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DEVICES

Cardiac resynchronization therapy with intraoperative epicardial mapping via minithoracotomy: 10 years' experience

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Abstract

Background: Cardiac resynchronization therapy (CRT) is considered an efficient method to improve the left ventricular (LV) dysfunction with left bundle branch block. However, coronary venous anatomy is not appropriate in about 10% of the cases; thus other alternatives, such as epicardial lead implantation via minithoracotomy are needed.

Methods: During the period 2007-2017, a total of 57 patients were operated at our institute via left anterior minithoracotomy after an unsuccessful transvenous CRT. The best position of the LV epicardial electrode was determined by intraoperative epicardial mapping, that is locating the latest activation spot relative to the right ventricular (RV) electrode. The authors analyzed the survival by Kaplan-Meier estimator with Tarone-Ware equality test and multiple Cox regression analysis, the changes of the LV ejection fraction (LVEF) and dimensions, the development of the impedance and threshold of the LV epicardial electrode, the possible associations between the survival and intraoperative sensed RV-LV activation delay.

Results: The intraoperative RV-LV activation delay was 92.250 ± 26.538 milliseconds. There were no intraoperative complications except ventricular fibrillation in three patients. Within 30 days there were neither wound healing complications nor pocket hematoma. There was no significant difference in survival with regard to gender or etiology, but significantly better survival was found in the cohort with intraoperative sensed RV-LV activation delay >86 milliseconds. The LVEF and dimensions improved following the operation and continued to be improved in the survivors.

Conclusion: CRT via minithoracotomy with epicardial mapping is a safe, efficient, simple, and reproducible second-line alternative to the transvenous method.

KEYWORDS
cardiac resynchronization therapy, epicardial mapping, heart failure, minithoracotomy

1 | INTRODUCTION

The number of patients with heart failure is increasing in spite of advances in medical management.[1] Conduction disturbances can further deteriorate cardiac function. Inter- and intraventricular dyssynchrony involves a complex pathology including subcellular, electrophysiological, biomechanical, and hemodynamic aspects resulting in adverse left ventricular (LV) remodelling and decreased contractile efficiency.[2] The first publication[3] regarding the positive actions of atriobiventricular pacing on quality of life and functional capacity was published in 2001, and some years later the improved survival and decreased hospitalization rate were also proved by the COMPANION study (comparison of medical therapy, pacing, and defibrillation in heart failure).[4,5] Cardiac resynchronization therapy (CRT) is currently considered a clinically proven nonpharmacological treatment in systolic heart failure with widened QRS complex due to left bundle branch block.[2,6–8] Dual, or recently multisite pacing of the left ventricle facilitates the synchronized contraction of its different segments.[3,9,10] In the standard transvenous method, the LV lead is positioned trough the coronary sinus (CS) in an appropriately sized vein branch seating in a suitable localization on the LV posterolateral wall in an ideal case.[3,4,9,10] However, in about 10% of the patients, the anatomy of the coronary venous system is not suitable for proper positioning, which would be mandatory for efficient resynchronization and for avoiding phrenic nerve stimulation.[11–13] In these cases the potential alternatives include transseptal approach through the interatrial septum,[12,14] transapical endocardial method via a minithoracotomy,[15] epicardial/epimyocardial approach through minithoracotomy[16,17] or video assisted thoracoscopy (VATS),[17,18] or, recently, robot-assisted surgical technique.[19] After an efficient CRT, the patients' functional capacity, complaints, hospitalization rate, and survival improve significantly compared to medical therapy alone,[3,4,9,10,20–22] and, on the other hand, CRT therapy allows better optimization of medical treatment in heart failure patients.[23] Nevertheless, in spite of appropriate positioning of the LV electrode, roughly one third of the patients are nonresponders to epicardial[24–26] or endocardial[12] CRT. However, there is no uniform definition of CRT response,[27] which would be essential in order to compare different studies. The present retrospective study addresses the feasibility and long-term analysis of epicardial CRT via minithoracotomy as an alternative to failed conventional CRT.

2 | MATERIALS AND METHODS

2.1 | Patient population, enrollment

This retrospective study was designed in compliance with the Declaration of Helsinki and approved by the Regional Ethics Committee of University of Pécs (6600/2017). During the period of January 01, 2007 to January 01, 2017, 284 CRT-P (CRT pacemaker) and 174 CRT-D (CRT defibrillator) implantation procedures were performed transvenously at our institute, of which n = 57 patients (12.4%, see baseline characteristics in Table 1) failed by means of correct positioning of the CS electrode or efficient resynchronization without phrenic nerve stimulation.

TABLE 1 Baseline characteristics of n = 57 patients enrolled for minithoracotomy. Values are presented as mean ± standard deviation, and also percentage is noted in parentheses when appropriate

Characteristics	Value
Male	40 (70%)
Age at minithoracotomy (years)	64.04 ± 7.90
Preoperative LVEF (%)	29.86 ± 5.88
Preoperative LVEDD (mm)	68.57 ± 9.58
Preoperative LVESD (mm)	57.58 ± 11.00
Ischemic etiology	26 (46%)
Previous cardiac surgery	6 (11%)
CRT-D	28 (49%)
Failed CRT was an upgrade	19 (33%)
Preoperative continuous RV pacing	6 (11%)
Follow-up time (days)	1789 ± 1256

Abbreviations: LVEDD; left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; CRT-D, cardiac resynchronization therapy with defibrillator capability.

The LV port was plugged, and the operation was finished habitually with the chosen biventricular generator. The tip of the right ventricular (RV) electrode was positioned to the apical septal segment in all CRT-D patients, whereas to the apical or mid antero- or inferoseptal segment in CRT-P patients. These patients were offered an epicardial LV electrode implantation via left anterior minithoracotomy in a second stage as an elective surgery with intratracheal narcosis 2-6 months later. All the patients accepted the alternative method of CRT. During the 10 years' inclusion-period we followed the actual AHA/ESC guidelines: New York Heart Association II-IV. Patients were enrolled with reduced LV ejection fraction (LVEF) (≤ 35%) and QRS duration ≥130 milliseconds. Decisions on whether patients should receive CRT-P or CRT-D implantation were also based on the guidelines. Data available until December 2019 were analyzed retrospectively, assuring a minimum of 3 years' follow-up period in the survivors. There were three patients with preoperative LVEF ≥40%; two of them had symptomatic heart failure due to permanent RV pacing, one patient improved on advanced medical therapy between the unsuccessful CS electrode implantation attempt and the minithoracotomy.

2.2 | Surgical technique, intraoperative epicardial mapping

After an informed consent and systemic anesthesia with normal (not selective) endotracheal intubation, the ICD antitachycardia function was disabled when appropriate. Selective intubation was not necessary since the incision was made on the absolute dullness of the heart (the majority of patients had enlarged hearts), and the pericardium was stitched to the chest wall at four points, therefore the lung did not interfere with the exploration. External defibrillator patches were placed only in three patients at high-risk of arrhythmia. Following skin disinfection and draping, the operation started with a left anterior

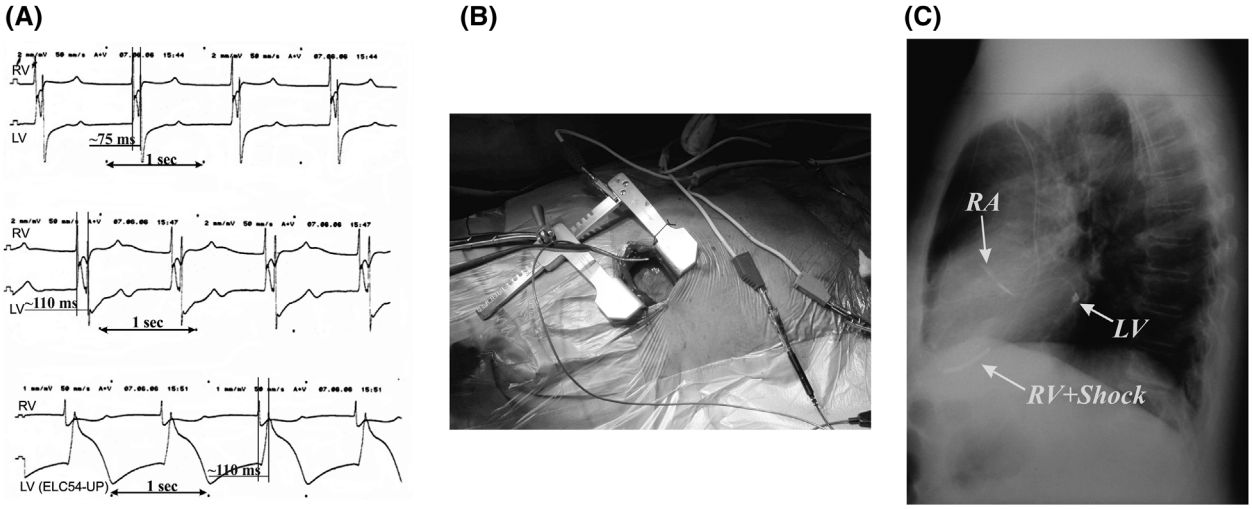

FIGURE 1 A, Invasive ECG strips for *epicardial mapping*. The right ventricular-left ventricular electrical activation delay is ~75 milliseconds on the top part. In a better position, it is ~110 milliseconds in the middle. In the bottom part at the same position (~110 ms) the wide transmembrane potential on the left ventricular channel is clearly visible due to the screw-in epimyocardial electrode (ELC54-UP). B, Intraoperative photo with the left anterolateral minithoracotomy. C, Chest X-ray showing atrial, right ventricular shock electrode, and the epicardial left ventricular electrode in the basal inferolateral-inferior segment
Abbreviations: LV, left ventricular channel, RV, right ventricular channel

minithoracotomy of 5-10 cm length, depending on the patient's stature, in the 4th or 5th intercostal space. Then a 5-6 cm horizontal pericardiotomy succeeded. Also, the previous generator pocket was opened; the generator was taken out, the RV electrode disconnected and connected to the external pacemaker programmer's atrial port (Biotronik 4708A RENAMIC, Biotronik SE & CO, Berlin, Germany) via a sterile quadripolar patient cable (Biotronik PK-141/2.8 m, Biotronik SE & CO). The RV port of this cable was attached to a temporary bipolar pacing wire (type depending on availability) in the operating field, which was used for *epicardial mapping* of the left ventricle, that is measuring the delay between the right and left sensed ventricular activation at the tips of the electrodes (Figure 1A). At the beginning of our CRT project, the above programmer was still not available, Biotronik ERA 300 Pacing System Analyser (Biotronik SE & CO) was used instead, with two external pacemaker cables (Biotronik PK-82/1.5 m, Biotronik SE & CO). The aim of the intraoperative epicardial mapping is to find the electrophysiologically farthest point of electrical activation on the LV wall relative to the RV electrode. The best point is usually expected to be posterobasally (basal inferior, inferior, mid inferior or mid inferolateral segments), which needed the careful impression and rolling of the left ventricle to the right side by a long Meier forceps with an inserted swab. Also, the temporary transvenous pacemaker wire was held in another Meier forceps during contacting the LV epicardium under direct eye-control in order to visualize and avoid any vessel or scar tissue. When the appropriate point was found, the permanent screw-in pacing electrode (Biotronik ELC-54UP, Biotronik SE & CO; Medtronic 5071 53 cm, Medtronic Inc., Minneapolis, MN; SJM Enpath 1084T 54 cm, St. Jude Medical [now Abbott], Sylmar, CA; SJM Myodex 1084T 54 cm, St. Jude Medical [now Abbott], Sylmar, CA) was placed there. After testing the electrode, the pericardium was partially closed, a soft 28 Ch chest drainage catheter was inserted at a lower intercostal level, and the epicardial electrode was subcutaneously driven to the generator pocket by its enclosed tunneler. The electrodes were connected to the generator and the system was placed back into the pocket. The chest wound and the generator pocket were finally closed layer by layer with absorbable suturing material with running technique.

After testing the pacing system by an external programmer, the antitachycardia function of the ICD was enabled, when appropriate. The patients were extubated on the operating table (except one patient), and they were put on underwater seal chest drainage at −20 H_2Ocm for 24 hours. Intraoperative epicardial mapping was developed and introduced by L. Melczer at our institution, jointly with L. Hejjel from the surgical side.[28] Figure 1B shows the intraoperative view of left anterolateral minithoracotomy, Figure 1C represents a lateral chest X-ray showing the epicardial LV electrode in the basal inferolateral-inferior segment.

2.3 | Follow-up, statistical analysis

Patient follow-up consisted of patient interrogation, physical examination, and an electrophysiological examination by the suitable pacemaker programmer at our pacemaker outpatient clinic 2-5 months after the implantation, followed by at least semi-annual or "on demand" appointments. Echocardiography was usually performed on an annual basis by cardiologist consultants: LVEF was calculated by Simpson method, LV end-diastolic (LVEDD) and end-systolic diameter (LVESD) were estimated visually in an appropriately chosen segment. Considering that most of the patients are from other cities and counties, we were seldom notified of the fact and time of their death, therefore we requested the validity of their health insurance from the National Health Insurance Fund of Hungary, which can cause a maximum of 2-3 days of delay from the time of decease. However, this delay is negligible compared to the study periods. In this retrospective study we

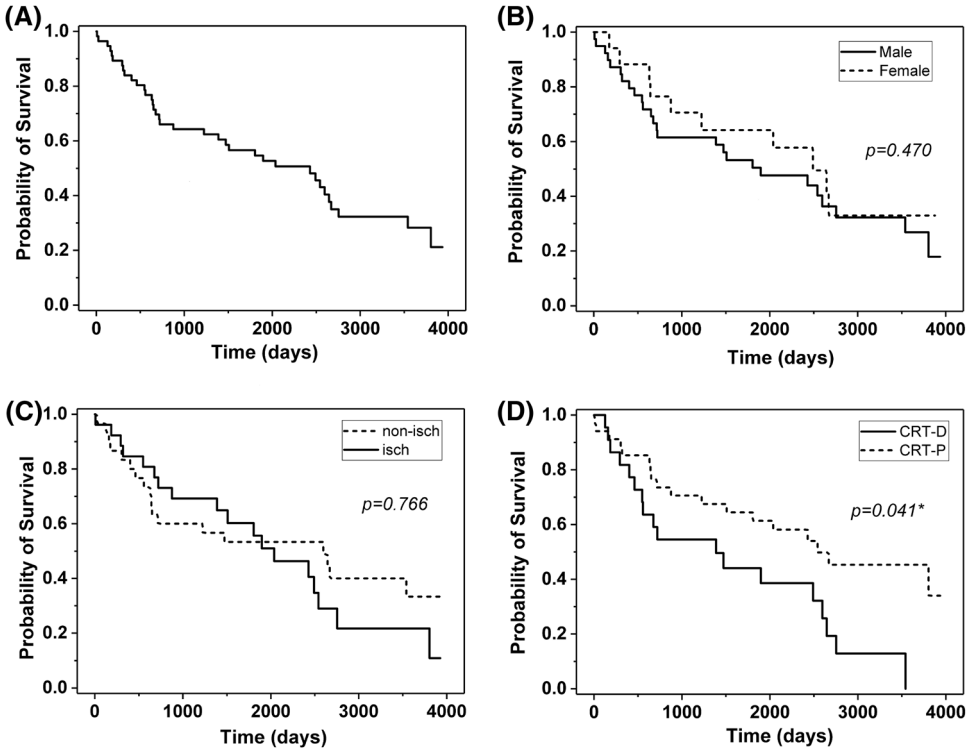

FIGURE 2 Kaplan-Meier survival analysis of all-cause mortality in the n = 55 patients: A, The entire minithoracotomy population; B, female and male; C, Ischemic versus nonischemic etiology; D, only the CRT-P versus CRT-D comparison resulted in significant difference, the *P* values are represented in the graphs

analyzed the survival (all-cause mortality) by Kaplan-Meier estimator with Tarone-Ware equality test in subgroups, the changes of the LVEF, LVEDD and LVESD, the development of the impedance and threshold of the LV epicardial electrode by means of Pearson's correlation. Also the possible associations between the survival and LVEF changes as a function of the intraoperative sensed RV-LV activation delay, the initial LV threshold and impedance were examined by Pearson's correlation. Although there is no common definition of responderity in the literature, we defined it as lack of hospitalization due to decompensation and lack of deterioration of LVEF in survivors during the first postoperative year. The statistical analyses and graphical representations were carried out in Origin Pro 2017 (OriginLab Corp., Northampton, MA). The $P \leq 5\%$ was considered statistically significant where appropriate.

3 | RESULTS

The n = 57 patients with minithoracotomy were followed at a mean of 1788 days, ranging from 7 to 3935 days. The intraoperative sensed RV-LV activation delay was 92.250 ± 26.538 milliseconds (ranging: 45-150 milliseconds, n = 35 was above 86 ms). In three patients of the six with previous heart surgery, the optimal positioning of the LV electrode was not possible because of serious adhesions and the high risk of tear or bleeding. In these patients the screw-in electrode was implanted in the apical region, resulting in 45, 48, and 56 milliseconds RV-LV delay.

The average operation time was 62 (ranging 55-130) minutes. There were no serious intraoperative complications excluding the ventricular fibrillation in three patients: one of them converted spontaneously and the remaining two were successfully defibrillated via the external pads. Ventricular extrasystoles, sometimes nonsustained ventricular tachycardias of short duration were common during manipulations on the heart when exposing the posterobasal surface.

Three patients were transported postoperatively to the intensive care unit: one needed longer ventilation because of respiratory failure, and two others required further observation after the intraoperative ventricular fibrillation and successful defibrillation. There were no significant pericardial or pleural effusions or pneumothorax in the postoperative period. The patients were discharged on an average of 5.4th postoperative day (range 4th-12th days). Within 30 days neither wound healing complications nor pocket hematoma occurred. We lost two patients on the 7th and 23rd postoperative days, respectively, due to intractable heart failure within the 30-day-mortality period; both of them were over 70 years. In the third postoperative month one patient had generator pocket infection, the system was removed and the patient refused any further pacemaker implantation and died on the 546th postoperative day. Another patient was heart transplanted on the 1541st day at the age of 55 years because of nonresponderity and worsening of heart failure. The last two patients were excluded from the Kaplan-Meier analysis. Until the end of the study period, the generator was replaced in 22 patients based on the elective replacement indicator.

Figure 2 represents the Kaplan-Meier survival analysis of all-cause mortality in the entire minithoracotomy population, and in different subgroups, however, the small number of cases limits their statistical

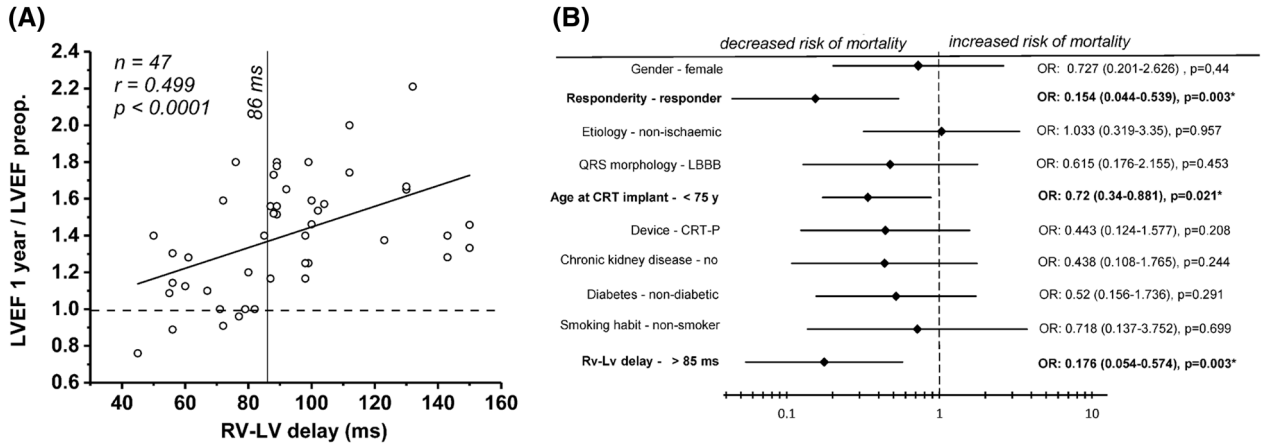

FIGURE 3 Intraoperative sensed right ventricular to left ventricular (RV-LV) activation delay and improvement of left ventricular ejection fraction at 1 year by linear correlation analysis (A) and forest plot showing relative risk of different factors for mortality (B). The positive slope of the linear regression line (A) is significantly different from zero with moderate positive correlation ($P < .0001$, Pearson's $r = 0.499$)

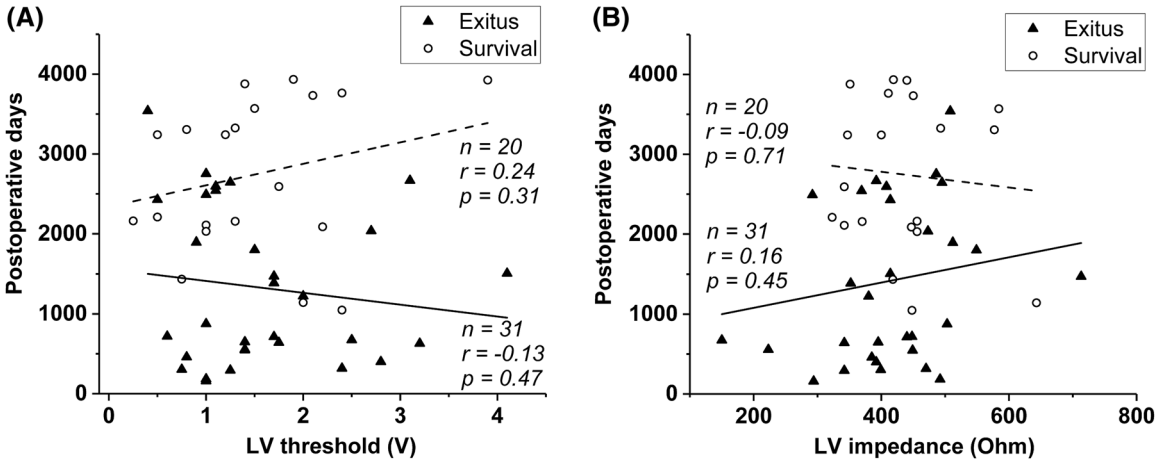

FIGURE 4 There was no significant association between survival and the initial (2-5 months) left ventricular electrode threshold (A) and impedance (B) by linear correlation in the deceased patients (continuous line) or in the survivors (dashed line). The number of patients in the cohorts, the Pearson's coefficient r, and the significance level *P* are presented in the graphs

strength. There was no significant difference with regard to gender and etiology, but CRT-D patients had significantly worse survival compared to CRT-P patients. The 5-year survival is around 40% in CRT-D patients versus 61% of CRT-P population.

Figure 3A shows the ratio of preoperative and 1-year postoperative LVEF as a function of the intraoperative RV-LV delay; the 86 milliseconds limit based on ([29]), see details later in the section Discussion. It is clearly demonstrated that the higher the delay, the better the improvement of LVEF.

The forest plot of odds ratios of mortality risk (Figure 3B) clearly shows significantly decreased mortality in responders (n = 39 in 47 survivors at 1 year), in patients under 75 years of age, and when RV-LV delay is above 85 milliseconds. The other parameters have no statistically significant strength.

The LV electrode threshold and impedance on the first postoperative control (after the healing period) influence the survival neither in deceased patients nor in survivors (Figure 4A,B). The LV pacing ratio was kept postoperatively as high as possible (mean: 95.6% ± 5.3%). The LVEF, LVEDD, and LVESD improved after the operation, and remained improved in survivors (Figure 5A-C).

During the mean 1197 (ranging 13-3867) days of electrophysiological follow-up, neither the LV electrode threshold nor impedance presented significant and strong or moderate correlation to the postoperative days from more than 300 samples (Figure 6A,B), reflecting preserved short- and long-term electrode function.

4 | DISCUSSION

CRT via left anterior minithoracotomy and intraoperative epicardial mapping is a viable alternative to transvenous CRT. According to our experience, about 60-70% surface area of the LV free wall is accessible, which can be limited by the stature of the patient, the thickness of the chest wall, the rotation and size of the heart, the mechanoelectrical

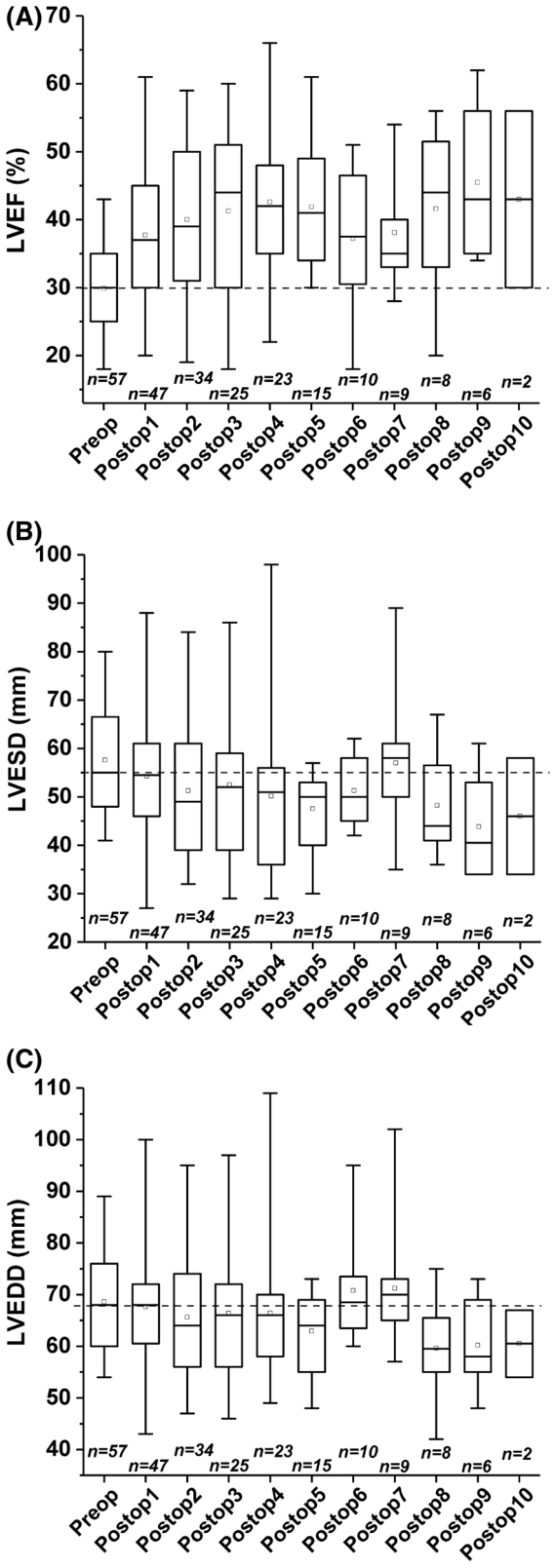

FIGURE 5 Sequential changes of the LVEF (A), LVESD (B), and LVEDD (C) with the n number of the actual survivors as a function of postoperative years

Abbreviations: LVEF, left ventricular ejection fraction (%), LVESD, left ventricular end-systolic diameter (mm), LVEDD, left ventricular end-diastolic diameter (mm)

irritability of the myocardium, and possible pericardial adhesions. The surgical exposure was good except in the three patients of the six with previous heart surgery. As we experienced, a good surgical access is not a guarantee of high RV-LV delay, it depends also on the position of the RV electrode and the electroanatomy of the broken LV myocardium.

Kaplan-Meier survival curves demonstrate sharp drops in survival at about 3 years and at around 7 years (Figure 2A). Comparing this trend to LVEF and echocardiographic dimensions (Figure 5A-C), different etiology can be suspected behind the two precipitous mortality periods: in the first case, the average of LVEF, LVESD, and LVEDD continuously improves during the initial 3 years - reflecting the relatively fast drop-out of nonresponders with worst parameters; in the second case the drop is preceded with gradual deterioration of echocardiographic parameters at 5-7 years - demonstrating the progression of heart failure in spite of the initial improvement in these patients following CRT. Referring to Figure 6 as well, the cause cannot be the dysfunction of the LV epicardial electrode since during the study period there was no significant temporal deterioration in electrode impedance or threshold.

It is interesting that in spite of several studies[8,26,29] considering female gender as a positive predictor of CRT responderity, there were no significant gender differences in Kaplan-Meier survival estimate found by Tarone-Ware test (Figure 2B) or in the forest plot (Figure 3B) in the present investigation, however, limitations due to the small number of cases must be taken into consideration. However, the female line is throughout a bit above the male line on Figure 2B, nevertheless, the small number of the patients can smudge the difference. Similarly, we could not demonstrate significant differences in survival regarding etiology (Figure 2C): in the short-term postoperative period, ischemic origin patients have better survival, at 5 years the two curves cross each other and, in accordance with the literature ,the nonischemic group has better survival thereafter (circa 40% versus 20% at 3000 days in the eight survivors). The crossing is due to a plateau phase between 2 and -7 years in the nonischemic cohort, as opposed to a monotonous, quasi-linear decrease in the ischemic group. Rickard et al[8] included 12 studies in their systematic review, and they associated nonischemic cardiomyopathy with superior outcomes exclusively in CRT-D patients, however they did not find sufficient evidence in CRT-P patients.

The significant difference among CRT-P and CRT-D group survivals (at 5 years 40% in CRT-D patients versus 61% of CRT-P patients) underlines the inherently higher risk of mortality of CRT-D patients in spite of the continuous defibrillator availability (Figure 2D). Interestingly, Döring et al[30] found no significant survival difference between 97 CRT-D and 80 CRT-P patients above 75 years by Kaplan-Meier analysis. On the other hand, Leyva et al[31] established CRT-D superior to CRT-P in a greater study population both in mortality and in composite end-point, especially in ischemic cardiomyopathy patients. Similarly to our observations, according to Liang et al,[32] CRT-D did not decrease all-cause mortality in their propensity score matched study on a total of 345 patients. The divergence of the above results calls for further studies in this area.

At the beginning of our CRT program we hypothesized that the higher the sensed activation delay between the two ventricular elec-

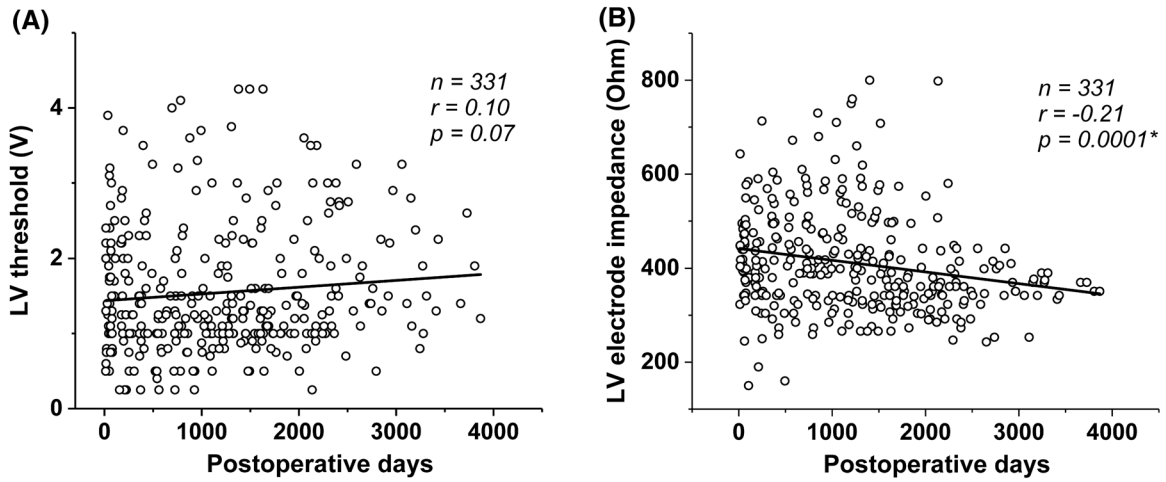

FIGURE 6 Long-term changes in left ventricular (LV) electrode threshold (A) and impedance (B). The n number of included data points, Pearson's r, and significance level *P* are presented. There is no significant strong or moderate correlation to time in case of either parameter

trodes, the better the synchronization on biventricular stimulation. This hypothesis gave rise to the idea of intraoperative epicardial mapping-based LV electrode positioning.[28] Kosztin et al[33] proved in a population of 125 transvenous CRT-patients with left bundle branch block that longer intraoperative RV-LV activation delay is associated with better clinical outcomes, including all-cause mortality during a median follow-up of 2.2 years. They defined a cutoff value at 86 milliseconds. In accordance with our results, in a meta-analysis[34] both acute and late QRS narrowing – that is, better electrical synchronization – was associated with clinical and echocardiographic improvements.

Comparing our survival results to those of other studies, Foley et al[35] had circa 30% survival in the upgrade to CRT group and circa 45% survival in the de novo CRT group at 2500 days with transvenous method, while we had circa 50% survival at the same time (Figure 2A) at 2500 days. Ailawadi et al[36] compared their surgical (n = 45) versus matched percutaneous (n = 135) CRT outcomes at a mean 32- and 39-month follow-up: they found no significant difference in functional benefits, however there was a higher risk of infection and acute kidney failure in the surgical cohort. Their survival at 60 months was around 30% in the surgical group, compared to our survival of circa 58% in the same period. We had no acute renal failure postoperatively, and there was only one late infection in the third postoperative month. Caliskan et al[17] investigated the role of steroid eluting versus bare LV screw-in electrodes implanted via left lateral minithoracotomy or VATS, focusing on the electrical performance in altogether 32 patients: they had no intraoperative complications, at a mean follow-up of 2.6 ± 1.9 years there was no significant difference in the electrical parameters of the LV electrode between the two groups. The Kaplan-Meier survival estimate showed no significant difference between the groups, the survival proved to be circa 85% in the steroid eluting and circa 70% in the bare cohort at about 30 months. In our study, at 30 months the survival was slightly inferior with approximately 65% rate (Figure 2A) with almost the same age distribution of patients and with implantation of mostly steroid eluting electrodes. In our population almost half of the group had ischemic etiology, whereas just about one third of the patients in the Caliskan study, and ischemic etiology is associated with worse outcomes in CRT according to large-scale studies. They did not detail the "selection of the optimal implantation site" and did not bring up RV-LV activation delay. Posteriorly we also analyzed our LV threshold and impedance changes with regard to steroid eluting (n = 48 patients) and non-steroid eluting electrodes (n = 9 patients): there were no significant differences between them.

The cornerstone of CRT is the positioning of the LV electrode relative to the RV electrode, followed by the "fine tuning" by programming atrioventricular and interventricular delay. The gold standard of optimization is echocardiography by measuring inter- and intraventricular segmental delays, however, this is a time-consuming and observer dependent method, not really suitable for intraoperative measurements. Optimal positioning of the electrode in the operating room can result in better outcomes and may reduce nonresponderity. Hence there are several ECG-based methods under testing in order to reach the best electrical synchronicity.[37] Del Greco et al[38] applied EnSite Precision Cardiac Mapping System in an electrophysiological laboratory to get the local electrical activation time map of the ventricles (near coronary veins) and to find the optimal position for the LV electrode. They reduced significantly the fluoroscopy time and angiography rate (dye) with the method; on the other hand it is a relatively time consuming procedure and requires an additional femoral venous access. Our method has the same philosophy with open chest; however, we need less time (5-10 minutes depending on the irritability of the heart) to find the optimal position on the epicardium by epicardial mapping, and there is no need for femoral venous puncture.

4.1 | Study limitations

The relatively small number of enrolled patients for minithoracotomy can limit the value of statistical analysis, however, as minithoracotomy is a second-line, more invasive procedure, in this case randomization is not an option to increase patient count.

5 | CONCLUSIONS

CRT via minithoracotomy with epimyocardial LV electrode implantation is a safe, efficient, and reproducible alternative to the transvenous method, owing to intraoperative epicardial mapping. At least 80-100 milliseconds sensed RV-LV delay is necessary for better short- and long-term results including LVEF and survival. Previous cardiac surgery can degrade the positioning due to adhesions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Study concept and design: Melczer and Hejjel. Analysis and interpretation of data: Hejjel, Németh, Melczer, and Kónyi. Drafting of the manuscript: Hejjel, Németh, Melczer, and Kónyi. Approval of article: Hejjel, Németh, Melczer, and Kónyi. Funding secured: Hejjel and Kónyi.

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