THROMBOEMBOLIC EVENTS IN LEFT VENTRICULAR ENDOCARDIAL PACING: LONG-TERM OUTCOMES FROM A MULTICENTRE UK REGISTRY

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ABSTRACT

Background: Endocardial left ventricular (LV) pacing is a viable alternative in patients with failed coronary sinus (CS) lead implantation. However, long-term thromboembolic risk remains unknown. Much of the data has come from a small number of centres.

Objectives: We examined the safety and efficacy of endocardial LV pacing to determine the long-term thromboembolic risk.

Methods: Registries from four UK centres were combined to include 68 patients with endocardial leads with a mean follow-up of 20 months. These were compared to a matched 1:2 control group with conventional coronary sinus (CS) leads. Medical records were reviewed and patients contacted for follow-up.

Results: Ischaemic stroke occurred in 4 patients(6%) in the endocardial arm providing an annual event rate (AER) of 3.6% over a 20 month follow-up; compared to 9(6.6%) patients amongst controls with an AER of 3.4% over a 23-month follow-up. Regression analyses showed a significant association between sub-therapeutic INR and stroke (p=0.0001) in the endocardial arm. There was no association between lead material and mode of delivery (transatrial/ventricular) and stroke. Mortality rate was 12 and 15 per 100 patient years in the endocardial and control arm respectively with end-stage heart failure being the commonest cause.

Conclusion: Endocardial LV lead in heart failure patients has a good success rate at 1.6yr follow-up. However, it is associated with a thromboembolic risk (which is not different from conventional CS leads) attributable to sub-therapeutic anticoagulation. Randomised control trials and studies on NOACs are required to ascertain the potential of widespread clinical application of this therapeutic modality.

Keywords: Endocardial LV lead; Thromboembolic risk; Long-term outcomes

CONDENSED ABSTRACT

This multicentre UK study shows that there was no significant difference in the long-term ischaemic stroke rates in patients with endocardial LV leads compared to conventional CS leads at 1.6 yr follow-up. The thromboembolic risk in both groups was attributable to sub-therapeutic anticoagulation.

WHAT'S NEW?

1. This is a case-control, multicentre UK study, investigating the long-term thromboembolic risks associated with LV endocardial leads compared to conventional CS leads.
2. First case-control study comparing stroke risk associated with endocardial LV leads to a control group (conventional CRT) and shows no significant difference between the groups (AER for stroke risk in endocardial and conventional arms being 3.6% and 3.4% respectively at a mean follow-up of 1.6yrs.
3. Thromboembolic risk associated with endocardial LV pacing is attributable to sub-therapeutic anticoagulation (at the time of thromboembolic event) and risk profile of the patients (rather than the actual procedure) and there is no difference in annual stroke rate between trans-atrial and trans-ventricular leads.

INTRODUCTION

Cardiac resynchronisation therapy (CRT) has been shown to improve functional class and reduce hospitalisation rates and mortality in heart failure patients.[1,2] However, conventional CRT is not always feasible and trans-venous coronary sinus lead placement has been reported to fail in 2.4% of new implants because of unfavourable anatomy or other reasons.[3] In addition, a substantial proportion (up to 40%) of CRT non-responders has been reported.[4] Recent data suggest that endocardial left ventricular (LV) pacing might be an alternative to conventional epicardial LV pacing as it leads to improvement in functional class and LV systolic function.[5]

Endocardial LV leads can be delivered via an atrial transseptal puncture[6] or via direct puncture of the inter-ventricular septum.[7] Regardless of the mode of delivery, LV endocardial lead placement exposes the lead to systemic circulation and hence the risk of systemic thromboembolism. It has been hypothesised that this risk might be lower in trans-ventricular leads due to the lack of residual flow across the ventricular septum combined with the absence of lead in the low pressure left atrium where lead thrombi are more likely to form.[7,8] However, lifelong anticoagulation remains a pre-requisite and a major concern is the unknown long-term thromboembolic risk associated with endocardial LV leads. Long-term follow-up data of thromboembolic complications in patients with transseptal endocardial LV leads comes from a small number of centres and are scarce.[9]

A recent meta-analysis of the complication rate from LV endocardial pacing reports on 23 studies including 384 patients with a follow-up of 22 months. The rate of stroke was 2.5 events per 100 patient years (95% confidence interval 1.5–4.3), and TIA 2.6 (1.1–6.1). This analysis was limited by a small number of patients in individual studies and the lack of a comparison or control group.[9]

The purpose of this multicenter study was to determine the long-term thromboembolic risk associated with LV endocardial pacing by comparing the

incidence of thromboembolic complications in patients with LV endocardial leads to those with conventional transvenous CS leads. We also examined the impact of mode of lead delivery (trans-atrial versus trans-ventricular) on the thromboembolic risk and degree of mitral regurgitation.

METHODS

Study design:

This is a retrospective, case-control study of patients undergoing endocardial LV lead placement from the device registries of four UK centres. Consecutive patients in whom endocardial LV lead was attempted were included in this study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutions human research committees. Prior to the procedure, all patients gave written informed consent.

Study patients:

All patients undergoing endocardial LV lead placement across four UK centres from 2010 to 2015 were included in the study. Patients were offered this procedure if they had a Class I indication for CRT[9] and had a previous failed coronary sinus approach. When appropriate patients were given the option of a surgically placed LV lead. An age and sex matched control group with successful conventional transvenous CS lead implants over the same time period was also included to compare the rate of thromboembolic events. Exclusion criteria included a contraindication to oral anticoagulation or presence of intra-cardiac thrombus on cardiac imaging.

Endocardial LV Lead procedure:

The LV endocardial leads were delivered via atrial transseptal or ventricular transseptal approaches as have been described previously by the authors.[6,7] Transthoracic echocardiography was undertaken prior to the procedure to exclude

presence of LV thrombus. The procedure was performed on therapeutic anticoagulation with warfarin at an international normalized ratio of 2 to 3. A small proportion (6%) of the procedures were performed on Non-vitamin K antagonist oral anticoagulants (NOACs). There was no fixed protocol on the use of uninterrupted anticoagulants. In a small number of patients bridging with clexane was used prior to the procedure. Patients were fully heparinised during the procedure and long-term oral anticoagulation (with heparin bridging if sub-therapeutic INRs) was initiated as soon as possible post LV endocardial lead placement. Procedures were performed under intravenous moderate sedation or general anaesthesia based on clinical need, patient preference or at the operators' discretion.

All patients were kept in hospital overnight post procedure. They underwent device check and chest radiography prior to discharge the following day.

Follow up:

Patients were typically discharged from hospital a day post procedure (i.e. approximately 24 hours post procedure). After hospital discharge, the local anticoagulation service and general practitioners managed the oral anticoagulation. All patients were followed up in clinic one to three months following their procedure and had a device check and transthoracic echocardiogram during the same visit. Lead sensing and threshold were determined on device check. Degree of mitral regurgitation post-procedure was ascertained by transthoracic echocardiography. The frequency of subsequent clinic visits was determined by clinical need. Additional review of medical notes and electronic health records was carried out to obtain a complete dataset.

Study end points:

The primary end point of the study was occurrence of a thromboembolic complication post LV endocardial lead placement. This was compared to the incidence of thromboembolic complications in the control group (conventional CS leads) to

determine overall thromboembolic risk associated with LV endocardial pacing. Impact of mode of lead delivery (trans-atrial versus trans-ventricular) on the thromboembolic risk was also investigated.

Secondary end-points included acute procedural success, complications (other than thromboembolic), worsening of mitral valve regurgitation (MR) post implant and all-cause mortality.

Statistical analyses:

Data analyses were carried out using SAS version 9.3, statistical software. Continuous data were presented as mean ± standard deviation or median (range) if not normally distributed. Categorical data were reported as a percentage. Continuous data were compared using unpaired t-test (if normally-distributed) and Mann-Whitney U test if not normally-distributed. Categorical data were compared using chi-square test. The use of regression analyses allowed testing of various independent variables in the dataset in a multivariable model to assess association with risk of stroke. A p-value of less than 0.05 was considered significant.

RESULTS

Study patients:

68 consecutive patients undergoing LV endocardial lead placement were included in the study. In addition to the cases, 136 patients undergoing conventional trans-venous CS lead placement were also recruited. The latter were matched to cases for age, gender and CHA_2DS_2-VASc score. Two controls per case were included. The cases and controls were well matched as shown in Table 1.

In the endocardial arm, 82% of patients were men with a mean age of 67 yrs. The aetiology of LV dysfunction was ischemic cardiomyopathy in 60%, with a mean LVEF of 27.4 ± 7.7% and trace/mild mitral regurgitation (97%). Nearly all the cases

(90%) had NYHA Grade III/IV heart failure symptoms. An additional indication (other than endocardial LV lead) for anticoagulation was present in 65% of the cases. Of these, 39 (89%) had AF, 2 prosthetic valves – mitral and aortic (5%), 2 previous LV thrombus (5%) and 1 (1%) recurrent DVTs. The mean CHA_2DS_2-VASc score was 3.5.

In the conventional CS arm, 75% of the patients were men with a mean age of 69 yrs. The aetiology of LV dysfunction was largely ischaemic (54%) and 85% of the patients were NYHA Grade III/IV. The mean CHA_2DS_2-VASc score was 3.6 and nearly 66% of the patients were anticoagulated for AF. – Table 1.

Procedural data:

The procedures were carried out at four different tertiary centres across the UK. The majority of patients (n= 39, 57%) had trans-atrial LV leads whereas 29 (43%) had trans-ventricular LV leads. All procedures were done electively and the majority (63%) performed under general anaesthetic. 88% of the cases had defibrillator implants.

In the endocardial arm, the mean procedure and fluoroscopy times were 200 ± 120 and 32 ± 28 min respectively with a mean radiation dose area product of 2289.4 $cGycm^2$. In comparison, the mean procedure and fluoroscopy times were 175 ± 90 and 30 ± 20 min in the conventional CS lead controls with a mean radiation dose area product of 3000 $cGycm^2$. There was no significant difference in the procedure and fluoroscopy times between the two groups (p = 0.09 and 0.55).

75% had a silicone-insulated pacing lead. Good R wave sensing and thresholds (mean ± SD; 10.8 ± 6.4 and 0.7 ± 0.3 V at 0.4 ms) were obtained in all patients.

Study endpoints:

Primary endpoint – Thromboembolic Events

No thromboembolic complications occurred during the index hospital stay. The cases were followed up for a mean period of 20 ± 16.4 months. Thromboembolic complications during follow-up included ischaemic stroke. These were defined as transient or permanent loss of function associated with imaging confirmation of a cerebral infarct. Four ischaemic strokes in four patients (n=68, 6%) over a mean of 20 months corresponding to 3.6 strokes per 100-patient years were reported.

All four patients who had a thromboembolic event were men with a mean age of 72 ± 4.24 yrs. None of them had had a previous stroke and 50% were known to have an atrial arrhythmia (AF/AFL). All were anticoagulated with warfarin, however, 3 out of the 4 (75%) had sub-therapeutic INRs at the time of hospital admission with stroke. Two patients had trans-atrial and two trans-ventricular endocardial LV leads. Mean time to stroke post procedure was 15.8 ± 4.01 months – Table 2.

The controls were followed-up for a mean duration of 23 ± 14.2 months (cases vs controls, p = 0.17). A total of 9 ischaemic strokes occurred in nine patients (n=136, 6.6%) over a mean of 23 months, corresponding to 3.4 strokes per 100-patient years. Most patients who had a thromboembolic event were men (78%) with a mean age of 71 ± 11.8 yrs. Eight out of the nine had AF and were anticoagulated with warfarin. 62% of these had sub-therapeutic INRs at the time of hospital admission with stroke. Mean time to stroke post procedure was 21.8 ± 11.2 months – Table 2.

A regression analyses showed significant association between sub-therapeutic INR and stroke (p=0.0001) in the endocardial LV group. There was no association between the mode of lead delivery (trans-atrial/ventricular), age, gender, LVEF and presence of AF and stroke (p-value 0.41, 0.33, 0.51, 0.99).

Secondary endpoints

Acute Procedural Success and Complications:

Acute procedural success for endocardial LV lead placement was 98.5%. One patient had a cardiac tamponade necessitating a pericardial drain and further procedure at a later date. Minor complications included three pocket haematomas requiring wound exploration post-procedure. During follow-up, two patients were noted to have lead displacement (at 7 and 60 days respectively) and required a further procedure. One patient underwent system extraction and surgical epicardial lead placement after device infection.

In the control group, the acute procedural success was 99% with one patient requiring a chest drain for pneumothorax. Minor complications included three haematomas, which were managed conservatively. During follow-up four patients were noted to have lead displacements (three RV and one LV) and required a repeat procedure. One patient underwent system extraction due to device infection.

Degree of MR pre and post implant:

There was no significant difference in the degree of mitral regurgitation pre and post procedure (grade 2; 23.5% versus 17.6%, n = 68, p = 0.39). This remained true on comparing trans-atrial versus trans-ventricular leads (grade 2; trans-atrial 23.6% versus 18.4%, p = 0.58; trans-ventricular 23.3% versus 23.3%, p = 1).

Mortality:

In the endocardial LV lead group, 14 patients died over a follow-up period of 20 months. None of the deaths was procedure related. Of these 11 (79%) died of end stage heart failure, 2 of pneumonia and 1 of septic shock post knee infection.

In the conventional CS lead arm, 39 patients died over a follow-up period of 24 months. Of these 32 (82%) died of end stage heart failure, 4 of end-stage renal failure, 2 of traumatic sub-dural haematoma and one of leukaemia.

There was no significant difference in the mortality rates between the two groups at a mean follow-up of 1.6 yrs (21% verus 28%, p = 0.28) and end-stage heart failure was the leading cause of death.

DISCUSSION

In the present study we report a multicentre UK experience with LV endocardial pacing especially with regards to long-term thromboembolic risk associated with this procedure. The main finding of the study is that endocardial LV pacing in heart failure patients is associated with a risk of 3.6 strokes per 100-patient years, which was not significantly different to the rate seen in the control group with conventional CS leads: 3.4 strokes per 100-patient years; p-value 0.94. This suggests that the stroke rate is related to the risk profile of these patients rather than to the endocardial leads. Stroke occurred remotely from the implant procedure and was significantly associated with a sub-therapeutic INR at the time of the thromboembolic event.

Endocardial LV pacing for cardiac re-synchronisation therapy has been proposed as an alternative to LV transvenous epicardial pacing with equal or superior cardiac performance. Advantages of the endocardial approach include improved ability to select LV lead position, the probability of superior haemodynamic benefit compared with conventional CS leads and a more physiological endocardial to epicardial LV electrical activation.[10,11] However, with the current evidence, it is not used as a first line pacing therapy due to concerns regarding its safety. Its clinical application (as an alternative to failed CS lead placement) is largely moderated by the undetermined long-term risk of cerebral thromboembolism (despite lifelong anticoagulation) and the need for lifelong anticoagulation.

Previously published data have come from a small number of centres and patient cohorts. Only a few studies have reported thromboembolic complications with LV endocardial pacing. Stroke incidence has varied from 9 to 16% and with short-term follow-up.[8,12,13] A more recent study reported 6.1 thromboembolic events per 100 patient years (n = 45) at 6 months follow-up. The majority of these were associated with sub-therapeutic anticoagulation.[14] All of these studies lacked a control group.

Our study is the first and largest case-control study to date, assessing the long-term thromboembolic risk associated with LV endocardial pacing across four tertiary centres in the UK. Although the incidence of stroke in the present study remains modest, it is significantly less than that reported before. Moreover, it is not different to the risk of stroke associated with conventional CS pacing, as seen in the control group. The only significant factor associated with the risk of stroke was sub-therapeutic INR.

Stroke and/or TIA occur more frequently in patients with heart failure than those without. The reported incidence of thromboembolic events in patients without a history of AF varied between 1.5 and 3. 5 events per 100-patient years.[15,16] This is similar to the incidence in our group (3.6 events per 100-patient years in cases and 4.4 events per 100-patient years in controls) even with a sizeable proportion of patients having AF. The controls had a higher event rate (although not significantly different) with a similar proportion of patients who were anticoagulated for AF.

It has been stipulated that the mode of lead delivery might have a bearing on the thromboembolic risk post LV endocardial pacing. The lack of residual flow across the ventricular septum, combined with the absence of lead in low-pressure left atrial chamber (where lead thrombi are more likely to form), may make lead thrombosis or paradoxical emboli less likely than with atrial transseptal route.[7,8,17] However, the present study did not show any association between the mode of lead delivery and thromboembolic risk (p=0.85), although the study is not adequately powered for this

comparison. Also, nearly 80% of the leads had silicone insulation and the study was not adequately powered to assess the impact of lead materials on thromboembolic risk.

The overall procedural success was high and complication rate low compared with other studies to date. There were no procedure related deaths and the all cause mortality was comparable to that in CRT trials.[2] The reported outcomes are likely to be a result of technical expertise and several precautionary measures that an LV lead implant mandates. Endocardial LV pacing does come with technical challenges including difficult transseptal punctures, bleeding risk associated with performing procedures on uninterrupted anticoagulation and therapeutic ACTs and the potential need of lead extraction, which might entail a surgical procedure in patients with severe heart failure.

The electrophysiologists performing the procedures in our study are experts in performing transseptal techniques. The implantation procedure was done on heparinised patients with therapeutic ACTs. Long-term anticoagulation was instituted as soon as possible after the procedure (if the patient was not already anticoagulated for another indication). The right level of anticoagulation was maintained by close follow-up, as joint care between anticoagulation clinic, general practitioners and hospital follow-up. Despite these precautions, the incidence of stroke post procedure was 3.6 per 100-patient years with sub-therapeutic INR being the only significant factor contributing to this risk. However, the rate of stroke during follow-up, although modest, was lower than that reported in other endocardial LV lead trials. Given the similar incidence of stroke in patients with endocardial LV leads and CS leads and the significant association with sub-therapeutic INRs, the observed risk of thromboembolic complications cannot be attributed to LV endocardial pacing alone. Maintaining the optimal level of anticoagulation, as a fine balance between haemorrhagic and thrombogenic risk is crucial. This remained a challenge in the current study wherein the vast majority of patients were anticoagulated with warfarin.

Non-vitamin K antagonist oral anticoagulants (NOACs) might decrease the risk associated with sub-optimal anticoagulation and facilitate the long-term care of these patients. Although they work well for stroke prevention in AF, studies assessing NOAC use in prosthetic valves have not been promising. The use of NOACs in patients with mechanical heart valves was associated with increased rates of thrombogenic complications when compared to warfarin. This was explained by the relative inability of NOACs to suppress activation of coagulation that occurs when blood is exposed to artificial surfaces of the valve prosthesis.[18] Hence, their potential for adequate anticoagulation in patients with endocardial LV leads remains uncertain.

STUDY LIMITATIONS

Some limitations of this study require consideration.

This is a retrospective case-control study. Patients were not randomised to receive LV endocardial pacing as a first line therapy. The results of this study reflect the practice of electrophysiologists who are well trained in transseptal techniques. These findings might not be generalisable to other centres, which lack a similar framework.

The study was not adequately powered to assess the thrombogenic properties of the lead insulation material or the mode of lead delivery. Also, the selection of advanced heart failure patients may have biased the results towards more thromboembolic complications.

CONCLUSIONS

It appears that endocardial LV pacing is a safe and effective alternative to conventional CS pacing. It is associated with a thromboembolic risk, particularly with sub-therapeutic anticoagulation. However, there is not enough long-term data regarding safety to justify this as a first-line approach at the current time.

Randomised control trials and further studies on NOACs are required to ascertain the potential of widespread clinical application of this therapeutic modality in heart failure patients.

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TABLES

Table 1: Baseline demographics

N = 204	Endocardial LV Lead N = 68	Conventional CS Lead N = 136	P-value
Age (yrs; mean±SD)	67 ± 12	69 ± 11	0.23
Sex (male; n, %)	56 (82)	102 (75)	0.26
Cardiomyopathy n(%)			
Ischaemic	41(60)	73(54)	0.41
Dilated	27(40)	63(46)	0.41
NYHA Grade n(%)			
I-II	7(10)	20(15)	0.32
III	43(63)	78(57)	0.41
IV	18(27)	38(28)	0.88
LVEF (%)	27.4 ± 7.7	28.2 ± 8	0.49
Intrinsic QRS duration (ms; mean±SD)	159 ± 26 ms	153 ± 29	0.15
QRS Morphology n(%)			
Left bundle branch block	42(62)	86(63)	0.88
Right bundle branch block	3(4)	5(4)	1
IVCD	2(3)	5(4)	0.72
Right ventricular paced	21(31)	40(29)	0.76
Atrial fibrillation n(%)	39(57)	75(55)	0.78
CHA_2DS_2-VASc Score (mean±SD)	3.5 ± 1.2	3.6 ± 1.1	0.55
Anticoagulated prior to procedure n(%)	44(65)	90(66)	0.88
Mitral Regurgitation n(%)			
Trace	43(63)	82(61)	0.78
Mild	23(34)	48(35)	0.88
Moderate	1(1.5)	4(3)	0.51
Severe	1(1.5)	2(1)	0.75

Table 1: Baseline demographics. The Endocardial LV lead group (cases) and Conventional CS leads (controls) both had 68 patients each. NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction.

Table 2: Patients with Thromboembolic Complications (Stroke)

S.No	Age (yrs)	Sex	Previous Stroke/TIA	Rhythm	Implantation Technique	Time to Event (mths)	Anticoagulation	INR at time of CVA	Sub-therapeutic INR
		Endocardial LV Leads (N=68)							
1	69	M	N	AF	TV	15.5	Warfarin	1.3	Y
2	78	M	N	SR	TV	12	Warfarin	2.9	N
3	72	M	N	AFL	TA	10	Warfarin	1.2	Y
4	69	M	N	SR	TA	20	Warfarin	1.4	Y
		Conventional CS Leads (N=136)							
1	69	M	N	SR	CS	24	None	NA	NA
2	50	M	N	AF	CS	30	Warfarin	2.5	N
3	83	M	Y	AF	CS	8	Warfarin	1.1	Y
4	70	M	N	AF	CS	20	Warfarin	2.9	N
5	82	M	N	AF	CS	36	Warfarin	3.4	N
6	70	F	N	AF	CS	6	Warfarin	1.2	Y
7	55	M	N	AF	CS	13	Warfarin	1.5	Y
8	81	M	N	AF	CS	24	Warfarin	1.2	Y
9	78	F	N	AF	CS	36	Warfarin	1.2	Y

Table 2: Patients with Thromboembolic Complications (Stroke). Clinical characteristics of patients who had a stroke are included here. 4 out of 68 in the Endocardial LV lead group (Cases) and 9 out of 136 in the Conventional CS Lead group (Controls) had a stroke on 1.6 yrs follow-up.