Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Neves Pereira MT, Tinoco M, Castro M, et al. **Assessing cardiac resynchronization therapy response in heart failure patients: a comparative analysis of efficacy and outcomes between transvenous and epicardial leads**. *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.2845

Assessing cardiac resynchronization therapy response in heart failure patients: a comparative analysis of efficacy and outcomes between transvenous and epicardial leads

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Contibutions: MTNP, MT, contributed equally. MTNP, MT, wrote the manuscript with contributions from MC, FC, LP; LC, SR, VM, VS, AL, reviewed the final version of the manuscript. All authors attest they meet the current ICMJE criteria for authorship, participated in the development of the manuscript and approved its final version.

Conflict of interest: there is no financial/personal interest or belief that could affect authors' objectivity. None author has any competing interests to disclose.

Ethics approval and consent to participate: the study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee (approval document no. 155/2023-CAF).

Patient consent for publication: not applicable.

Funding: this study did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials: data and materials are available from the corresponding author upon request.

Abstract

Cardiac resynchronization therapy (CRT) is an effective treatment for selected heart failure (HF) patients. Although transvenous implantation is the standard method, it is not feasible in some patients, so the epicardial lead emerges as an alternative.

We aim to compare CRT response, procedure-related complications, and the occurrence of clinical outcomes between patients with transvenous and epicardial leads.

In a single-center retrospective study, we enrolled consecutive HF patients submitted to CRT implantation with a defibrillator between 2013 and 2022. Clinical response was defined as an improvement of at least one of the New York Heart Association classes with no occurrence of cardiovascular death or HF hospitalization in the first year of follow-up. Echocardiographic response was attained with an increase in left ventricular ejection fraction 10% or a reduction of left ventricular end-diastolic volume >15% at 6-12 months after CRT implantation. Major adverse cardiovascular events (MACE) (cardiovascular mortality and HF hospitalization) and all-cause mortality were evaluated.

From a total of 149 patients, 38% (n=57) received an epicardial lead. Clinical (63% *versus* 60%, p=0.679) and echocardiographic (63% *versus* 60%, p=0.679) responses were similar between the transvenous and epicardial groups. Patients in the transvenous group had a shorter hospital stay (2 *versus* 7 days, p<0.001). Procedure-related complications were comparable between groups (24% *versus* 28%, p=0.572), but left ventricular lead-related complications were more frequent in the transvenous group (14% *versus* 2%). During a median follow-up of 4.7 years, the rate of MACE was 30% (n=44), with no differences in both groups (p=0.591), neither regarding HF hospitalization (p=0.917) nor cardiovascular mortality (p=0.060). Nevertheless, the epicardial group had a higher rate of all-cause mortality (35% *versus* 20%, p=0.005), the majority occurring during long-term follow-up (>12 months), with no deaths in the postoperative period.

Considering the comparable rates of CRT response, procedure-related complications, and MACE between groups, we conclude that epicardial lead is a feasible alternative for CRT when transvenous lead implantation is not possible. The occurrence of a higher number of all-cause deaths in epicardial patients in the long-term follow-up was mainly due to infectious complications (unrelated to the lead) and the progression of oncological/chronic diseases.

Key words: cardiac resynchronization therapy, heart failure, epicardial lead, transvenous lead, cardiac resynchronization therapy response, outcomes.

Introduction

Cardiac resynchronization therapy (CRT) is a well-established therapeutic option for appropriately selected heart failure (HF) patients with reduced left ventricular ejection fraction (LVEF) and interventricular conduction delay (QRS 130ms), resulting in morbidity and mortality reduction [1,2]. Moreover, the last randomized trials also demonstrated improvement of functional capacity and quality of life in HF patients [1,3,4]. Nevertheless, approximately 30% of patients don't have a favourable response to CRT [5].

CRT delivers biventricular pacing (BiVP) to correct electromechanical desynchrony, contributing to reverse remodeling with reduction of end-systolic (LVESV) and end-diastolic volumes (LVEDV), reduction of functional mitral regurgitation (FMR) and increase in LVEF in most cases [6,7].

Achievement of an optimal left ventricular (LV) lead position in patients undergoing CRT is of utmost importance to achieve an effective BiVP and, consequently, reverse remodelling [6,8]. Transvenous implantation of the LV lead through the coronary sinus (CS) into an epicardial LV target vein is the method of choice. Nevertheless, this procedure is unsuccessful in up to 10% of cases due to unfavourable or abnormal CS anatomy, high pacing threshold in fibrotic areas and painful phrenic nerve stimulation [6,8,9].

Epicardial lead placement through a left lateral mini-thoracotomy has emerged as an alternative to overcome these challenges, having a class IIA recommendation (level of evidence B) by the current guidelines, alongside other techniques such as His bundle pacing [7]. Indeed, despite previous controversies, the latest evidence demonstrated not only safety, but also good durability and performance of the epicardial lead in comparison to the transvenous lead [6,9,10].

Nevertheless, there is few recent evidence evaluating CRT response and LV lead performance. The present study was designed to: i) evaluate the CRT response in HF patients considering the type of LV lead (transvenous and epicardial); ii) assess short and long-term procedure-related complications and LV lead performance between LV leads; and iii) compare the occurrence of clinical adverse outcomes, including the composite of major adverse cardiovascular events (MACE) namely HF hospitalizations (HFH) and cardiovascular (CV) mortality and all-cause mortality in both groups.

Materials and Methods

Study population and study design

This was a single-centre retrospective observational cohort study. Participants were consecutively recruited from a population of patients with HF with reduced ejection fraction who implanted a CRT with defibrillator (CRT-D) from January 2013 to September 2022. This

included patients referred to our centre after unsuccessful CS cannulation. According to European Society of Cardiology guidelines in force, all patients had a reduced ejection fraction (LVEF <35%), remained in New York Heart Association (NYHA) class II-IV despite a minimum of 3 months of optimal medical therapy (OMT) and had a life expectancy greater than 1 year at the time of device implantation [1,7]. Patients with missing data regarding echocardiographic or serial device interrogation variables and those with a follow-up inferior to 1 year were excluded. Patients were under renin-angiotensin system inhibitors, beta blockers, mineralocorticoid receptor antagonists and SGLT2 inhibitors, unless if contraindicated or not tolerated, translating the update of guidelines throughout the study period.

All clinical data, echocardiographic parameters and information regarding device implantation and interrogation parameters during surveillance were collected from each participant electronic health record.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee.

Device implantation

The CRT-D devices used were manufactured by *St. Jude Medical/Abbot®, Medtronic®, Boston Scientific®, LivaNova/Microport®* and *Biotronik®*.

CRT-D implantation was performed according to standard protocols, under local anaesthesia. The right atrial (RA) and right ventricular (RV) leads were positioned conventionally. CS cannulation was performed with the assistance of an electrophysiology catheter and electrogram guidance, and was followed by a CS venography to select the target vein. Subsequently, the quadripolar LV lead was implanted in the most suitable side branch of the CS, preferably in the posterolateral or lateral veins.

When placement of the transvenous lead was not feasible, an epicardial lead (*Greatbatch Medical Myopore® Bipolar Sutureless Myocardial Pacing Lead)* was implanted through a left lateral mini-thoracotomy in a separate procedure, under general anaesthesia. The exposed ventricular segments were macroscopically visualized to avoid areas with scar tissue, fibrosis, and/or fat. Pacing and sensing thresholds were analyzed in different positions, and the electrode was attached over the area with the most delayed activation time, using an active fixation technique. The electrode was then tunneled and connected to the previously implanted pacemaker generator [11].

Echocardiography analysis

All patients underwent echocardiographic evaluation at baseline and 6 to 12 months after CRT-D implantation.

Standard parameters including left atrium (LA), RV and LV dimensions and systolic and diastolic ventricular function were performed according to the European Association of Cardiovascular Imaging (EACVI) recommendations. RV systolic dysfunction (RVSD) was considered when S' velocity was inferior to 9.5 cm/s [12]. FMR was assessed qualitatively and graded on a scale of mild to severe.

Response to cardiac resynchronization therapy

The response to CRT was evaluated based on clinical and echocardiographic response and the occurrence of clinical adverse outcomes.

Clinical response to CRT was established as NYHA class improvement (at least 1 class) in the absence of MACE in the first year of follow-up.

Echocardiographic CRT response was defined as an absolute increase in LVEF 10% or reduction of LVEDV 15% at the echocardiographic revaluation performed 6 to 12 months after CRT implantation [13-15]. A super-response to CRT was defined as the recovery of LV systolic function with LVEF 50% [16]. FMR improvement was also considered in the subpopulation of patients with moderate to severe and severe FMR in the baseline echocardiogram and was defined as a reduction of at least one qualitative grade in FMR severity.

Left ventricular lead performance

All CRT-D interrogations were performed by the Arrhythmology team. Lead-specific parameters including pacing threshold (volts), sensing (mV) and lead impedance (Ω) as well as the BiVP (%) were collected at implantation and after 1 year of follow-up.

Procedure-related complications

The overall procedure-related complications rate was reviewed and defined as postoperative (from implantation until patient discharge), short-term (within the first 3 months after discharge), middle term (>3 to 12 months) and long-term complications (> 12 months). Complications included pneumothorax, acute heart failure/cardiogenic shock, nosocomial infection, stroke, CS dissection, ventricular fibrillation, lead-related (dislodgment, fracture or other significant changes in lead parameters), device endocarditis and *Twiddler* syndrome. The total number of complications experienced by the patients has been accounted for.

Clinical adverse outcomes during follow-up

Clinical adverse outcomes were also evaluated during the follow-up and included: 1) the composite of MACE (CV mortality and HFH), and the individual outcomes of 2) all-cause mortality, 3) CV mortality and 4) HFH. Unknown cause of death was assumed when the search for information about the death aetiology was not feasible due to missing data.

Statistical analysis

Statistical analysis was performed using the software IBM SPSS for Windows®, version 25. Normality of quantitative data was verified by the Kolmogorov–Smirnov test and variables are presented as mean and standard deviation (SD) [normally distributed] or median and interquartile range (IQR) [non-normally distributed]. Categorical variables are presented as absolute and relative frequencies.

Statistical significance was assessed using T-test or Mann-Whitney U test for quantitative variables and Pearson chi-square test or Fisher exact test for categorical variables, as appropriate. Outcome data were analyzed using the Kaplan-Meier method and log-rank test. A statistically significant difference was defined as a 2-sided p-value <0.05.

Results

Baseline characteristics

A total of 149 patients (mean age of 68 ± 11 years; 69% male gender) were included in the analysis. Ninety-two patients (62%) received a transvenous lead and 57 (38%) received an epicardial lead. The reasons which led to epicardial lead implantation are presented in *Supplementary Table 1*, being the absence of suitable tributaries veins and unfeasible CS cannulation the most frequent. The median follow-up of our study was 4.7 [IQR 2.4-6.9] years. The majority of the patients underwent *de novo* CRT-D implantation, with only 12 (8%) patients having been upgraded from a prior device (7 from implantable cardioverter-defibrillator and 5 from pacemaker).

The predominant HF etiology was non-ischemic (n=88, 59%) and most of patients were in NYHA class III-IV (n=91, 61%). Left bundle branch block (LBBB) was the predominant QRS morphology in the baseline (n=124, 83%) and 38% (n=56) had atrial fibrillation (AF).

When compared to transvenous lead group, patients with an epicardial lead had a higher prevalence of diabetes mellitus (61% vs 37%, p=0.004) and ischemic heart disease (IHD) (54% vs 33%, p=0.009). There were no other significant differences considering gender, baseline NYHA class, use of guideline-directed medical therapy (GDMT) and echocardiographic parameters (Table 1).

Response to cardiac resynchronization therapy

After CRT-D implantation, 101 patients (71%) experienced a functional status improvement by at least one NYHA class, and 15 patients (10%) improved two classes. No significant differences were found regarding clinical improvement between groups (p=0.638). Clinical response rate was also similar between them (63% in transvenous vs 60% in epicardial, p=0.679).

The magnitude of improvement in LVEF (9.5±10.2% in transvenous vs 12.1±11.6% in epicardial, p=0.162), as well as in LVEDV (-21.1±48.0 ml vs -25.0±47.2 ml, p=0.658) were also comparable, culminating in similar rates of CRT echo response (63% in transvenous vs 60% in epicardial, p=0.985).

In the overall population, when comparing the 92 patients who achieved CRT clinical response with the 92 patients who had CRT echo response, there was an overlap of 63 (69%) patients who had improved both clinical status and LV remodelling, with no differences between groups (p=0.135) (Table 2). Additionally, there was a trend for higher prevalence of super-responders in the epicardial group (24.6% vs 15.2%, p=0.156).

Regarding the comparison between patients who undergone *de novo* CRT implantation and upgrade, the rates of clinical and echo CRT response were similar (p=0.807 and p=0.903, respectively), with no differences according to the LV lead.

It is noteworthy that no significant differences in GDMT were observed between the groups at 6-12 months of follow-up. Specifically, 98% of patients were on renin-angiotensin system inhibitors, 82% on mineralocorticoid receptor antagonists, 85% on beta-blockers, and 21% on SGLT2 inhibitors (p-values of 0.696, 0.156, 0.198, and 0.098, respectively).

Regarding the 42 (28%) patients with significant FMR at baseline, an improvement of at least one degree was observed in 29 (69%) patients, with no differences achieved between groups (p=0.138). The group of FMR improvement had a lower prevalence of atrial fibrillation (31% vs 69%, p=0.021) and, indeed, the absence of AF was the only independent predictor of FMR improvement (HR: 0.064, 95% CI: 0.006 – 0.693, p=0.024). As expected, improvement of FMR was associated to a higher rate of clinical (31% vs 66%, p=0.036) and echocardiographic response (15% vs 52%, p=0.027). At 6-12 months after CRT, left atrial volume indexed (LAVI), LV mass and LVEDV were significant lower on the FMR improved group (p=0.005; p=0.004 and p=0.036, respectively), in simultaneous with a lower QRS width (p=0.043).

Considering electrocardiographic parameters at 1 year of follow-up, there weren't significant differences in QRS duration narrowing between transvenous and epicardial groups (-13ms vs -18msl, p=0.194). The BiVP at 1 year, similarly to postoperative values, was also comparable (p=0.131). There weren't differences between the groups regarding the prevalence of

prominent R wave in V1, prominent S in DI or prominent R in DII in follow-up ECG (p=0.667).

Left ventricular lead performance

The LV lead impedance in the epicardial group was lower comparing to transvenous, either in the postoperative period (371±115 Ohm vs 610 ± 224 Ohm, p<0.001) and at 1 year (392 ±123 Ohm vs 679 ± 281 Ohm, p<0.001). However, there weren't significant variations regarding LV impedance (p=0.494) or other lead-parameters throughout the observation period (Figure 1 and *Supplementary Table 2*).

Procedure-related complications

The median postoperative length of hospital stay was significantly longer in the epicardial lead group (7 [6-13] vs 2 [1-9] days, p<0.001).

A total of 47 procedure-related complications in 38 patients (26%) were reported, with comparable rates between the groups (p=0.572), either in postoperative, short, middle and long-term follow-up (Table 3).

During the postoperative period, 4 patients in the epicardial group experienced hemodynamic instability (3 cases of cardiogenic shock and 1 of ventricular fibrillation), but all of them fully recovered before discharge.

In the follow-up period, LV lead-related complications occurred in 13 (n=14%) patients in the transvenous group. Conversely, there was only 1 (2%) LV lead-related complication (fracture) in the epicardial group during long-term follow-up.

Only 3 (2%) patients experienced device infection (2 in the transvenous group and 1 in the epicardial group), requiring extraction.

In the long-term follow-up, there was one reported device-related death in the epicardial group which was attributed to device endocarditis.

Clinical adverse outcomes during follow-up

During a median follow-up of 4.7 [2.4-6.9] years the rate of MACE was 30% (n=44), with no significant differences between the groups (28% in the transvenous group vs 32% in the epicardial group, p=0.591). Nine percent of patients (n=14) died due to CV causes and 28% (n=42) experienced HFH, with no significant differences based on the LV lead (p=0.060, p=0.917).

However, the all-cause mortality rate (26%, n=38) was significantly higher in the epicardial group compared to the transvenous group (35% vs 20%, p=0.005). It is important to note that 18% (n=7) of patients died from unknown causes, while the remaining 17 deaths were

attributed to infections (n=9; 24%), progression of oncological disease (n=4; 11%), non-cardiac postoperative complications (n=2; 5%), CKD failure (n=1; 3%) and liver failure (n=1; 3%).

The majority of all-cause mortality events occurred during long-term follow-up (n=35, 92%), with only 2 deaths (1 in each group) during mid-term follow-up and 1 death in the short-term follow-up in the epicardial group. Figure 2 shows the Kaplan-Meier survival curves for event-free survival between the groups, and *Supplementary Table 3* provides the event frequencies.

When clinical adverse outcomes were assessed in patients with procedure-related complications (n=38; 26%), there were no significant differences in terms of MACE (31% vs 29%, p=0.844) or all-cause mortality rates (23% vs 26%, p=0.686) compared to patients without complications throughout the entire follow-up period.

Discussion

Our study comprises a real-world cohort of HF patients who underwent CRT-D implantation via LV transvenous or isolated epicardial lead surgery, enabling an extensive and long-term comparison of CRT response, lead performance and safety.

The main findings of our study were the followings: i) the absence of difference in CRT response rate between patients with transvenous and epicardial LV leads; ii) the similar performance and safety of both LV leads and iii) the comparable incidence of MACE between both groups.

Thirty-eight percent of our patients received an epicardial lead, mostly due to the absence of suitable tributaries veins and unfeasible CS cannulation. Despite recent technological advancements, recent studies have reported LV lead implantation failure followed by epicardial lead placement in up to 10% of cases [9,17]. Our increased rate of epicardial lead placement could be explained by the referrals from other hospitals after failed CS cannulation.

The transvenous and epicardial groups were comparable, except for a higher prevalence of IHD (54% vs. 33%, p=0.009) and diabetes mellitus (61% vs. 37%, p=0.004) in the epicardial group. In IHD, scar burden is typically more pronounced, leading to higher pacing thresholds [18,19]. Recent evidence also demonstrated an association between high pacing thresholds and diabetes [19]. Elevated pacing thresholds present challenges in CRT, and justified epicardial lead placement in 7% of our cohort.

In our cohort, the rates of clinical and echocardiographic CRT response were both 62% (n=92), with no differences between transvenous and epicardial groups (63% vs 60%, p=0.679). It is noteworthy that among the 92 patients who achieved echocardiographic CRT response, only 63 (68%) improved at least one functional class. This data highlights the common disparity between clinical and echocardiographic improvements, consistent with some studies reporting

discordant responses in up to half of the cohorts [20-22]. In fact, there is no universal definition to a "positive CRT response", and most of trials have used different combinations of clinical status, ventricular remodelling indices and MACE [23].

Besides the impact in LV reverse remodelling indices, the role of CRT in patients with significant FMR is another crucial prognosis modifier [1,7,24]. In our population, 69% of patients achieved an improvement in FMR, irrespective of the LV lead used. Notably, our rate of FMR improvement slightly exceeded previous reports [7,24,25].

Importantly, the notable lack of difference in CRT response rate that we found between transvenous and epicardial leads, either in terms of functional status and reverse remodelling, is consistent with the available evidence [6,17,26].

Although the LVEF and QRS duration are the only parameters considered in the current recommendations for guiding CRT in HF patients, studies have shown that myocardial scar and the LV site of the latest activation in relation to the LV lead position are also associated with CRT response [1,7]. Most studies agree that the most suitable location for LV lead placement is in a coronary vein located in the latest activated region, remote from the scar. The rationale is that pre-exciting viable late-activated myocardium enhances synchrony, which is associated with acute hemodynamic improvements and favourable outcomes [27,28], while pacing in the scar site may lead to high thresholds or even pro-arrhythmic effects [29].

Post-hoc analyses from the larger trials regarding the best LV lead position in CRT were not always consistent [30-32]. An optimal LV lead position remote from the myocardial scar was associated with improved survival [33,34], and the latest evidence demonstrated that scar burden appears to independently predict clinical events and LV functional improvement, regardless of the type of cardiomyopathy, and even when considering the presence of LBBB and QRS duration [35]. Remarkably, late electrical activation may coincide with regional scar in approximately one-third of the patients, preventing optimal LV lead placement [27,36].

Indeed, although imaging identifies suitable LV lead segments, clinical challenges arise due to variable venous coronary anatomy, hindering accessibility to the targeted segment [37]. The use of an epicardial approach for LV lead implantation provides direct visual oversight, allowing for the avoidance of scar tissue and selection of the site with the maximum electrical delay, and effectively overcomes vascular challenges due to unfavourable cardiac vein anatomy [17,38].

Epicardial lead implantation has been found to be safe and comparable to transvenous leads in terms of LV lead performance [26,39-41]. Besides the advantage of optimal lead positioning, it reduces the risk of dislodgment or phrenic nerve stimulation, decreases the need for fluoroscopy, and eliminates the need for contrast. However, it requires general anesthesia and may pose challenges like epicardial fat and adhesions. In our long-term follow-up, we

observed successful outcomes with a safety profile comparable to transvenous leads [17,38,41].

As expected, hospital stays were longer for patients with epicardial leads due to the impact of mini-thoracotomy (median 7 vs 2 days, P<0.001) [10,17,38,40].

In the epicardial group, it is worth mentioning that four patients experienced postoperative hemodynamic instability, contributing to a longer hospital stay. However, all patients achieved complete recovery, and there were no reported deaths during the perioperative phase. It is important to note that there was only one case of device-related death in the epicardial group, occurring more than 12 months after the procedure, due to device endocarditis.

In terms of lead dislodgement, the epicardial lead has an important advantage over the transvenous lead due to their active fixation [6,12]. Indeed, the occurrence of short and late LV lead dislodgement was restricted to the transvenous group (13%), most in the first 3 months after device implantation, leading to a higher rate of re-interventions, as stated in previous reports [6,17].

Regarding LV lead performance, our study showed that epicardial leads performed well during long-term follow-up, consistent with other studies [6,9,10]. Pacing thresholds and sensing values remained stable in the first year. LV lead impedances differed between the two types, with transvenous leads having higher impedances, due to the fact that epicardial leads are anchored in the myocardium, providing stable and low-resistance electrical contact. However, both lead types maintained appropriate and consistent values throughout the follow-up period [6]. When compared to transvenous leads, the revision or removal of an epicardial lead, such as in cases of device-related infection, requires an additional surgical procedure involving re-thoracotomy. This poses a significant risk, making it an important consideration in the selection of LV lead type to CRT [6,9]. Additionally, the presence of fibrosis and adhesions from previous epicardial interventions presents challenges in ventricular tachycardia ablation. This anatomical constraint has clinical implications, as epicardial ablations are becoming more frequent and crucial in so many clinical scenarios.

Furthermore, it is also important to take into consideration that epicardial leads do not provide the same options for device optimization as multipolar electrodes, which are currently the most commonly used. Unlike multipolar lead connectors, epicardial leads do not allow for multipoint pacing, offer fewer selectable stimulation vectors based on programming, and are not compatible with magnetic resonance imaging [6].

In our cohort, the incidence of MACE over a median follow-up of 4.7 years was 30%, with no differences between transvenous and epicardial leads (p=0.591). CV death and HFH rates were 9% and 28%, respectively, also similar between groups. Our prognosis data were consistent with previous reports [6,26,42].

The higher all-cause mortality in the epicardial group (35% vs 20% in transvenous, p=0.005) aligns with recent evidence. [6,42] Although one hypothesis was the higher procedural risk as an explanation to the superior all-cause mortality in patients who received an epicardial lead, our data showed that the vast majority (92%) of deaths occurred during long-term follow-up, with no perioperative mortality, which contrasts with previous studies [42]. Indeed, patients in the epicardial group experienced higher long-term mortality rate due to infectious complications (unrelated to device lead) and progression of oncological diseases or other chronic conditions. This may be partially attributed to a higher prevalence of comorbidities like diabetes and IHD in epicardial group, as reported in previous studies [6,42], translating a potential bias arising from the retrospective nature of our single-center study.

Limitations and strengths

One important limitation that should be acknowledged is the small population size, which inevitably lowered the statistical power of this study. Additionally, due to its retrospective nature, it was not feasible to collect data about the etiology of some patients' death, which potentially may have influenced the categorization of deaths into CV and non-CV.

Nevertheless, we presented a comprehensive characterization of a real-world population with advanced HF, and our study has one of the longest follow-up durations reported to date. We defined the response to CRT by considering all evidence-based parameters, since clinical response to LV remodelling and outcomes analysis. We also took into account patients' rhythm, biventricular pacing rate, and lead-specific parameters to adjust for any potential confounding factors that could influence CRT response between groups.

Additionally, throughout the entire observation period, we rigorously assessed the causes of death and all procedure-related complications, aiming to provide a full analysis of performance and safety of both LV lead.

Conclusions

The implantation of an epicardial lead is a safe and effective method for CRT, providing a valuable alternative when transvenous lead implantation is unsuccessful. However, it is crucial to carefully evaluate the decision for a patient to receive an epicardial lead, considering the increased invasiveness and the singular spectrum of complications associated with the surgical approach.

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Online supplementary material:

Supplementary Table 1. Reasons which led to epicardial lead implantation.

Supplementary Table 2. Leads specific parameters (pacing threshold, impedance and sensing) at post-implant and at 1-year evaluations after device implantation, according to the LV lead type.

Supplementary Table 3. Clinical events during the follow-up period of the study after cardiac resynchronization therapy implantation.

Table 1. Differences in baseline characteristics of overall population and according to the transvenous and epicardial LV lead groups.

Baseline characteristics	All (n=149)	Transvenous lead (n = 92)	Epicardial lead (n = 57)	p-value
Age (years-old), mean ± SD	68 ± 11	68 ± 11	70 ± 10	0.272
Male gender, n (%)	102 (68%)	58 (63%)	44 (77%)	0.071
Arterial hypertension, n (%)	118 (79%)	73 (79%)	45 (79%)	0.953
Diabetes mellitus, n (%)	69 (46%)	34 (37%)	35 (61%)	**0.004**
Dyslipidaemia, n (%)	111 (74%)	67 (73%)	44 (77%)	0.552
CKD, n (%) (eGFR< <60ml/min/1.72m^2)	53 (36%)	33 (36%)	20 (35%)	0.923
Etiology of heart failure, n (%)				**0.009**
Ischaemic	61 (41%)	30 (33%)	31 (54%)	
Non-ischaemic	88 (59%)	62 (67%)	26 (46%)	
NYHA functional class				0.799
Class II, n (%)	58 (39%)	35 (38%)	23 (40%)	
Class III-IV, n (%)	91 (61%)	57 (62%)	34 (60%)	
Guideline-directed medical therapy, n (%)				
ACEI/ARB/ARNI	147 (99%)	91 (99%)	56 (98%)	0.731
BB	142 (95%)	89 (97%)	53 (93%)	0.292
MRA	131 (88%)	84 (91%)	47 (83%)	0.107
SGLT2 inhibitor	23 (15%)	10 (11%)	13 (23%)	0.051
Diuretics	110 (74%)	67 (73%)	43 (76%)	0.831
Type of admission, n (%)				0.263
Elective	110 (74%)	65 (71%)	45 (79%)	
Upgrade	11 (7%)	4 (4%)	7 (12%)	
Non-elective	39 (26%)	27 (29%)	12 (21%)	
HF decompensation	25 (17%)	14 (15%)	11 (19%)	
Syncope/dysrhythmia	13 (9%)	12 (13%)	1 (2%)	
Upgrade	1 (1%)	1 (1%)	0 (0%)	
Electrocardiographic:				
Atrial fibrillation, n (%)	56 (38%)	30 (33%)	26 (46%)	0.111
LBBB, n (%)	124 (83%)	80 (87%)	44 (77%)	0.121
QRS width (ms), median [IQR]	161 [150-174]	160 [148-172]	162 [154-182]	0.075
Echocardiographic:				
LAVI (ml/m^2), mean ± SD	46.8 ± 20.9	46.5 ± 22.1	47.4 ± 18.6	0.415
LVMI (g/m^2), mean ± SD	139.3 ± 7.7	135.7 ± 37.7	144.7 ± 37.4	0.765
LVEDV (ml), mean ± SD	179.0 ± 62.0	179.8 ± 65.1	177.6 ± 57.2	0.824
LVESV (ml), mean ± SD	131.7 ± 55.4	131.8 ± 58.2	131.7 ± 50.8	0.829
LVEF (%), mean ± SD	27.6 ± 5.6	27.6 ± 5.5	27.6 ± 5.7	0.528
S' RV (cm/s), mean ± SD	10.2 ± 2.4	10.3 ± 2.4	10.2 ± 2.4	0.840
RVSD, n (%)	46 (31%)	29 (32%)	17 (30%)	0.827
FMR, n (%)	128 (86%)	77(84%)	51 (89%)	0.778
Mild	86 (58%)	48 (52%)	38 (67%)	0.317
Moderate	26 (17%)	19 (21%)	7 (12%)	
Severe	16 (11%)	10 (11%)	6 (10%)	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, β blocker; CKD, chronic kidney disease; FMR, functional mitral regurgitation; HF, heart failure; LBBB, left bundle branch block; LV, left ventricle; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricle ejection fraction; LVES, left ventricular end-systolic volume; LVMI, left ventricle mass index; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RV, right ventricular; RVSD, right ventricular systolic dysfunction; SGLT2, Sodium-glucose co-transporter-2.

Table 2. Clinical and echocardiographic parameters of CRT response evaluated at 6 to 12 months after CRT-D implantation, according to the type of LV lead. *Only patients with significant (moderate to severe and severe) FMR were selected to be evaluated regarding their improvement.

	All (n=149)	Transvenous lead (n=92)	Epicardial lead (n=57)	p-value
NYHA class, n (%)				0.714
Class I-II	137 (92%)	84 (91%)	53 (93%)	
Class III	12 (8%)	8 (9%)	4 (7%)	
NYHA class improvement, n (%)				0.638
1 class	106 (71%)	67 (73%)	39 (69%)	
1 class	91 (61%)	59 (64%)	32 (57%)	
2 classes	15 (10%)	8 (9%)	7 (12%)	
Clinical response, n (%)	92 (62%)	58 (63%)	34 (60%)	0.679
LVEF (%)	38.0 ± 11.0	37.1 ± 10.3	39.7 ± 11.7	0.182
LVEF (%)	10.6 ± 10.5	9.5 ± 10.2	12.1 ± 11.6	0.162
LVEF 10%, n (%)	77 (52%)	47 (51%)	30 (53%)	0.855
LVEDV (ml)	157.8 ± 73.8	158.8 ± 77.1	149.7 ± 66.8	0.500
LVEDV (ml)	-22.6 ± 47.6	-21.1 ± 48.0	-25.0 ± 47.2	0.658
LVEDV 15%, n (%)	68 (46%)	41 (45%)	27 (47%)	0.874
Echo response, n (%)	92 (62%)	58 (63%)	34 (60%)	0.679
Super response, n (%)	28 (19%)	14 (15%)	14 (25%)	0.156
FMR, n (%) (n=x)	128	77 (84%)	51 (89%)	0.589
Mild	(86%)	48 (52%)	38 (67%)	0.317
Moderate	86 (58%)	19 (21%)	7 (12%)	
Severe	26 (17%)	10 (11%)	6 (11%)	
	16 (11%)			
FMR improvement, n (%) (n=42*)		(n=29)	(n=13)	0.138
No change	13 (31%)	11 (38%)	2 (15%)	
1 degree	22 (52%)	12 (41%)	10 (77%)	
2 degrees	7 (17%)	6 (21%)	1 (8%)	

FMR, functional mitral regurgitation; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association;

Table 3. Procedure-related complications in postoperative period (from implantation until patient discharge), short term (within first 3 months after discharge), middle term (between 3 to 12 months) and long term (> 12 months) follow-up between transvenous and epicardial lead groups.

	All (n=149)	**Transvenous leads (n=92)**	**Epicardial leads (n=57)**	**p-value**
Postoperative length of stay (days), median [IQR]	6 [2-10]	2 [1-9]	7 [6-13]	**P < 0.001**
Procedure-related complications	47 in 38 pts (26%)	30 in 22 pts (24%)	17 in 16 pts (28%)	0.572
• **Postoperative**	19	9	10	0.151
Pneumothorax	5	4	1	
Acute HF/Cardiogenic shock	1/3	0	1/3	
Nosocomial infection	3	0	3	
Stroke	1	0	1	
Coronary sinus dissection	1	1	0	
Ventricular fibrillation	1	0	1	
Lead-related complication				
RA/RV lead dislodgment	2	2	0	
LV lead dislodgement	2	2	0	
• **Short term**	15	11	4	0.542
Lead-related complication				
RA/RV lead dislodgment	10	6	4	
LV lead dislodgment	5	5	0	
• **Middle term**	6	5	1	0.256
Lead-related complication				
RA/RV lead dislodgment	1	1	1	
LV lead dislodgment	4	3	0	
Twiddler syndrome	1	1	0	
• **Long term**	7	5	2	0.347
Device endocarditis	3	2	1	
Lead-related complication				
LV lead dislodgment	2	2	0	
LV lead fracture	2	1	1	

IQR, interquartile range; LV, left ventricle; HF, heart failure; pts, patients; RA, right atrium; RV, right ventricle.

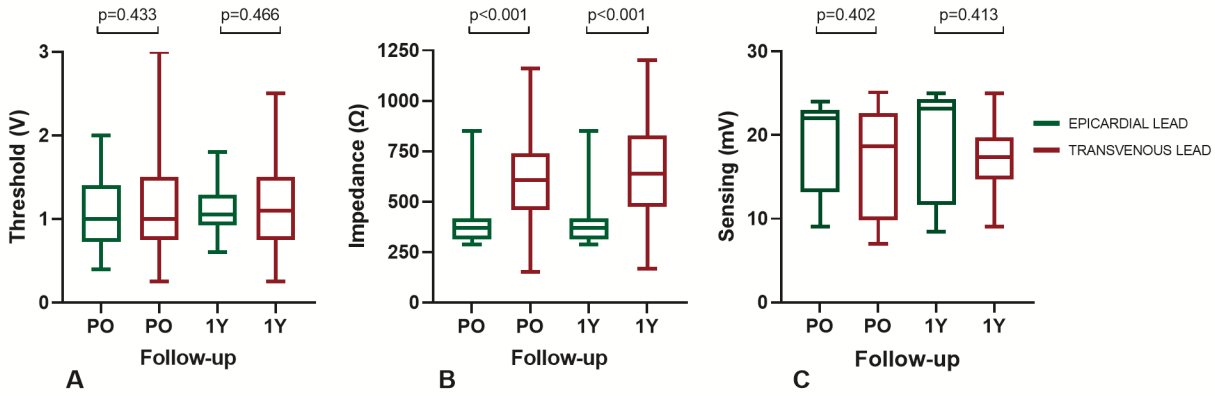

Figure 1. Changes in pacing threshold (A), impedance (B) and sensing (C) of epicardial and endocardial LV leads assessed during the postoperative period and at 1 year of follow-up. PO, postoperative; 1Y, 1 year.

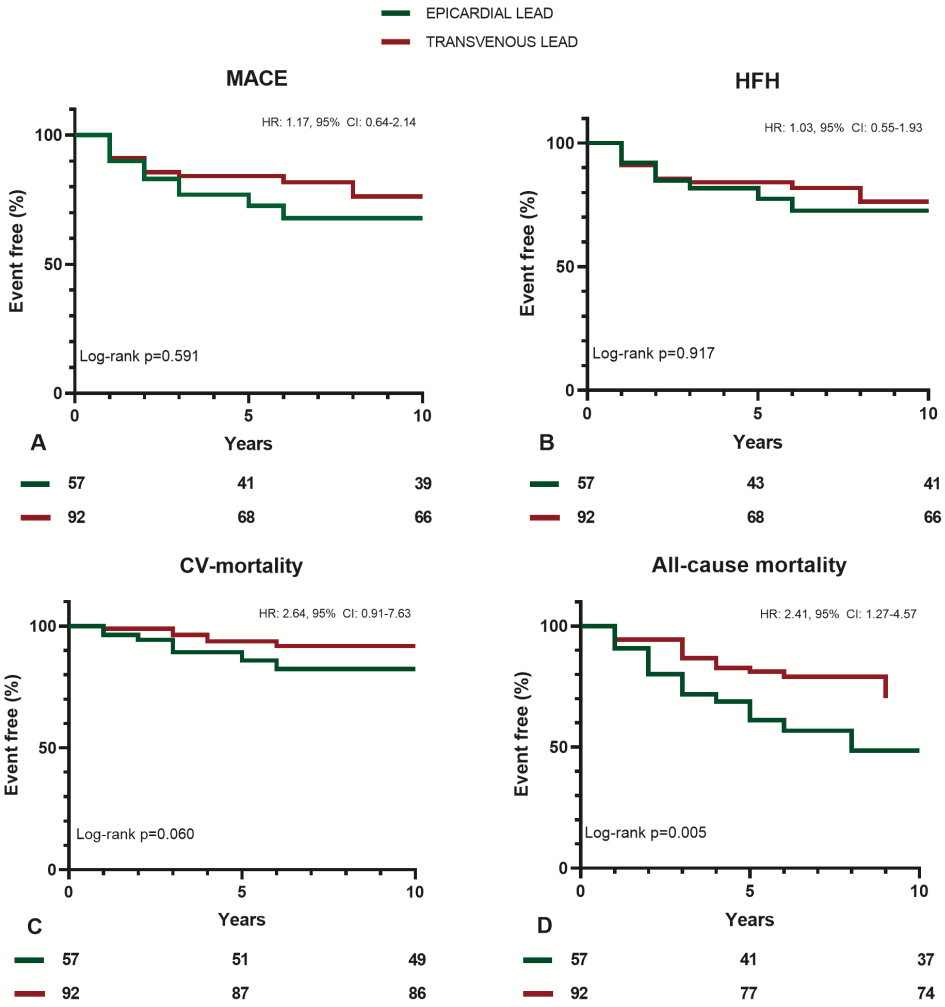

Figure 2. Kaplan-Meier survival curves of time to MACE (A), HFH (B), CV death (C) and all-cause death (D) in Epicardial and Transvenous groups. CV, cardiovascular; HFH, heart failure hospitalization; MACE, major adverse cardiovascular events.