Cardiac Dysfunction and Prolonged Hemodynamic Deterioration after Implantable Cardioverter-Defibrillator Shock in Patients with Systolic Heart Failure

Running title: Toh et al.; ICD Shock and Cardiac Function

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Journal Subject Codes: [22] Ablation/ICD/surgery, [31] Echocardiography
Abstract:

Background - We investigated the acute effects of implantable cardioverter-defibrillator (ICD) shock on the myocardium, cardiac function, and hemodynamics in relation to left ventricular (LV) systolic function.

Methods and Results - We studied 50 patients who underwent ICD implantation and defibrillation threshold (DFT) testing: 25 patients with LV ejection fraction (EF) $\geq$45% and 25 patients with LVEF<45%. We measured cardiac biomarkers (creatine kinase (CK), CK-MB, myoglobin, cardiac troponin T and I, and N-terminal pro-brain natriuretic peptide). LV relaxation was assessed by global longitudinal strain rate during the isovolumetric relaxation period (SRIVR) using speckle-tracking echocardiography. Blood sampling and echocardiography were performed before, immediately after, and 5 minutes and 4 hours after DFT testing. Mean arterial pressure (MAP) was measured directly during DFT testing. Cardiac biomarkers showed no significant changes in either group. LVEF was decreased until 5 minutes after DFT testing and had recovered to the baseline at 4 hours in the reduced LVEF group ($p<0.001$), while LVEF reduction was not observed in the preserved LVEF group ($p=0.637$). Global SRIVR was decreased until 5 minutes after DFT testing and had recovered to the baseline at 4 hours in both groups (preserved-LVEF: 0.39±0.14 vs. 0.23±0.13* vs. 0.23±0.13* vs. 0.40±0.13 s$^{-1}$, *$p<0.001$ vs. baseline; reduced-LVEF: 0.15±0.05 vs. 0.08±0.04† vs. 0.09±0.04† vs. 0.15±0.05 s$^{-1}$, †$p<0.001$ vs. baseline, repeated-measures ANOVA). Time to recovery of MAP to the baseline was prolonged in the reduced LVEF group ($p<0.001$).

Conclusions - ICD shock transiently impairs cardiac function and hemodynamics especially in patients with systolic dysfunction, although significant tissue injury is not observed.

Key words: echocardiography; hemodynamics; implanted cardioverter defibrillators; ventricular fibrillation; cardiac function
Introduction

Both primary and secondary prevention trials have demonstrated that implantable cardioverter-defibrillators (ICDs) reduced mortality from sudden cardiac death due to malignant ventricular arrhythmia (1,2). Despite this survival advantage, several studies have demonstrated that ICD shock, whether it is appropriate or not, is associated with increased risk of mortality among patients with reduced left ventricular (LV) systolic function (3-6). Moreover, defibrillation threshold (DFT) testing at the time of ICD implantation sometimes invokes several critical complications, especially in patients with reduced LV contractility (7-9). These complications include transient ischemic attack or stroke, cardiopulmonary arrest due to refractory ventricular fibrillation (VF) or pulseless electrical activity, cardiogenic shock, embolic events, and death. Although ICD shock is related to short- and long-term critical complications in patients with LV systolic dysfunction, the association between electrical defibrillation and cardiac function has been investigated in only a few animal experimental studies (10-12) and there are few clinical data regarding the effect of ICD shock on cardiac function and its association with tissue damage and subsequent hemodynamic change in patients with systolic heart failure.

Recently, strain and strain rate (SR) derived from 2-dimensional speckle-tracking echocardiography have enabled us to quantify myocardial deformation without angle dependency (13), and global SR during the isovolumetric relaxation period (SRIVR) provides more accurate assessment of LV relaxation than conventional parameters (14). In this study, we investigated the effects and mechanisms of ICD shock on myocardial functions by echocardiography, direct central arterial pressure measurement, and measurement of cardiac biomarkers with respect to LV systolic function.
Methods

Study sample

The study population consisted of 50 consecutive patients who were admitted to our institution to undergo transvenous ICD implantation and DFT testing between April 2008 and December 2009. The underlying heart diseases were ischemic cardiomyopathy in 13 patients, dilated cardiomyopathy in 9 patients, hypertrophic cardiomyopathy in 6 patients, cardiac sarcoidosis in 3 patients, and idiopathic ventricular fibrillation in 19 patients. The patients were divided into two groups according to preoperative LV ejection fraction (EF): a preserved LVEF group of patients with LVEF $\geq 45\%$ and a reduced LVEF group of patients with LVEF $< 45\%$ (15,16). All of the tests that were performed were approved by the medical ethical review committees of Okayama University Hospital. Informed consent was obtained from each patient.

Study protocol

The study protocol is summarized in Figure 1. ICD implantation was performed using local anesthesia combined with sedation only for DFT testing. At the end of ICD implantation, we induced VF by T-wave shock after monitored anesthesia care using a bolus injection of thiopental (4 mg/kg). For minimizing change in loading condition during monitored anesthesia care, saline infusion rate was set at 0.33 ml/min. Defibrillation shock was fixed to 20 joules and automatically delivered from the ICD after detection of VF. We repeated the same protocol 5 minutes after the first DFT testing and did not use a step-down protocol in any of the subjects. We performed venous blood sampling and echocardiographic examination before, immediately after, and 5 minutes and 4 hours after two consecutive DFT testing. Vascular access was achieved through the femoral artery, and central arterial pressure was continuously monitored in the ascending aorta during DFT testing.
Analysis of laboratory data

To evaluate myocardial injury by DFT testing, we measured cardiac biomarkers: serum levels of creatine phosphokinase (CK), CK-MB fraction (CK-MB), myoglobin, cardiac troponin T (cTNT), cardiac troponin I (cTNI), and N-terminal pro-brain natriuretic peptide (NT-proBNP). CK activity was measured with CicaLiquid reagents (Kanto Chemical, Tokyo, Japan) on a Bio Majaestry analyzer (Nihondenshi, Tokyo, Japan) with upper normal limits of 287 U/L for males and 163 U/L for females. The CK-MB activity was determined using a commercially available immuno-inhibition assay (CicaLiquid CK-MB, Kanto Chemical, Tokyo, Japan) with an upper normal limit of 25 U/L. Myoglobin was measured using a commercially available radioimmunoassay (Daiicchi III, TFB Inc., Tokyo, Japan) with an upper normal limit of 60 ng/ml. cTNT was assessed by an electrochemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany). The lower limit of detection was 0.01 ng/ml and the discrimination level used for myocardial injury was 0.10 ng/ml. cTNI was determined using a two-site immunoenzymatic assay (Access AccuTnI, Beckman Coulter, CA, USA) with an upper normal limit of 0.50 ng/ml. NT-proBNP was measured using an electrochemiluminescence immunoassay on an Elecsys 1010 analyzer (Roche Diagnostics, Mannheim, Germany) with an upper normal limit of 125 pg/ml.

Analysis of echocardiographic data

All echocardiographic studies were performed with Vivid 7 (GE Healthcare, Milwaukee, WI). We measured LV volume and EF according to the recommendations of the American Society of Echocardiography (17). From mitral flow velocity pattern, we measured peak mitral inflow early diastolic and atrial filling (E and A) velocities and the E wave deceleration time. Peak early diastolic mitral annular velocities were measured at septal and lateral mitral annular sites by
pulsed tissue Doppler imaging and then the average values were used for analysis (e’ velocity). E/e’ was calculated as a surrogate for LV filling pressure. Longitudinal SR analysis was performed using the speckle-tracking system in an EchoPAC PC (GE, Milwaukee, WI) as previously described (14). In brief, after tracing the entire LV endocardium, the displacement of speckles of the myocardium was analyzed automatically through the cardiac cycle in the speckle-tracking system. Then the SR curve of each segment was displayed and approved. LV global SR was calculated with the use of the entire length of the LV myocardium, and peak global SR during the isovolumetric relaxation period was defined as global SR\textsubscript{IVR}. The global SR\textsubscript{IVR} values from the 3 apical views were averaged and used for analysis. All echocardiographic measurements and analysis were performed offline by an experienced investigator (N.T.) with no clinical information on the patients.

The following measures were taken to obtain adequate echocardiographic images for analysis promptly and maintain operative field sterility: 1) we enrolled only patients with optimal echocardiographic images, 2) the transducer position was fixed at apical impulse for minimizing loss of time and maintaining sterility, because an apical window was sufficient for acquiring all data as mentioned above, and 3) the operative field and catheter insertion site were carefully covered with sterile surgical drapes.

**Analysis of hemodynamic data**

Continuous measurements of systolic and diastolic arterial pressures were performed at the ascending aorta during DFT testing. Mean arterial pressure (MAP) was obtained by direct integration of the blood pressure curve. Time to reach baseline MAP was defined as the interval between the second ICD shock and the time MAP returned again.
Statistical analysis

Data are expressed as mean values ± standard deviation. Unpaired t test was used to detect statistical differences for continuous variables with normality of data distributions between two groups, and categorical data and percentage frequencies were analyzed by Fisher’s exact test. Serial data (before and after the procedure) were analyzed by linear mixed effects models, and two-way repeated-measures ANOVA was conducted. If a significant difference between 2 groups or among 4 time points was detected by a global test, ad hoc multiple comparison was performed. Central arterial pressures before and after DFT testing were compared by paired t test. Ten subjects were randomly selected from each group and analyzed blindly by two independent investigators (N.T. and H.O.) to assess intraclass correlation coefficient for evaluating reproducibility for longitudinal SR measurements. A value of p < 0.05 was considered to be statistically significant. All analyses were performed with JMP 9 (SAS Institute, Cary, NC).

Results

Clinical characteristics

Table 1 shows the characteristics of the study population. There were no significant differences in age, gender, and body surface area between the two groups. New York Heart Association functional class was higher in the reduced LVEF group than in the preserved LVEF group. The reduced LVEF group more frequently included ischemic and dilated cardiomyopathies than the preserved LVEF group. Idiopathic ventricular fibrillation was the major cause of ICD implantation in the preserved LVEF group. Concomitant cardiovascular drug therapy was common in the reduced LVEF group.

Serial changes of serum markers before and after DFT testing

Serial changes of serum markers are listed in Table 2. At baseline, there were no differences in
biomarkers except for NT-proBNP between the groups before DFT testing. Baseline NT-proBNP was significantly higher in the reduced LVEF group than in the preserved LVEF group (p < 0.002).

All patients received two consecutive 20-joule shocks with a 5-minute interval. All induced VFs were successfully terminated by the first 20-joule shock, and shocks neither higher nor lower than 20 joules were delivered. Although, by repeated-measures ANOVA, the response to DFT testing in CK-MB and NT-proBNP differed between the groups, DFT testing did not cause significant changes in CK, CK-MB, myoglobin, and NT-proBNP in either group. DFT testing slightly increased cTNT in the preserved LVEF group and cTNI in the reduced LVEF group, but these values did not exceed the normal ranges (Table 2).

**Serial changes of echocardiographic parameters before and after DFT testing**

Serial changes of echocardiographic parameters in both groups are demonstrated in Table 3. In baseline echocardiographic data, LV end-diastolic volume and end-systolic volume were significantly greater in the reduced LVEF group (both p < 0.001). Parameters of transmitral flow showed no significant differences between the two groups. The e’ velocity was significantly lower and E/e’ was greater in the reduced LVEF group than those in the preserved LVEF group (p < 0.001 and p = 0.042, respectively). Global SRIVR was less in the reduced LVEF group than in the preserved LVEF group (p < 0.001).

By repeated-measures ANOVA, the response to DFT testing differed between the groups in all echocardiographic parameters listed in Table 3. In the reduced LVEF group, LVEF decreased immediately after DFT testing and had recovered to the baseline level 4 hours after the test, while it showed no significant changes after DFT testing in the preserved LVEF group (Table 3). Among Doppler parameters, e’ velocity showed modest decreases immediately after
DFT testing in both groups, but the differences were not statistically significant. Reduction of global SRIVR was sustained until 5 minutes after DFT testing and had recovered to the baseline level at 4 hours in both groups (Figure 2 and 3).

Intraclass correlation coefficients for longitudinal global SR for comparison between the 2 observers and among 1 observer were 0.950 (p < 0.001) and 0.971 (p <0.001), respectively.

Changes of central arterial pressure before and after DFT testing

After monitored anesthesia care, although systolic and diastolic blood pressures were significantly decreased in both groups (preserved LVEF group: 127 ± 14 vs. 121 ± 13, p = 0.004, 74 ± 12 vs. 67 ± 8 mmHg, p = 0.016; reduced LVEF group: 112 ± 18 vs. 103 ± 18, p = 0.013, 66 ± 8 vs. 58 ± 9 mmHg, p = 0.005), decrease in heart rate was not significant (preserved LVEF group: 63 ± 9 vs. 61 ± 8 bpm, p = 0.092; reduced LVEF group: 70 ± 10 vs. 68 ± 13 bpm, p = 0.337).

Central arterial pressures before and after DFT testing are shown in Table 4. The reduced LVEF group had lower systolic and diastolic arterial pressures and MAP than those in the preserved LVEF group before DFT testing. DFT testing caused transient, yet significant, decreases in systolic and diastolic arterial pressures and MAP in both groups. Time to recovery of MAP to the baseline level was more prolonged in the reduced LVEF group than in the preserved LVEF group (43 ± 24 vs. 12 ± 10 sec, p < 0.001).

Discussion

In the present study, we firstly found that ICD shock caused LV systolic dysfunction in patients with reduced LVEF and also LV diastolic dysfunction irrespective of baseline LVEF in the clinical setting. Impaired ventricular relaxation lasted at least 5 minutes after ICD shock in both
groups as demonstrated by sustained reduction of global SR_{IVR}. However, serum cardiac markers were unaffected or did not exceed normal values at any time point in either group, suggesting that transient ventricular dysfunction was not a result of myocardial injury. Moreover, time to recovery of central arterial pressure to the baseline level was significantly longer in patients with reduced LVEF than in patients with preserved LVEF.

**Effect of ICD shock on cardiac function**

The impact of internal cardioversion on LV systolic function remains controversial. Some previous echocardiographic studies showed that LV systolic function was unaffected after internal cardioversion during ICD implantation (18,19), but LV systolic function was assessed by LVEF from the apical 4-chamber view only or LV fractional area change from a single plane transgastric short-axis view using transesophageal echocardiography. In contrast, a previous animal study demonstrated that contractile dysfunction was provoked after defibrillator shock given directly to the myocardium (10). In the present study, LV systolic dysfunction after DFT testing was limited in patients with reduced LVEF and this result does not contradict previous observations that cardiac output was deteriorated only in patients with low LVEF after inductions of ICD shock (20,21).

In contrast to the effect of DFT testing on systolic function, DFT testing promoted transient diastolic dysfunction in all patients irrespective of preoperative LVEF in the present study. Experimental studies revealed that the time constant of LV relaxation was prolonged and LV end-diastolic pressure was increased after direct current shock even in normal hearts (11,12). These results indicated that the electrical defibrillation impaired LV relaxation and deteriorated LV diastolic function. This is the first study demonstrating that defibrillation shock induced transient LV diastolic dysfunction in humans. We confirmed that reduced global SR_{IVR}, which is
a new surrogate of LV relaxation, was sustained for at least 5 minutes after DFT testing and had recovered to the baseline level 4 hours after DFT testing in both groups, indicating that ICD shock impaired LV relaxation but that it was temporal in the clinical setting. Transient impairment of both systolic and diastolic LV dysfunctions by DFT testing in patients with reduced LVEF is associated with hemodynamic instability. Prolonged recovery of central arterial pressure may have a pivotal role in the occurrence of DFT testing-related critical complications (8).

The mechanisms of cardiac dysfunction after ICD shock remain uncertain. Serum cardiac biomarkers were not increased by DFT testing and it was likely that significant myocardial injury did not occur. One possible explanation is abnormal Ca$^{2+}$ transient induced by defibrillation (22-24). It has been reported that electrical shock prolonged the time decay of the Ca$^{2+}$ transient and elevated diastolic intracellular calcium concentration even in normal myocytes (23) and that abnormal Ca$^{2+}$ handling leads to impairment of LV relaxation (22,25). Also, excessive intracellular Ca$^{2+}$ overload results in contractile dysfunction (26). Since intracellular Ca$^{2+}$ handling alters and diastolic intracellular Ca$^{2+}$ concentration elevates in the failing heart (25,27), defibrillation shock could transiently induce both diastolic and systolic dysfunctions in patients with reduced LVEF. Another possible mechanism is occurrence of myocardial interstitial edema after defibrillation shock. Myocardial interstitial edema is a characteristic morphological change after ICD shock (12) and is associated with reduced LV distensibility and impaired relaxation (28). However, myocardial edema is thought to be a result of thermal myocardial injury after ICD shock (12) and we could not demonstrate either myocardial edema by echocardiography or tissue injury determined by biological markers in the present study. Thus, the impact of myocardial interstitial edema on cardiac dysfunction remains obscure in this study.
Implications of echocardiographic parameters

Although both global \( \text{SR}_{IVR} \) and \( e' \) velocity reflect the property of LV relaxation, statistically significant reduction of \( e' \) velocity was not observed after DFT testing, and decreased global \( \text{SR}_{IVR} \) was sustained for 5 minutes after DFT testing. This discrepancy may result from the fact that global \( \text{SR}_{IVR} \) is a measurement of whole heart motion, whereas \( e' \) velocity is a localized measurement of mitral annular movement. The present results also support the superiority of global \( \text{SR}_{IVR} \) to \( e' \) velocity for assessing LV relaxation.

Study Limitations

First, since the number of subjects in this study was limited, further research is needed to obtain a definitive conclusion regarding the association of ICD shock and subsequent cardiac dysfunction. Second, we cannot exclude the possibility of an effect of VF itself on cardiac dysfunction. Even though the duration of VF is short, VF causes cardiac dysfunction as a result of reduced blood flow and tissue perfusion. However, previous experimental studies have demonstrated that electrical defibrillation itself also impaired intracellular \( \text{Ca}^{2+} \) dynamics and that it was associated with cardiac dysfunction (22-24), and a previous clinical study has also proved that ICD shock strength, not VF, was most relevant to reduction in cardiac index (29). Thus, we believe that DFT testing after induced VF played a crucial role in cardiac dysfunction observed in this study. Third, all patients were under monitored anesthesia care during DFT testing and awakened during post-procedural investigation. However, the effect of anesthesia on the results might be small, because echocardiographic parameters before DFT testing were comparable to those at 4 hours after DFT testing even though these data were acquired during sedated and waking periods, respectively. Central arterial pressure measurements were performed during the sedated period in all subjects. Fundamentally, it is impossible to deliver
appropriate ICD shock during the waking period in patients. Fourth, because DFT testing is required in all patients undergoing ICD implantation in our institution, we were not able to include a control group with monitored anesthesia care and without DFT testing in this study, although the inclusion of such a control group would be helpful for assessing the impact of anesthesia on cardiac function and hemodynamics. Fifth, we cannot foreclose the possibility that high prevalence of antihypertensive agent usage was associated with prolonged recovery of central arterial pressure in patients with reduced LVEF. Lastly, it is uncertain whether the current results can properly explain the mechanism of the adverse effect on long-term outcome after ICD shock. However, the present results showed that ICD shock caused cardiac dysfunction at least temporarily and that subsequent hemodynamic instability, especially in patients with reduced LVEF, has the potential for worsening the clinical outcome after ICD shock in patients with heart failure.

**Conclusions**

ICD shock caused LV systolic dysfunction in patients with reduced LVEF and also LV diastolic dysfunction irrespective of LVEF, although tissue injury determined by serum cardiac biomarkers was not observed. Furthermore, in patients with reduced LVEF, hemodynamic instability was prolonged. Therefore, even though the effects of ICD shock on cardiac function and hemodynamics are transient, clinicians should select an optimal medical therapy for avoiding ICD shock, and the necessity of DFT testing should be reconsidered, especially in patients with reduced LVEF.

**Acknowledgments:** The authors thank Yasuharu Tanabe, RDCS and Nobuhisa Watanabe, RDCS for obtaining the excellent echocardiographic data and Yuuki Takenaka, MT for valuable assistance with DFT testing.
Conflict of Interest Disclosures: None

References:


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Table 1. Baseline and Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preserved LVEF (n=25)</th>
<th>Reduced LVEF (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>55 ± 13</td>
<td>57 ± 14</td>
<td>0.661</td>
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<tr>
<td>Gender, male</td>
<td>20 (80)</td>
<td>15 (60)</td>
<td>0.217</td>
</tr>
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<td>Body surface area, m²</td>
<td>1.72 ± 0.20</td>
<td>1.66 ± 0.19</td>
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<td>NYHA functional class</td>
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<td>&lt;0.001</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>NYHA II</td>
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<td>20</td>
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</tr>
<tr>
<td>NYHA III</td>
<td>0</td>
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<td></td>
</tr>
<tr>
<td>Cardiac disease history</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>1 (4)</td>
<td>12 (48)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>0 (0)</td>
<td>9 (36)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>5 (20)</td>
<td>1 (4)</td>
<td>0.190</td>
</tr>
<tr>
<td>Cardiac sarcoidosis</td>
<td>0 (0)</td>
<td>3 (12)</td>
<td>0.235</td>
</tr>
<tr>
<td>Idiopathic ventricular fibrillation</td>
<td>19 (76)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concomitant cardiovascular therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors/ ARBs</td>
<td>6</td>
<td>19</td>
<td>0.001</td>
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<tr>
<td>β-Blockers</td>
<td>9</td>
<td>23</td>
<td>&lt;0.001</td>
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<td>0.609</td>
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<tr>
<td>Diuretics</td>
<td>3</td>
<td>23</td>
<td>&lt;0.001</td>
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<tr>
<td>Class III antiarrhythmic agent</td>
<td>9</td>
<td>5</td>
<td>0.345</td>
</tr>
<tr>
<td>Statins</td>
<td>3</td>
<td>5</td>
<td>0.702</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD.
LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers.
### Table 2. Serial Changes of Cardiac Biomarkers Before and After DFT testing

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>Immediately after</th>
<th>5 minutes after</th>
<th>4 hours after</th>
<th>Preserved LVEF vs Reduced LVEF (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CK, U/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preserved LVEF</td>
<td>102 ± 59</td>
<td>101 ± 56</td>
<td>101 ± 56</td>
<td>101 ± 50</td>
<td>0.154</td>
</tr>
<tr>
<td>Reduced LVEF</td>
<td>89 ± 59</td>
<td>88 ± 58</td>
<td>87 ± 58</td>
<td>94 ± 49</td>
<td></td>
</tr>
<tr>
<td><strong>CK-MB, U/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preserved LVEF</td>
<td>8 ± 2</td>
<td>8 ± 2</td>
<td>8 ± 2</td>
<td>8 ± 2</td>
<td>0.004</td>
</tr>
<tr>
<td>Reduced LVEF</td>
<td>9 ± 3</td>
<td>9 ± 3</td>
<td>9 ± 2</td>
<td>9 ± 3</td>
<td></td>
</tr>
<tr>
<td><strong>Myoglobin, ng/mL</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Preserved LVEF</td>
<td>62 ± 32</td>
<td>62 ± 33</td>
<td>61 ± 33</td>
<td>60 ± 35</td>
<td>0.830</td>
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<tr>
<td>Reduced LVEF</td>
<td>62 ± 22</td>
<td>62 ± 19</td>
<td>61 ± 19</td>
<td>62 ± 19</td>
<td></td>
</tr>
<tr>
<td><strong>cTNT, ng/mL</strong></td>
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<td></td>
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</tr>
<tr>
<td>Preserved LVEF</td>
<td>0.02 ± 0.02</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td>0.05 ± 0.03 *</td>
<td>0.005</td>
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<tr>
<td>Reduced LVEF</td>
<td>0.04 ± 0.03</td>
<td>0.04 ± 0.03</td>
<td>0.04 ± 0.03</td>
<td>0.05 ± 0.03</td>
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<tr>
<td><strong>cTNI, ng/mL</strong></td>
<td></td>
<td></td>
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<tr>
<td>Preserved LVEF</td>
<td>0.14 ± 0.09</td>
<td>0.15 ± 0.11</td>
<td>0.15 ± 0.10</td>
<td>0.23 ± 0.16</td>
<td>0.017</td>
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<tr>
<td>Reduced LVEF</td>
<td>0.17 ± 0.11</td>
<td>0.19 ± 0.12</td>
<td>0.18 ± 0.12</td>
<td>0.29 ± 0.16 *</td>
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</tr>
<tr>
<td><strong>NT-proBNP, pg/mL</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Preserved LVEF</td>
<td>214 ± 325</td>
<td>206 ± 312</td>
<td>212 ± 327</td>
<td>190 ± 297</td>
<td>&lt;0.001</td>
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<tr>
<td>Reduced LVEF</td>
<td>1491 ± 1811</td>
<td>1519 ± 1845</td>
<td>1501 ± 1820</td>
<td>1531 ± 1761</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

*P < 0.05 vs. variables at baseline (repeated-measures ANOVA, post hoc analysis).

DFT = defibrillation threshold; CK = creatine phosphokinase; cTNT = cardiac troponin T; cTNI = cardiac troponin I; NT-proBNP = N-terminal pro-brain natriuretic peptide; other abbreviations as in Table 1.
Table 3. Serial Changes of Echocardiographic Parameters Before and After DFT testing

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>Immediately after</th>
<th>5 minutes after</th>
<th>4 hours after</th>
<th>Preserved LVEF vs Reduced LVEF (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVEF, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preserved LVEF</td>
<td>61 ± 6</td>
<td>61 ± 7</td>
<td>61 ± 7</td>
<td>62 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduced LVEF</td>
<td>27 ± 9</td>
<td>23 ± 9 *</td>
<td>22 ± 8 *</td>
<td>27 ± 9</td>
<td></td>
</tr>
<tr>
<td><strong>E/A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preserved LVEF</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduced LVEF</td>
<td>0.9 ± 0.8</td>
<td>0.8 ± 0.6</td>
<td>0.8 ± 0.6</td>
<td>0.8 ± 0.6</td>
<td></td>
</tr>
<tr>
<td><strong>E-wave deceleration time, ms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preserved LVEF</td>
<td>246 ± 54</td>
<td>230 ± 48</td>
<td>238 ± 50</td>
<td>244 ± 53</td>
<td>0.030</td>
</tr>
<tr>
<td>Reduced LVEF</td>
<td>272 ± 82</td>
<td>244 ± 71</td>
<td>259 ± 66</td>
<td>268 ± 85</td>
<td></td>
</tr>
<tr>
<td><strong>Peak e' velocity, cm/s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preserved LVEF</td>
<td>7.3 ± 3.8</td>
<td>5.1 ± 3.4</td>
<td>6.6 ± 4.6</td>
<td>6.7 ± 4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduced LVEF</td>
<td>3.4 ± 1.9</td>
<td>2.8 ± 1.6</td>
<td>3.2 ± 2.0</td>
<td>3.6 ± 2.5</td>
<td></td>
</tr>
<tr>
<td><strong>E/e'</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preserved LVEF</td>
<td>9.6 ± 5.2</td>
<td>13.1 ± 8.0</td>
<td>10.2 ± 6.8</td>
<td>9.2 ± 4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduced LVEF</td>
<td>14.0 ± 8.5</td>
<td>16.8 ± 9.4</td>
<td>14.5 ± 10.0</td>
<td>13.0 ± 8.9</td>
<td></td>
</tr>
<tr>
<td><strong>Global SR_{IVR}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preserved LVEF</td>
<td>0.39 ± 0.14</td>
<td>0.23 ± 0.13 †</td>
<td>0.23 ± 0.13 †</td>
<td>0.40 ± 0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduced LVEF</td>
<td>0.15 ± 0.05</td>
<td>0.08 ± 0.04 †</td>
<td>0.09 ± 0.04 †</td>
<td>0.15 ± 0.05</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

*P < 0.05 vs. variables at baseline (repeated-measures ANOVA, post hoc analysis); †P < 0.01 vs. variables at baseline (repeated-measures ANOVA, post hoc analysis).

LV = left ventricular; e’ = early diastolic mitral annular velocity; SR_{IVR} = strain rate during the isovolumetric relaxation period; other abbreviations as in Table 1 and 2.
Table 4. Central Arterial Pressure Measurements and Recovery Time of MAP After DFT testing

<table>
<thead>
<tr>
<th></th>
<th>Preserved LVEF</th>
<th>Reduced LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline systolic arterial pressure, mmHg</td>
<td>121 ± 13</td>
<td>103 ± 18 *</td>
</tr>
<tr>
<td>Baseline diastolic arterial pressure, mmHg</td>
<td>67 ± 8</td>
<td>58 ± 9 *</td>
</tr>
<tr>
<td>Baseline MAP, mmHg</td>
<td>85 ± 10</td>
<td>73 ± 11 *</td>
</tr>
<tr>
<td>Systolic arterial pressure immediately after DFT testing, mmHg</td>
<td>87 ± 15 †</td>
<td>67 ± 22 *†</td>
</tr>
<tr>
<td>Diastolic arterial pressure immediately after DFT testing, mmHg</td>
<td>39 ± 8 †</td>
<td>33 ± 7 *†</td>
</tr>
<tr>
<td>MAP immediately after DFT testing, mmHg</td>
<td>55 ± 9 †</td>
<td>44 ± 11 *†</td>
</tr>
<tr>
<td>Time to reach baseline MAP, sec</td>
<td>12 ± 10</td>
<td>43 ± 24 *</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

*P < 0.01 vs. preserved LVEF; †P < 0.01 vs. variables at baseline.

MAP = mean arterial pressure; other abbreviations as in Table 1 and 2.

Figure Legends:

Figure 1. Outline of clinical study protocol

ICD = implantable cardioverter-defibrillator; DFT = defibrillation threshold.

Figure 2. Serial changes of global SR_{IVR} before and after DFT testing in patients with preserved LVEF. A representative case of preserved LVEF.

A. Before DFT testing, global SR_{IVR} (yellow arrow) was 0.38 s^{-1} and LVEF was 71%.

B. Immediately after DFT testing, global SR_{IVR} was 0.20 s^{-1} and LVEF was 71%.

C. At 5 minutes after DFT testing, global SR_{IVR} was 0.12 s^{-1} and LVEF was 73%.

D. At 4 hours after DFT testing, global SR_{IVR} was 0.36 s^{-1} and LVEF was 70%.

SR_{IVR} = longitudinal strain rate during the isovolumetric relaxation period; LVEF = left ventricular ejection fraction; AVC = aortic valve closure; MVO = mitral valve opening; other abbreviations as in Figure 1.
**Figure 3.** Serial changes of global $\text{SR}_{\text{IVR}}$ before and after DFT testing in patients with reduced LVEF. A representative case of reduced LVEF.

**A.** Before DFT testing, global $\text{SR}_{\text{IVR}}$ (red arrow) was 0.23 s$^{-1}$ and LVEF was 39%.

**B.** Immediately after DFT testing, global $\text{SR}_{\text{IVR}}$ was 0.08 s$^{-1}$ and LVEF was 34%.

**C.** At 5 minutes after DFT testing, global $\text{SR}_{\text{IVR}}$ was 0.08 s$^{-1}$ and LVEF was 33%.

**D.** At 4 hours after DFT testing, global $\text{SR}_{\text{IVR}}$ was 0.23 s$^{-1}$ and LVEF was 37%.

Abbreviations as in Figure 1 and 2.
ICD Implantation
Monitored anesthesia care

DFT testing
(20 Jour x 2,
5 minutes interval)

Before

Immediately after
5 minutes after
4 hours after

Continuous central arterial pressure monitoring

Echocardiography
Blood sampling

Echocardiography
Blood sampling

Echocardiography
Blood sampling

Echocardiography
Blood sampling
Strain rate (s⁻¹)

A

B

C

D

AVC

MVO

Strain rate (s⁻¹)

Strain rate (s⁻¹)

Strain rate (s⁻¹)

Strain rate (s⁻¹)
Strain rate (s⁻¹)

A

B

C

D

AVC

MVO

AVC

MVO

AVC

MVO
Cardiac Dysfunction and Prolonged Hemodynamic Deterioration after Implantable Cardioverter-Defibrillator Shock in Patients with Systolic Heart Failure

Norihsa Toh, Nobuhiro Nishii, Kazufumi Nakamura, Takeshi Tada, Hiroki Oe, Satoshi Nagase, Kunihisa Kohno, Hiroshi Morita, Kengo F. Kusano and Hiroshi Ito

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