Optimal Strength and Number of Shocks at Upper Limit of Vulnerability Testing Required to Predict High Defibrillation Threshold Without Inducing Ventricular Fibrillation

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Background: The upper limit of vulnerability (ULV) closely correlates with the defibrillation threshold (DFT). The aim of this study was to establish the optimal protocol for using the ULV test to predict high DFT (>20 J) without inducing ventricular fibrillation (VF).

Methods and Results: The 10-J and 15-J ULV test with 3 coupling intervals (−20, 0, and +20 ms to the peak of T-wave) and the DFT test were performed in 96 patients receiving implantable cardioverter defibrillator. ULV ≤10 J was confirmed in 47 (49%). ULV ≤15 J was confirmed in 70 (77%) of 91 patients (15-J ULV test could not be done in 5). The sensitivity and negative predictive value of both ULV >10 J and >15 J for predicting high DFT were 100%. The specificity and positive predictive value of ULV >15 J were higher than those for ULV >10 J (85% vs. 55%, 43% vs. 22%, respectively). The rate of VF inducibility for confirming ULV ≤15 J was lower than that for ULV ≤10 J (23% vs. 51%, $P<0.0001$). On analysis of single 15-J ULV test only at the peak of T-wave, VF was not induced in 79 of 91 patients, but 4 of these had high DFT.

Conclusions: The 15-J ULV test with 3 coupling intervals could correctly identify high-DFT patients and reduce the necessity for VF induction at defibrillator implantation. (*Circ J* 2013; **77**: 2490–2496)

Key Words: Defibrillation; Defibrillation threshold; Implantable cardioverter defibrillator; Upper limit of vulnerability; Ventricular fibrillation

Implantable cardioverter defibrillators (ICDs) are established as the optimal approach to prevent sudden cardiac death due to malignant ventricular arrhythmias.^{1–3} And cardiac resynchronization therapy combined with ICD (CRTD) has been indicated in patients with advanced heart failure associated with electrical and/or mechanical dyssynchrony.^{4–7} At the time of implantation, an ICD generally has to be tested to ensure that it can reliably sense ventricular fibrillation (VF) and deliver a direct-current shock with an acceptable safety margin to terminate the VF once or twice. This test, however, requires repetitive VF induction and thus has potentially life-threatening complications.^{8–11} Therefore, defibrillation testing with minimal risk is required.

The upper limit of vulnerability (ULV) is the weakest shock

strength at which VF can no longer be induced when a shock is delivered during the cardiac vulnerable period. A close correlation between the ULV and the defibrillation threshold (DFT) has been validated in some studies of humans and other animals,^{12–14} and the safety and reliability of ICD implantation and programming of the lower first-shock strength using vulnerability testing without VF induction as a surrogate for DFT assessment has been demonstrated.^{15–21}

The present study evaluated the usefulness of vulnerability testing to confirm acceptable DFT at the time of ICD implantation and to predict high DFT (>20 J). Optimal strength and number of shocks at ULV testing to predict high DFT without inducing VF were assessed.

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Vulnerability testing was started at 10J in the early enrolled 49 patients (**Figure**). The first 10J T-wave shock was delivered at the St-T peak interval after 8 right ventricular pacing beats with

Table 1. Patient Characteristics

Variable	Outcome (n=96)
Age (years)	63±14
M/F	80/16
Underlying heart disease	
Ischemic cardiomyopathy	39
Non-ischemic cardiomyopathy	41
No structural heart disease	16
LVEF (%)	43±18
CRTD	15
Indication for defibrillator	
VF or cardiac arrest	32
VT	48
Non-sustained VT	16
Anti-arrhythmic drugs	22
Amiodarone	15
Sotalol	7
Class I	4
β-blockers	70
ACEI or ARB	70

Data given as mean±SD or n. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRTD, cardiac resynchronization therapy defibrillator; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; VT, ventricular tachycardia.

CL=500ms. If VF was not induced, a subsequent 10-J shock was delivered at −20ms and +20ms to the St-T peak interval. If three 10-J shocks with different timing did not induce VF, we determined that the ULV was ≤10J, and then subsequent shocks were decreased to 5 or 1 J, and delivered in the same sequence until VF was induced. If VF was not induced by a series of induction shocks, VF was induced by alternative methods such as a high frequency burst for defibrillation testing.

Vulnerability was tested at 1-min intervals between shocks. If VF was induced, defibrillation was tested. Five minutes after VF defibrillation, the energy of the next ULV test shock was increased to 15 J and delivered in the same manner. If VF was also induced at 15 J, it was determined that the ULV was >15 J. If VF was not induced by any 15-J T-wave shocks, the ULV was determined as ≤15 J.

The aim of this study was to estimate the DFT without inducing VF. The first 10-J T-wave shocks, however, induced VF in many patients (53%) using this protocol. Therefore, we changed the first induction shock to 15 J in the next 47 patients (Figure). The protocol for the 15-J shocks was the same as that described for the 10-J shocks.

During defibrillation testing for induced VF, we evaluated only whether DFT was ≤20J or not. The first defibrillation shock was set at 20J and the second was set at the maximum delivered energy of each device. If the first 20-J shock could not defibrillate (DFT >20J), the first shock was increased by 5 J until VF was defibrillated in subsequent defibrillation tests. We defined DFT as the smallest shock strength that defibrillated twice.

In both vulnerability and defibrillation testing, shock energy was unified as delivered energy. Therefore, the programmed (charged) energy was adjusted to obtain the required delivered energy for the Guidant defibrillator (delivered energy of 10, 15 and 20J was equivalent to charged energy of 11, 17 and 23J, respectively).

If a patient became hemodynamically unstable or fell into VF several times during these tests, vulnerability and defibrillation

testing were stopped according to the decision of the operator.

Statistical Analysis

Baseline characteristics are given as mean±SD and were analyzed for statistical significance using paired t-test for continuous variables and Fisher's exact test for categorical variables. $P<0.05$ was considered statistically significant.

Results

Table 1 lists the patient characteristics. Anti-arrhythmic drugs (amiodarone, n=15; sotalol, n=7; mexiletine, n=2; pirmenol, n=1; procainamide, n=1) were given to 26 patients and β-blockers were given to 70 (73%) at the time of the procedure.

Device Implantation

At the time of ICD implantation, the mean R wave amplitude on the ventricular sensing lead was 12.6±5.11 mV (range, 5.0–29.1 mV). The stimulation threshold was <1.5 V at 0.5 ms in all patients. Dual-chamber ICDs and CRTDs were implanted in 73 and 15 patients, respectively. No major perioperative complications developed that required additional procedures.

Vulnerable Period

The mean St-T peak interval was 351±35 ms. No visible T-wave alternans developed at right ventricular pacing at 500 ms CL.

Vulnerability and Defibrillation Testing

The ULV test was started at 10J in the early enrolled 49 patients (Figure). VF was induced at 10J in 26 patients (53%; ULV >10J) and not induced in 23 (47%; ULV ≤10J). Among the 26 patients in whom VF was induced at 10-J ULV test, 21 of them underwent testing at 15J. Among these 21 patients, the 15-J ULV test induced VF in 11 patients (ULV >15J) and did not induce VF in 10 patients (10J < ULV ≤15J; Figure C). But the 15-J ULV test could not be done in 5 patients because of unstable hemodynamics (hypotension or bradycardia) after VF defibrillation. Interestingly, 2 of these 5 patients had high DFT (Figure B).

The ULV test was started at 15J in the next 47 patients (Figure). VF was induced by 15-J ULV test in 10 (21%; ULV >15J) and not induced in 37 (79%; ULV ≤15J). The ULV test at 10J was done in the 37 patients with ULV ≤15J. VF was induced by 10J ULV in 13 patients (35%; 10J < ULV ≤15J; Figure E) and VF was not induced in 24 patients (65%; ULV ≤10J).

Among the 47 patients without VF induction on the 10-J ULV test, 39 patients underwent the 5-J ULV test and VF was induced in 28 patients (5J < ULV ≤10J). The 1-J ULV test was done in 19 patients (11 patients without VF induction by the 5-J ULV test and 8 patients who did not undergo the 5-J ULV test) and VF was induced in 17 patients (1J < ULV ≤5J in 10 patients and 1J < ULV ≤10J in 7 patients). In the remaining 2 patients, high frequency burst pacing was required for inducing VF.

ULV and High DFT

In all of the 96 patients, ULV ≤10J was confirmed in 47 patients (49%; Figure A) and ULV >10J was confirmed in 49 patients (51%; Figure B–E). In total, 11 patients (11%) had high DFT (>20J) and ULV was >10J in all of these 11 patients. In 38 of 49 patients with ULV >10J, however, DFT was <20J (acceptable DFT). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of ULV >10J for predicting high DFT were 100%, 55%, 22% and 100%, respectively (Table 2).

Because 15-J ULV test could not be done in 5 patients (Figure B), the decision as to whether ULV was ≤15J or >15J

Table 2. Confirmation of ULV ≤ 10 J and ≤ 15 J, and DFT

	DFT ≤ 20 J (n)	DFT > 20 J (n)	Total (n)	SS (%)	SP (%)	PPV (%)	NPV (%)
ULV ≤ 10 J	47	0	47				
ULV > 10 J	38	11	49	100	55	22	100
Total	85	11	96				
ULV ≤ 15 J	70	0	70				
ULV > 15 J	12	9	21	100	85	43	100
Total	82	9	91†				

†Five patients could not undergo ULV testing at 15 J. DFT, defibrillation threshold; NPV, negative predictive value; PPV, positive predictive value; SP, specificity; SS, sensitivity; ULV, upper limit of vulnerability.

Table 3. ULV Test at 10 J and 15 J; VF Inducibility and High DFT (> 20 J)

	DFT ≤ 20 J (n)	DFT > 20 J (n)	Total (n)	SS (%)	SP (%)	PPV (%)	NPV (%)
10-J ULV test with 3 CI							
No VF	47	0	47				
VF	31	8	39	100	66	20	100
Total	78	8	86				
15-J ULV test with 3 CI							
No VF	47	0	47				
VF	12	9	21	100	80	42	100
Total	59	9	68				
15-J ULV test with 1 CI							
No VF	52	4	56				
VF	7	5	12	55	88	42	93
Total	59	9	68				

CI, coupling interval. Other abbreviations see in Tables 1, 2.

Table 4. Patient Characteristics vs. ULV Level

Variables	ULV ≤ 10 J (n=47)	ULV > 10 J (n=49)	P-value	ULV ≤ 15 J† (n=70)	ULV > 15 J† (n=21)	P-value
Age (years)	63±14	62±14	0.93	62±15	64±11	0.50
M/F	39/8	41/8	>0.99	58/12	18/3	>0.99
Underlying heart disease						
Ischemic cardiomyopathy	23	16	0.14	29	8	>0.99
Non-ischemic cardiomyopathy	16	25	0.10	29	9	>0.99
No structural heart disease	8	8	>0.99	12	4	>0.99
LVEF (%)	43±17	43±18	0.88	45±18	38±17	0.10
LVDd (mm)	57±9	55±14	0.38	55±10	57±16	0.51
LVDs (mm)	44±12	42±17	0.51	42±13	45±19	0.35
CRTD	4	11	0.09	8	5	>0.99
Anti-arrhythmic drugs	14	12	0.65	20	6	0.59
β -blockers	36	34	0.49	53	13	0.27
ACEI or ARB	37	33	0.25	51	14	0.17
St-T peak interval (ms)	349±34	353±35	0.58	348±33	353±37	0.55
DFT ≥ 20 J	0	11	0.0005	0	9	<0.0001

Data given as mean±SD or n. †Five patients could not undergo ULV testing at 15 J. LVDd, left ventricular end-diastolic dimension; LVDs, LV end-systolic dimension; St-T, stimulus-T wave. Other abbreviations see in Tables 1, 2.

was made in 91 patients. ULV ≤ 15 J was confirmed in 70 patients (77%; **Figure A,C,E**) and ULV > 15 J was confirmed in 21 patients (23%; **Figure D**). A high DFT was not found in patients with ULV ≤ 15 J, whereas 9 of 21 patients with ULV > 15 J had a high DFT. The sensitivity, specificity, PPV and NPV of ULV > 15 J for predicting high DFT were 100%, 85%, 43% and 100%, respectively (**Table 2**).

The rate of VF inducibility to confirm ULV ≤ 15 J was lower than that for ULV ≤ 10 J (23% vs. 51%, $P<0.0001$).

10-J ULV vs. 15-J ULV Test

A total of 86 patients underwent 10-J ULV test and VF was induced in 39 patients (45%; **Table 3**). And 68 patients underwent 15-J ULV test and VF was induced in 21 patients (31%). The

Table 5. Patient Characteristics vs. Presence of High DFT (>20 J)

Variables	DFT ≤20 J (n=85)	DFT >20 J (n=11)	P-value
Age (years)	62±14	66±11	0.35
M/F	72/13	8/3	0.39
Underlying heart disease			
Ischemic cardiomyopathy	36	3	0.52
Non-ischemic cardiomyopathy	33	8	0.05
No structural heart disease	16	0	0.20
LVEF (%)	44±18	33±17	0.05
LVDd (mm)	55±11	63±16	0.05
LVDs (mm)	42±14	51±19	0.07
CRTD	12	3	0.37
Anti-arrhythmic drugs	23	3	>0.99
β-blockers	62	8	>0.99
ACEI or ARB	60	10	0.28
St-T peak interval (ms)	349±34	367±39	0.10

Data given as mean±SD or n. Abbreviations see in Tables 1, 2, 4.

sensitivity and NPV of VF inducibility for both the 10-J and 15-J ULV test for predicting high DFT were 100%. Importantly, the specificity and PPV of VF inducibility for the 15-J ULV test were higher than those for the 10-J ULV test (Table 3). Furthermore, the rate of VF inducibility for the 15-J ULV test was lower than that for the 10-J ULV test (31% vs. 45%, $P=0.07$).

Patient Characteristics and ULV

Patient characteristics did not differ significantly between ULV ≤10J and >10J, and ULV ≤15J and >15J. Patients with high DFT, however, were more often identified with ULV >10J than ≤10J ($P=0.0005$), and with ULV >15J than ≤15J ($P<0.0001$; Table 4).

Optimal Number of Shocks at ULV Test

We delivered 3 shocks within the vulnerable period (−20, 0, +20 ms to the peak of T-wave wave). The effectiveness of the 15-J ULV test with single shock only at the peak of the T-wave was analyzed. VF was induced by single shock at 15 J in 12 of 68 patients, and a high DFT was found in 5 (42%) of these 12 patients. Among 56 patients without VF induction by the single 15-J ULV test, 4 patients (7.1%) had a high DFT. The sensitivity, specificity, PPV and NPV of VF inducibility by single 15-J shock for predicting a high DFT were 55%, 88%, 42% and 93%, respectively (Table 3). The sensitivity of single 15-J ULV test was considerably lower than that for the 15-J ULV test with 3 coupling intervals, and the NPV of single ULV test was <100%.

Defibrillation Testing and High DFT

The ICD immediately sensed VF in all patients during defibrillation testing, and the R wave was not under-sensed during VF even when sensitivity was sufficiently blunted. Induced VF could not be terminated by a first rescue 20-J shock in 11 patients (high DFT). System modification such as repositioning of the shock lead or changing of the direction of the shock wave was required in 4 of them to achieve an adequate DFT safety margin ($DFT \leq \text{maximum device output energy} - 10J$).

Prevalence of non-ischemic cardiomyopathy ($P=0.05$), lower left ventricular (LV) ejection fraction ($P=0.05$), larger LV end-diastolic and end-systolic dimension ($P=0.05$ and 0.07 , respectively) were more common in patients with high DFT but the

differences did not reach significance (Table 5).

Number of Induction Shocks and Procedure Duration

The mean number of induction T-wave shocks was 5.7 ± 2.3 ; the total duration of the test was 14.2 ± 2.4 min and the amount of time required to confirm effective defibrillation energy (twice) or acceptable ULV (≤ 10 or $\leq 15J$) was 6.2 ± 4.7 min for all patients.

Complications

Neither major complications nor prolonged unstable hemodynamics requiring inotropic agents or mechanical support were encountered in this series.

Discussion

The major findings can be summarized as follows. The ULV test at 10 and 15 J is a reliable method to identify patients with an acceptable DFT ($\leq 20J$). In patients with acceptable DFT, the rate of VF inducibility by 15-J ULV test was significantly lower than that for the 10-J ULV test. Single ULV test at the peak of T-wave sometimes underestimated the ULV. Baseline patient characteristics could not predict high DFT, but ULV could.

Based on these findings, the 15-J ULV test with 3 coupling intervals (−20, 0, and +20 ms to the peak of T-wave) was thought to be a reliable method to identify high-DFT patients without inducing VF.

Previous Reports

To date, a close correlation between the ULV and DFT at the time of defibrillator implantation has been reported.^{12–14} These findings suggest that vulnerability testing can be safely and reliably substituted for conventional defibrillation testing. Regarding device implantation without induction of VF, the 15-J ULV test was more feasible compared with the 10-J ULV test. Hwang et al showed that the ULV was $\leq 20J$ in 75% of 60 patients, and all of them had DFT $\leq 20J$.²⁴ Swerdlow et al showed that inductionless implantation is feasible in >80% of patients based on vulnerability testing at 15J.²⁵

The ASSURE study compared vulnerability safety margin testing vs. defibrillation safety margin test with a single VF induction/defibrillation;¹⁵ 14-J vulnerability testing with 3 coupling intervals was carried out in 420 patients. VF was not induced in 322 patients (76.7%) and defibrillation was achieved with 21-J shocks in 317 of them (98.4%). Among the 98 patients (23.3%) in whom VF was induced at 14-J vulnerability testing, 21 (21.4%) had DFT >21 J. The predictive value of VF inducibility for detecting high DFT in the present study was comparatively higher than that of ASSURE. The ICD device produced by Guidant was used in the ASSURE study. In the Guidant ICD system, the programmed energy of 14J is converted into 12J at shock delivery and the programmed energy of 21 J is converted into 18J at shock delivery. Vulnerability test at “12J” in the ASSURE study seems to be a reason for the relatively lower predictive value of VF inducibility for detecting high DFT.

Determination of Vulnerable Period and Underestimation of ULV

The vulnerable zone was defined as a combination of coupling intervals and the strength of the T-wave shock. It is shown as a 2-D, diamond-shaped space defined by the coupling interval on the abscissa and shock strength on the ordinate.²⁶ Swerdlow et al investigated the timing of the peak of the human vulnerable zone using right ventricular pacing at a CL of 500 ms and showed that the peak of the human vulnerable zone is narrow and includes a median of only two 20-ms intervals.¹³ They re-

ported that a 20-ms difference could cause underestimation of the ULV, and the most reliable method to define the ULV is to scan the vulnerable period of the T-wave shock within a window of 40 ms (in 20-ms steps) before and after the T-wave peak. We determined the vulnerable period as a window of 20 ms before and after the T-wave peak. Although this method might underestimate the ULV, none of the patients with either ULV ≤ 10 J or ≤ 15 J had a high DFT.

A single T-wave shock underestimates the actual ULV in the present study. In the TULIP study vulnerability test was done at a single coupling interval on the T-wave of the ECG lead II.¹⁶ Although this simplified method reduced the number of required induction shocks and the procedure time, the accuracy of measuring ULV might be reduced.

A T-wave shock was delivered after ventricular pacing at a CL of 400 ms in the TULIP study.¹⁶ Most of the ULV studies used a basic CL of 500 ms. Pacing CL might affect the width of the vulnerable period. Furthermore, a shortened pacing CL might cause beat-to-beat instability of repolarization such as T-wave alternans.

Inducibility of VF During Vulnerability Testing

All the patients in whom VF was not induced by ULV test at both 10 J and 15 J had an acceptable DFT (≤ 20 J). And in all the patients with high DFT, VF was induced by both 10-J and 15-J ULV test. The 10-J and 15-J ULV test, however, induced VF in 31 and in 12 patients with acceptable DFT, respectively. The higher delivered energy at ULV test might lower VF inducibility in patients without a high DFT, but it might involve a risk of missing a high DFT. Further detailed prospective study to identify the ideal energy at ULV test is required.

Avoidance of VF induction at defibrillator implantation is required in patients with severe heart failure. Unfortunately in these patients, VF is likely to be induced even by the vulnerability test. Patients with more advanced heart failure were more likely to have high DFT in the ASSURE study.¹⁵ In contrast, the parameters of cardiac function such as LV ejection fraction and LV dimensions did not predict high DFT in the present study, but ULV could predict high DFT. Although several studies have attempted to identify the predictive factors associated with high DFT,^{27–31} it has been difficult to identify high-DFT patients without vulnerability or defibrillation testing.

Study Limitations

The present study had some limitations. Shock energy other than 10 or 15 J might be optimal in vulnerability testing. Some patients might have a lower limit of vulnerability >10 J or >15 J. This likelihood, however, seems to be vanishingly small because none of the patients without VF induced on 10-J ULV testing had high DFT.

Without inducing VF, R-wave sensing during induced VF cannot be ensured. But in patients with sinus rhythm R-wave sensing amplitude >5 mV, R-wave sensing during VF was thought to be almost always reliable, and critical delay in detecting VF was not observed in previous reports.²¹

Determination of the vulnerable period using 12-lead ECG is essential for the ULV test. This process requires extra time and adequate experience. Recently, the usefulness of automated vulnerability test for predicting high DFT has been reported.²¹ The vulnerable period that was automatically calculated by their software was well correlated with the St-T peak interval. The 18-J vulnerability test at 4 coupling intervals could correctly detect high-DFT patients with 19% of VF inducibility. The automated ULV test may be able to increase the utility of the ULV test in clinical practice.

Multiple induction shocks might increase DFT. More than 10 multiple induction shocks were sometimes required in the present study. If these induction shocks increased the DFT, DFT might be overestimated, but we did not identify a significant dissociation between ULV and DFT.

Clinical Implications

At the time of defibrillator implantation, the 15-J ULV test with 3 coupling intervals (-20 , 0 , and $+20$ ms to the peak of T-wave) was thought to be a reliable method to detect high DFT. The vulnerable period should be determined as -20 , 0 and $+20$ ms to the St-T peak interval using multi-lead ECG during pacing at a CL of 500 ms. If any of the 3 T-wave shocks cannot induce VF, no further induction is required and implantation without VF induction can be completed.

Although the ULV test can decrease the necessity for VF induction, VF tends to be induced by the ULV test in patients with depressed LV function, in whom VF induction is hoped to be avoided. Accordingly, we have considered the indication of the ULV test as follows. For the secondary prevention of sudden cardiac death, ULV test should be done. And, if VF is induced, defibrillation safety margin should be ensured, and system revision should be done if needed. For primary prevention, the ULV test might be avoided in patients with severely depressed LV function. Importantly, the necessity of ULV test should be decided on a patient-by-patient basis.

Conclusion

The ULV test at 10 and 15 J with 3 coupling intervals (-20 , 0 , and $+20$ ms to the peak of T-wave) is a reliable method to identify patients with an acceptable DFT (≤ 20 J). Baseline patient characteristics did not predict high-DFT patients, but ULV could detect high-DFT patients. For the purpose of defibrillator implantation without inducing VF, the 15-J ULV test was more feasible than the 10-J test.

Disclosures

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