Left ventricular lead location and the risk of ventricular arrhythmias in the MADIT-CRT trial

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Aims
We aimed to evaluate the influence of left ventricular (LV) lead position on the risk of ventricular tachyarrhythmias in cardiac resynchronization therapy (CRT) patients.

Methods and results
Left ventricular (LV) lead position was evaluated by biplane coronary venograms and anterior/posterior, lateral chest X-rays in patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT). The LV lead location could be defined in 797 of 1089 patients (73%). The LV lead was placed at the LV apex in 110 (14%) patients, in the anterior position in 146 (18%), in the lateral position in 448 (56%), and in the posterior position in 93 (12%) patients. After adjustment for clinical covariates, lateral or posterior lead location was associated with significantly lower risk of ventricular tachycardia (VT)/ventricular fibrillation (VF) [hazard ratio (HR) = 0.57, 95% confidence interval (CI): 0.38–0.85; P = 0.006] when compared with an anterior lead location. Patients with anterior lead position had similar risk of VT/VF as patients with implantable cardioverter defibrillator (ICD)-only (HR = 1.04, 95% CI: 0.72–1.81; P = 0.837). There was no difference in the risk of mortality between posterior or lateral and anterior LV lead locations.

Conclusion
Cardiac resynchronization therapy with posterior or lateral LV lead position is associated with decreased risk of arrhythmic events in comparison with anterior lead location and ICD-only patients. There is no evidence for increased risk of VT/VF episodes associated with CRT.

Keywords
Cardiac resynchronization therapy † Ventricular tachycardia † Ventricular fibrillation † Left ventricular lead position

Introduction
Cardiac resynchronization therapy (CRT) improves survival and cardiac function in moderate or severe heart failure (HF), NYHA class III, IV, and wide QRS or dyssynchrony.1 Cardiac resynchronization therapy reduces the risk of HF hospitalizations and improves quality of life. Reverse remodelling of myocardial structures can be characterized by the increase of LV ejection fraction (LVEF) and reduced left ventricular (LV) volumes.2–6 The Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT) showed that CRT with defibrillator (CRT-D) was associated with significant reduction in the risk of HF or death compared with implantable cardioverter defibrillator (ICD) among mildly symptomatic or asymptomatic patients (NYHA class I or II) with a low ejection fraction and a wide QRS.7

However, HF patients remain at increased risk of ventricular tachycardia (VT) or ventricular fibrillation (VF) even after receiving CRT. The Cardiac Resynchronization in Heart Failure (CARE-HF) extension trial reported 7.8% of sudden cardiac death during the mean follow-up of 29.4 months in patients receiving CRT.8 In the Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Heart Failure (COMPANION) study, 19.3% of the CRT-D patients experienced appropriate ICD therapy by the second year after device implantation.
Implantable cardioverter defibrillator shock therapy is associated with worse outcome.\textsuperscript{6,9} There are several risk factors contributing to the occurrence of ventricular tachyarrhythmias, ischaemic events, depressed LV function, increased ventricular wall stress, renal dysfunction and atrial fibrillation.\textsuperscript{6,10} Some data also indicate that there is a potential pro-arrhythmic risk of biventricular pacing itself.\textsuperscript{11–15}

It is unknown whether the position of the LV lead might play a role in the development of VT/VF, possibly by enhancing electrical heterogeneity. A recent study suggested that different LV lead positions were not associated with higher risk of ventricular arrhythmias.\textsuperscript{16} However, this has not yet been investigated in a prospective trial in patients with mildly symptomatic or asymptomatic HF. Therefore, the aim of our study was to analyse the association between the LV lead position and the risk of VT/VF episodes in patients enrolled in the MADIT-CRT trial.

Methods

Study population

The design, protocol, and results of the MADIT-CRT study have been reported previously.\textsuperscript{17} Briefly, 1820 patients who had ischaemic or non-ischaemic cardiomyopathy, an ejection fraction (LVEF) < 30%, prolonged intraventricular conduction with a QRS > 130 ms were randomized to receive CRT-D or ICD therapy in a 3:2 ratio. Patients were excluded if they had an existing indication for CRT, received a pacemaker, were in NYHA class III/IV < 90 days before enrolment, underwent coronary artery bypass graft surgery or percutaneous coronary intervention, or had myocardial infarction within the past 90 days prior to enrolment.

The study was in compliance with the Declaration of Helsinki, the protocol was approved by the institutional review board at each of the participating centres, and all patients provided informed consent prior to enrolment.

Device programming and interrogation

Commercially available transvenous ICD and CRT-D devices (Boston Scientific) were used in the trial. Standard techniques were used to implant the devices. Device testing and programming were performed as reported in the study protocol.\textsuperscript{17} Devices were programmed to monitor + therapy, with protocol recommendation to a setting of the VT zone at 180 b.p.m. and the VF zone at 250 b.p.m. Sensitivity was programmed according to physician discretion. Detection was 1.0 s for the VF zone and 2.5 s for the VT zone. The study protocol suggested programming the VT zone first therapy to burst-type anti-tachycardia pacing (ATP), then shock therapy; second therapy should be shock at defibrillation threshold plus at least 10 J. The remaining therapies should be maximal energy shocks. All device interrogation disks were sent to an independent core laboratory for categorization and final evaluation of detected arrhythmias.

Patient follow-up

Patients had an ambulatory follow-up 1 month after CRT-D or ICD implantation and every 3 months thereafter until the termination of the trial. The mean follow-up of the enrolled patients was 29.4 months. All patients had a clinical evaluation and ICD interrogation with retrieval of stored electrograms at each follow-up visit or at any meaningful clinical event.

Evaluation of left ventricular lead locations

Left ventricular lead position was evaluated by biplane coronary venograms and anterior/posterior, lateral chest X-rays in patients enrolled in the MADIT-CRT. At the time of CRT implantation, coronary venous angiograms were obtained in at least two orthogonal views (right anterior oblique—RAO; left anterior oblique—LAO) as well as fluoroscopic images in the same views after definitive LV lead placement. Anterior–posterior and lateral chest X-rays were performed after the procedure or prior to discharge. The stored images were copied onto a CD-ROM and sent to the core laboratory at the University of Rochester Medical Center for central reading. The study protocol recommended positioning the LV lead in the lateral or postero-lateral side-branch of the coronary sinus if possible.

The final LV lead position was assessed in the longitudinal axis view (RAO 20°–40°) and the short axis view (LAO 20°–40°) together with the anterior/posterior and lateral chest-X ray. In case the LV lead images were not available in both angle views, stored at completely different angles, or showed poor quality making lead assessment impossible, the lateral chest-X rays were used to define the final lead position.

We were able to analyse the LV lead location in 797 of 1089 (73%) patients who received CRT-D devices and were followed over a mean of 30.6 (± 10.9) months. The following patients were not included in the analysis: those who needed a cross-over to ICD only (n = 66, 6.1%) or who had a cross-over to CRT-D (n = 2, 0.2%), who were withdrawn prior to device implantation (n = 56, 5.1%), who underwent LV lead repositioning > 1 week after the initial CRT device implantation because of lead dislodgement (n = 54, 5%), those who had epicardial LV lead placement (n = 36, 3.3%), or cases with incomplete data sets of device implantation venograms and X-rays (n = 78, 7.2%).

The LAO view, representing the short-axis view of the heart, was used to classify the LV wall into three equal parts: anterior, lateral (antero-lateral, lateral, postero-lateral), and posterior. The RAO view, representing the long axis of the heart, was used to distinguish the lead position to be basal, mid-ventricular, or apical.\textsuperscript{18,19} We defined an anterior, lateral, and posterior LV lead locations along the short axis, including all basal and mid-ventricular lead locations. We also grouped patients with apical vs. non-apical (basal and mid-ventricular) LV lead location along the short axis (Figure 1). We compared the anterior, lateral, posterior, and apical LV lead locations; the anterior vs. lateral-posterior and apical lead locations along short axis as well as the apical vs. non-apical lead positions along the long-axis of the heart.

Endpoints

The primary endpoint of the current study was the first occurrence of appropriate therapy for VT or VF or death assessed as the cumulative probability of first events or risk of events. All ICD interrogations were adjudicated by an independent, blinded core laboratory reviewing the electrograms of the episodes for categorization and final evaluation of the detected arrhythmias. Definition of VT was set to a rate of 180 (recommended programming) up to 250 b.p.m., V rate > A rate if 1:1 A:V, VV changes drive AA changes. Ventricular fibrillation was defined as ventricular rate >250 b.p.m. with disorganized ventricular electrograms. Only appropriate therapy, ATP, or shock delivery for VT or VF was considered in the present analysis.

We analysed VT/VF and rapid VT/VF episodes (rate ≥ 200 b.p.m.) as separate endpoints. We evaluated VT/VF events requiring ICD shock or death, as well as recurrent VT/VF events (two or more VT/VF
episodes in one patient). We also analysed all-cause mortality of the subgroups.

**Statistical analysis**

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between the pre-specified subgroups, stratified by implanted device and LV lead position, using non-parametric Wilcoxon or Kruskal–Wallis tests for continuous variables and χ² test for dichotomous variables, as appropriate. Baseline LV dysynchrony, 12-month LV dyssynchrony, and change in LV dyssynchrony were evaluated among the subgroups using the Kruskal–Wallis test.

Cumulative probability of first VT/VF or death episodes was displayed according to the Kaplan–Meier method, with comparisons of cumulative event rates by the log-rank test. Multivariate Cox proportional hazards regression analysis was used to identify and evaluate the impact of LV lead location on the endpoint of first VT/VF or death, whichever occurred first. The Cox model was adjusted for the following covariates: female gender, aetiology of cardiomyopathy, LVEF, apical LV lead location, QRS duration, and morphology (left bundle branch block—LBBB; right bundle branch block—RBBB). Crude event rates were reported as counts of events. As these are composite descriptive measures of risk, ignoring risk variation across patients, no statistical analysis was done.

Propensity analysis was additionally performed to evaluate the robustness of our findings. The propensity score was developed using logistic regression, which showed RBBB, LVEF, and blood urea nitrogen to be statistically significant predictors of lead position.

Adjusted hazards ratios (HRs) with their 95% confidence intervals (CIs) are reported. A P-value of <0.05 was considered statistically significant and all statistical tests were two-sided. Analyses were conducted with the SAS software (version 9.2, SAS institute, Cary, NC, USA).

**Results**

The LV lead location was evaluated in 797 of 1089 patients (73%). The LV lead was placed in the lateral position in 448 (56%), in the posterior position in 93 (12%), in the anterior position in 146 (18%), and in the apical position in 110 (14%) patients. Of the 797 CRT-D patients with LV lead assessment, 166 (20.8%) reached the combined endpoint of VT/VF or death and 133 patients (16.7%) reached the arrhythmia endpoint of VT/VF episodes. Forty-seven patients (5.9%) died during the follow-up: 15 with cardiac pump failure, 7 from sudden death, 2 from acute coronary ischaemic event, 19 with non-cardiac death, and in 4 patients, the cause of death was indeterminable. Of the seven patients who had sudden death, three had an anterior, three a lateral, and one patient a posterior lead position.

**Relation of the left ventricular lead location and the risk of ventricular tachyarrhythmias**

During the follow-up, VT/VF episode occurred in 62 patients (13.7%) with the LV lead located in the lateral, in 15 patients (16.1%) in the posterior, in 36 patients (24.6%) in the anterior, and in 20 patients (18.2%) in the apical LV lead position (Figure 1). Patients with apical LV lead location had similar incidence of VT/VF as patients with non-apical LV lead position. Therefore, this analysis is mainly focusing on patients with lateral-posterior vs. anterior LV lead location, comparing them with ICD patients as a control group. Patients with anterior LV lead locations had similar frequency of VT/VF/death (Figure 2) and VT/VF episodes (not shown) as ICD-only treated patients. The lateral or posterior LV lead location was associated with significantly lower
incidence of VT/VF or death (Figure 3A) \(P = 0.002\) or VT/VF alone compared with the anterior lead location (Figure 3B) \(P = 0.006\). These findings were similar in both ischaemic and non-ischaemic cardiomyopathy (data not shown) and also in patients with LBBB ECG pattern (Figure 4A). In patients with non-LBBB ECG pattern, the effect was similar, but did not reach statistical significance when analysing cumulative probability of VT/VF/death (Figure 4B) and VT/VF episodes \(P = 0.101\), not shown) with anterior or lateral-posterior LV lead locations.

Rapid ventricular tachyarrhythmic episodes with VT ≥ 200 b.p.m. or VF (rapid VT–VF) or death occurred less often in patients with lateral-posterior LV lead locations (3-year event rate 16%) compared with anterior LV lead locations (3-year event rate 24%, \(P = 0.014\)) (data not shown). Consistent findings were revealed when analysing VT/VF episodes requiring shock therapy or death (data not shown).

**Clinical characteristics by device type and left ventricular lead location**

The clinical characteristics of patients with anterior \(n = 146\) and lateral-posterior \(n = 541\) lead positions and the cohort with ICD-only therapy \(n = 710\) are shown in Table 1. Patients with a lateral-posterior lead location were less likely to have RBBB-QRS morphology than patients with anterior leads (11 vs. 19%, \(P = 0.006\)). The frequency of moderate or severe HF >3 months prior to enrolment, LVEF at enrolment, and baseline antiarrhythmic drug treatment were similar in the three groups.

Reverse remodelling with a decrease of LV volumes after 1 year was similar in patients with lateral-posterior and anterior LV leads. Left ventricular transverse dyssynchrony, measured as the SD of the 12-myocardial segments using speckle tracking imaging in patients with anterior and lateral-posterior LV lead location, was
similar at baseline (186 ± 68 vs. 189 ± 61 ms, \(P = 0.589\)), after 12 months (135 ± 60 vs. 148 ± 57 ms, \(P = 0.064\)), or when measuring the change of dyssynchrony after 12 months (−51 ± 86 vs. −41 ± 75 ms, \(P = 0.481\)).

**Left ventricular lead location and the risk of ventricular tachycardia/ventricular fibrillation events in multivariate analysis**

We assessed the risk of VT/VF/death, VT/VF events, rapid VT/VF events, and death in Cox analysis after adjustment for relevant clinical covariates and compared the combined lateral and posterior LV lead positions with anterior lead locations and with ICD-only treatment. The lateral or posterior lead location was associated with a significantly lower risk of first VT/VF/death episode only (HR = 0.58, \(P = 0.004\)) and VT/VF (HR = 0.57, \(P = 0.006\)) compared with anterior LV lead location, as well as when compared with ICD-only patients (Table 2). Patients with anterior lead position had a risk of first VT/VF similar to patients with ICD-only (HR = 1.04; 95% CI: 0.72–1.50; \(P = 0.837\)). Lateral or posterior LV lead locations were associated with decreased risk of rapid VT/VF (HR = 0.53, \(P = 0.018\)) when compared with anterior LV lead location.

Again, no difference of first VT/VF was found in the Cox model when comparing apical LV lead locations with non-apical locations (HR = 1.12, 95% CI: 0.70–1.81; \(P = 0.638\)).

CRT-D patients with lateral or posterior LV lead location had similar risk of all-cause mortality as patients with an anterior LV lead location. LV lead location did not modify the effects of CRT-D on all-cause mortality. However, patients with lateral or posterior LV lead placement had significantly lower risk of death when compared with patients with ICD only.

When using propensity score analysis, the results regarding the lateral-posterior vs. anterior hazard ratio (HR = 0.56, 0.39–0.82, \(P = 0.003\)) were similar to the original results.

**Recurrent ventricular tachycardia/ventricular fibrillation episodes by left ventricular lead location**

From 133 patients who had previous VT/VF events, 21 (58.3%) patients with anterior and 36 (46.8%) patients with lateral-posterior LV lead location experienced recurrent VT/VF events (defined as more than two episodes in one patient) during the follow-up.

**Discussion**

Our analysis of the impact of LV lead position on the occurrence of ventricular tachyarrhythmic events showed that the lateral-posterior LV lead position was associated with decreased risk of first VT/VF when compared with patients with ICD only and with patients with an anterior LV lead location.

It is important to stress that the majority (65%) of the anterior leads were placed at the basal part of the anterior LV wall, whereas
We recently demonstrated that apical position showed higher incidence of HF or death compared with all other LV lead locations; however, apical LV lead position is not associated with higher arrhythmia risk in this patient cohort.

There are some reports analysing the influence of LV lead location and primary outcome showing that LV lead location might not be a major determinant of response to CRT. 

There is another report from Kleemann et al., who investigated LV lead position and potential arrhythmic events in 187 patients receiving CRT (anterior lead location was found in 40 patients). They did not find significant difference in the susceptibility to arrhythmic events regarding LV lead positioning. However, they compared anterior and apical lead locations with posterior and posterior-lateral positions. The incidence of sudden cardiac death was not different among the lead positions.

Several studies reported potential pro-arrhythmic effects of CRT independent of LV lead location. During CRT, pacing the right ventricle from the endocardium and the left ventricle from the epicardium may increase transmural heterogeneity of repolarization and subsequently create QT and TDR prolongation, leading to the development of R-on-T extrasystoles and torsades de pointes. We did not observe significant differences in QRS duration changes (pre-implant vs. 1 day after implant) or in the QTc and JTc interval changes in the pre-specified subgroups (data not shown). In our study, there was no evidence for any pro-arrhythmic effects of CRT, since none of the CRT subgroups showed more VT/VF events than ICD-only patients.

Other studies suggest anti-arrhythmic effects of CRT, which might be partly explained by the CRT-induced reverse remodelling. Higgins et al. found that ICD therapy occurred less often with biventricular pacing compared with no pacing. A possible mechanism might be the reduction of heterogeneity, avoidance of pause-dependent VT, or decrease of the norepinephrine level. McSwain et al. did not find CRT to be associated with a measurable increase in the incidence of polymorphic VT or a decrease in monomorphic VT episodes analysing arrhythmic events in two CRT-D trials. We observed decreased risk of first VT/VF events in patients with lateral-posterior LV lead position, but not in patients with anterior and particularly anterior-basal lead position despite similar amount of LV reverse remodelling. The difference of the risk of arrhythmic events between anterior and lateral or posterior lead location was present after adjustment for clinical covariates. There were no significant differences between anterior and lateral-posterior LV lead locations regarding baseline LV volumes and LVEF. In both ischaemic and non-ischaemic cardiomyopathy, lateral-posterior lead locations were associated with a lower risk of VT/VF when compared with anterior LV lead location.

The reason why, at least in our study, the lateral-posterior LV lead positions bear a lower risk of ventricular tachyarrhythmic events whereas the risk remains unchanged with anterior LV pacing is difficult to explain. Although most clinical characteristics were similar with an anterior and lateral or posterior position, two baseline characteristics may have contributed to no suppression of VT/VF events with anterior LV pacing. The percentage of patients with RBBB ECG configuration was significantly higher in the anterior LV lead position compared with the lateral-posterior position. Pacing the anterior LV wall in patients with RBBB may not reduce electrical heterogeneity to the same amount as in patients with LBBB ECG morphology. This is supported by our study on the impact of QRS morphology in the MADIT-CRT trial and other trials in HF patients with mild-to-moderate HF. Not only patients with LBBB had less HF or death than patients with RBBB morphology, but also the incidence of VT/VF episodes was significantly lower in patients with LBBB morphology compared with non-LBBB patients.

The fact that patients with anterior LV lead positions had trend towards more frequent prior myocardial infarctions than patients with lateral and posterior positions might also contribute to the difference in VT/VF occurrence. Pacing the left ventricle in close proximity to scar tissue may enhance electrical instability.

We must acknowledge that the question of why VT/VF events are significantly suppressed with a lateral or posterior but not with an anterior LV lead remains partly unanswered. In addition, our earlier findings of more HF events with apical lead location do not correlate with an increase in VT/VF events.

Potential limitations of our analysis include the non-randomized fashion of this study, which might leave potential bias. We acknowledge that the groups analysed were not equal in size and we found differences in baseline clinical characteristics among the groups.

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<th>Parameter</th>
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<th>P-value</th>
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The model is adjusted for female, ischaemic, QRS ≥150 ms, LBBB, RBBB, apical LV lead location, and LVEF.

35% were positioned on the mid-ventricular anterior wall. This suggests that the LV lead positioned at the basal anterior wall does not reduce VT/VF episodes despite the reverse remodelling of the left ventricle.

We must acknowledge that the question of why VT/VF events are significantly suppressed with a lateral or posterior but not with an anterior LV lead remains partly unanswered. In addition, our earlier findings of more HF events with apical lead location do not correlate with an increase in VT/VF events.

Potential limitations of our analysis include the non-randomized fashion of this study, which might leave potential bias. We acknowledge that the groups analysed were not equal in size and we found differences in baseline clinical characteristics among the groups;
however, our findings were coherent even after adjusting for potential imbalances of baseline clinical characteristics in the Cox multivariate model. Our results might warrant conducting further randomized trials in this field.

In conclusion, our study on LV lead position and its impact on VT/VF events in MADIT-CRT showed that CRT therapy with posterior or lateral LV lead position is associated with decreased risk of ventricular arrhythmic events in comparison with an anterior LV lead location or ICD-only treated patients. However, CRT-D with anterior LV lead positions does not increase arrhythmic events, clearly indicating that CRT carries no pro-arrhythmic effects. Therefore, in CRT-D patients with LV lead placement at the anterior position, more aggressive treatment of ventricular arrhythmias might be preferable.

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