Upper Limit of Vulnerability During Defibrillator Implantations Predicts the Occurrence of Appropriate Shock Therapy for Ventricular Fibrillation

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Background: The utility of the upper limit of vulnerability (ULV) test in patients undergoing defibrillator implantation has been reported, so the purpose of this study was to evaluate the difference in the clinical outcomes between patients with ULV ≤ 15 J or >15 J.

Methods and Results: A total of 165 patients receiving an implantable cardioverter-defibrillator underwent a vulnerability test. At the time of the implantation, we delivered a 15-J shock on the T-peak and ± 20 ms later to cover the most vulnerable part of the cardiac cycle. The clinical outcomes were prospectively analyzed. A 15-J shock induced ventricular fibrillation (VF) in 30 patients (ULV >15 J) and did not in 135 (ULV ≤ 15 J). The characteristics of the 2 groups were comparable. After a mean follow-up of 757 days, Kaplan-Meier curve analysis showed that the ULV ≤ 15 J group experienced less VF than the ULV >15 J group (log-rank $P=0.003$). The occurrence of ventricular tachycardia was similar between the 2 groups ($P=0.140$). Furthermore, the effectiveness of ATP was comparable. After adjusting for other known predictors of shock therapy, a ULV >15 J was independently associated with the occurrence of VF (hazard ratio: 6.25; 95% confidence interval: 1.913–20.40; $P<0.01$).

Conclusions: A high ULV value was associated with a high incidence of VF, which suggests that cardiac vulnerability to electrical shock may be linked to electrical instability. (*Circ J* 2014; **78**: 1606–1611)

Key Words: Defibrillation; Fibrillation; Implantable cardioverter-defibrillator; Shock; Upper limit of vulnerability

Implantable cardioverter-defibrillators (ICDs) are the standard therapy for patients at risk of sudden cardiac death (SCD).^{1–3} Defibrillation threshold (DFT) tests have traditionally been part of the ICD implantation to determine a sufficient safety margin. However, the DFT test is associated with the risk of intractable ventricular fibrillation (VF), cerebral hypoperfusion, and myocardial ischemia. The upper limit of vulnerability (ULV) is the weakest shock strength at which VF is not induced when the shock is delivered during the vulnerable period of the cardiac cycle. The correlation between the ULV and DFT has been validated in multiple studies.^{4–6} Clinically, the vulnerability test can be applied to a safety-margin strategy without inducing VF and several protocols have been reported.^{7,8}

The mechanism of cardiac vulnerability to electrical shock is still unclear, similar to the mechanism of defibrillation. The purpose of this study was to evaluate the clinical outcome and

characteristics of patients with a high ULV in an attempt to better understand the mechanisms of cardiac vulnerability.

Methods

Study Design

This was a prospective observational study in order to identify the prespecified effect of the ULV as a predictor of life-threatening arrhythmia occurrence. The primary endpoint was the occurrence of ventricular tachyarrhythmia. We prospectively reviewed 175 consecutive patients who underwent implantation or replacement of an ICD, including a cardiac resynchronization therapy device with defibrillation backup (CRT-D), from February 2009 to December 2012. All patients met the standard guidelines for primary and secondary prevention with an ICD or CRT-D device.⁹ In 165 patients, vulnerability tests were performed at the end of the implantation; 10 patients

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were excluded because of severe LV dysfunction in 4, bilateral femoral artery stenosis in 2, alternative DFT testing because of poor right ventricular (RV) sensing in 2, and rejection in 2. Patients who had the device implanted on the right side were also excluded from this study. A baseline clinical history and physical examination were obtained and 12-lead ECG was recorded in each patient. A blood test, including the brain natriuretic peptide (BNP) level, was obtained just before device implantation. Further, echocardiographic studies were performed 10 days before implantation. The left ventricular ejection fraction (LVEF) was assessed by the modified biplane Simpson's method. Medications at the time of the implantation were also noted.

Implantation Technique

All patients underwent successful implantation or replacement of the ICDs. Commercially available devices (Medtronic, Minneapolis, MN, USA; Boston Scientific, Indianapolis, IN, USA; St. Jude Medical, St. Paul, MN, USA) were used in the trial. The RV leads were all implanted in the RV apex. The choice of a single or dual coil was at the operator's discretion. Written informed consent was given by all patients prior to device implantation.

Vulnerability Test

We have reported that the 15-J ULV test with 3 coupling intervals could correctly identify high-DFT patients.¹⁰ All patients were anesthetized with propofol. First, we performed ventricular pacing with 8 pulses at a coupling interval of 500ms via the RV lead to measure the stimulus-T wave peak time of the last paced beat to determine the vulnerable period. Second, we delivered a 15-J shock on the T-wave with 3 coupling intervals (-20, 0, and +20ms from the peak of the T-wave). If VF was not induced by these procedures, a ULV ≤ 15 J was noted and the test was finished. On the other hand, if VF was induced, a ULV > 15 J was noted, and subsequently we delivered a 25-J shock for defibrillation. If the defibrillation failed, a maximal energy shock was delivered. This protocol is summarized in **Figure 1** and the details have been

described previously.¹⁰

Device Programming

The "ventricular tachycardia (VT) zone" and "VF zone" were programmed. For patients in whom VT was not expected to occur, such as those with Brugada syndrome, a single VF zone was programmed. For patients with a history of sustained monomorphic VT, their therapy zones were programmed appropriately to detect each tachycardia. For the VF zone, the devices were programmed to initially deliver the maximal shock therapy. Antitachycardia pacing (ATP) during charging was programmed. Otherwise, for the VT zone, the first therapy was 3–6 ATP sequences. A failed ATP was followed by a shock at 10J and then maximal shocks as necessary. In the high-DFT patients, the maximal shock energy was delivered first for each zone. Other specific ATP strategies were determined by the responsible physician. ATP was considered to be unsuccessful when the therapy progressed to an ICD discharge after reaching the maximal number of attempts without termination of the VT.

Follow-up

The patients were followed in our ICD follow-up dispensary every 3–4 months. Clinical evaluation and device interrogation were carried out at each follow-up visit. The treating physicians were aware of the study-group assignments. Stored intracardiac electrograms (IEGMs) were reviewed by at least 2 independent electrophysiologists using standard criteria to confirm appropriate defibrillator therapy. We evaluate the IEGMs at the time of appropriate therapy and classify the episodes into true VT or true VF based on the IEGMs. True VF was defined as a tachycardia with a cycle length < 300 ms and the standard deviation (SD) of the V-V interval > 30 ms. If inappropriate ICD therapy occurred and it was necessary to reprogram the device, the physicians could change the device programming.

Statistical Analysis

Continuous data are presented as the mean $\pm$ SD. Differences

Table 1. Baseline Characteristics of Patients Undergoing Implantation or Replacement of an ICD

	ULV ≤15 J (n=130)	ULV >15 J (n=35)	P value
Follow-up, days	775±391	717±402	0.46
Age, years	64±14	65±13	0.84
Male, n (%)	98 (75)	30 (86)	0.19
BMI, kg/m ²	22.6±3.9	22±3.1	0.13
BSA, m ²	1.63±0.19	1.65±0.19	0.69
Primary prevention, n (%)	45 (37)	19 (54)	0.22
Single coil, n (%)	12 (9)	5 (14)	0.15
NYHA class	1.8±0.4	1.7±0.5	0.52
Ischemic, n (%)	48 (37)	7 (20)	0.06
Nonischemic, n (%)	51 (39)	18 (51)	0.19
HCM, n (%)	10 (8)	1 (3)	0.22
Nonstructural disease, n (%)	17 (13)	7 (20)	0.3
Other, n (%)	4 (3)	2 (6)	0.21
CRT-D, n (%)	33 (25)	14 (40)	0.09
AF, n (%)	29 (22)	9 (26)	0.67
LVEF, %	45±17	46±18	0.27
LVDD, mm	55±10	56±12	0.28
LVDS, mm	43±14	43±14	0.29
QRS, ms	121±14	119±12	0.55
Amiodarone, n (%)	28 (21)	3 (8)	0.01
Sotalol, n (%)	11 (8)	4 (11)	0.4
β-blocker, n (%)	106 (82)	26 (74)	0.34
ACI/ARB, n (%)	89 (68)	27 (77)	0.32
BNP, pg/ml	196±77	222±90	0.22

ACI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BSA, body surface area; CRT-D, cardiac resynchronization therapy device with defibrillation backup; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVDD, left ventricular end-diastolic dimension; LVDS, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; ULV, upper limit of vulnerability.

between mean data were compared using Student's t-test for Gaussian variables. For non-Gaussian variables, the data were compared by the Mann-Whitney test for independent samples, or by Wilcoxon's nonparametric test for paired samples. Categorical data are presented as percentages, and differences in proportions were compared using chi-square analysis. The cumulative event proportions were calculated by Kaplan-Meier analysis, and the differences in the outcome were assessed by a log-rank test. Cox regression analysis was performed to assess the associations between the risk factors at enrolment and the occurrence of VF.

Adjusted hazard ratios of the prespecified predictors of ICD therapy such as age,¹¹ NYHA class,¹² LVEF,¹³ QRS duration,¹⁴ BNP concentration,¹⁵ history of atrial fibrillation (AF),^{16,17} indications for secondary prevention,¹⁸ use of amiodarone and β-blockers,¹⁹ and ULV >15J were calculated with Cox proportional hazards regression models. P<0.05 was considered statistically significant. The statistical analyses were performed using SPSS ver. 20.0 software (Chicago, IL, USA).

Results

Baseline Characteristics

In this prospective cohort study, a total of 165 patients were enrolled. The median age was 64 years, and 78% were male. The median NYHA was 1.8. With regard to the cardiac diseases, 33% had ischemic and 42% had nonischemic cardiomyopathy and 15% had nonstructural heart disease. Other cardiac

diseases were valvular heart disease, arrhythmogenic RV cardiomyopathy, vasospastic angina, and congenital heart disease. Overall, 90% of the patients received a dual-coil ICD and 10% received a single-coil ICD. The indications for ICD therapy were primary prophylaxis in 39% and secondary prophylaxis in 61% of cases. Age, sex, indication for defibrillator therapy, cardiac disease, NYHA class, history of AF, LVEF, QRS width, and BNP level were comparable between the ULV ≤15J and ULV >15J groups. The only difference between the 2 groups was the use of amiodarone, which was significantly more often prescribed in the ULV ≤15J group than in the ULV >15J group (21% vs. 8%, P<0.05) at the time of ICD implantation. A summary of the baseline characteristics is shown in **Table 1**.

Follow-up

During 757±396 days of follow-up, 12 patients died, but none was SCD. Appropriate shocks and ATPs were documented in 17 and 36 patients, respectively. Of those, 12 true VF episodes were documented. All shocks could terminate the VF on the first attempt, excluding 1 patient in the ULV ≤15J group who experienced a failure of terminating the VF with maximal shock energy. Fortunately, the VF terminated spontaneously before the third shock. After that event, we re-programmed the tilt and vector of the shock energy, and confirmed the termination of VF by DFT test.

Kaplan-Meier analysis showed that the occurrence of true VF was significantly higher in the ULV >15J group than in

the ULV ≤15J group (Figure 2, log-rank $P=0.003$), despite the occurrence of true VT being comparable between the 2 groups (Figure 3, log-rank $P=0.140$). Multivariate Cox regression analysis revealed that ULV >15J was an independent predictor of the occurrence of VF (Table 2; hazard ratio: 6.25; 95% confidence interval: 1.913–20.40; $P<0.01$). The success rate of ATP was comparable between groups (74% vs. 90%, $P=0.35$, Table 3). VT acceleration by ATP was documented in 2 patients in the ULV ≤15J group, and in none of the ULV >15J group.

Discussion

This prospective study demonstrated that ULV >15J was an independent predictor of the occurrence of VF in ICD patients. Further, the occurrence and efficacy of appropriate ATP therapy were similar between the 2 groups.

Our results imply that an increase in the ULV is associated with electrical instability of the ventricle. As far as we know, there has not been a previous clinical report directly showing the relationship between the ULV/DFT and the occurrence of ventricular arrhythmias. The mechanism of cardiac vulnerability to electrical shock is still unclear, although some reports have challenged this difficult problem. Shocks on T-waves produce strong virtual electrode polarizations (VEPs) that re-

Table 2. Cox Regression Analysis for the Occurrence of VF

	EXP	P value	95% CI
Univariate analysis			
Age	0.95	0.01	0.924–0.989
NYHA	0.88	0.53	0.715–1.885
QRS	0.82	0.80	0.311–5.022
Prior documented VF	1.08	0.75	0.873–11.33
ICM	0.92	0.56	0.512–1.764
NICM	1.08	0.66	0.438–3.133
Nonstructural heart disease	1.14	0.24	1.041–2.203
AF	1.20	0.78	0.324–4.443
LVEF	1.01	0.54	0.976–1.047
ULV >15J	4.78	<0.01	1.533–14.92
Amiodarone	0.37	0.31	0.122–1.899
β -blocker	0.49	0.26	0.149–1.659
	HR	P value	95% CI
Multivariate analysis			
Age	0.94	<0.01	0.913–0.982
ULV >15J	6.25	<0.01	1.913–20.40

CI, confidence interval; ICM, ischemic cardiomyopathy; NICM, non-ischemic cardiomyopathy; VF, ventricular fibrillation. Other abbreviations as in Table 1.

Table 3. Success Rate of ATP

	All	ULV ≤15J	ULV >15J	P value
Total, n	36	27	9	
Cycle length of true VT, ms	342±33	346±28	339±45	0.72
1st sequence success, n (%)	23 (63)	16 (59)	7 (79)	0.31
Termination with more ATP, n (%)	5 (14)	4 (15)	1 (11)	0.78
Spontaneous term, n (%)	6 (17)	5 (19)	1 (11)	0.6
Acceleration, n (%)	2 (6)	2 (7)	0	0.4
Success rate, %	77	74	90	0.35

ATP, antitachycardia pacing. Other abbreviations as in Tables 1,2.

sult in post-shock reentrant arrhythmias via a mechanism of phase singularity.²⁰ Anisotropy has been shown to be crucial for the generation of VEPs.²¹ Using a 2-dimensional bi-domain model, Mazeh et al showed that heterogeneity of the fiber angles plays an important role in the mechanisms underlying the ULV.²² On the other hand, Maharaj et al²³ conducted simulations of shock-induced VF using a 3-dimensional realistic bi-domain model and demonstrated that inclusion of transmural heterogeneity in ionic currents results in an increase in the ULV. Propagation proceeds through the post-shock excitable area in the LV free wall, while tissue rendered refractory at the shock-end recovers. Transmural dispersion of the repolarization increases the likelihood of the establishment of reentry within the LV free wall, and explains the increase in the ULV. In another report, the post-shock propagation in the LV free wall was particularly described using a similar model.²⁴ Those authors showed that a post-shock activation propagated intramurally through an excitable tunnel in the LV free wall. The fate of the post-shock activation wave might have been related to the propagated intramural graded response and the recovery from the refractory period of the epicardium. Both these reports suggest that anisotropy of the fibers and transmural heterogeneity of the ventricle play key roles in cardiac vulnerability to electrical shock. Both are well-known factors promoting wavebreaks and the generation of fibrillation.^{25–28} The results of our study may arise from these mechanisms. Furthermore, dynamic factors, including the restitution of the action potential duration and conduction velocity,^{29,30} electrotonic currents,³¹ and Ca_i cycling properties,^{32,33} have also been recognized as playing an important part in electrical instability. Those factors, together with the tissue heterogeneity, act synergistically to promote wavebreaks and may increase the ULV/DFT.

Multiple protocols of the vulnerability test have been reported. The pacing cycle length, vulnerable period, shock energy, and number of shocks necessarily differ among these reports.^{7,8,10,34} Furthermore, an automated vulnerability safety-margin system has been invented, which measures the T-wave timing using the ECG of the implanted device system.³⁵ Similar to those protocols, the high safety and feasibility of our protocol have been reported.¹⁰ Although differences in the protocol of the vulnerability test might have influenced our results, it may have been relatively small because the peak of the T-wave is in the middle of the vulnerable period in any protocol.

Clinical Implications

Our results suggest the possibility that VF events may be highly recurrent in patients with an increased ULV. In those patients, an electrical strategy including antiarrhythmic medications, β -blockers, or catheter ablation should be considered more intensively in clinical practice.

Although a multitude of clinical, laboratory and echocardiographic factors that increase the risk of a high DFT have been identified, it is difficult to predict a high DFT before ICD implantation. Our results point to being able predicting high-DFT patients through the relationship between arrhythmogenicity and vulnerability. Promising noninvasive methods for predicting SCD, such as T-wave alternans,^{36,37} may be related to the ULV/DFT. This possibility merits additional research effort.

Study Limitations

First, we had a small sample size, so additional studies are required to validate our findings using a larger number of patients in a multicenter trial. Second, the physicians were aware of the study-group assignments during follow-up, so there might have

been some bias in the prescribing of drugs that could have influenced the DFT such as amiodarone and β -blockers. Third, the difference between a single-coil and dual-coil ICD was not considered. In silico, the reaction to a shock on the T-wave differs between a single and dual coil,²⁴ which could influence the outcome, although the proportions of single and dual coils was comparable between the 2 groups.

Conclusions

An increase in the ULV might be an independent predictor of the future occurrence of VF regardless of heart disease. Cardiac vulnerability to electrical shock may be related to electrical instability.

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