Implantable cardioverter defibrillator treatment : benefits and pitfalls in the currently indicated population

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Chapter 11

Right Ventricular Stimulation Threshold at ICD implant Predicts Device Therapy in Primary Prevention Patients with Ischemic Heart Disease

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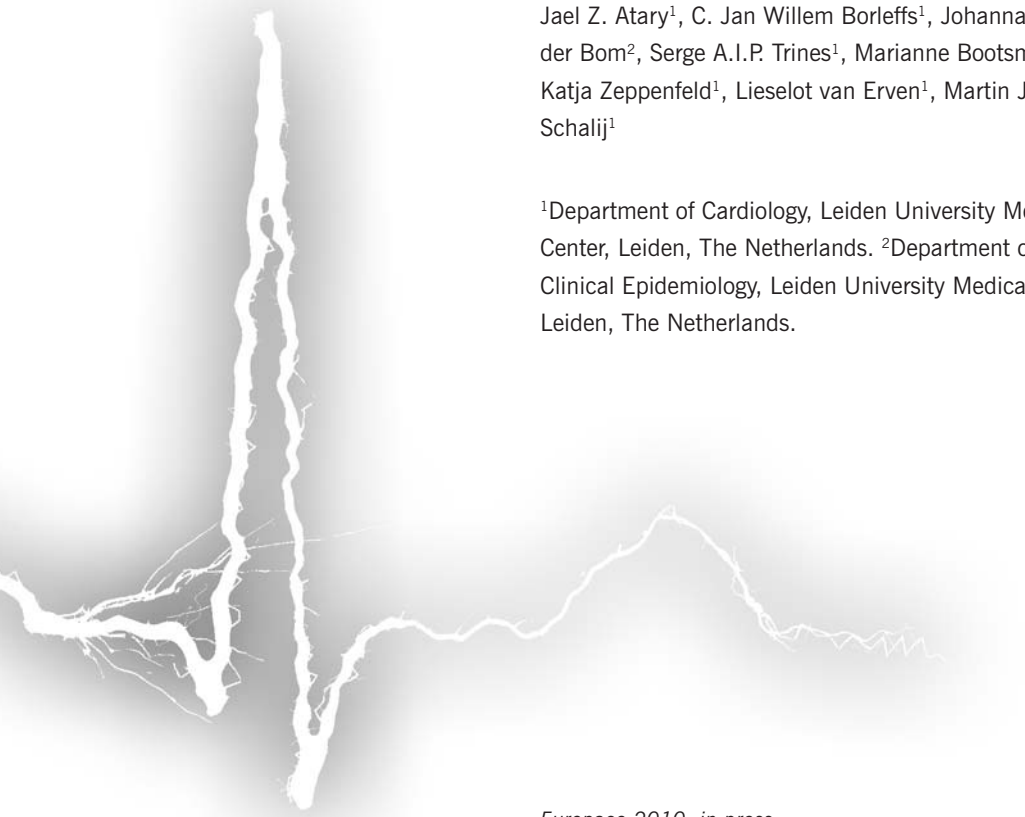

Europace 2010; in press

Abstract

Background: Myocardial excitability is known (amongst other reasons) to be related to the degree of ischemia, contractile dysfunction and heart failure. It was hypothesized that the right ventricular (RV) stimulation threshold has prognostic value with respect to the occurrence of ventricular arrhythmias (VAs) and patient survival in recipients of an implantable cardioverter defibrillator (ICD).

Methods: Ischemic heart disease patients receiving an ICD at Leiden University Medical Center as primary prevention for sudden cardiac death were included in this study. RV-thresholds were determined at ICD implant. Data was collected on VAs triggering ICD therapy and on all-cause mortality.

Results: A total of 689 consecutive patients were included (87% male, age 63±11 years, left ventricular ejection fraction [LVEF] 29±11%) and followed for a median 28 months. Post-implant RV-threshold was 0.7±0.5volt (V) at 0.5ms pulse duration. Best dichotomous separation was reached at a cut-off of 1V. During follow-up, 167(24%) patients received appropriate ICD therapy, 88(13%) had appropriate shocks and 134(19%) died. Cumulative appropriate shock incidence for patients with RV-threshold ≥1V (n=166) was 16% at 1 year, 24% at 3 years and 34% at 5 years compared to 4%, 11% and 17% for patients with a RV-threshold <1V (n=523). Adjusted Hazard Ratio (HR) of RV-threshold ≥1V was 1.8 (95% CI 1.3-2.6) for appropriate therapy, 3.3 (95%CI 2.0-5.4) for appropriate shocks and 1.6 (95%CI 1.1-2.5) for mortality.

Conclusion: The RV stimulation threshold at ICD implant has a strong independent prognostic value for the occurrence of ventricular arrhythmias triggering appropriate ICD therapy, appropriate shocks and mortality.

Introduction

Following the results of several large randomized trials, current guidelines for prevention of sudden cardiac death (SCD) advocate implantation of an implantable cardioverter defibrillator (ICD) in patients with a low left ventricular ejection fraction (LVEF) without a prior life-threatening ventricular arrhythmia.[1-5] This strategy has led to an increasing number of ICD implantations in recent years and currently, a low LVEF is still the most effective and consistent parameter used to select patients at risk of SCD.[6-9] However, the rate of ventricular arrhythmias, triggering appropriate device therapy is relatively low (35-40%)[10] in this group of patients, warranting better risk-stratification for ICD implantation.

As the structure of cardiac tissue is affected by the pathological processes of infarction and subsequent fibrosis, the electrophysiological properties of the myocardium are altered significantly.[11-13] The changes in cardiac tissue structure caused by myocardial infarction may increase the risk of ventricular arrhythmias to occur. Furthermore these changes may increase the myocardial excitability threshold.[11-13] Consequently an increased excitability threshold may reflect an increased risk of ventricular arrhythmias.

In the current study, it was hypothesized that alterations of myocardial excitability caused by ischemic heart disease and reflected in part by changes in the stimulation threshold, may be of clinical use as a risk parameter for ventricular arrhythmias in primary prevention ICD patients.

Methods

Patients and protocol

Since 1996, all patients who received an ICD system in the Leiden University Medical Center were prospectively documented in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center). Patients included in this study received an ICD between 1999 and 2007. Characteristics at baseline, data of the implant procedure, and data of all follow-up visits were recorded. For the current study, only patients with ischemic heart disease and a primary indication for defibrillator implantation were evaluated. We excluded patients with congenital structural, monogenetic heart disease, or non-ischemic heart disease for the present analysis. Furthermore, patients without a documented RV-threshold at implant were excluded for the present analysis.

Eligibility for ICD implantation in this population was based on international guidelines for the prevention of sudden cardiac death which, due to evolving guidelines may have changed over time. In the majority of patients, indication for an ICD was based on a depressed LVEF with or without non sustained ventricular tachycardia. Ischemic heart disease was defined as a history of myocardial infarction (presence of an unstable coronary

lesion on angiography and/or the elevation of cardiac biomarker(s) above normal levels), or a history of significant coronary artery disease (an angiographically estimated diameter stenosis of at least 50% in at least one coronary artery and exercise induced myocardial ischemia/perfusion defect) that resulted in coronary revascularization.

ICD implantation

All defibrillator systems used were implanted transvenously without thoracotomy. The right ventricular lead was positioned in the right ventricular apex near the septum and adjustments, if necessary, were made to achieve an optimal pacing threshold. During the implant procedure standard testing of sensing and pacing thresholds and defibrillation threshold testing was performed. Used systems were manufactured by Biotronik (Berlin, Germany), Medtronic (Minneapolis, MN, United States), Boston Scientific (Natick, MA, United States, formerly CPI, Guidant [St. Paul, MN, United States]) and St. Jude Medical/Ventritex (St. Paul, MN, United States).

In this primary prevention patient cohort, defibrillators were programmed as follows: a monitor zone was programmed in all patients to detect ventricular arrhythmias faster than 150 bpm. No therapy was programmed in this zone. Ventricular arrhythmias faster than 188 bpm were initially attempted to be terminated with two bursts of antitachycardiapacing (ATP) and, after continuation of the arrhythmia, with defibrillator shocks. In the case of a ventricular arrhythmia faster than 210 bpm, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 bpm with supraventricular tachycardia (SVT) discriminators enabled. Settings were adapted, only when clinically indicated (i.e. hemodynamic well tolerated ventricular tachycardia at high rate; ventricular tachycardia in the monitor zone). The stimulation threshold was determined by automatic decrementation of the stimulus voltage at constant pulse duration of 0,5ms after implant.

Follow-up and Endpoints

All patients visited the clinic for follow-up assessments every 3 to 6 months. Patients were followed up to February 2009. At each patient visit, a trained device specialist or cardiologist performed device interrogation and determined sensing, pacing thresholds, and lead impedance.

The primary endpoint was ventricular arrhythmia triggering appropriate defibrillator therapy (antitachycardia pacing [ATP] or shock) or appropriate shock only. Secondary endpoint was all-cause death.

ICD evaluation

All printouts were checked for appropriate and inappropriate ICD therapy (ATP or shocks). Therapies were classified as appropriate when they occurred in response to ventricular tachycardia (VT) or ventricular fibrillation (VF) and as inappropriate when triggered by

sinus or SVT, T-wave oversensing, or electrode dysfunction. Cutoff rate of the monitor or first therapy zone was noted.

Statistical Analyses

Continuous data are expressed as mean (±standard deviation) or as median (25^{th}/75^{th} percentile); dichotomous data are presented as numbers and percentages. Differences at baseline were tested for statistical significance using a Chi-square test using Yate's correction or student t-test for independent samples where appropriate. Event rates over time were analyzed by method of Kaplan-Meier with corresponding log-rank test for differences in distribution between the curves. Since follow-up was performed every three to six months, patients without data in the past six months were censored at the date of their last visit.

We used multivariable Cox regression analyses to assess the association between stimulation threshold and ventricular arrhythmias independent of an increasing number of other risk factors including age (years), gender (male/female), cardiac resynchronization therapy (yes/no), LVEF (%), history of atrial fibrillation/atrial flutter (any/none), use of amiodarone (yes/no), use of beta-blocker (yes/no), use of sotalol (yes/no), anterior MI (yes/no), lateral MI (yes/no), inferior MI (yes/no), and posterior MI (yes/no) as potential confounders. Hazard Ratio (HR) is reported with the corresponding 95% confidence interval (CI). All tests were two-sided, a p-value of < 0.05 was considered statistically significant. Missing values of all the variables were seen only for the variable atrial fibrillation/atrial flutter, in less than 0.3% (n=2/689) of all patients. The regression models were done on the patients without missing values.

A receiver operating characteristic (ROC) curve analysis was used to measure the ability of the RV-threshold to discriminate between patients that received appropriate therapy and patients that did not.

Results

Patient population

A total of 1086 consecutive ICD recipients with a primary prevention indication were registered in the electronic database system. Fifty patients (5%) were excluded due to incomplete follow-up data, 332 patients (31%) due to non-ischemic heart disease and 15 patients (1%) due to non-documented baseline RV-threshold measurements. The remaining 689 patients were included in the present analysis and followed for a median 28 months (interquartile range (IQR) 16 to 46 months).

The majority of patients (87% male, 63 ± 11 years, LVEF 29 ± 11%) had a history of myocardial infarction (84%) or coronary revascularization procedure (PCI 28%, CABG

Table 1. Baseline characteristics.

	All patients n = 689	RV threshold <1V n = 523	RV threshold ≥1V n = 166	p-value
Male sex	600 (87)	459 (88)	141 (85)	0.35
Age (years)	63 ± 11	63 ± 11	63 ± 11	0.81
Hypertension	318 (46)	239 (46)	79 (48)	0.72
Diabetes	176 (26)	130 (25)	46 (28)	0.40
Smoking	151 (22)	118 (23)	33 (20)	0.50
Prior myocardial infarction	578 (84)	436 (83)	142 (86)	0.55
Anterior†	304 (53)	237 (54)	67 (47)	0.13
Inferior†	161 (28)	112 (26)	49 (35)	0.043*
Lateral†	76 (13)	54 (12)	22 (16)	0.32
Posterior†	49 (9)	36 (8)	13 (9)	0.76
Prior PCI	192 (28)	145 (28)	47 (28)	0.92
Prior CABG	296 (43)	226 (43)	70 (42)	0.86
hypercholesterolemia	463 (67)	364 (70)	99 (60)	0.051
Family History of CAD	300 (44)	220 (42)	80 (48)	0.21
Atrial fibrillation/flutter documented	170 (25)	123 (24)	47 (28)	0.26
QRS width	126 ± 34	125 ± 34	130 ± 34	0.10
Creatinine clearance (ml/min)	78 ± 35	78 ± 32	77 ± 43	0.70
Ejection Fraction	29 ± 11	29 ± 10	29 ± 13	0.90
Cardiac resynchronization therapy	335 (49)	263 (50)	72 (43)	0.13
Medication				
Beta-blocker	425 (62)	345 (66)	80 (48)	<0.001*
Sotalol	75 (11)	47 (9)	28 (17)	0.006*
ACE-inhibitor/ATII-antagonist	580 (84)	443 (85)	137 (83)	0.54
Diuretics	502 (73)	375 (72)	127 (77)	0.27
Statin	560 (81)	426 (82)	134 (81)	0.82
Aspirin	332 (48)	255 (49)	77 (46)	0.76
Oral anticoagulation	400 (58)	304 (58)	96 (58)	1.00
Amiodarone	110 (16)	70 (13)	40 (24)	0.002*

Values are expressed as n (%) or as mean ± standard deviation. * p <0.05
†Patients could fall into more than one infarction location category (i.e. anterolateral, inferoposterior infarction).

43%)(Table 1). Median RV-threshold was 0.5V (IQR 0.5 to 0.8V) at 0.5ms pulse duration. ROC curve analysis of the RV-threshold suggested that a cutoff of 1V provided the best clinically useful dichotomous separation for assessment of the primary endpoint. A RV stimulation-threshold ≥1V was observed in 166 (24%) patients.

Baseline characteristics distributed according to RV-threshold are reported in table 1. With the exception of infarct localization (higher number of inferior wall infarctions in the >1 RV threshold group (p=0.04)) baseline characteristics were similar. Cardiac resynchronization therapy was combined with the defibrillator device in approximately 50% of cases of either group (RV-threshold <1V: 50%, RV-threshold ≥1V: 43%; p = 0.13). Concerning the use of drugs: Patients with a higher threshold more often used sotalol and amiodarone than patients with a threshold < 1V. Patients with lower threshold more often used beta-blockers. The use of other drugs was similar in both groups.

Device therapy

During follow up, a total of 1615 episodes of ventricular arrhythmia were appropriately terminated by the ICD in 24% (n=167) of patients either by ATP or by shock delivery. A total number of 278 shocks were delivered appropriately by the ICD in 13% (n=88) of patients. Furthermore, 68 patients (10%) experienced inappropriate shocks. Figure 1 shows the distribution over time of first appropriate therapy and -shocks for the total patient cohort.

Appropriate therapy during follow-up occurred more often in patients with a RV-threshold ≥1V (37%, 62 of 166 patients) when compared to patients with a RV-threshold <1V (20%, 105 of 523 patients). Furthermore, the number of patients that experienced appropriate

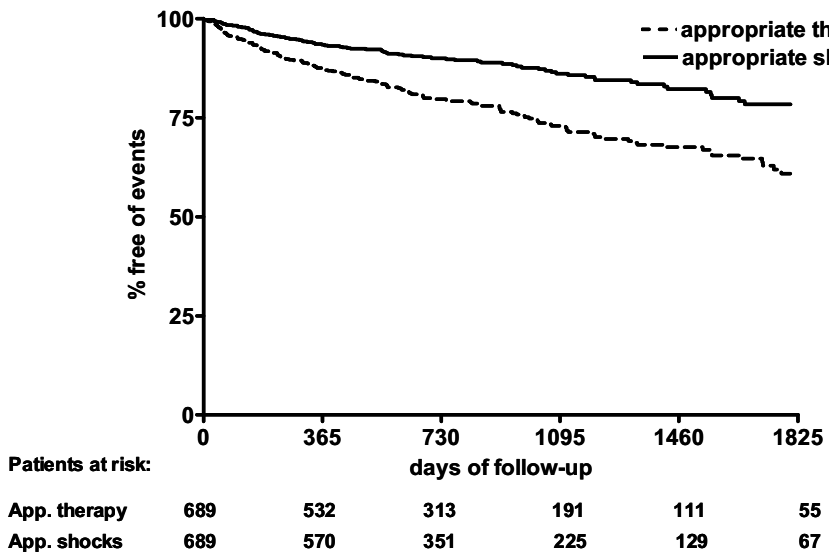

Figure 1: Kaplan-Meier Plot of Cumulative Incidence of first appropriate ICD therapy and appropriate shocks in the total study population.
App = appropriate; ICD = Implantable Cardioverter Defibrillator

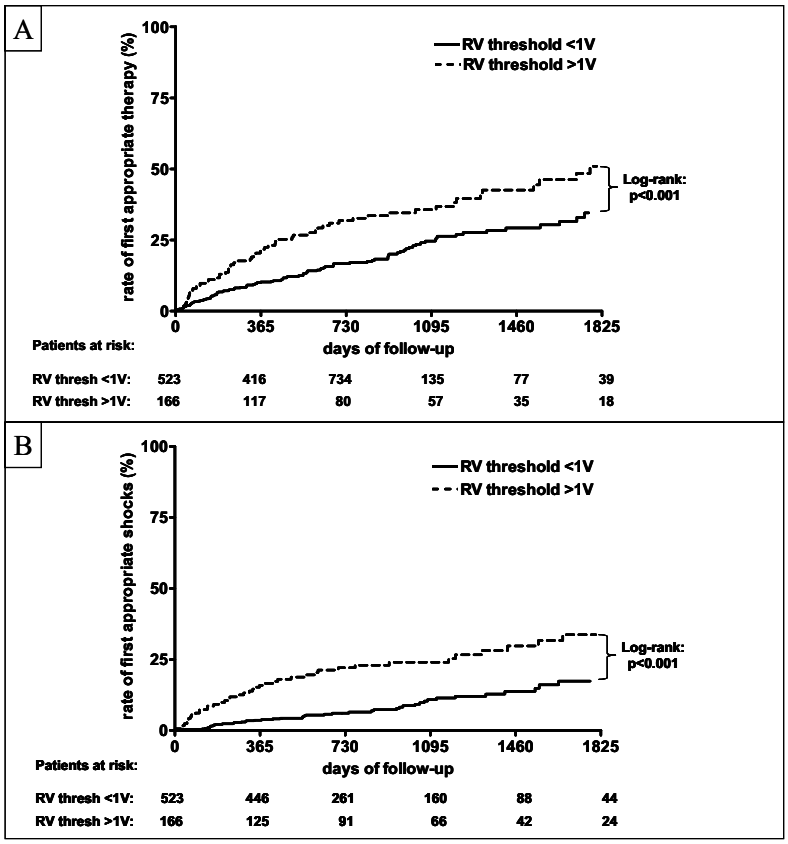

Figure 2: A. Kaplan-Meier Plot of Cumulative Incidence of first appropriate ICD therapy.
B. Kaplan-Meier Plot of Cumulative Incidence of first appropriate ICD shocks.
RV = Right Ventricular; Thresh = threshold; other abbreviations as in Figure 1.

ICD shocks was more than three times higher in the group with a RV-threshold ≥1V (26%, 43 of 166 patients) than in the group with a RV-threshold <1V (9%, 45 of 523 patients).

Figure 2 illustrates the time course of first appropriate therapy (panel A) and for first appropriate shocks (panel B) for patients with a RV-threshold <1V and a RV-threshold ≥1V. A significantly higher cumulative incidence of first ICD therapy and shocks was observed in the group with a RV-threshold ≥1V. Cumulative appropriate shock rate for patients with a RV-threshold ≥1V was 16% (95%CI 10-22%) at 1 year, 24% (95%CI 17-31%) at 3 years and 34%(95%CI 24-43%) at 5 years compared to 4% (95%CI 2-5%) at 1 year, 11% (95%CI 7-14%) at 3 years and 17% (95%CI 12-23%) at 5 years for patients with a RV-threshold <1V (log-rank p<0.001).

Post-implant RV-threshold ≥1V was found to be an independent and significant predictor of first appropriate ICD therapy (adjusted HR model 3: 2.0, 95%CI 1.4-2.9) and appropri-

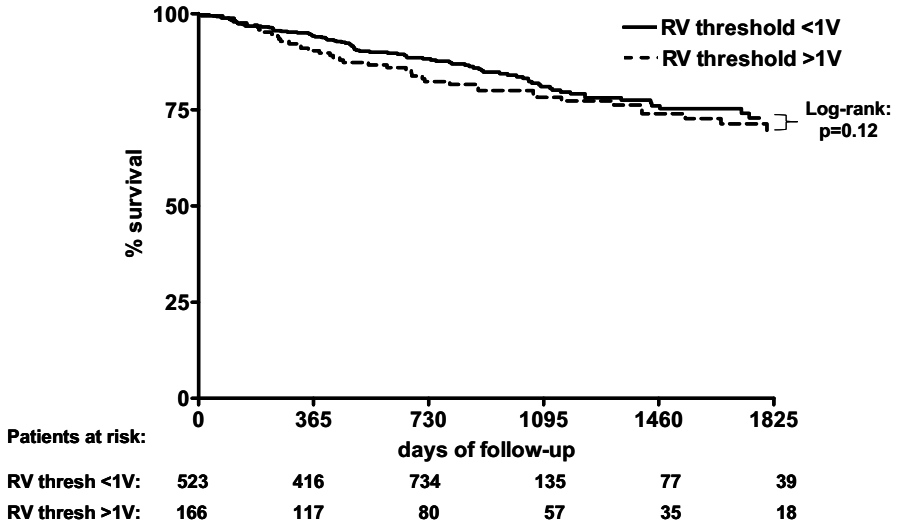

Figure 3: Kaplan-Meier Plot of Cumulative Incidence of Death.
Abbreviations as in Figure 2.

ate shocks (adjusted HR model 3: 3.3, 95%CI 2.0-5.4) after correcting for other potential confounders as listed.

As the measured RV-threshold increased, the percentage of patients experiencing appropriate shocks increased. The area under the ROC curve for RV-threshold was significantly greater than 0.5 (area under ROC curve 0.7; 95%CI 0.6-0.7; $p<0.001$). A high specificity was observed at a cut-off value around ≥1V (specificity 80% [95%CI 76-83%]) at the expense of sensitivity (49% [95%CI 38-60%]). The negative predictive value of the RV-threshold cut-off value of 1V was 91%.

Mortality

One-hundred and thirty-four (19%) patients died during the follow-up period. Total mortality in patients with a RV-threshold ≥1V (28%, 47 of 166 patients) was higher compared to the group of patients with a RV-threshold <1V (17%, 87 of 523).

Cumulative survival (%) for the two study groups is displayed in Figure 3. A trend exists toward decreased patient survival in the patient group with a RV-threshold ≥1V. Cumulative survival in this group is 90% (95%CI 86-95%) at 1 year, 78% (95%CI 72-85%) at 3 years and 70% (95%CI 61-78%) at 5 years, compared to 94% (95%CI 92-96%) at 1 year, 81% (95%CI 77-85%) at 3 years and 73% (95%CI 67-79%) at 5 years in the group with a RV-threshold <1V. The log-rank test for this difference was not statistically significant ($p=0.12$).

However, post-implant RV-threshold ≥1V was found to be an independent and significant predictor of mortality after correcting for potential confounders as listed in table 2. After

adjustment the mortality rate was 60 percent higher among those with RV-threshold ≥1V as compared to patients with RV-threshold <1V (adjusted HR model 3: 1.6, 95%CI 1.1-2.5) (Table 2).

Discussion

In this cohort of ICD treated patients with ischemic heart disease and a primary prevention indication for ICD treatment, a post-implant right ventricular stimulation threshold ≥1V was independently associated with (1) a higher occurrence of ventricular arrhythmias triggering appropriate therapy, (2) a 3-fold higher occurrence of ventricular arrhythmia triggering appropriate shocks and (3) a 60% higher risk of mortality compared to patients with a threshold <1V.

Risk stratification for SCD

LV function is an established indicator for an increased risk of SCD.[6-8] Results of a series of randomized trials have resulted in a rise in the number of ICD implantations due to a great expansion in the indications for primary prevention ICD use.[1, 3-5] However, the relatively low percentage of ICD patients who receive appropriate therapy (35-40% of patients in MADIT II and SCD-Heft)[1, 10] suggested a considerable risk heterogeneity in the low LVEF-population. This has prompted a series of studies and secondary analyses from the major ICD trials in an attempt to identify factors that can be used to stratify patients with reduced LVEF into high- and low risk subgroups.[14-22] Given the complexity and limitations of some of these proposed stratification strategies, the RV stimulation threshold is a relatively easy to use, straightforward prognostic parameter. It may assist clinicians in identifying ICD treated patients at high risk of receiving appropriate ICD therapy and a higher risk of death, therefore facilitating better evaluation of the prognosis post-implant.

Ischemic heart disease, poor excitability and arrhythmogenesis

Prior myocardial infarction leaves a residue of poorly excitable cardiac tissue. Findings from a canine study suggested that disruptions in cell-to-cell electrical continuity may contribute to slow conduction in the infarcted region.[12] In later experiments a persistent reduction of the space constant existed in chronically infarcted canine myocardium 5-8 days after persistent occlusion and reperfusion which is directly related to slow conduction velocity.[13] The investigators hypothesized that these alterations were due to a depression in action potential depolarization, an increase in internal axial resistance (by modification of the low resistance gap junctions, therefore increasing anisotropy) and an increase in the axial resistance of the extracellular space (due to the fibrotic matrix in which surviving cells are distributed within the mottled infarcted myocardium). Furthermore, wavefront-obstacle

interactions in a poorly excitable medium may reflect an arrhythmogenic process that permits formation of separate new wavelets which in vivo may lead to flutter, fibrillation, and sudden cardiac death.[23]

Arrhythmias leading to sudden cardiac death are often associated with the presence of inhomogeneities (obstacles) in cardiac tissue and reduced excitability of cardiac cells. Observations of fast arrhythmias in a medium of reduced excitability, combined with medium inhomogeneities provide a substrate for formation of multiple wavelets leading to high-frequency arrhythmias.[11, 24-26]

Device therapy and stimulation threshold

Stimulation thresholds vary immediately following implant due to lead-myocardium maturation and chronically due to changes in underlying myocardium, ischemia, infarction, metabolic state, or drug therapy.[27-30] The present findings suggest that properties of the baseline RV stimulation threshold may be used clinically as an indicator of chronic changes caused by ischemic heart disease, increasing the risk of arrhythmic events requiring ICD therapy and the risk of mortality. A high RV stimulation threshold was used as a marker of the degree of poor myocardial excitability to indirectly indicate potentially arrhythmia-prone conditions. The association was found to be independent of infarction location despite the essentially local measurement position at the RV apex, which implies that the parameter reflects not only a localized effect but rather a sum of effects. While the cumulative survival analysis was not able to demonstrate a significant difference in mortality incidence between the two study groups (Figure 3), post-implant RV-threshold ≥1V was nevertheless found to be independently associated with a 60% increased hazard of mortality after adjusting for confounders as listed in table 2. As its association with ventricular arrhythmia triggering appropriate shocks was strongest, the risk parameter may be most valuable for the estimation of fast, potentially life-threatening, arrhythmias.

Though the optimal cut-off value of the RV stimulation threshold for its best predictive value may vary slightly in post-MI patient subgroups with different baseline characteristics or for a different time point of baseline measurement, its ability to identify patient with a higher risk of arrhythmic events leading to appropriate ICD therapy and shocks will most likely not be affected. This is supported by results of the multivariate analyses that showed that the effect was independent of other predictors. Antiarrhythmic drugs such as beta-blockers tend to increase the stimulation threshold, but paradoxically in the current study were used more frequently in the group with RV-threshold <1V, suggesting a limited clinical effect. Amiodarone treatment was more prevalent in patients with RV-threshold ≥1V, but whether the type III antiarrhythmic drug has similar effects is as yet unclear. Virtually all antiarrhythmic drugs may influence the pacing threshold but usually become clinically important only at high serum concentrations.[29]

Limitations

This is a single-center follow-up study based on data of routine clinical practice. However, missing data in the enrolled population was seen in less than 1% which limited potential over- or underestimation of findings. Guidelines for ICD eligibility might have changed over time, creating a more heterogeneous patient population than in the strict controlled conditions of a clinical trial. Potentially confounding effects of these heterogeneities were limited by using the multivariable Cox analysis to assess the independent association between stimulation threshold and ventricular arrhythmias. Of note, clinical usefulness of the stimulation threshold before the implantation of the ICD still remains to be investigated. Findings of the present study would need to be confirmed by further studies and may eventually be included in a risk score for occurrence of ventricular arrhythmias. Lastly, while appropriate ICD therapy was used as a primary endpoint throughout the current study, it should be noted that it is not a perfect surrogate for life-threatening ventricular arrhythmia or SCD.

Conclusion

In ICD treated patients with a primary prevention indication and ischemic heart disease the RV stimulation threshold at implantation has an independent prognostic value for the prediction of potentially life-threatening ventricular arrhythmia and death.

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