are candidates for CRT are clearly relatively high-risk for surgery, and a significant proportion of CRT candidates are not felt to be candidates for a surgical epicardial lead.

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Several techniques to achieve LV endocardial pacing have been described, and within these techniques, there are multiple variations. All these techniques have been investigated in multiple small studies.

In order to assess the relative benefits and risks of LV endocardial pacing, we will make a systematic assessment of the studies so far and their results. The main concern about these techniques has been the long-term thromboembolic (TE) risk, and better establishing this by meta-analysis was the main aim of the review. We intended to establish the rate of TE complications in patients exposed to lead-based LV endocardial pacing, and in addition to assess the rate of response to CRT in this population.

Methods

The review and meta-analysis was conducted according to the PRISMA statement. A systematic search of PubMed, Web of Science and the Cochrane Library was performed by the authors (primarily J.G.) to identify relevant articles published until the end of February 2016. We used the keywords ‘endocardial pacing’ and ‘endocardial LV pacing’. Hand searching of the reference lists of included publications allowed identification of articles not found in our primary search strategy.

All publications reporting the results of endocardial implantation of LV leads for CRT were included. We included all study designs, and allowed conference abstracts, acknowledging that this may reduce the quality of included data but with the intention of maximising the numbers of patients included. We excluded publications that were entirely or largely duplicates of previously reported data.

The titles of all publications identified were screened and those that did not meet our inclusion criteria were excluded. Subsequently we reviewed the text of remaining publications. Where CRT response rates were provided, we recorded these in a standardized method, defining clinical response as a ≥1 point decrease in New York Heart Association (NYHA) class (as this was by some way the most consistently reported parameter) and echocardiographic response as a >5% increase in LV ejection fraction (EF). Similarly, we classified any TE events that were reported. We assessed whether patients were followed up in a systematic fashion with specified review times, or if this was not clearly reported.

Significant heterogeneity was expected, and so a random effects meta-analytical approach was applied to all analyses. A normal-normal model was used for log-normalized response rates. For complication rates, we used the binomial-normal model, which provides appropriate weight to studies with low event numbers. We also used random-effects meta-analysis to estimate the mean of population parameters where appropriate. Analyses were performed using R version 3.2 with the metafor package. A significance level of 0.05 was used for testing and confidence intervals, and all testing was two-tailed. Rate comparisons were made using a Chi-squared test of the incidence rate ratio. Publication bias was assessed with use of funnel plots and Egger’s test.

Studies identified

We identified 1560 studies, of which 29 met initial inclusion criteria for the meta-analysis. We excluded 6 studies as they included duplicate data, leaving 23 valid studies published between 1999 and 2016. Twenty studies used the trans-atrial septal technique with various modifications, one used the trans-apical surgical hybrid technique and two studies used the trans-ventricular septal technique. One study used a wireless endocardial ultrasound transducer. All studies identified by the search were in English.

No studies were randomized or had a formal comparator group. Other than three studies, all studies were single centre, and only one study included more than 40 patients. Four studies were single-patient case reports. Reporting quality was generally poor, and blinding was not used for response determination. Follow up was clearly systematic in only 30% of studies. Although ALYSNC was multicentre, it appears that analysis was performed locally in each centre, rather than with a core lab arrangement. Risk of bias was thus judged as high in all included studies. A summary of the included studies is shown in Table 1.

Review

There is a body of pre-clinical evidence suggesting potential benefit of endocardial CRT, which has been reviewed previously. There is evidence to suggest that endocardial pacing may be less arrhythmogenic and may result in greater acute response to biventricular pacing than does conventional epicardial pacing via the coronary sinus, although this evidence is entirely in animals. This may be explained by either an intrinsic benefit of pacing from the endocardium and quicker access to cardiac conduction tissue, or by greater freedom to choose and target a pacing site.

Atrial trans-septal endocardial lead placement

The most used method of endocardial pacing is the atrial transseptal approach initially described by Jais in 1998. Multiple modifications of the technique have been described over the past decade, but it has remained complex, with most groups using a combined femoral and superior approach to puncture the atrial septum and deliver a lead from the subclavian vein, and using modifications of existing equipment to allow this. Experience of this technique has been reported in several small single-centre publications, often focused more on technique than on clinical outcomes, with limited reporting of response parameters. Complications appear to be more consistently reported, although follow-up length was often limited and it was often unclear as to how often patients were seen in follow up, and the completeness of the patient group.

Most studies used standard six French pacing leads, although since the availability of the Medtronic SelectSecure lead (which is a 4.2-French bipolar lumenless lead delivered through a catheter) this has been frequently used, on the basis that the smaller surface area may be less thrombogenic. Practice around anticoagulation has varied, but most studies report using an INR target of 2.5–3.5.

Trans ventricular apical pacing

A series of 20 cases of a hybrid surgical/endocardial procedure has been described, using surgical access to the LV apex via a mini-thoracotomy, followed by placement of an endocardial LV pacing lead through the apex. The 6 French lead was then tunneled up to the generator in a standard subclavicular position, with right ventricular and right atrial leads implanted conventionally. They used an international normalized ratio (INR) target of 3–3.5. Initial clinical results
in 12 patients were encouraging with a response rate reported as 100%.13

**Transventricular septal**

Our group has previously reported the development of a ventricular transseptal approach, designed to ameliorate some of our perceived concerns about the atrial transeptal route, and requiring superior access alone.33–35 In theory, the absence of lead in the left atria might reduce stroke risk and avoid worsening of mitral regurgitation attributable to crossing the valve. We punctured the high interventricular septum with radiofrequency energy applied to a wire via a steerable catheter, and then placed a mixture of standard 6-French and 4.2-French lumenless leads.33,34 We used an INR target of 2.5–3.5.

Another group have reported a small series using this technique.35 Larger studies

Rademakers et al. report the retrospective cumulative experience of two centres over 7 years, with 45 patients in whom an atrial transseptal approach was used, and six in whom a transapical approach was used (three due to failed atrial transseptal and three due to the presence of a mitral valve prosthesis).12 In the majority of cases, they used the 4.2-French lumenless lead. Their centres used a relatively high INR target of 3.5–4.5. The 51 patients were systematically followed up for a median of 24 months, with loss to follow up of only one patient, representing a significant cumulative exposure. They reported eight TE events in seven patients, although the CHADS-VASc or similar score was not reported, making it difficult to assess baseline risk. A persistent concern about placing leads across the mitral valve has been the potential for worsened mitral regurgitation (MR), but they did not observe this (Table 2).

Recently, Medtronic (MN, USA) has developed LV lead implant equipment specifically designed to allow puncture of the inter-atrial septum under guidance by transesophageal echocardiography and delivery of an endocardial LV lead, with access solely from the left subclavian/axillary vein access typically used for CRT procedures. This was used in the large ALternate Site Cardiac ReSYNChronization (ALSYNC) study, which included 138 patients and is by some way the largest and most rigorously conducted study of endocardial pacing.11 Patients were recruited from 18 centres on the basis of failed attempts at conventional CRT or non-response to CRT (22.5% of patients). The study includes a minimum of 12 months

### Table 1  Studies included in the meta-analysis

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<th>Technique</th>
<th>Design</th>
<th>Centres</th>
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TAS, trans-atrial septal; TVS, trans-ventricular septal; TVA, trans-apical. Follow up given as mean with standard deviation where available. When range is given this is minimum to maximum.
of systematic follow-up for all included patients, a mean of 17 ± 6, and up to 36 months for some patients. The 4.2-French Select Secure lead was again used, and they used an INR target of 3 with a range of 2–4. Again, they did not observe worsening of MR, and in fact report improvement in 33%. About 50% of patients had atrial fibrillation and 76% were already on oral anticoagulation at study start; their mean CHADS-VASc score was 3.4 ± 1.3. There were 14 failed implant attempts, 11 of which were due to failure to cross the interatrial septum, and 5 pocket haematomas.

With this larger patient group, they were able to assess TE risk in more detail. Five strokes (all reported to be non-disabling) occurred in patients with endocardial leads, as well as 14 transient ischaemic attacks (TIA) events in nine patients. Long-term assessment of the lead electrical performance revealed very stable parameters over the study period.

Other technologies

A system has been designed for LV leadless pacing, using ultrasound to deliver energy to an endocardial transducer, which converts it to electrical energy to activate the myocardium (EBR systems WISE). The 9 mm long transducer is inserted trans-arterially. The ultrasound pulse generator and battery units are implanted over the apex of the heart, but require a suitable acoustic window. The ultrasound pulse is designed to endothelialize rapidly, minimizing the risk of thrombus formation. The company have subsequently redesigned the implant equipment to reduce the risk of LV perforation.

In the initial trial of 17 patients, the system could be implanted in 16 (94%). Patients had a 66% response rate based on improvement in NYHA class, comparable with standard CRT. In three of the failed implants pericardial effusions occurred, one of which resulted in the patient’s death. There were no thrombotic strokes or transient ischaemic attacks (TIA), however, and these would not be expected as the transducer is designed to endothelialize rapidly, minimizing the risk of thrombus formation. The company have subsequently redesigned the implant equipment to reduce the risk of LV perforation.

We decided not to include this paper in the meta-analysis, as the main aim of our paper was to establish the safety of the lead-based techniques, and the TE risk arising from this technique is likely to be much lower.

A trial based in Maastricht (ClinicalTrials.Gov NCT01609738) is investigating LV septal pacing from a lead tunnelled into the LV endocardium but not entering the left ventricle, but are recruiting candidates for pacemakers, aiming to achieve capture of residual sub-atrioventricular nodal conducting tissue and thus more physiological pacing. Early results are positive.36

Results

As shown in Table 1, the range of numbers of patients included in each study was wide. The ALSYNC study11 contributed 35% of the total patients; the median patients per study in the remaining studies was 7. Most included patients had undergone a failed coronary sinus implant of an LV lead lead for CRT, but across all studies, 10% of patients were reported as being included on the basis of non-response to CRT.

Although this is not well illustrated by the demographics, narratively it is clear from included studies that the majority of patients were not straightforward patients but tended to be complex and high risk. Given the third-line status of these techniques in most centres (behind surgical epicardial placement for suitable candidates), and their novel nature, this would be expected.

Response to CRT

Sixteen studies, including 262 patients (68% of total patients), reported clinical response outcomes. Positive response after CRT (≥1 decrease in NYHA class) was reported for 191 patients (73% of patients), although the range of reported response rates was wide and unevenly distributed between studies such that the overall meta-analysis estimate of response rate was 82% (95% CI 71–89%) as shown in Figure 1. ALSYNC reported an overall response rate of 59%, with 60% of failed implants and 52% of non-responders responding at 6 months. The estimate of response rate in the remaining studies was 92%; the difference in response rates between ALSYNC and the remaining studies was significant (P = 0.02). There were no significant overall differences in response rates between techniques detected by meta-regression (P = 0.2 of no significant differences). A funnel plot of the response rates (not shown) suggests significant publication bias towards high response rates, and Egger’s test suggests significant asymmetry of published results (P < 0.0001).

Echocardiographic response, as defined by >5% increase in EF, was reported by only three studies, although these included 171 patients (65% of total patients). One study also reported echocardiographic response by end-systolic volume change. The meta-analytical estimate of echocardiographic response rate was 64.3% (56.8–71.2).

Adverse outcomes

Thromboembolic complications were reported by all 23 studies, which followed up patients for 22 ± 23 months, representing 554 patient-years of follow up. Summary results of meta-analysis are shown in Figure 2.

There were relatively small numbers of events reported overall, and considerable heterogeneity between studies, with 13/23 (57%) of studies reporting no events. Heterogeneity for any adverse
outcome as measured by $I^2$ was 77.9%, representing moderate-severe heterogeneity. This heterogeneity can also be appreciated in Figure 3. The length of follow-up did not appear to predict the events rate.

The bulk of these events was from ALSYNC, contributing 38% of total patient-years of follow up, and Rademaker’s study, contributing 19%. Narratively, many studies relate the majority of stroke and TIA events to periods of reduced anticoagulation and difficulty in maintaining a consistent INR level.

There were no significant differences in complication rates between techniques detected by meta-regression ($P = 0.7$ of no significant differences).

### Discussion

#### Response rates

Some authors have suggested that endocardial pacing might increase response rates over standard CRT, and as discussed above there is some animal evidence in terms of acute haemodynamic response for this. It appears from the response meta-analysis results that clinical response rates after endocardial pacing, at 82%, are better than the 50–70% of expected using standard lead placement via the coronary sinus. There is, however, a clear disconnect between the results of ALSYNC and the other studies. Part of this effect is likely to be the group of non-responders in ALSYNC who only had a 52% response rate. Non-responders to CRT are a challenging population who are
expected to be less likely to improve and are known to frequently have multiple reasons, such as comorbidities, that prevent functional improvement after CRT, so that it could be argued that achieving a response even in this proportion is an excellent result.

Even without this group, the high response rates reported in other studies were not seen in ALSYNC. This phenomenon of higher response rates being reported by smaller trials with less bias-resistant design features has been observed in other CRT trials. According, we do not think our analysis is convincing evidence that response to CRT is more common in the endocardial pacing population, given that no difference was seen in the largest and best-conducted study.

**Thrombosis risks**

All patients who have a LV endocardial pacing lead implanted will have a risk of thrombus forming on the lead, potentially causing systemic embolism and stroke. It is reasonably well established that there is a risk of thrombus forming on intracardiac leads. One group systematically examined the leads of patients with right-sided leads having ablation procedures using intracardiac ultrasound, finding some thrombus in 32% of patients. Transient thrombus was identified on right atrial leads in 29% of patients, on RV leads alone in 1%, and on both in 5%.

The annualized thrombosis rates calculated from this dataset are undoubtedly significant. None of the trials have a control arm and so there is no definitive method to identify a comparison rate.

**Figure 3** Random-effects meta-analysis of stroke or TIA thromboembolic (TE) events per 100 patient-years, with all studies shown to illustrate heterogeneity and the wide confidence intervals for the smaller studies. Studies are ordered by the number of patient-years of follow up, and subgroup estimates are shown for the studies with long follow up (defined as > 20 patient-years) and for the remaining studies. The difference in TE event rate between the shorter and longer follow up groups was not significant ($P = 0.6$).
The patients included in these trials, as discussed, were high-risk patients with heart failure. The mean CHADS-VASc score was 3.4 from limited reporting, as detailed above. Thromboembolism rates in this population would be expected to be high.

One comparison population would be the WARPCEF trial, which randomized 2305 patients with heart failure to warfarin or aspirin. The population was younger and less sick with mean NYHA class 2.2, and only ~30% had a defibrillator or pacemaker. Over 42 ± 22 months follow-up, the rate of stroke in the warfarin arm was 0.84 per 100 patient-years. This is significantly lower than the stroke rate in the endocardial pacing population which was 2.5 per 100 patient-years (P for comparison =0.007). An analysis of data from the SAVE trial followed 2231 patients with myocardial infarction for 42 ± 10 months, mean age 59, LVEF 31%, 28% on warfarin. They found a stroke rate of 1.5 per 100 patient-years (P for comparison = 0.11). They also noted a much increased rate of stroke in patients with EF <28% (as did >50% of patients in the current analysis), who had a stroke rate of approximately 2.5 per 100 patient-years. Neither of these studies reported TIA rates.

A recent large analysis of Danish registry data investigated the ability of the CHADS-VASC score to predict stroke in patients with heart failure, both with and without AF. Heart failure patients without AF (and not on warfarin) had an annual stroke rate of 2.0% with a CHADS-VASC score of 3 (a likely minimum for the endocardial pacing population) and 3.0% for a score of 4. With AF and not on warfarin, risks were 3.2% and 4.3%, although the addition of warfarin would be expected to approximately halve these risks.

In patients with atrial fibrillation, there is extensive data on assessing stroke risk. The rate of stroke or embolism in patients with a CHADS-VASC score of 3 on warfarin can be estimated from published data at 1.4% per year, and with a CHADS-VASC score of 4 at 2.1%, in comparison with the rate of 2.5% in the endocardial pacing population. This and the studies discussed above all estimate the risk of stroke, and not of TIA.

This would suggest that the added risk of endocardial pacing is of the order of 1 additional stroke per 100 patient years or less, on top of a baseline risk of 1–3 strokes per 100 patient-years. It is also clear that anticoagulation in this population must be meticulous. The use of non-warfarin oral anticoagulants has been very little studied, and their use was excluded in most studies. One group used them without reported complication in a small number of patients.

Limitations
This analysis is limited by the small numbers of patients included in the majority of studies. There is clearly a significant heterogeneity between study results, illustrated in particular by the differences in reported results from the multi-centre ALSYNC study and the other studies, which are all small and single centre. It is also challenging to accurately assess the expected risks of the patients included, who were likely to be very high-risk and complex patients. We were able to assess CHADS-VASc scores from four studies only. This limits the accuracy of comparisons of stroke or other outcome rates. Although we have made comparisons between the techniques used in the different studies, these were severely limited by the numbers of patients included. It is not clear from most papers how systematic the follow up of included patients was, which might have resulted in under-reporting of adverse events and thus under-estimation of risks. There was also severe heterogeneity in the amount of outcome and complication data reported in studies. We collected all available data but this meta-analysis is still limited by the data reported in the studies.

Conclusions
It would appear that the rate of thromboembolism in patients with endocardial LV leads is probably increased over that expected in a similar population, although it does not seem that the magnitude of the increase is large. The rate of death in this cohort appears to be as expected.

The meta-analysis estimate of the rate of response to CRT is greater than for most studies of conventional CRT, but study results are highly inconsistent between the smaller and larger studies in this area and there was evidence to suggest significant publication bias. Taking the large ALSYNC study as the closest available to a gold standard would suggest that there is not a significant benefit in terms of response over conventional CRT.

The increased long-term TE risk of endocardial pacing might potentially be offset by a significant improvement in response rates, although the only way to definitively assess the risk-benefit ratio of endocardial pacing would be a randomized trial comparing it to alternative therapeutic options.

The experience so far of endocardial pacing would suggest that it can be achieved feasibly in experienced hands with reasonable short-term risk, but there is currently no compelling evidence that it has any advantage above standard CRT if an optimal pacing site can be reached with conventional methods. The need for endocardial pacing using the current lead-based techniques as a second or third-line procedure has already decreased, as conventional CRT is now successful in most patients. Furthermore, the development of leadless endocardial pacing technologies may well obviate the need for these techniques in the near future.
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