

Effects of defibrillation shock in patients implanted with a subcutaneous defibrillator: a biomarker study

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Aims

Implantable cardioverter defibrillator (ICD) shocks are associated with a subsequent increased risk of death, and an elevation of cardiac enzymes has been measured after defibrillation testing (DFT). In an experimental swine study, subcutaneous ICD (S-ICD) shocks caused less myocardial damage than traditional ICD shocks. The aim of our study was to investigate the association between S-ICD shock and acute cardiac damage in humans, as evaluated by means of sensitive and highly specific circulating biomarkers.

Methods and results

We calculated the variation in the serum levels of high-sensitivity cardiac troponin I (hs-CTnI) and creatine kinase-MB mass concentration (CK-MB mass), measured before and after an S-ICD shock delivered during intraoperative DFT. We also measured the degree of haemodynamic stress, as the variation in the serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and copeptin (CP), after the S-ICD shock. We analysed 30 consecutive patients who received an S-ICD and who underwent DFT by means of a single 65 J shock. The levels of biomarkers did not change from baseline to 1 h post-shock, i.e. hs-CTnI (from 0.029 ± 0.005 ng/mL to 0.030 ± 0.005 ng/mL, $P = 0.079$) and CK-MB mass (from 1.37 ± 0.17 ng/mL to 1.41 ± 0.18 , $P = 0.080$) and remained stable 6 and 24 h after DFT. The plasma NT-proBNP did not change, whereas CP levels were significantly higher at 1 h post-shock evaluation. However, 6 h after DFT, the levels had returned to the baseline and remained stable at 24 h.

Conclusion

The S-ICD shock did not seem to cause myocardial injuries. Although CP levels temporarily rose after DFT, they returned to basal levels within 6 h, which suggests that DFT does not have long-term prognostic implications. ICD shocks are associated with a subsequent increased risk of death, and an elevation of cardiac enzymes has been measured after DFT. We showed that serum levels of biomarkers of myocardial damage did not increase after high-energy DFT in patients who had undergone S-ICD device implantation. This suggests that S-ICD shock does not have long-term prognostic implications.

Keywords

Subcutaneous ICD • Ventricular fibrillation • Biomarkers

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What's new?

- In our study, serum levels of biomarkers of myocardial damage were not found to be elevated after high-energy shock in patients who had undergone subcutaneous implantable cardioverter defibrillator (S-ICD) device implantation.
- The S-ICD shock did not seem to cause stable increase in haemodynamic stress biomarkers, either in patients with preserved cardiac function or in those with reduced ejection fraction.
- This suggests that S-ICD defibrillation testing does not cause acute myocardial injuries in humans.

Introduction

Sudden cardiac arrest is the most common cause of death in developed countries.¹ The implantable cardioverter defibrillator (ICD) has consistently been found superior to the best available drug therapy for the prevention of sudden cardiac death in patients with previous cardiac arrest and in high-risk patients with depressed ventricular function or arrhythmogenic conditions.¹ For this reason, ICDs are the gold standard for sudden cardiac death prevention. The subcutaneous ICD (S-ICD) is a novel defibrillator equipped with an extrathoracic subcutaneous electrode. The defibrillation coil lies directly between two sensing electrodes and the S-ICD generator acts as the 3rd electrode, used for sensing and defibrillation. The S-ICD should be regarded as an alternative to transvenous defibrillators in patients with an indication for an ICD when pacing therapy for bradycardia support, cardiac resynchronization, or antitachycardia pacing is not needed.¹ The S-ICD also may be a useful alternative to the transvenous ICD system when venous access is difficult, after the removal of a transvenous ICD for infections or in young patients with a long-term need for ICD therapy.¹

It has been clearly demonstrated that appropriate and inappropriate ICD shocks for ventricular arrhythmias are associated with a subsequent 2- to 10-fold increased risk of death.² Several non-randomized studies have shown an elevation of cardiac enzymes measured after defibrillation testing (DFT), when performed during ICD implantation or before hospital discharge.³⁻⁵ A recent prospective, randomized, multicentre trial confirmed that the ICD shock itself, and not ventricular fibrillation (VF), seems to cause myocardial micro-damage, as evaluated by high-sensitivity troponin assessment.⁶

In an experimental swine study,⁷ S-ICD shocks seemed to cause less myocardial damage than traditional ICD shocks. However, there are no data on the effect of S-ICD shocks on the myocardium in humans in the literature. The aim of our prospective study was to investigate the association between S-ICD shock and acute cardiac damage, as evaluated by means of sensitive and highly specific circulating biomarkers.

Materials and methods

Study population

Of the 167 patients who received an ICD at Monaldi Hospital between October 2015 and July 2016, 32 met the criteria for S-ICD implantation according to the current guidelines and were enrolled in the study.

Study protocol

This study was single centre and prospective. Ethics approval was obtained from the institutional review committee, and all patients provided written, informed consent before participating in the study.

Study endpoints

The primary study endpoint was the degree of myocardial micro-damage, assessed by calculating the variation in the serum levels of high-sensitivity cardiac troponin I (hs-CTnI) and creatine kinase-MB mass concentration (CK-MB mass), measured before and after an S-ICD shock delivered during intraoperative DFT. The secondary endpoint was the degree of haemodynamic stress, measured as the variation in the serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and copeptin (CP), after the S-ICD shock. Variations in biomarker serum levels according to ejection fraction were compared.

Device implantation and defibrillation test

All patients underwent S-ICD implantation according to the manufacturer's recommendations. The optimal configuration proved to be that in which the shock coil was placed in the left parasternal position and the pulse generator was placed over the 6th rib in the left mid-axillary line. For shock coil placement, we adopted the two-incision technique, thereby avoiding superior parasternal incision. All patients underwent standardized intraoperative DFT. The detection rate was lowered to a minimal value of 170 b.p.m. DFT was performed on VF induced by a single 50 Hz alternating current burst lasting 4 s. The first shock energy was programmed to 65 J, resulting in a safety margin of at least 15 J. In the case of ineffective first shock delivery, the second shock energy was programmed to 80 J in reversed polarity. An ineffective second shock delivery would have required external defibrillation. An ineffective first shock required further tests in either reverse polarity or after repositioning of the subcutaneous lead and/or the pulse generator.

Biomarker measurements

Baseline serum levels of hs-CTnI (ng/mL), CK-MB mass (ng/mL), NT-proBNP (pg/mL), and CP (pmol/L) were measured before S-ICD implantation when the patient was in stable haemodynamic conditions and had been free from clinical sustained ventricular arrhythmia for at least 4 weeks. Blood sampling was repeated at the end of the surgical S-ICD implantation procedure, before the shock delivery and 1, 6 and 24 h after DFT.

Blood samples used to measure serum biomarker levels were centrifuged at 2500g for 15 min at 4°C, within 30 min of collection, and the serum was stored at -70°C until analysis.

High-sensitivity cardiac troponin I was measured by means of STAT contemporary sensitive and high-sensitivity assays on a Siemens Dimension Vista 1500 according to the manufacturer's instructions. The hs-CTnI measurements were taken using a sandwich chemiluminescent immunoassay based on LOCI advanced technology. The upper reference limit was 0.045 ng/mL.

Creatine kinase-MB mass and NT-proBNP were measured quantitatively using an electrochemiluminescence immunoassay based on electrochemiluminescence technology, sandwich principle (cobas 8000 modular analyser series, Roche, Mannheim, Germany). The upper reference limits were 3.6 ng/mL and 125 pg/mL, respectively.

Copeptin was detected by means of an automatic immunofluorescent assay (BRAHMS Copeptin proAVP KRYPTOR, Germany) according to the manufacturer's recommendations. The upper reference limit was 10 pg/mL.

The clinical biochemistry laboratory of our institution has implemented and maintains a Quality Management System which fulfils the

requirements of the standard ISO 9001:2008 for the following fields of activities: provision of chemical analysis—clinical trials in the areas of highly automated clinical chemistry, haematology and coagulation, immunoassay, autoimmunity, flow cytometry, high-performance liquid chromatography assays, and medicines—immunosuppressant, nephelometry-specific protein, and CSF (registration number: IT-74072).

Statistical analysis

Continuous data were expressed as mean \pm standard deviation; categorical data were expressed as percentages. Differences between mean data over time were determined by means of repeated-measures analysis of variance with Bonferroni's correction. A *P*-value <0.05 was considered significant for all tests. All statistical analyses were performed by means of SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The clinical characteristics of the study population are reported in Table 1. The patients had a mean age of 43 ± 14 years, and the

Table 1 Clinical characteristics of the study population

Patients (n)	32
Age (years)	43 ± 14
Gender (male/female)	24/8
Body mass index (kg/m ²)	22.4 ± 1.4
Ischaemic DCM (%)	7 (21.9)
Non-ischaemic DCM (%)	7 (21.9)
HCM (%)	7 (21.9)
BS (%)	5 (15.6)
ARVD (%)	6 (18.7)
Ejection fraction	49 ± 14
Beta-blockers (%)	22 (68)
Angiotensin-converting enzyme inhibitor therapy (%)	14 (43.7)
Angiotensin receptor blocker therapy (%)	6 (18.7)
Diuretic (%)	12 (37.5)
Sotalol (%)	5 (15.6)
Amiodarone (%)	5 (15.6)

Data are represented as mean \pm SD or n (%).

ARVD, Arrhythmogenic Right Ventricular Dysplasia; BS, Brugada syndrome; HCM, hypertrophic cardiomyopathy.

majority (75%) were male. Seven patients were affected by ischaemic dilated cardiomyopathy (DCM), seven patients by non-ischaemic DCM, six patients by arrhythmogenic right ventricular dysplasia, seven by hypertrophic cardiomyopathy and five by Brugada syndrome.

All S-ICDs were implanted for primary prevention of sudden cardiac death. DCM patients underwent implantation at least 3 months after the optimization of medical therapy. All patients underwent successful S-ICD implantation and DFT. In all patients, the first shock (65 J) was effective; no additional shocks were delivered, and no serious complications were noted.

Endpoint analysis

The primary and secondary analyses were performed in 30 patients. The remaining two DCM patients were excluded from the analysis, as blood samples were not collected according to the study protocol.

Primary endpoints: myocardial injuries

The baseline serum levels of hs-CTnI and CK-MB mass were 0.029 ± 0.005 ng/mL and 1.37 ± 0.17 ng/mL, respectively. All patients showed normal values of hs-CTnI and CK-MB mass at the baseline; these were not increased after the S-ICD implantation procedure or at the 1-h post-shock evaluation (0.030 ± 0.005 ng/mL, *P* = 0.079; 1.41 ± 0.18 , *P* = 0.080) and remained stable 6 and 24 h after DFT (Table 2).

Secondary endpoints: haemodynamic stress

The mean baseline plasma NT-proBNP and CP levels were 425.1 ± 71.3 pg/mL and 31.8 ± 9.1 pg/mL, respectively. Normal values of CP and NT-proBNP were found in 18 of 30 (60%) patients at the baseline. N-terminal pro-B-type natriuretic peptide was not increased after the S-ICD implantation procedure or at the 1-h post-shock evaluation (427.2 ± 73.8 pg/mL, *P* = NS) and remained stable 6 and 24 h after DFT.

Copeptin levels were not increased after the S-ICD implantation procedure but were significantly higher at the 1-h post-shock evaluation (107.6 ± 14.8 pg/mL, *P* < 0.0001); 6 h after DFT, however, they had returned to the baseline and remained stable at 24 h (Figure 1).

Table 2 Biomarker values at baseline and over time in the overall study population

	Baseline	Pre-shock	Post-shock	6 h	24 h	<i>P</i> -value (pre vs. post)
hs-CTnI (ng/mL)	0.029 ± 0.005	0.028 ± 0.005	0.030 ± 0.005	0.029 ± 0.005	0.029 ± 0.005	0.079
Copeptin (pg/mL)	31.8 ± 9.1	36.0 ± 8.9	107.6 ± 14.8	29.4 ± 7.1	31.6 ± 9.3	<0.0001
NT-proBNP (pg/mL)	425.1 ± 71.3	423.6 ± 73.2	427.2 ± 73.8	427.8 ± 72.1	424.6 ± 72.2	NS
CK-MB mass (ng/mL)	1.37 ± 0.17	1.38 ± 0.18	1.41 ± 0.18	1.36 ± 0.17	1.38 ± 0.17	0.080

Data are represented as mean \pm SD.

Biomarker evaluations according to ejection fraction and underlying disease

We divided the study population into two groups according to the ejection fraction. Twelve (40%) patients affected by DCM had an ejection fraction $\leq 35\%$. At the baseline, this subgroup presented normal values of hs-CTnl and CK-MB mass but increased NT-proBNP and CP values (Table 3). The CP values were significantly increased at the 1-h post-shock evaluation; 6 h after DFT, however, they had returned to the baseline, and remained stable at 24 h, as in the overall study population (Figure 2). The values of hs-CTnl, CK-MB mass and NT-proBNP were not significantly increased at the 1-h post-shock evaluation (Figure 3).

Stratifying the study population according to the underlying disease, we noticed comparable changes in biomarkers over time (Table 4).

Discussion

Background

The S-ICD constitutes a major advance in ICD technology in the last 10 years. Despite its current limitations, in routine clinical practice, an increasing number of patients requiring an ICD might be potential candidates for a subcutaneous device.⁸ According to a recently published multinational consensus statement on optimal ICD programming and testing, DFT is recommended (Class I indication) in patients undergoing S-ICD implantation.⁹ However, the S-ICD system requires significantly higher energy shocks than transvenous ICD. At present, there are no literature data on the association between

defibrillation shock and acute cardiac damage in patients with S-ICD. The aim of our study was to evaluate myocardial injury and haemodynamic stress, as assessed by means of serial perioperative evaluation of serum biomarkers following subcutaneous intraoperative DFT.

Clinical biomarkers

Myocardial injury is detected when blood levels of sensitive and specific biomarkers, such as cardiac troponin or the MB fraction of creatine kinase, are increased. Cardiac troponin I and T are components of the contractile apparatus of myocardial cells and are expressed almost exclusively in the heart. Although elevations of these biomarkers in the blood reflect injury leading to the necrosis of myocardial cells, they do not indicate the underlying mechanism. High-sensitivity troponin assays detect concentrations of the same proteins that conventional sensitivity assays are aimed at detecting, though at much lower concentrations; they therefore markedly improve sensitivity in detecting cardiac myocyte necrosis.¹⁰

In our study, we used the specific myocardial injury markers hs-CTnl and CK-MB mass to evaluate acute injury leading to the necrosis of myocardial cells secondary to subcutaneous intraoperative DFT; this approach differs from that of previous studies, in which troponin T and troponin I were observed.^{3,6}

B-type natriuretic peptide can be produced both in the atria and in the ventricles and is up-regulated in failing ventricular myocardium. In response to increased myocardial stretch and wall stress, ventricular myocytes secrete the pro-hormone pre-proBNP, which is then cleaved into biologically active BNP and the inactive byproduct NT-proBNP. Elevated BNP levels have been demonstrated to response to

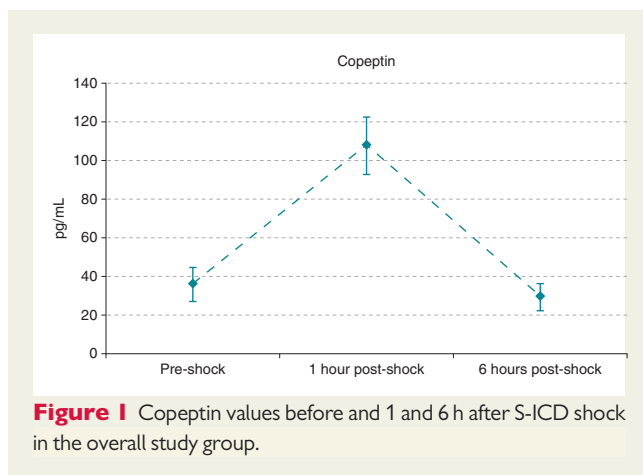


Figure 1 Copeptin values before and 1 and 6 h after S-ICD shock in the overall study group.

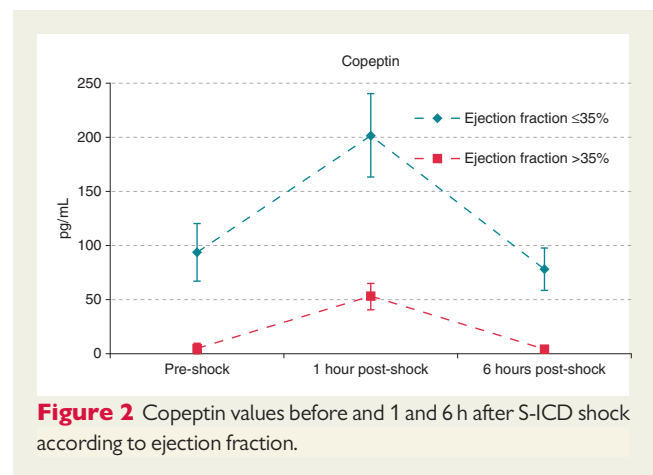
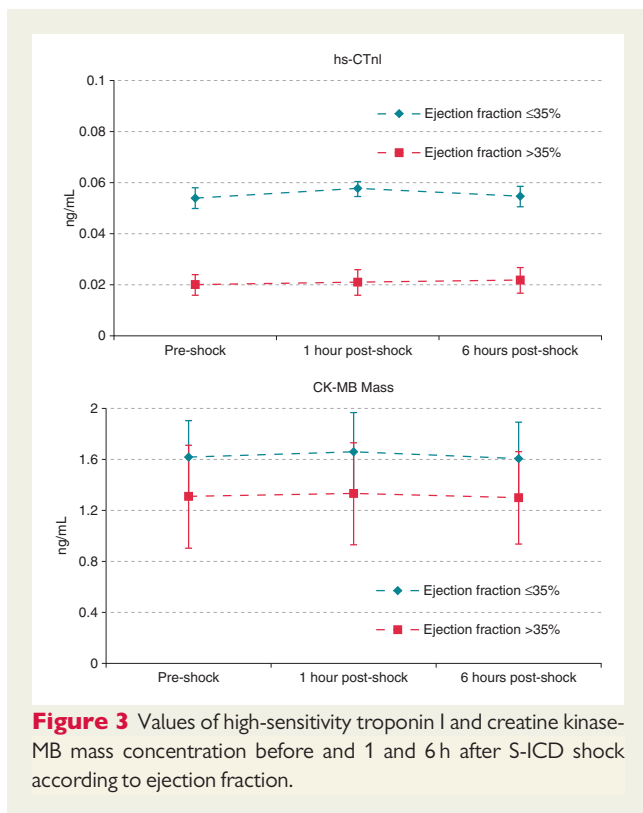


Figure 2 Copeptin values before and 1 and 6 h after S-ICD shock according to ejection fraction.

Table 3 Biomarkers values at baseline and over time in the subgroup with reduced ejection fraction ($\leq 35\%$, $n = 12$)

	Baseline	Pre-shock	Post-shock	6 h	24 h	P-value (pre vs. post)
hs-CTnl (ng/mL)	0.0537 \pm 0.004	0.0541 \pm 0.004	0.0577 \pm 0.003	0.0547 \pm 0.004	0.0540 \pm 0.005	0.0738
Copeptin (pg/mL)	91.7 \pm 25.4	93.9 \pm 26.6	201.9 \pm 38.5	78.3 \pm 19.6	92.8 \pm 26.3	0.0049
NT-proBNP (pg/mL)	1014.7 \pm 60.3	1015.8 \pm 65.1	1040.4 \pm 62.9	1031.7 \pm 46.1	1016.2 \pm 61.5	0.8936
CK-MB mass (ng/mL)	1.618 \pm 0.30	1.617 \pm 0.29	1.659 \pm 0.31	1.604 \pm 0.29	1.617 \pm 0.31	0.0915

Data are represented as mean \pm SD.



increased angiotensin II and sympathetic tone. In primary care settings, NT-proBNP has a good diagnostic performance in identifying patients who are at risk of developing HF, even if they have few symptoms and less severe signs of HF. N-terminal-pro-B-type natriuretic peptide is also a sensitive marker of myocardial ischaemia in that it increases much more markedly than conventional markers in the early phase of myocardial damage, especially in non-ST elevation MI patients.¹¹

Copeptin, the C-terminal portion of proavopressin, is a glycosylated polypeptide comprising 39 amino acids and harbouring a leucine-rich core segment. It is a neurohormone of the Arginine vasopressin (AVP) system and is co-secreted with AVP by the hypothalamus. Copeptin has been suggested as a marker of individual stress level.¹² It is well known that sympathetic hyperactivation is strongly associated with the endogenous stress level,¹³ and it has been suggested that adrenergic substances, including norepinephrine, stimulate AVP release.

Copeptin has yielded promising clinical results in a variety of cardiovascular and non-cardiovascular conditions. It may serve as an independent predictor of both mortality and rehospitalization for heart failure and displays greater superior prognostic value than BNP and NT-proBNP¹⁴; if used in combination with other markers, including NT-proBNP and hs-cTnT, it has excellent prognostic value.¹⁵

Previous studies

Defibrillation testing, which is conducted by inducing and terminating VF, is widely considered to be a part of the standard protocol for transvenous ICD implantation. However, several studies have

suggested that shock causes myocardial injury^{3,16} and unstable cardiac haemodynamics.¹⁷ A recent prospective, randomized, multi-centre trial conducted by Semmler *et al.*⁶ on 194 ICD recipients showed that ICD implantation was associated with an elevation of serum levels of hsTnT and that the postoperative release of hsTnT was significantly higher in patients who had undergone intraoperative ICD testing than in those who had not. The authors concluded that the ICD shock delivered during DFT, and not the VF, caused hsTnT to rise after device implantation. Ishigaki *et al.*¹⁸ found that patients who underwent ICD implantation and received a 15 J shock during DFT exhibited evidence of myocardial damage, as indicated by increased serum levels of cardiac troponin T and heart-type fatty acid-binding protein. In contrast, 10 J of DFT (9 J or 10 J) was associated with an acceptable rate of successful DFT and no significant elevation of either marker. A summary of previous studies reporting changes of cardiac troponin and CK-MB mass after transvenous ICD shock is reported in Table 5.

The S-ICD system can deliver a maximum of five 80 J shocks, and it has been hypothesized that higher energy shocks delivered to tissues within the shock field from a subcutaneous lead would result in more tissue injury near the delivery electrodes than if a transvenous lead were used.¹⁹ However, in an animal study aimed at evaluating acute cardiac and chest wall damage after shocks delivered by an S-ICD in swine, Killingsworth *et al.*⁷ showed that the S-ICD group, which underwent DFT with higher energy 80 J shocks, had lower troponin I values, indicating less cardiac injury than the control pigs, which received 35 J transvenous shocks. The authors suggested that the strength of the electric shock within the heart was probably greater when the transvenous lead was used than when the subcutaneous lead was used. However, no data in humans are available to confirm these observations. More recently, Garcia *et al.*²⁰ compared S-ICD and transvenous ICD shocks delivered after VF induction in 14 pigs. High-sensitivity troponin T levels were significantly higher in the transvenous ICD group, whereas creatine phosphokinase activity levels were significantly higher in the S-ICD group from 1 h to 24 h after the procedure. Therefore, they concluded that S-ICD shocks were less cardiotoxic than T-ICD shocks.²⁰

Main findings

Intraoperative DFT offers the unique clinical opportunity to evaluate the impact of the S-ICD shock on acute cardiac damage and cardiovascular haemodynamics, as evaluated by means of serum levels of biomarkers. In our study, the S-ICD shock did not seem to cause myocardial injuries, either in patients with preserved cardiac function or in those with reduced ejection fraction. Although CP levels temporarily rose after DFT, probably due to haemodynamic stress following VF induction and shock delivery, they returned to basal levels within 6 h, which suggests that DFT does not have long-term prognostic implications. However, it is not clear whether the main determinant of the CP increase was the ICD shock itself or the induced VF.

Limitations

Our study did not directly compare S-ICD and transvenous ICD in terms of the potential damage caused by DFT. However, it is the first to evaluate the impact of the S-ICD shock on acute cardiac damage and cardiovascular haemodynamics in humans by means of novel,

Table 4 Biomarker values at baseline and over time in the population stratified by underlying disease

	Baseline	Pre-shock	Post-shock	6 h
Ischaemic DCM (n = 6)				
hs-CTnl (ng/mL)	0.062 ± 0.039	0.062 ± 0.030	0.063 ± 0.033	0.063 ± 0.034
Copeptin (pg/mL)	85.7 ± 88.0	85.9 ± 82.2	172.1 ± 119.8	71.3 ± 59.8
NT-proBNP (pg/mL)	793.8 ± 389.9	785.3 ± 411.6	782.8 ± 425.5	782.0 ± 404.8
CK-MB mass (ng/mL)	1.53 ± 0.44	1.58 ± 0.51	1.61 ± 0.51	1.54 ± 0.45
Non-ischaemic DCM (n = 6)				
hs-CTnl (ng/mL)	0.049 ± 0.021	0.047 ± 0.017	0.050 ± 0.018	0.048 ± 0.018
Copeptin (pg/mL)	51.8 ± 29.2	56.9 ± 29.5	151.9 ± 70.6	50.1 ± 28.0
NT-proBNP (pg/mL)	829.1 ± 327.6	844.5 ± 370.2	858.1 ± 365.4	852.8 ± 336.9
CK-MB mass (ng/mL)	1.55 ± 0.88	1.54 ± 0.86	1.58 ± 0.89	1.52 ± 0.86
HCM (n = 7)				
hs-CTnl (ng/mL)	0.012 ± 0.002	0.012 ± 0.002	0.013 ± 0.001	0.013 ± 0.001
Copeptin (pg/mL)	9.9 ± 11.3	20.1 ± 18.2	74.8 ± 57.5	10.3 ± 12.9
NT-proBNP (pg/mL)	203.5 ± 128.2	176.4 ± 69.2	176.1 ± 65.8	195.1 ± 95.2
CK-MB mass (ng/mL)	1.34 ± 1.57	1.36 ± 1.61	1.37 ± 1.60	1.38 ± 1.60
BS (n = 5)				
hs-CTnl (ng/mL)	0.007 ± 0.003	0.008 ± 0.004	0.008 ± 0.004	0.008 ± 0.004
Copeptin (pg/mL)	3.1 ± 1.7	3.9 ± 1.4	45.4 ± 20.5	4.6 ± 2.8
NT-proBNP (pg/mL)	134.4 ± 33.7	148.2 ± 40.2	151.4 ± 37.3	141.6 ± 39.4
CK-MB mass (ng/mL)	1.29 ± 0.80	1.27 ± 0.78	1.31 ± 0.81	1.27 ± 0.76
ARVD (n = 6)				
hs-CTnl (ng/mL)	0.012 ± 0.003	0.010 ± 0.001	0.012 ± 0.002	0.012 ± 0.002
Copeptin (pg/mL)	7.2 ± 2.3	10.3 ± 5.8	88.8 ± 36.0	9.5 ± 5.1
NT-proBNP (pg/mL)	152.6 ± 57.8	158.8 ± 66.9	163.5 ± 70.0	158.3 ± 57.5
CK-MB mass (ng/mL)	1.10 ± 0.80	1.14 ± 0.85	1.14 ± 0.83	1.07 ± 0.77

Data are represented as mean ± SD.

ARVD, Arrhythmogenic Right Ventricular Dysplasia; BS, Brugada syndrome; HCM, hypertrophic cardiomyopathy.

Table 5 Previous studies reporting changes of cardiac troponin and creatine kinase-MB mass concentration after transvenous implantable cardioverter defibrillator shock

	hs-CTnl	CK-MB mass	Number of patients	Patient characteristics	Shocks delivered
Francis et al. ³	↑ (2 h) ↑ (8 h) (*)	↑ (2 h) → (8 h)	31	90% DCM, mean EF 28%	1 or 2 at ≤ 35 J
Hurst et al. ⁴	↑ (8 h)	↑ (8 h)	49	94% DCM, mean EF 34%	7 ± 3 at ≤ 35 J
Schlüter et al. ⁵	→ (1 h) ↑ (4 h) → (24 h)	↑ (1 h) ↑ (4 h) → (24 h)	14	100% DCM, mean EF 45%	2 (from 1 to 10) at ≤ 31 J
Semmler et al. ⁶	↑ (6 h) (#)	→ (6 h)	194	98% DCM, mean EF 29%	Median 2 at ≤ 42 J
Ishigaki et al. ¹⁸	↑ (2 h) → (24 h) (\$)	–	20	100% DCM, mean EF 55%	1 at 15 J

↑, significant increase; →, no change; DCM, dilated cardiomyopathy; EF, ejection fraction; *, cardiac troponin I; #, high-sensitivity cardiac troponin T; \$, cardiac troponin T.

high specificity biomarkers. Device testing during implantation was performed by means of a 65 J shock on induced VF. However, after implantation, the device is able to deliver up to five consecutive biphasic 80 J shocks per episode and can automatically reverse shock polarity if the initial shock is unsuccessful. Therefore, no conclusion can be drawn as to the potential damage caused by multiple shocks during follow-up.

Conclusions

Serum levels of biomarkers of myocardial damage were not found to be elevated after high-energy DFT in patients who had undergone S-ICD device implantation, regardless of their ejection fraction value. We did not find a stable increase in haemodynamic stress biomarkers after high-energy DFT. Our prospective observational study is the

first to suggest that S-ICD DFT does not cause acute myocardial injuries in humans. Further studies are necessary to confirm our results and to directly compare S-ICD with transvenous ICD in terms of the damage caused by DFT.

Conflict of interest: none declared.

References

- Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Europace* 2015;**17**:1601–87.
- Proietti R, Labos C, Davis M, Thanassoulis G, Santangeli P, Russo V et al. A systematic review and meta-analysis of the association between implantable cardioverter-defibrillator shocks and long-term mortality. *Can J Cardiol* 2015;**31**:270–7.
- Francis CK, Kuo YH, Azzam I, Selim S, Patel N, Beri R et al. Brain natriuretic peptide and biomarkers of myocardial ischemia increase after defibrillation threshold testing. *Pacing Clin Electrophysiol* 2012;**35**:314–9.
- Hurst TM, Hinrichs M, Breidenbach C, Katz N, Waldecker B. Detection of myocardial injury during transvenous implantation of automatic cardioverter-defibrillators. *J Am Coll Cardiol* 1999;**34**:402–8.
- Schlüter T, Baum H, Plewan A, Neumeier D. Effects of implantable cardioverter defibrillator implantation and shock application on biochemical markers of myocardial damage. *Clin Chem* 2001;**47**:459–63.
- Semmler V, Biermann J, Haller B, Jilek C, Sarafoff N, Lennerz C et al. ICD shock, not ventricular fibrillation, causes elevation of high sensitive troponin T after defibrillation threshold testing—the prospective, randomized, multicentre troponin shock-trial. *PLoS One* 2015;**10**:e0131570.
- Killingsworth CR, Melnick SB, Litovsky SH, Ideker RE, Walcott GP. Evaluation of acute cardiac and chest wall damage after shocks with a subcutaneous implantable cardioverter defibrillator in swine. *Pacing Clin Electrophysiol* 2013;**36**:1265–72.
- Botto GL, Forleo GB, Capucci A, Solimene F, Vado A, Bertero G et al. The Italian subcutaneous implantable cardioverter-defibrillator survey: S-ICD, why not? *Europace* 2007;**19**:1826–32.
- Wilkoff BL, Fauchier L, Stiles MK, Morillo CA, Al-Khatib SM, Almendral J et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. *Europace* 2016;**18**:159–83.
- Twerenbold R, Jaffe A, Reichlin T, Reiter M, Mueller C. High-sensitive troponin T measurements: what do we gain and what are the challenges? *Eur Heart J* 2012;**33**:579–86.
- Ogawa A, Seino Y, Yamashita T, Ogata K, Takano T. Difference in elevation of N-terminal pro-BNP and conventional cardiac markers between patients with ST elevation vs non-ST elevation acute coronary syndrome. *Circ J* 2006;**70**:1372–8.
- Katan M, Morgenthaler N, Widmer I, Puder JJ, König C, Müller B et al. Copeptin, a stable peptide derived from the vasopressin precursor, correlates with the individual stress level. *Neuro Endocrinol Lett* 2008;**29**:341–6.
- Yalta K, Sivri N, Yalta T, Geyik B, Aksoy Y, Yetkin E. Copeptin (C-terminal pro-vasopressin): a promising marker of arrhythmogenesis in arrhythmia prone subjects?. *Int J Cardiol* 2011;**148**:105.
- Gegenhuber A, Struck J, Dieplinger B, Poelz W, Pacher R, Morgenthaler NG et al. Comparative evaluation of B-type natriuretic peptide, mid-regional pro-A-type natriuretic peptide, mid-regional pro-adrenomedullin, and Copeptin to predict 1-year mortality in patients with acute destabilized heart failure. *J Card Fail* 2007;**13**:42–9.
- Alehagen U, Dahlström U, Rehfeld JF, Goetze JP. Association of copeptin and N-terminal proBNP concentrations with risk of cardiovascular death in older patients with symptoms of heart failure. *JAMA* 2011;**305**:2088–95.
- Cevik C, Perez-Verdia A, Nugent K. Implantable cardioverter defibrillators and their role in heart failure progression. *Europace* 2009;**11**:710–5.
- Tokano T, Bach D, Chang J, Davis J, Souza JJ, Zivin A et al. Effect of ventricular shock strength on cardiac hemodynamics. *J Cardiovasc Electrophysiol* 1998;**9**:791–7.
- Ishigaki D, Kutsuzawa D, Arimoto T, Iwayama T, Hashimoto N, Kumagai Y et al. The association between defibrillation shock energy and acute cardiac damage in patients with implantable cardioverter defibrillators. *J Arrhythm* 2016;**32**:481–5.
- Allred JD, Killingsworth CR, Allison JS, Dossall DJ, Melnick SB, Smith WM et al. Transmural recording of shock potential gradient fields, early postshock activations, and rebrillation episodes associated with external defibrillation of long-duration ventricular fibrillation in swine. *Heart Rhythm* 2008;**5**:1599–606.
- Garcia R, Inal S, Favreau F, Jayle C, Hauet T, Bruneval P et al. Subcutaneous cardioverter defibrillator has longer time to therapy but is less cardiotoxic than transvenous cardioverter defibrillator. Study carried out in a preclinical porcine model. *Europace* 2008;**20**:873–9.