

# **Endocardial Left Ventricular Pacing across the Inter- Ventricular Septum for Cardiac Resynchronization Therapy - Clinical Results of a Pilot Study**

**Short title:** Endocardial pacing across the interventricular septum

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## **Disclosures / Conflict of Interest**

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## **Abstract:**

### **Background**

Cardiac Resynchronization Therapy (CRT) is an effective treatment for selected patients with heart failure, but can be limited by the inability to place the left ventricular (LV) lead via the coronary sinus.

### **Objective**

We have developed an alternative approach, placing the LV lead endocardially via an interventricular septal puncture; this study was designed to assess the feasibility and safety of this technique.

### **Methods**

All patients were anticoagulated with warfarin (INR 2.5-3.5). A superior approach ventricular transseptal puncture using radiofrequency energy was performed. An active-fixation pacing lead was delivered to the mapped site of latest electrical activation on the endocardial LV.

### **Results**

20 patients were recruited, 15 with failed transvenous LV lead placement and 5 non-responders to CRT. Age was  $67 \pm 12$ , 80% male, QRS duration  $157 \pm 14$ ms, ischemic 45%, NYHA class  $2.9 \pm 0.4$ , LV ejection fraction (LVEF)  $28 \pm 7\%$  (mean  $\pm$  SD). The procedure was successful in all with no serious complications.

Clinical composite score improved at 6 months in 65%, and worsened in 35%. LVEF improved  $>5\%$  in

88%, from  $28 \pm 7\%$  to  $41 \pm 9\%$ . 6-minute walking distance improved  $>10\%$  in 64%, from  $248 \pm 125$  to  $316 \pm 109$ m. One patient suffered a lacunar ischemic stroke after 5 months with partial neurological recovery, associated with labile INRs. After  $2.0 \pm 1.0$  years follow-up, three patients have died, (two pneumonia, one heart failure), and two patients have suffered transient ischemic attacks.

## Conclusion

LV endocardial pacing via interventricular septal puncture in patients in whom standard CRT is not possible is similarly effective and durable, with significant but potentially acceptable risks.

## Keywords

Cardiac Resynchronization Therapy; Pacing Leads; LV endocardial pacing; LV pacing site; heart failure

## Abbreviations

CI: Confidence Interval

CRT: Cardiac Resynchronization Therapy

CS: Coronary Sinus

LV: Left Ventricular

## Introduction

Cardiac Resynchronization Therapy (CRT) has been shown to decrease both hospitalizations and mortality and to improve symptoms and quality of life in patients with impaired systolic function and prolonged QRS duration on the electrocardiogram (ECG).<sup>1</sup> Placement of the left ventricular (LV) lead via the coronary sinus (CS) can be challenging due to adverse CS anatomy or procedural complications.<sup>2</sup> A meta-analysis including 164 studies of LV lead implantation has shown a contemporary rate of failure to place an LV lead of 2.4% (95% confidence interval 1.9-3%)<sup>3</sup>. LV lead revision is needed in 5.7 patients per 100 patient-years, although this is more often early post implant<sup>3</sup>. Replacement of chronic LV leads is not feasible via the coronary sinus in at least 20% of cases<sup>4</sup>.

The most established alternative to LV lead placement via the coronary sinus is surgical epicardial lead placement, which is limited by an acute and possibly long-term increase in adverse outcomes<sup>5,6</sup>, as well as concern about lead failure rates<sup>7</sup>. Furthermore, access to the posterolateral basal LV, where leads are optimal in most patients, is relatively difficult and leads are often placed anteriorly<sup>8</sup>.

The alternative is endocardial LV pacing. The atrial trans-septal approach to LV endocardial pacing was initially described in 1998 and has undergone multiple modifications, but has remained complex, usually requiring a combined femoral and superior approach to puncture the atrial septum and deliver a lead<sup>9</sup>. Several studies have reported results on small numbers of patients with relatively limited follow-up. The ALSYNC study has reported results of this route in a larger 138 patient cohort<sup>10</sup>. These techniques are complex, leave lead material in the low-pressure left atrial chamber where lead thrombi are more likely to form<sup>11</sup> and may expose the mitral valve to damage or insufficiency<sup>9</sup>.

Despite the limitations of current techniques, a developing body of evidence suggests that endocardial LV pacing may have hemodynamic benefits over epicardial pacing via the CS<sup>9,12,13</sup>.

Endocardial pacing has also been shown to produce less dispersion of repolarisation than epicardial stimulation, which may reduce arrhythmic risk<sup>14</sup>.

Endocardial LV pacing procedures are likely to be at higher risk than conventional lead placement via the coronary sinus, due to the increased complexity and the necessary presence of artificial material in the left ventricular cavity. The latter exposes patients to a potential risk of thrombotic embolization and in particular stroke and therefore all prior LV endocardial pacing trials have used oral anticoagulation with warfarin. This carries an additional risk associated with bleeding.

We have developed an alternative route, placing the LV lead endocardially through an interventricular septal puncture<sup>15,16</sup>. We now report the results of a formal pilot study assessing this technique.

## Methods

The study was approved by the local Research Ethics Committee and is registered at ClinicalTrials.Gov (NCT01818765). We included adults who satisfied the ESC criteria for CRT<sup>17</sup>, who had had a failed attempt or attempts at placing a left ventricular epicardial lead via the conventional coronary sinus route, and in whom the treating clinicians had assessed that with available technology a viable lead could not be placed via this route. All potential patients had the risks and benefits of surgical epicardial versus transvenous endocardial lead placement discussed, including the use of lifelong oral anticoagulation.

In addition, we recruited non-responders to conventional CRT (non-response defined as no improvement in NYHA status and a <15% reduction in end systolic or diastolic volume on echo at 6 months), with non-optimal LV lead position (which we defined as a LV lead position outside the anterolateral, lateral or posterolateral basal and mid-ventricular segments) and without other evident reasons for non-response. All patients were carefully assessed for their suitability for long-

term warfarin therapy, and commenced on it if not already anticoagulated, at least a month before the procedure to allow stability.

## **Clinical Follow-Up**

Our primary objective was to investigate if left ventricular endocardial pacing via the trans-ventricular septal route is safe and feasible and accordingly our primary end-point was freedom from adverse effects at 6 months post-procedure. As a secondary end-point we assessed response to CRT using the Packer Clinical Composite Score (CCS), which categorises heart failure patients as improved, unchanged or worsened, categorising all patients who die or are hospitalised as worsened<sup>18</sup>. In addition, we used the NYHA class, the EQ-5D-5L quality of life score and the 6-minute walk test to assess clinical response. Echocardiographic response was assessed with 2-D echocardiography at baseline and 6 months by an accredited echocardiographer and defined as a >5% absolute increase in LV ejection fraction (EF) and >15% relative decrease in LV end-systolic volume (ESV).

Patients were followed up in person at 3 months and 6 months and then until two years telephonically. All comparisons were made between the baseline and 6-month assessments, using the Wilcoxon signed-rank test for non-parametric variables such as NYHA class and EQ-5D-5L scores, and paired T-tests for the other normally distributed continuous variables.

## **Procedural methods**

We have previously described our implant technique<sup>15</sup>. All procedures were performed under general anesthesia with continuation of warfarin (INR 2-3). We gained access via the subclavian/axillary vein and a steerable sheath (Agilis; St Jude Medical, MN, USA) was guided by left ventriculography to position the straight end of a standard 0.035" guidewire against the interventricular septum. Radiofrequency energy was applied using a surgical diathermy pen to the

wire and the septum was punctured. The dilator and sheath were then passed into the LV, and intravenous heparin was given.

A decapolar catheter (Enquiry, St Jude Medical) and the NavX electro-anatomic mapping system (St Jude Medical) were used to produce an endocardial LV geometry and activation map during RV pacing to locate the site of latest electrical activation (LEA), which was the latest-activated area without low activation amplitudes suggesting scar.

The sheath was exchanged for a split-able, steerable sheath (SelectSecure; Medtronic, MN, USA) and used to deliver a pacing lead to the site of late electrical activation. Standard active fixation 6 French pacing leads (Medtronic 5076) and also the lumen-less 4.1 Fr lead (SelectSecure; Medtronic) were used. All patients were anticoagulated with INR 2.5-3.5 after the procedure.

## Results

### Patients

20 patients were recruited, 15 (75%) patients with prior attempts at CRT but no successful LV lead placement, and 5 (25%) patients who already had functioning LV leads and were recruited as non-responders with non-optimal LV lead placement. Of these patients, four had coronary sinus LV leads and one had a surgical epicardial lead. Patient characteristics are summarised in Table 1.

Eleven additional patients were assessed in detail and not recruited. Four of the 11 non-recruited patients decided in favour of a surgical epicardial lead. In one patient we were able to place an LV lead via the conventional CS route and in a second programming changes allowed LV lead capture. Three patients were felt to have too many advanced co-morbidities to benefit from CRT. Two patients with prior low LVEF were found to have improved LV function at re-assessment. One patient died before having decided if she wanted to participate.

16/20 (80%) patients were already taking warfarin before consideration of study entry; the others were started on warfarin pre-procedure. 12/20 (60%) patients had persistent AF, and 4/20 (20%) had paroxysmal AF but were in sinus rhythm at the time of implant. The CHADS-VASc score was a mean of 3.7, median 4, with interquartile range 3-5.

## **Procedural results**

We were able to place a LV endocardial lead in all 20 cases where this was attempted. In one patient, guidewire micro-fracture prevented transmission of radiofrequency energy and thus septal puncture, until the problem was recognised and the guidewire replaced. Overall, time from venous access to successful passage of the sheath into the LV was  $25 \pm 19$  minutes. The SelectSecure lead was used in 10 patients, and the 5076 in the remaining 10. Final lead position, based on the site of late electrical activation, was anterolateral in 65% and 35% lateral, 80% were basal and 20% were midventricular.

Two patients developed significant post-operative wound haematomas, requiring early re-operation to control bleeding. In one patient, who also had extraction of a right atrial lead during the procedure, a pre-existing right ventricular lead became displaced after the procedure and required revision. There were no incidences of pneumothorax, wound infection or LV lead displacement. No patient suffered a peri-procedural neuro-embolic complication. Accordingly, 17/20 (85%) patients were free of an acute procedural complication.

## **Freedom from adverse events**

In the first 6 months, one patient suffered a lacunar ischaemic stroke after 5 months with partial neurological recovery, in association with labile INRs. Another patient, who had a history of previous TIA and known severe carotid artery disease, had a probable TIA 6 weeks after the procedure. No change in medication was made and he had no further events. A further patient had a TIA more than 3 years post-procedure.



No ventricular arrhythmias occurred in the first 6 months. No patients suffered lead failure. Thus the primary end point of freedom from possible procedure-related serious adverse events at 6 months was 15/20 (75%). No residual flow across the septal puncture site was detected with transthoracic echocardiography.

Two patients died in the first 6 months, for reasons unrelated to the procedure. One, who had been an early clinical and echocardiographic responder to CRT at 3-month follow-up, died of community-acquired pneumonia after 4 months. The other was a non-responder to CRT with severe heart failure, who was included on the basis of an apical anterior LV lead position, persistent broad QRS despite optimised CRT and persistent severe symptoms. He did not improve, and died 5 months after the procedure of progressive heart failure.

Over longer-term follow up, one additional patient died 13 months post procedure, also attributed to community-acquired pneumonia. He was a non-responder to CRT who had no improvement symptomatically after endocardial pacing, but did improve in terms of EF and LV volumes. He had a history of prior slow ventricular tachycardia; this recurred 9 months after the procedure but was controlled medically.

A total of 40 patient-years of follow-up is available, with per-patient follow-up duration of  $2.0 \pm 1.0$  years.

## **Clinical Response Results**

As discussed above, two patients had died before the 6-month assessment. Two patients refused face to face follow up and only telephone assessment of NYHA class could be made, and thus 16/18 (89%) surviving patients were assessed fully at 6 months.

Clinical response at 6 months was variable dependent upon the method of assessment. The primary response outcome of clinical composite score improved at 6 months in 13/20 (65%) and worsened in 7/20 (35%), including in the latter category the two patients who had died. Clinical response by

clinical composite score was similar between patients recruited on the basis of failed lead placement (10/15; 67%) and in prior non-responders (3/5; 60%, retrospective analysis not defined in protocol).

As shown in Table 2 and Figure 1 and 2 below, there were significant improvements in NYHA class, 6MWT and quality of life as measured by the EQ 5D-5L. Echocardiographic response rates were higher than clinical response, as shown in Table 3. Echocardiographic response rates on the basis of LV EF were non-significantly higher in failed implants (10/12; 83%) than in prior non-responders (3/4; 70%;  $P=0.7$  by Fisher's exact test).

Lead capture thresholds were stable in all patients over 6 months, as shown in Figure 3, with expected decreases in both between implant and first follow up. Two patients had  $>1$  V increases in LV threshold, but subsequent thresholds have been stable.

## Discussion

Endocardial LV pacing via the trans-ventricular septal approach appears from this small cohort to be reasonably safe, with 85% of patients free of acute procedure-related complications. Those that did occur were manageable. The BRUISE-CONTROL study demonstrated that performing CRT procedures on therapeutic anticoagulation is safe<sup>19</sup>. Our 11% rate of significant haematoma is higher than the 3.5% observed in their warfarin arm and higher than in the ALSYNC study, where there was a 3% haematoma rate<sup>20</sup>. This may be due to the additional intra-procedural heparin given during the procedure.

Displacement of a 1-year old RV lead was unexpected but is unlikely to be specifically related to our technique. The procedure can also be performed in a reasonable time, likely to be faster than in the ALSYNC study, although as a result of the electro-anatomical mapping we did not place the LV lead immediately after gaining access and were unable to directly compare the two procedures. Placing the lead was generally quite straightforward, as the puncture direction leads the sheath towards the lateral basal LV, where the late activation areas are in most patients.

223 Response results were broadly within the range expected and are comparable to those of standard  
224 CRT<sup>1,21</sup>. Our echocardiographic response rate at 88% was higher than the 60% seen in most studies<sup>21</sup>  
225 and our 65% clinical response rates based on the CCS were also as expected, as 65-70% of patients  
226 are found to improve<sup>21</sup>.

227 Our lower clinical response rates are likely to be a feature of the high-risk and comorbid patient  
228 group recruited, rather than a limitation of the technique. Candidates who were relatively well and  
229 had failed conventional lead placement were unlikely to be recruited as they were suitable for  
230 surgical lead placement, leaving us with a complex and extensively comorbid patient group in whom  
231 response was often limited by cardiopulmonary comorbidities. Assessment of both response and  
232 safety in our small cohort is unavoidably limited by the small number of patients recruited.

233 It is clear that long term adverse events are the key issue after LV endocardial pacing. Our group has  
234 tried to assess this by a meta-analysis of studies published to date, in which we found with 384  
235 patients and 554 patient-years of follow-up, a stroke rate of 2.5 events per 100 patient-years (95% CI  
236 1.5-4.3)<sup>22</sup>. A multi-center registry of patients with endocardial LV leads found a rate of stroke or TIA  
237 of 3.6% per year<sup>23</sup>. These are similar to the rate in our study which was also 2.5 strokes per 100  
238 patient-years. Use of published data to calculate personalised risk in our patient group based on the  
239 CHADS-VASC score<sup>24</sup> gave a mean annual risk of stroke or embolism of 2.4±1.2% on warfarin  
240 therapy, although this does not fully account for higher risks in heart failure patients<sup>25</sup>. This would  
241 suggest that there is probably only a very small increase in the stroke rate over that expected in this  
242 patient group. As has been reported in other similar studies<sup>10,23</sup>, the stroke which occurred was  
243 associated with poor control of INR levels, and careful screening for good INR control is essential.

244 The optimal level of anticoagulation to be used in patients with endocardial LV leads remains  
245 undefined. We used an INR target of 2.5-3.5, but this was empirical and it may be that a lower INR  
246 target would have been adequate. It might be that the use of non-warfarin direct oral anticoagulants  
247 (NOACs) will provide more reliable INR control and thus be safer. There is minimal experience of

NOACs in patients with endocardial LV leads, with only one trial reporting use in a small number of patients<sup>26</sup>. Although our patients did not have any bleeding events, this risk that would be increased by this higher INR target. The risk of extracting endocardial LV leads is unknown, with minimal worldwide experience, but a risk of stroke associated with an such extraction needed would be expected. Collaborative efforts between centers performing endocardial LV pacing are likely to be needed in order to gather large patient cohorts and to follow them up over the longer term. This should allow accurate assessment of the rate of endocardial LV lead-related thrombosis and also potentially a comparison between the trans-ventricular and trans-atrial septal techniques for LV endocardial pacing. Endocardial pacing using lead-based technology is likely, at least in the short term, to remain a third-line option, with significant risks and no clear evidence of advantage over conventional CRT via the coronary sinus.

For most patients with failed placement of a LV lead via the coronary sinus, options other than LV endocardial lead based pacing are likely to be best. In some cases a different operator or technique might be able to achieve pacing via the coronary sinus. Surgical epicardial lead placement remains a viable option despite some concerns. Wireless endocardial pacing technology is maturing and is now commercially available in the WICS system<sup>27</sup>. This has a subcutaneous ultrasound energy transmitter and a small endocardial transducer placed via the retrograde aortic route which is designed to endothelialize and does not mandate oral anticoagulation. The downside of this system is the relatively bulky battery and transmitter modules, although these are now smaller in a second-generation version. This wireless system is likely to a better option for many patients, unless specific patient characteristics (e.g. lack of acoustic window or prosthetic aortic valve) prevent its use, given the likely lower thrombotic risks.

## Conclusions

- LV endocardial pacing across the interventricular septum as a third-line option for LV lead placement had moderate risks in the short and long-term, in this small study.
- There may be a small increase in the rate of stroke over that expected in these patients, of the order of 1 additional events per 100 patient-years.

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St Jude Medical Limited kindly donated consumables for the study, but had no other involvement in the study design, undertaking, or analysis.

## Tables

Parameter	Result
N	20

Age	67 ± 12
Male	80%
QRS Duration	157 ± 14
Ischaemic aetiology	45%
NYHA class	2.9 ± 0.4
Ejection fraction	28 ± 7%

**Table 1 –Patient details; mean ± standard deviation.**

	Baseline	6m	Mean Change	Criterion	Responders	P	Test
<b>NYHA Class</b>	2.9 ± 0.4	2.1 ± 0.8	-0.8	≥1 class decrease	9/18 (50%)	0.001*	WSRT
<b>6 MWT (m)</b>	248 ± 125	316 ± 109	47	≥10% increase	10/16 (63%)	0.01*	TT
<b>EQ 5D-5L Total</b>	14 ± 5	10 ± 5	-3	>1 decrease	9/16 (56%)	0.006*	WSRT
<b>EQ 5D-5L VAS</b>	52 ± 26	62 ± 33	2	>5 increase	8/15 (53%)	NS (0.4)	WSRT
<b>BNP (pmol/L)</b>	81 ± 96	95 ± 129	20	≥10% decrease	6/13 (46%)	NS (0.6)	TT

**Table 2 – Clinical response rates. (6 MWT – 6 minute walk test; BNP – bone natriuretic peptide;**

**WRST – Wilcoxon signed rank test; TT – Paired T-Test.)**

	Baseline	6m	Mean Change	Criterion	Responders	P
<b>ESV (ml)</b>	119 ± 63	81 ± 48	-34mL	≥15% decrease	13/16 (81%)	P<0.001**



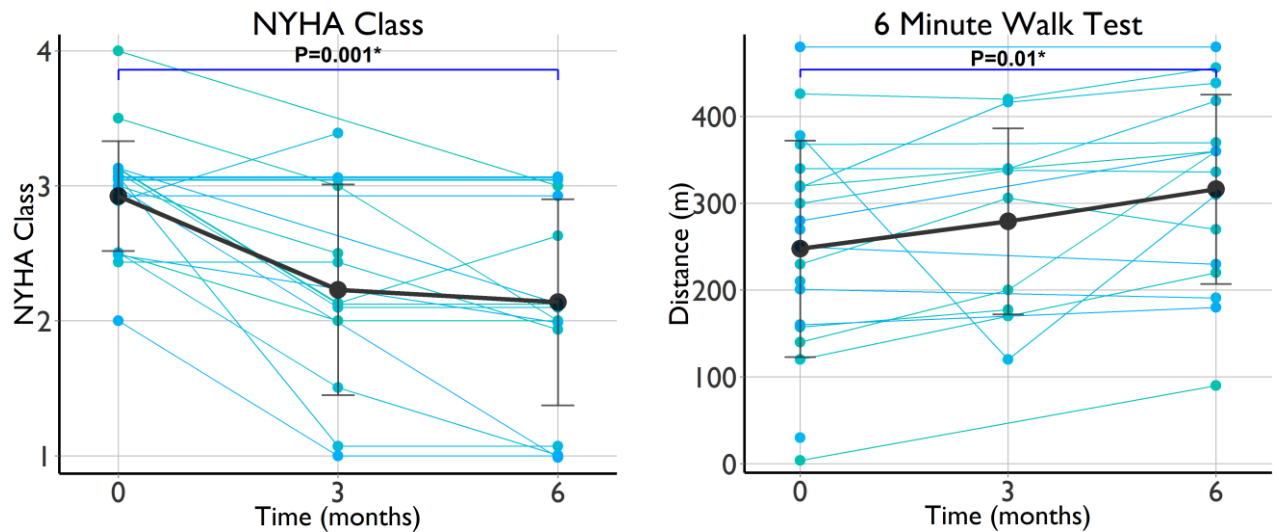
<b>Ejection fraction</b>	28 ± 7%	41 ± 9%	13.8%	≥5% increase	14/16 (88%)	P<0.001**
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374 Table 3 – Echocardiographic response rates. Paired T-tests used for both comparisons. (ESV: end-  
375 systolic volume,

376

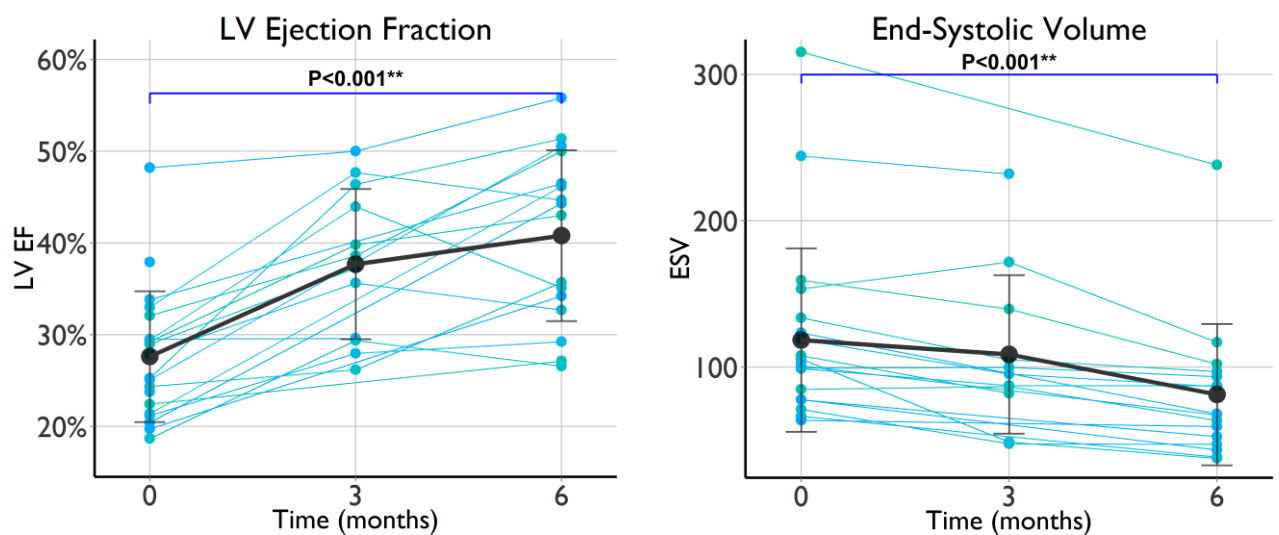
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## Figures



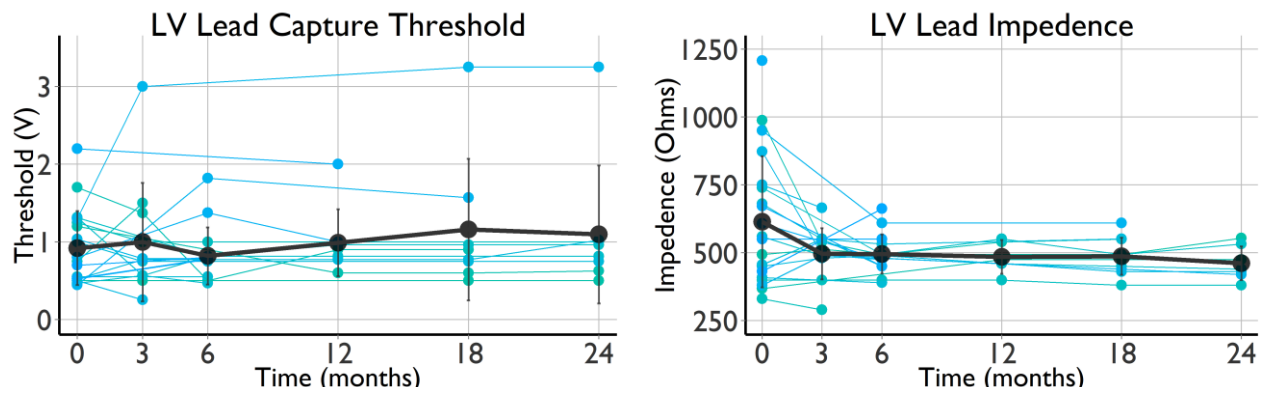
**Figure 1**

1 - Clinical response as measured by NYHA class and 6-minute walk test distance



**Figure 2**

2 – Echocardiographic response as measured by left ventricular (LV) ejection fraction and LV end systolic volume.



**Figure 3**

3 – Long-term electrical parameters. Left; lead capture threshold in Volts. Right: Lead impedance in Ohms. Note limited numbers of patients in whom long-term results are available.