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Original article

# Impact of left ventricular pacing threshold on ventricular arrhythmia occurrence in cardiac resynchronization therapy

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ABSTRACT

*Background:* Cardiac resynchronization therapy (CRT) is an established heart failure (HF) treatment option, however its effect on ventricular arrhythmias (VAs) is controversial. Regional scar burden and high left ventricular (LV) pacing threshold (PT) are associated with poor outcome in CRT patients. The aim of our study was to analyze the impact of intraoperative LVPT on VA occurrence.
*Methods:* Eighty consecutive patients with advanced HF scheduled for a CRT defibrillator device [aged 63.3 ± 10.9 years; New York Heart Association II–III 86.2%; 52 males (65%); 34 ischemic etiology (42.5%); 71 sinus rhythm (88.7%); QRS duration 168 ± 25.7 ms] were evaluated using single-photon emission computed tomography myocardial perfusion imaging. Regional myocardial viability was calculated as the mean tracer activity in the corresponding segments at the LV lead pacing site. Fluoroscopic position and intraoperative LVPT were determined at implant after the final LV lead position was determined.
*Results:* LVPT was inversely associated with regional myocardial viability ($\rho$ −0.785, $p < 0.001$). After a median follow-up of 36 months (24–57) months VAs were registered in 27 patients (33.7%). Patients with VAs had higher median intraoperative LVPT compared to those without VAs [2.2 V (1.9–2.8) vs. 0.8 V (0.6–1.2), $p < 0.001$]. In a multivariate logistic regression model intraoperative LVPT was identified as a strong independent predictor of VAs.
*Conclusion:* Increased intraoperative LVPT during CRT could be associated with lower regional myocardial viability at LV lead location. CRT patients with higher LVPT could have an increased risk of VA occurrence.


## Introduction

Cardiac resynchronization therapy (CRT) has been shown to reduce mortality in selected patients with heart failure (HF) [1], however its impact on ventricular arrhythmias (VAs) remains controversial. Several randomized controlled studies have demonstrated that while CRT significantly reduces mortality and HF progression, patients remain at increased risk of VAs [2,3]. Some data also indicate that left ventricular (LV) lead pacing alone could impose a potential proarrhythmic risk [4,5].

Global scar burden and myocardial viability at the LV lead position play an important role in CRT response and VA occurrence [6–9]. A high LV pacing threshold (PT) at resynchronization device implantation may be a contributing factor to the adverse CRT outcome and could indicate a regional myocardial scar [10]. In addition, our previous study demonstrated that lower regional viability in the vicinity of the LV lead pacing site could be associated with increased risk of malignant tachyarrhythmias [11].

In this analysis, we sought to determine the relationship between LVPT and myocardial viability at the LV lead position. We also hypothesized that high LVPT would be associated with potential occurrence of VAs.

## Methods

The study complies with the Declaration of Helsinki. The study protocol was approved by The National Medical Ethics Committee and all patients gave a written informed consent before entering the study.

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*Study subjects*

Eighty consecutive HF patients who met the inclusion criteria for CRT device with a defibrillator (CRT-D) implantation between October 2009 and September 2014 were included. The inclusion criteria were the following: (1) an electrocardiogram showed a wide QRS complex (≥130 ms) and the morphology of left bundle branch block [12], (2) ischemic and non-ischemic cardiomyopathy with New York Heart Association (NYHA) class II–IV symptoms refractory to optimal medical therapy, (3) LV ejection fraction (LVEF) ≤35%, (4) patients were at least 18 years old and not pregnant, (5) gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) images were obtained before CRT-D implantation. In case of device malfunction, inadequate biventricular pacing (<90%) or lead failure/dislodgement (resulting in acute threshold increase) during follow-up patients were not included in the study. Ischemic etiology was based on the angiographically proven >70% stenosis of at least one major epicardial coronary artery or documented myocardial infarction. Patients with cardiac arrest or registered sustained ventricular tachycardia before CRT implantation were classified as patients with history of VAs. Clinical and laboratory examinations, medical therapy, chest X-ray, electrocardiographic, and echocardiographic parameters were recorded at baseline and 6 months after CRT-D implantation.

*Device implantation, programming and pacing threshold measurement*

Transvenous implantations of CRT-D devices were performed using standard techniques under local anesthesia. Commercially available devices (Medtronic; Minneapolis, MN, USA and Sorin Group; Saluggia, Italy) and leads were used. Active-fixation bipolar pacing leads were preferred in the right atrium and ventricle, and passive bipolar LV leads in the coronary venous system. Anatomical approach was used for LV lead positioning with lateral or postero-lateral vein as a preferred target. Operators were blinded to preimplantation MPI findings. Final LVPT was measured using bipolar pacing at 0.5 ms pulse width and the value obtained intraoperatively was used for analysis. Devices were programmed in the DDD mode with lower rate of 50 bpm or VVI mode with lower rate of 70 bpm in case of chronic atrial fibrillation (AF). Devices had a two-zone detection setting: ventricular tachycardia (VT) zone at 180 bpm and ventricular fibrillation (VF) zone at 210 bpm. Atrioventricular and interventricular delay optimization with echocardiography was performed at implantation.

*Evaluation of left ventricular lead position*

Final LV lead position was determined from 2 orthogonal views: 30° left anterior oblique (LAO) and the 30° right anterior oblique (RAO) fluoroscopic images. The LAO view was used to classify the LV wall into anterior, lateral (antero-lateral, postero-lateral), and posterior part. The RAO view was used to determine basal, mid, or apical lead position (Fig. 1A). This LV lead classification system was validated in previous studies [8,13]. LV lead positions were analyzed by two experienced cardiologists blinded to MPI findings and outcome data. If a discrepancy was present, the fluoroscopic images were reviewed again by the same analysts together to reach a consensus.

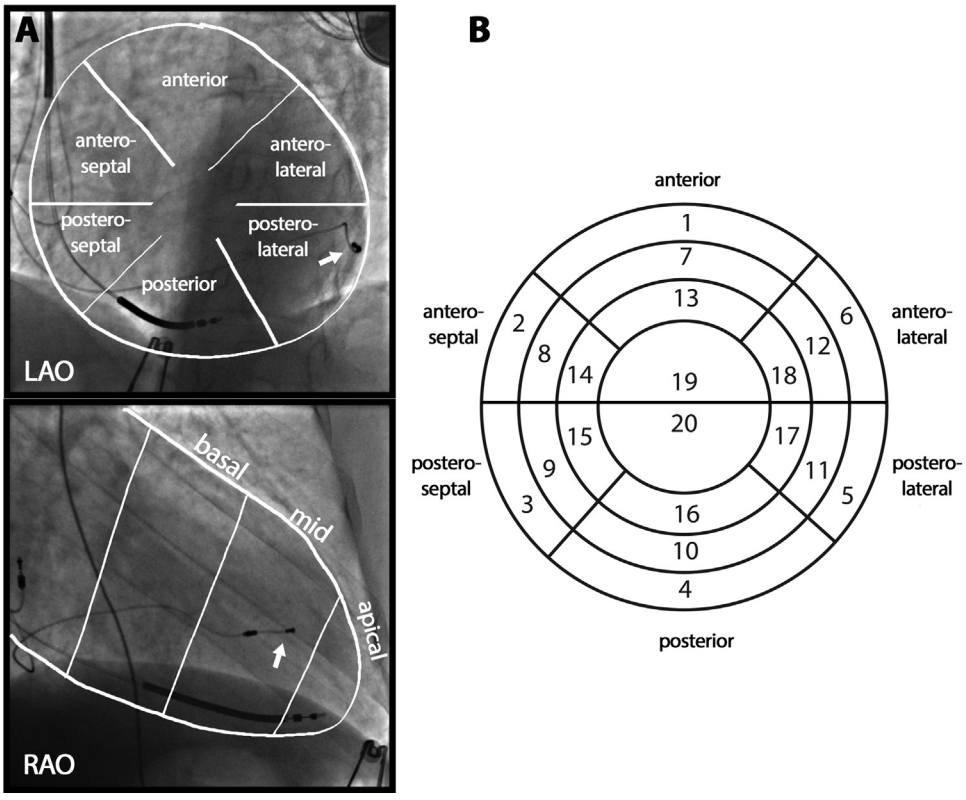


**Fig. 1.** Assessment of left ventricular (LV) lead location based on 20-segment LV model. (A) Fluoroscopic images in 30° left anterior oblique (LAO) (upper panel) and 30° right anterior oblique (RAO) (lower panel) were used to determine the final intraoperative LV lead position (arrow). RAO view was used to determine the LV lead position in the basal-apical direction: basal, mid, and apical part of the LV. LAO view was used to divide LV along the short axis of the heart into 6 equal parts: anterior, antero-lateral, postero-lateral, posterior, postero-septal and antero-septal part. Fluoroscopic lead position based on upper algorithm was projected onto the 20-segment model of myocardial perfusion imaging (B). Segments 1–6 presented basal, 7–12 mid and 13–18 apical part of the LV, segments 19 and 20 represent the apex. For example, if the LV lead was implanted in the mid portion of the postero-lateral vein the corresponding segments were 4, 5, 10, and 11.

*Myocardial perfusion imaging*

Gated SPECT images before CRT implantation were acquired according to previously described rest $^{99m}$Tc-sestamibi protocol [14]. MPI studies were interpreted by two independent nuclear imaging specialists using a standard 20-segment model [15]. Segmental tracer uptake was analyzed quantitatively and presented as a percentage of myocardial counts per segment normalized to maximum uptake in myocardium and displayed as bull's eye maps. Global myocardial viability was determined by number of viable segments per patient (≥50% of normal myocardium). Regional viability was calculated as the mean tracer activity in the corresponding segments at the LV lead position. Viability in the anatomic vicinity of the LV lead tip was determined by comparing fluoroscopic (30° LAO, 30° RAO) lead position at implantation with the tracer activity of adjoining myocardial segments assessed by SPECT imaging (Fig. 1B) [16].

*Echocardiography methods*

Transthoracic two-dimensional echocardiography was performed at baseline and at least 6 months after CRT device implantation. Left ventricular end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF were quantified using manual planimetry of two- and four-chamber views and Simpson's technique. Decrease in LVESV ≥15% 6 months after CRT was defined as LV reverse remodeling or echocardiographic CRT responder [10].

*Patient follow-up*

Device interrogations and clinical evaluations were performed in our device outpatient clinic at implant, one- and six-months post-implantation, and every six months thereafter. Additional follow-up was made in the case of a device shock or new HF symptoms onset. Ventricular tachyarrhythmia episodes were validated by two independent electrophysiologists blinded to the study outcome. Sustained episodes of ventricular tachycardia or ventricular fibrillation that were appropriately sensed and treated with anti-tachycardia pacing (ATP) or shock by the CRT-D device were defined as ventricular arrhythmias. Electrical storm was defined as ≥3 VAs within 24 h.

*Statistical analysis*

The Kolmogorov–Smirnov test was used to verify normal distribution. Normally distributed continuous variables were expressed as means and standard deviations. In non-normal distributed continuous variables, data were expressed as median together with the 25th and 75th percentiles (inter-quartile range). Categorical data were summarized as frequencies and percentages. For comparison of continuous variables paired and unpaired Student *t*-test was used for normally distributed variables and the Wilcoxon matched-pair test or the Mann–Whitney *U* test for non-normally distributed variables. The data for categorical variables were analyzed by using the Fisher exact test or chi-square test. Univariate and multivariate logistic regression analysis were performed to determine the relation between potential risk factors at baseline and the occurrence of VAs. Variables selected in the univariate analysis ($p < 0.05$) were entered into multivariate analysis. Because viability at LV lead position and intraoperative LV pacing threshold were strongly related, these variables were included separately in multivariate analysis. For this purpose, separate multivariate logistic regression models were constructed. The odds ratio (OR) and 95% confidence interval (CI) were reported. The optimal intraoperative LV pacing threshold to predict occurrence of VAs was determined by receiver-operating characteristic (ROC) curve analysis. For all tests, a two-tailed *p*-value ≤0.05 was considered statistically significant. Data were analyzed using SPSS version 23 (SPSS Inc., Chicago, IL, USA).

## Results

*Study population characteristics*

Eighty patients with a mean age of 63.3 ± 10.9 years were included in the study. The sample consisted of 52 male (65%) patients. Ischemic etiology was present in 34 patients (42.5%) and was more common in the VA group (63% vs. 32.1%; $p = 0.016$). Most of the patients were in NYHA class III (61; 76.3%). Mean QRS duration was 168 ± 25.7 ms and patients were predominantly in sinus rhythm (71; 88.8%). Median LVEF was 25% (21–30). Patients were managed with optimal contemporary tolerated medical therapy (Table 1). The LV lead was inserted in the postero-lateral vein in 54 patients (67.5%). There were 14 patients with history of VA before device implantation. Reverse echocardiographic remodeling was noted in 40 patients (50%). After CRT-D implantation, patients were further followed for 36 months (24–57) for VA occurrence (Table 1). No patients were lost to follow-up. During long-term follow-up, 10 patients died due to cardiac pump failure, 2 patients received an LV assist device and 5 patients had heart transplantation. Non-cardiac death was reported in three patients.

*Occurrence of ventricular arrhythmias*

During long-term follow-up, 27 patients (33.7%) experienced VAs. Of these patients, 8 (15%) experienced more than two appropriate device discharges during long-term follow-up. A total of 61 VAs were registered. Fifty-nine were classified as monomorphic ventricular tachycardias (43 terminated after ATP and 16 after ICD shock was discharged). In addition, two polymorphic VTs were recorded that degenerated into VF. Five patients experienced an electrical storm, all presenting with monomorphic VTs. In four patients VT ablation procedure was performed. Comparison of baseline, clinical, and echocardiographic parameters between groups of patients with VAs and no VAs is summarized in Table 1. Patients with registered VAs were more likely to have a larger baseline LVESV and LVEDV and were without reverse remodeling after 6 months of CRT. Patients with a history of VAs before implantation were comparable in both groups. Antiarrhythmics and HF therapy were also similar. LV lead was predominantly located in the postero-lateral vein in both groups [VAs vs. non-VAs: 34 (64.2%) vs. 27 (69.2%); $p = 0.454$].

*Intraoperative left ventricular pacing threshold, myocardial perfusion imaging, reverse remodeling, and the occurrence of ventricular arrhythmias*

Patients without VAs had lower intraoperative LV pacing thresholds (0.97 V ± 0.48 V vs. 2.26 V ± 0.64 V; $p < 0.001$), more viable segments (17.4 ± 2.7 vs. 14.4 ± 3.6; $p = 0.001$) and higher viability of the corresponding segments at LV lead position (67.5% ± 3% vs. 49.6% ± 7.8% of tracer activity; $p < 0.001$). In addition, among patients with registered VAs, intraoperative LV pacing threshold and the extent of regional viability is also related to occurrence of electrical storm. Patients with electrical storm had higher intraoperative LV pacing threshold (2.54 V ± 0.9 V vs. 1.33 V ± 0.76 V) and lower regional viability (47.3% ± 12% vs. 62.4% ± 11.2%; $p = 0.005$). Patients with LV reverse remodeling after CRT had a lower mean intraoperative LV pacing threshold compared to non-responders (0.98 V ± 0.52 V vs. 1.87 V ± 0.83 V; $p < 0.001$).

**Table 1**
Characteristics of all patients and comparison of group with and without the occurrence of ventricular arrhythmias in long-term follow-up.

| | All ($n=80$) | No VAs ($n=53$) | VAs ($n=27$) | $p$-Value |
|---|---|---|---|---|
| Clinical characteristics | | | | |
| Age (years) | 63.3 ± 10.9 | 64.4 ± 10.9 | 61 ± 11.8 | 0.196 |
| Male (%) | 52 (65) | 29 (54.7) | 23 (85.2) | 0.007 |
| History of VAs before CRT (%) | 14 (17.5) | 10 (18.9) | 4 (14.8) | 0.763 |
| Ischemic cardiomyopathy (%) | 34 (42.5) | 17 (32.1) | 17 (63) | 0. 016 |
| NYHA class I/II/III/IV | 1/8/61/10 | 1/7/37/8 | 0/1/24/2 | 0.281 |
| QRS duration (ms) | 168 ± 25.7 | 169.5 ± 26.3 | 167 ± 27.7 | 0.673 |
| 6-MWT (m) | 330.5 ± 107.6 | 324.9 ± 102.3 | 341.4 ± 118.6 | 0.520 |
| AF (%) | 9 (11.3) | 7 (13.2) | 2 (7.4) | 0.710 |
| Diabetes mellitus (%) | 14 (17.5) | 8 (15.1) | 6 (22.2) | 0.536 |
| Serum creatinine (mmol/L) | 92 (77.25–114) | 92 (73–115) | 92 (82–114) | 0.228 |
| proBNP (ng/L) | 2098 ± 1449,6 | 2000 ± 1540 | 2291 ± 1258 | 0.400 |
| Echocardiographic parameters | | | | |
| LVEF (%) | 25 (21–30) | 25 (21–30) | 25 (20–30) | 0.291 |
| LVESV (mL) | 181 (135.5–225.8) | 170 (131–211.5) | 210 (115–265) | 0.024 |
| LVEDV (mL) | 240 (198.5–280) | 219 (188.5–271.5) | 274 (226–339) | 0.013 |
| LV reverse remodeling (%) | 40 (50) | 35 (66) | 5 (18) | <0.001 |
| MPI | | | | |
| Nb. of viable segments[a] | 16.4 ± 3.5 | 17.4 ± 2.7 | 14.4 ± 3.6 | 0.001 |
| Viability at LV lead position (%) | 62.1 ± 12 | 67.5 ± 3 | 49.6 ± 7.8 | <0.001 |
| Pacing threshold at implantation (V) | 1.31 ± 0,7; 1.1 (0.7–2.1) | 0.97 ± 0,48; 0.8 (0.6–1.2) | 2.26 ± 0.64; 2.20 (1.9–2.8) | <0.001 |
| LV R-wave amplitude at implantation (mV) | 13.7 ± 3.3 | 13.7 ± 3.3 | 13.7 ± 3.3 | 0.968 |
| Medical therapy | | | | |
| Beta blockers (%) | 77 (96.3) | 50 (94.3) | 27 (100) | 0.547 |
| ACE-I/ARB (%) | 78 (97.5) | 51 (96.2) | 27 (100) | 0.547 |
| Spironolactone (%) | 74 (92.5) | 48 (90.6) | 26 (96.3) | 0.658 |
| Amiodarone (%) | 12 (15) | 9 (17) | 3 (11.1) | 0.742 |
| Digoxin (%) | 9 (11.3) | 6 (11.3) | 3 (11.1) | 0.999 |
| CRT implantation | | | | |
| Postero-lateral vein (%) | 54 (67.5) | 34 (64.2) | 20 (74.1) | 0.454 |
| Antero-lateral vein (%) | 26 (32.5) | 19 (35.8) | 7 (25.9) | 0.454 |
| Clinical outcome | | | | |
| Duration of follow-up (months) | 36 (24–57) | 46 (24–64) | 26 (20–36) | <0.001 |
| Death (%) | 18 (22.5) | 7 (13.2) | 11 (40.7) | 0.01 |
| VAD (%) | 2 (2.5) | 0 | 2 (7.4) | 0.111 |
| Transplant (%) | 5 (6.3) | 3 (5.7) | 2 (7.4) | 0.999 |
| Electrical storm (%) | 5 (6.3) | 0 | 5 (18.5) | 0.003 |

VAs, ventricular arrhythmias; CRT, cardiac resynchronization therapy; NYHA class, New York Heart Association class; MPI, myocardial perfusion imaging; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume; 6-MWT, 6-min walking distance test; proBNP, brain natriuretic peptide; AF, atrial fibrillation; LV, left ventricle; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; VAD, ventricular assist device.
[a] Tracer uptake 50% or more of normal myocardium according to 20-segment model (Fig. 1B).

To investigate whether the intraoperative LV pacing threshold predicts the occurrence of VAs, we performed univariate and multivariate logistic regression analysis. The univariate analysis showed that ischemic cardiomyopathy, LVEDV, LV reverse remodeling, global myocardial viability, viability at lead position [OR 0.76 (per 1% of tracer activity), 95% CI (0.68–0.86); $p < 0.001$], and intraoperative LV pacing threshold [OR 24.9 (per 1 V), 95% CI (6.63–93.6); $p < 0.001$] were predictive for occurrence of VAs. Other clinically relevant variables: previous VAs, baseline LVEF, NYHA class, and amiodarone therapy were non-significant in univariate analysis (Table 2). Because the mean viability at LV lead position and intraoperative LV pacing threshold had very strong negative correlation (correlation coefficient −0,78; $p < 0.001$), these two factors were separately assessed in multivariate analysis. Intraoperative LV pacing threshold and viability at LV lead position remained independently related to the occurrence of VAs in multivariate models adjusting for etiology, LVESV, LVEDV, LV reverse remodeling, and global myocardial viability (Table 2).

To define the optimal cut-off value of intraoperative LV pacing threshold to predict VA occurrence, ROC curve analysis was performed. Fig. 2 shows a ROC curve of intraoperative LVPT to predict the occurrence of VAs (AUC = 0.938, 95% CI 0.88–0.99). The cut-off value of 1.45 V had a sensitivity of 89% and specificity of 81%.

## Discussion

The results of our study stress the importance of assessing intraoperative LVPT during CRT device implantation. Regardless of HF etiology, we demonstrated a strong relationship between intraoperative LVPT and regional myocardial viability at the LV pacing site. High LVPT was associated with increased risk of malignant tachyarrhythmias in CRT-D recipients during long-term follow-up.

The rate of VA occurrence in our patient cohort was similar to previous studies [17,18]. Several baseline clinical characteristics in CRT patients including absence of optimal medical therapy [2], renal failure [2], NYHA class IV [2,17], and LV systolic diameter >61 mm have been identified as predictors of Vas [18]. Although our results show that patients who experienced VAs had higher baseline LV volumes, we could not find the relationship of these clinical variables with the arrhythmia occurrence. In our study, only myocardial viability at LV lead position and LVPT at implantation remained independent predictors of VAs. Differences in study population characteristics and HF therapy may account for the discrepancy of the results. Patients in the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure) trial [2] and Ventak CHF (congestive heart failure)/Contak CD [17] trials were receiving less β-blocker therapy compared with our study population and had shorter follow-up

**Table 2**
Univariate and multivariate logistic regression for the occurrence of VAs.

| Variable | OR | 95% CI | *p*-Value |
|---|---|---|---|
| Univariate analysis | | | |
| History of VAs before CRT | 1.34 | 0.38–4.74 | 0.653 |
| Ischemic cardiomyopathy | 0.28 | 0.11–0.73 | 0.01 |
| NYHA class I–III vs. IV | 2.95 | 0.51–13.3 | 0.252 |
| LVEF (%) | 0.96 | 0.88–1.04 | 0.288 |
| LVESV (mL) | 1.01 | 1.00–1.02 | 0.029 |
| LVEDV (mL) | 1.01 | 1.00–1.01 | 0.017 |
| LV reverse remodeling | 8.56 | 2.8–26.4 | <0.001 |
| Nb. of viable segments[a] | 0.75 | 0.64–0.89 | 0.001 |
| Viability at LV lead position (%) | 0.76 | 0.68–0.86 | <0.001 |
| Pacing threshold at implantation (V) | 24.9 | 6.63–93.6 | <0.001 |
| Amiodarone | 1.64 | 0.4–6.62 | 0.49 |
| Multivariate analysis (model 1) | | | |
| Ischemic cardiomyopathy | 0.35 | 0.06–2.23 | 0.269 |
| LVESV (mL) | 1.01 | 0.96–1.05 | 0.774 |
| LVEDV (mL) | 1.0 | 0.96–1.04 | 0.952 |
| LV reverse remodeling | 1.62 | 0.27–9.81 | 0.602 |
| Nb. of viable segments[a] | 1.03 | 0.76–1.4 | 0.866 |
| Pacing threshold at implantation (V) | 19.84 | 4.37–90.1 | <0.001 |
| Multivariate analysis (model 2) | | | |
| Ischemic cardiomyopathy | 0.53 | 0.93–3.01 | 0.482 |
| LVESV (mL) | 0.99 | 0.95–1.04 | 0.751 |
| LVEDV (mL) | 1.00 | 0.97–1.04 | 0.85 |
| LV reverse remodeling | 2.55 | 0.44–14.7 | 0.259 |
| Nb. of viable segments[a] | 1.12 | 0.82–1.52 | 0.474 |
| Viability at LV lead position (%) | 0.76 | 0.65–0.88 | <0.001 |

OR, odds ratio; CI, confidence interval; CRT, cardiac resynchronization therapy; LV, left ventricular; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume; NYHA, New York Heart Association; VAs, ventricular arrhythmias.
[a] Tracer uptake 50% or more of normal myocardium according to 20-segment model (Fig. 1B).

period. Furthermore, a recent cardiac magnetic resonance (CMR)-based study with similar patient cohort suggested that only myocardial scar variables independently predict arrhythmic events in CRT patients [9].

There are several SPECT MPI-based publications on detrimental effect of high scar burden in CRT recipients [6,7,19]. However, only few studies have systematically examined the impact of anatomical LV lead location and regional myocardial viability on CRT outcome [8,19]. With a low proportion (11%) of LV leads concordant to LV scar, Xu et al. [19] did not show a significant impact of regional myocardial viability on CRT response. On the other hand, in a study with ischemic CRT patients, regional scar and reversible ischemia adjacent to LV pacing site were independent predictors of HF hospitalization and death [8]. Furthermore, in our previous study we showed that lower regional LV viability could be associated with increased risk of malignant tachyarrhythmias [11]. In addition, a substudy of MADIT-CRT (multicentre automatic defibrillator implantation trial with cardiac resynchronization therapy) trial demonstrated that patients with anterior LV lead position and prior adjacent myocardial infarction had an increased risk of malignant arrhythmias [20].

Previous studies that evaluated the impact of regional LV myocardial viability on CRT outcome did not report on the relationship between LVPT and adjoining scar [8,19,20]. Therefore, with the present study we further extended the possible clinical implications of the LV lead positioning during CRT implantation by demonstrating a close inverse association of intraoperative LVPT and regional myocardial viability. To the best of our knowledge, only one study investigated the impact of LVPT at the time of implant on CRT outcome [10]. In a similar patient cohort and in line with our results, high LVPT was associated with lower clinical CRT response and increased risk of death from any cause [10]. Although arrhythmia occurrence in the latter study was not reported, it is conceivable to implicate that at least part of the outcomes could have been influenced by VAs [2,3].

The key finding of our study is that high intraoperative LVPT may be associated with regional myocardial scar and increased risk of malignant tachyarrhythmias. The LVPT cut-off value of 1.45 V (sensitivity of 89%, specificity of 81%) was a good predictor of VAs in long-term follow-up. There are several mechanisms that could explain possible enhancement of electrical instability by LV epicardial pacing in the area of reduced myocardial viability. Reversal of the normal direction of activation during LV epicardial pacing could augment intrinsic transmural heterogeneity of repolarization and alter mechanical dyssynchrony patterns, which potentially contribute to the occurrence of arrhythmia [4]. In myocardial scar tissue, fibrosis facilitates the emergence of triggers

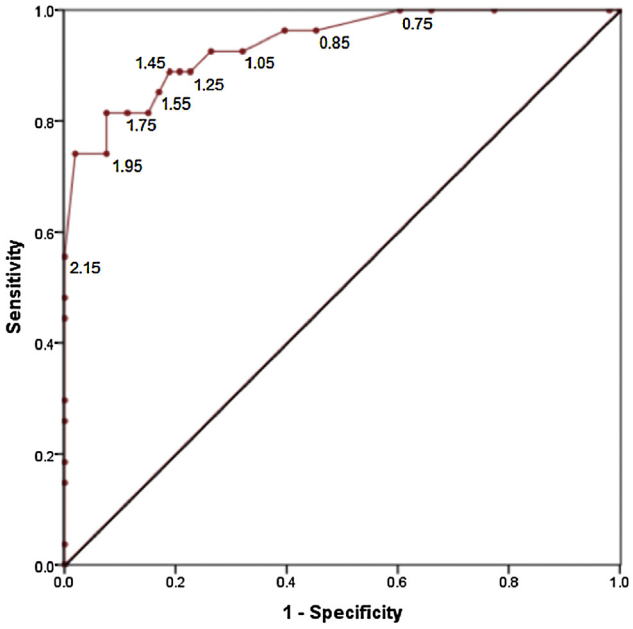


**Fig. 2.** Receiver-operating characteristic curve analysis pacing threshold at implantation (V) and the occurrence of ventricular arrhythmias (area under the curve = 0.938).

such as after depolarization-induced premature ventricular complexes. Irrespective of etiology, fibrosis separating myocyte bundles creates a fixed substrate vulnerable to functional and anatomic reentry by enabling slow conduction and susceptibility to unidirectional conduction block [21]. Epicardial LV pacing stimulus during CRT may penetrate the reentry circuit and produce unidirectional block in slow conduction zones initiating VA. In a cohort of 64 patients undergoing VT ablation, re-entry circuit was the underlying mechanism among all CRT patients as electroanatomical mapping demonstrated that LV epicardial lead was located within scar in 80% of arrhythmic cases with ischemic and non-ischemic cardiomyopathy [22].

Finally, presence of regional scar tissue in the area of the final lead position may also preclude LV improvement after CRT and prevent antiarrhythmic effect of LV reverse remodeling [3]. The present study extends these observations as the presence of LV reverse remodeling after CRT was significantly higher in patients without VAs. A recent meta-analysis of 23 studies showed that CRT responders are less likely to experience VAs compared to CRT non-responders, suggesting that CRT with LV epicardial stimulation may be inherently proarrhythmic in the absence of LV reverse remodeling [23]. With the results of our study and data from the literature it is difficult to clarify weather non-viable myocardium is responsible for worse echocardiographic outcome and consequently higher incidence of malignant tachyarrhythmias. Further prospective studies are needed to establish whether high LVPT associated with reduced regional viability really has an arrhythmogenic effect.

### *Clinical implications*

The results of our study highlight the importance of achieving low intraoperative LVPT during CRT device implantation. Higher LVPT is an issue of substantial importance, not just in terms of increased battery drain and potentially diminished echocardiographic response [6–8,10], but also in view of the current controversy regarding the need of implantable defibrillator backup. Patients with increased scar burden should be considered for CRT-D as they could pose a higher risk of VA occurrence [9,11]. However, localization of scar requires specialized imaging techniques and personnel that may not be promptly available before CRT device implantation. Prespecified LV location may not always be feasible as high intraoperative PT could indicate local scar tissue. Therefore, during CRT device implantation, alternative LV lead pacing site with lower LVPT should be pursued to avoid possible enhancement of electrical instability.

### *Limitations*

The present study has some limitations. Its retrospective design and number of patients limits the strength of our findings. Collection of data at a single center may result in treatment bias, which could influence the outcomes. However, our study cohort was representative of patients who receive CRT devices in general and the rate of VA occurrence was similar to previous studies [17,18]. Furthermore, fluoroscopic LV lead position projection onto the 20-segment model is limited. However, the definition applied to this analysis is a commonly used method that has gained wide acceptance [6–8]. A recent CMR-based study showed that apart from the presence of scar tissue also its heterogeneity predicts VA occurrence [9]. Comparatively lower spatial resolution of scar quantification by SPECT MPI compared with CMR limits the strength of our findings. Still, SPECT MPI is widely available in clinical practice with a high level of standardization and reproducibility [14,15]. Finally, apart from local scar, intraoperative LVPT can be influenced by several factors such as suboptimal tissue contact, lead stability, and patient-specific variables (e.g. medication, electrolyte imbalance) [24]. However, during long-term follow up in our patient cohort, no substantial LV lead issues were noticed. Further studies are needed to establish a causal relationship.

## Conclusions

Increased LVPT during CRT device implantation could be related to lower regional myocardial viability at LV lead pacing site. CRT patients with higher intraoperative LVPT may have an increased risk of VA occurrence. Placement of LV lead at sites with lowest LVPT should be pursued to avoid possible enhancement of electrical instability.

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## Conflicts of interest

The authors declare that there is no conflict of interest.

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