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Evaluation of acute cardiac and chest wall damage after shocks with a subcutaneous implantable cardioverter-defibrillator in swine

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Abstract

Background—A subcutaneous implantable cardioverter defibrillator (S-ICD) could ease placement and reduce complications of transvenous ICDs, but requires more energy than transvenous ICDs. Therefore we assessed cardiac and chest wall damage caused by the maximum energy shocks delivered by both types of clinical devices.

Methods—During sinus rhythm, anesthetized pigs (38±6 kg) received an S-ICD (n = 4) and five 80-Joule (J) shocks, or a transvenous ICD (control, n = 4) and five 35-J shocks. An inactive S-ICD electrode was implanted into the same control pigs to study implant trauma. All animals survived 24-hours. Troponin I and creatine kinase muscle isoenzyme (CK-MM) were measured as indicators of myocardial and skeletal muscle injury. Histopathological injury of heart, lungs, and chest wall was assessed using semi-quantitative scoring.

Results—Troponin I was significantly elevated at 4- and 24-hours (22.6±16.3 and 3.1±1.3 ng/ml; baseline 0.07±0.09 ng/ml) in control pigs but not in S-ICD pigs (0.12±0.11 and 0.13±0.13 ng/ml; baseline 0.06±0.03 ng/ml). CK-MM was significantly elevated in S-ICD pigs after shocks (6544±1496 and 9705±6240 U/L; baseline 704±398 U/L) but not in controls. ECG changes occurred post-shock in controls but not in S-ICD pigs. The myocardium and lungs were histologically normal in both groups. Subcutaneous injury was greater in S-ICD compared to controls.

Conclusion—Although CK-MM suggested more skeletal muscle injury in S-ICD pigs, significant cardiac, lung, and chest wall histopathological changes were not detected in either group. Troponin I data indicate significantly less cardiac injury from 80-J S-ICD shocks than 35-J transvenous shocks.

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Keywords

Implantable cardioverter defibrillator; troponin I; creatine kinase; inflammation; swine

Introduction

The ICD system began with an epicardial patch with connection to an abdominally placed pulse generator^{1, 2} and has evolved to today's ICD system with a transvenous lead connected to a pectorally placed pulse generator. More recently, data on a completely subcutaneous ICD (S-ICD) system that eliminates the need for venous access were reported by Bardy et al.³ However, significantly higher energy shocks were required with the S-ICD system when paired defibrillation threshold testing of the S-ICD and transvenous ICD system was performed (36.6 ± 19.8 J vs. 11.1 ± 8.5 J, $n = 49$ patients).³ The increased energy required for defibrillation by the subcutaneous ICD raises the question of whether the shocks cause more damage than shocks by transvenous ICDs.⁴⁵

The goal of this study was not to determine defibrillation efficacy as has been reported^{3, 6} but to use an animal model to determine the potential for acute damage to the heart, lungs, and surrounding tissues caused by the delivery of the higher energy S-ICD system compared to a currently implanted transvenous system. The S-ICD system can deliver a maximum of five 80 J shocks so this acute injury study was based on a worse case scenario of the maximum energy output and the maximum number of shocks. We used an analogous worse case scenario for a commercially available transvenous defibrillation system for comparison. Thus, the transvenous devices were also programmed to their maximum programmable energy of five shocks at 35 J. We hypothesized that higher energy shocks delivered to tissues within the shock field from a subcutaneous lead would result in more tissue injury near the shocking electrodes compared to a transvenous lead, but because the strongest shock electric field strength within the heart was probably higher with the transvenous lead than the subcutaneous lead,⁷ that the transvenous lead would result in more cardiac injury. Post-shock changes in the electrocardiogram, cardiac troponin I, and creatine kinase muscle isoenzyme (CK-MM) were measured as indicators of myocardial and skeletal muscle injury, respectively. Histopathology of the heart, lungs, skeletal muscle and tissues within the defibrillation shock field was performed 24-hours after shock delivery.

Methods

Eight pigs (38 ± 6 kg) were anesthetized with intramuscular (IM) atropine (0.04 mg/kg), tiletamine HCl/zolazepam HCl (4.4 mg/kg), and xylazine (4.4 mg/kg). All animals were intubated, and anesthesia was maintained by inhalation of isoflurane (1.5 to 2.5%) administered in 100% oxygen. Animals were given intravenous 0.9% saline and mechanically ventilated throughout the experiment. Injections of the antibiotic cefazolin (25 mg/kg IM) and the analgesic buprenorphine (0.01 mg/kg IM) were given before surgery was begun. Core body temperature, arterial blood gas values, and electrolyte levels were monitored and maintained within the normal range throughout the experiment.

Four pigs (S-ICD group) received the totally subcutaneous S-ICD system consisting of an electrode (Cameron Health Model 3010 Q-TRAK) implanted with the distal portion parallel to the left sternal border and the proximal end connected to the pulse generator (Cameron Health Model 1010 SQ-RX Pulse Generator) implanted in a left lateral pocket. All incisions were closed using standard surgical technique. The S-ICD group received five 80-J sequential biphasic shocks. Shocks were synchronously delivered to the R wave in sinus

rhythm with the time between shocks spaced to mimic actual system performance in the presence of persistent ventricular fibrillation. The median time between shocks was 30 s.

In 4 control pigs, a conventional transvenous dual coil right ventricular (RV) defibrillation lead (Guidant Reliance Model# 0147) was implanted with fluoroscopic guidance and standard technique. An active-can ICD (Guidant Renewal 3 HE) was implanted subcutaneously over the left lateral neck. The RV lead was connected to the ICD and the incisions were closed using standard surgical technique. In addition, an S-ICD system electrode was implanted in a parasternal location. A subcutaneous device pocket was also formed to cause surgical implant trauma as a further control. Control pigs received five 35-J sequential biphasic shocks from the implanted ICD delivered via the transvenous lead delivered with timing similar to the control group, but received no shocks via the S-ICD electrode. The median time between shocks was 33 s.

The ECG was recorded continuously throughout shock delivery to detect ST segment changes, T-wave changes, ventricular ectopy, asystole, and bradycardia. Arterial blood pressure and ECG data were analyzed immediately before, after, and 10 minutes following shock delivery. Blood samples for cardiac troponin I and CK-MM measurement were obtained at baseline, and at 4- and 24-hours after shocks. Serum samples were stored at -20C and analyzed by a commercial veterinary laboratory (Antech Diagnostics).

Animals were recovered from anesthesia and survived for 24-hours, after which they were anesthetized again as described above and euthanized with potassium chloride (2 mM/kg intravenously). Tissues around the electrode shock coils, implanted lead, pulse generator, heart, lungs, and surrounding structures were examined grossly in all animals. No hematoma, marked discoloration, softening or hardening of tissues was observed in any case, and therefore histological sections were not selected based on any observed abnormality. Instead, histological sections of the soft tissue and muscle along the S-ICD electrode and pulse generator pockets were taken at 5-cm intervals related to the presence of the electrode, coil, and ICD for each animal. Tissues were fixed by immersion or perfusion (heart) in 10% buffered formalin. Histological sections of the skin, subcutaneous tissue, and muscle along the S-ICD electrode and pulse generator pocket were collected at regular spacing such that 10 to 12 slides of tissue along the implants were examined for each animal; thereby allowing for comparison of tissues receiving shocks with tissues receiving no shocks in the subcutaneous field. Similarly, in the control group, the transvenous electrode coil area and the tissue surrounding the Guidant pulse generator (shocks delivered) and the S-ICD pulse generator (no shocks delivered), were examined grossly and histological samples were collected at regular intervals. The heart was examined grossly and then cut into ~1 cm thick transverse slices. Transmural heart sections were collected from the anterior, lateral and posterior walls of the left ventricle, the septum, and from the RV. The right ventricular myocardium near the shocking electrode was examined histologically in the controls. Representative lung sections were also collected. Tissue sections were stained with hematoxylin and eosin. A semi-quantitative score was used to grade histopathological injury with 0 as normal, 1+ mild, 2+ moderate, and 3+ as significant hemorrhage, tissue injury, and inflammation.

Data Analysis

Data were expressed as mean $\pm$ standard deviation (SD). Statistical differences between the two groups over time were determined with analysis of variance and post hoc Fisher LSD testing. Results were considered significant if $P < 0.05$.

Results

The capacitor size was 145 μ F and pulse width was 10.5 ms in the control ICD compared to 95 μ F with a pulse width of 7.6 ms in the S-ICD. The peak voltage and peak current delivered were 750 V and 18.8 amps in the control ICD and 1350 V and 27 amps in the S-ICD. The shock impedance was 40 ± 4 ohms in the control group implanted with the transvenous lead and 52 ± 11 ohms in the S-ICD group. Troponin I was similar at baseline but significantly elevated at 4-hours after shock delivery in controls receiving transvenous shocks compared to the S-ICD group (Table 1). Troponin I in the control group remained significantly elevated at 24-hours compared to baseline levels but was significantly less than the 4-hour troponin I measurement. Troponin I was increased in S-ICD animals at 4- and 24-hours after shocks but this increase was not significantly different than the baseline measurement (Table 1). Total CK-MM was significantly elevated at 4- and 24-hours post shock compared to the baseline measurement in the S-ICD group (Table 1). CK-MM was also elevated in the control animals at 4- and 24-hours but these values did not reach statistical significance.

Post-shock ectopy was noted in 3 of the 4 control animals ranging from 1 to 5 ventricular ectopic beats. Other ECG changes including ST-segment depression and T-wave inversion occurred following shocks in all 4 control animals (Figure 1). No ectopic beats were detected post-shock in the S-ICD animals. T-wave changes were detected in one S-ICD animal 10 minutes post-shock (Figure 1). There were no significant differences in heart rate or systemic arterial blood pressure between the 2 groups before or after shocks.

The subcutaneous tissue over the chest wall of the S-ICD animals with implantation and shocks as well as control animals with S-ICD implantation and no shocks had histopathological changes consistent with surgery 24 hours earlier (Figure 2). Specifically, there was hemorrhage, edema and acute inflammation in the adipose tissue and adjoining skeletal muscle. Overall, the histological injury changes were similar between both groups with a small increase in the injury grade of the subcutaneous tissues of S-ICD animals compared to the control animals (Table 2).

Three control animals had minor endocardial changes associated with the transvenous lead (Figure 3). A red blood cell-rich thrombus was associated with the tip of the lead in one animal, whereas inflammation, very small areas of hemorrhage and minor endocardial fibrin deposition with inflammation were seen in the RV of 2 other control animals. Transverse myocardial sections were normal in both the S-ICD and control animals. The lungs were similar between both groups with no histopathological evidence of electric shock injury.

Discussion

The major findings of this study are as follows: (1) in spite of higher energy 80-J shocks, the S-ICD group had lower troponin I values, indicating less cardiac injury than the control pigs receiving 35-J transvenous shocks; (2) the semi-quantitative histological grading of subcutaneous and skeletal muscle injury was mild to moderate in both groups due to surgical implantation with a small increase in the injury score with shock delivery in the S-ICD animals; (3) CK-MM data suggested more skeletal muscle injury in S-ICD pigs receiving shocks from electrodes in the subcutaneous space based on lower CK-MM values in control pigs implanted with a subcutaneous lead but no shock delivery; and (4) neither the lungs nor the myocardium in either group of animals had any histological indication of shock injury.

To isolate the impact of the shock on tissue damage caused by the S-ICD in this study, all shocks were delivered synchronously in normal sinus rhythm. This study was not designed to analyze conversion efficacy of the delivered shocks, which has been previously

investigated.^{3, 6} The 80 J maximum output of the S-ICD used in this study is a 15 J safety margin over the 65 J shock level, which twice successfully defibrillated 58 of the 59 patients in the Bardy study.³ DFT analysis was not performed in this study because the additional shocks would confound the intended analysis, and the induced arrhythmias might introduce an ischemic burden that could affect the cardiac enzymes used to assess damage resulting from the shock. Previous studies measuring cardiac enzymes post resuscitation suggest that mechanical trauma associated with cardiopulmonary resuscitation and ischemia associated with ventricular fibrillation and acute coronary occlusion cause tissue damage rather than does the transthoracic shock itself.^{8, 9} A review of published data suggests that the damage threshold for perfused hearts is well above any external defibrillation shock energy delivered clinically.¹⁰

Troponin I data indicated less cardiac injury following 80-J S-ICD shocks than 35-J transvenous shocks. These data are consistent with data from Allred et al. who reported that during external defibrillation, much less of the shock voltage appears across the heart compared to defibrillation shocks delivered during transvenous defibrillation. The authors reported that only ~10% of the stored voltage appears across the ventricles during a transthoracic shock and that the maximum electric field caused by a transthoracic shock within the heart was only one-third to one-fifth that reported for internal defibrillation even though the transthoracic shock was much larger.⁷

Although CK-MM is found in both cardiac and skeletal muscle, it has been used for detection of both exercise-stressed skeletal muscle and after muscle lengthening exercise.¹¹ In this study, CK-MM was significantly elevated in S-ICD animals at 4- and 24-hours compared to baseline. In addition, the CK-MM was much higher in the S-ICD animals at 24-hours after receiving subcutaneous shocks compared to control animals receiving S-ICD subcutaneous implant but no shocks. The elevated CK-MM could be the result of both myocardial and skeletal muscle release; however, because the troponin-I was insignificantly elevated at both time points in the S-ICD animals, whereas the histological injury in the tissue surrounding the S-ICD lead with shocks was slightly greater, we interpreted the increased CK-MM to be largely due to skeletal muscle injury. The general increase in CK-MM in control animals is likely due to a combination of lead implantation and intracardiac shock delivery.

Relatively minor tissue injury and inflammation were detected in both groups of animals following subcutaneous lead placement whether or not shocks were delivered. Endocardial changes in animals with transvenous leads have been reported and can be induced by mechanical trauma as well as shock delivery.¹² Microscopic cardiac myofibrillar degeneration characterized by swollen myocardial cells, loss of cross striations, and dense eosinophilic transverse contraction bands were not detected in either group of animals. Thus, histopathological results suggest that the higher energy used with the S-ICD system did not cause myocardial injury at 24-hours post shock.

Limitations

This study was performed using anesthetized pigs, which have a different shaped thorax and a different heart location compared to humans. Ethically, a maximal injury study could not be performed in humans but could be performed in anesthetized animals. Thus, we chose the porcine model to test defibrillation damage to the heart and surrounding tissues based on our previous work and on a large body of literature on cardiopulmonary resuscitation research performed using swine.

A commercially available transvenous defibrillation system was used as a control for comparison since it is the current standard of care for prevention of sudden cardiac death.

The goal was to determine the amount of myocardial injury caused by the worst case scenario of 5 maximum output shocks with the subcutaneous system. Thus, we used an analogous worst case scenario for the transvenous system. Previous studies performed to assess the extent of myocardial injury after transvenous ICD implantation reported cumulative energy delivered of 111.2 ± 62.7 J,¹³ 112 ± 57 J (range 36–418 J),¹⁴ 38 J (mean, range 17–194 J),¹⁵ and 114 J (mean, range 94–174 J),¹⁶ which are within the range that we delivered. However, with improved transvenous ICD technology and left pectoral implants, the first shock success for spontaneous ventricular arrhythmias varies from 83–93%.¹⁷ Thus, from a clinical standpoint, a patient would rarely receive 5 shocks at the maximum output of the transvenous ICD system.¹⁸

We have recently completed another protocol similar to that used in this study except that a single 30 J transvenous shock (a 10 J safety factor for a 20 J DFT) was given in pigs after 10 s of VF.¹⁹ The troponin I level was much lower (1.86 ± 0.52 ng/ml) than for the five 35 J shocks in this study (22.6 ± 16.3 ng/ml), suggesting that damage from a single shock with a standard ICD is much less than for 5 successive maximum output shocks. However, the troponin I level for a single 30 J transvenous shock is still significantly higher than for 5 successive maximum output shocks from the subcutaneous defibrillator in the manuscript (0.12 ± 0.11 ng/ml).

Conclusion

Troponin I data indicate less cardiac injury from 80-J S-ICD shocks than 35-J transvenous shocks in this swine study. The S-ICD shocks resulted in more subcutaneous soft tissue injury. Cardiac and pulmonary injury were not detected.

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Abbreviations

S-ICD	subcutaneous implantable cardioverter-defibrillator
ICD	implantable cardioverter-defibrillator
CK-MM	creatinine kinase muscle isoenzyme
AST	aspartate aminotransferase

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Figure 1.

Examples of ECG changes detected following shocks from a transvenous lead and a S-ICD lead. The most common ECG changes detected after transvenous shocks were ST-segment depression or T-wave inversion (A). One ECG change was detected following S-ICD shocks, which was a tall T-wave 10 minutes post shock delivery (B). Panel C shows the surface ECG (upper trace) and arterial blood pressure (lower trace) from a control animal. A single PVC and a compensatory pause followed a transvenous shock. Post-shock ectopy was noted in 3 of the 4 control animals ranging from 1 (Panel C) to 5 ventricular ectopic beats. No ectopy was recorded in the S-ICD animals.

Figure 2.

Example of histopathological findings from tissue surrounding the S-ICD coil and pocket in which shocks were delivered (A and C, S-ICD group) or no shocks were delivered to control for surgical implant trauma in control animals (B and D). Tissue near the distal tip of the S-ICD electrode is shown in A. The epidermis and dermis were normal (not shown). The subcutaneous tissue contained hemorrhage, edema, and mild to moderate acute inflammation (identified with straight arrows). There was also moderate inflammation and hemorrhage in the skeletal muscle adjacent to the subcutaneous tissue (curved arrow). Control tissue with implantation but no shock (B) had normal epidermis with focal acute inflammation in the dermis. Moderate acute inflammation and edema were detected in the subcutaneous tissue and adjacent skeletal muscle (arrows). The pocket with shocks (C) demonstrated edema and mild inflammation (arrow) in the subcutaneous tissue that was similar in degree to tissues without shocks (D) suggesting injury was largely due to the surgery rather than shock delivery. Bar = 0.5 mm.

Figure 3.

Example of histopathological findings from a control animal receiving shocks from a transvenous lead. A thrombus is seen on the endocardial surface of the RV that was adjacent to the transvenous electrode (A, dashed arrow) as well as subendocardial focal inflammation (arrow). Edema and acute inflammation were also detected in the subcutaneous tissue and skeletal muscle in the defibrillator can pocket (B, arrow) following implantation and shocks delivered by the control ICD. Bar = 0.5 mm.

Table 1

Enzymes at baseline and following shocks with a subcutaneous or a transvenous control electrode

	Baseline	4-hours	24-hours
Troponin I (ng/ml)			
S-ICD	0.06±0.03	0.12±0.11	0.13±0.13
Control	0.07±0.09	22.58±16.3 [*] , [†]	3.09±1.34 [*]
CK-MM (U/L)			
S-ICD	704±398	6544±1496 [*]	9705±6240 [*] , [†]
Control	691±303	2446±1092	3900±2060

Values are expressed as mean±SD.

^{*} P<0.05 compared to baseline[†] P<0.05 between the two groups at that time point

CK-MM = creatine kinase-muscle isoenzyme; S-ICD = subcutaneous ICD system

Table 2

Semi-quantitative grading of histological injury following S-ICD shocks

Tissue Injury & Hemorrhage	S-ICD Coil			S-ICD Pocket		TV Pocket
	S-ICD (shock)	Control (no shock)		S-ICD (shock)	Control (no shock)	Control (shock)
Electrode Tip	1.8	1.3	Pocket Center	2.0	1.7	1.3
Coil Distal	1.8	1.0	Pocket 12:00 o'clock	1.8	1.5	1.8
Coil Proximal	1.8	1.8	Pocket 3:00 o'clock	1.3	1.8	1.8
			Pocket 6:00 o'clock	1.8	1.0	2.0
			Pocket 9:00 o'clock	2.0	1.0	1.8
<i>Average</i>	<i>1.8</i>	<i>1.4</i>		<i>1.8</i>	<i>1.4</i>	<i>1.7</i>
Inflammatory Infiltrate						
Tip Distal	1.8	1.3	Pocket Center	1.8	1.5	1.3
Coil Distal	1.5	1.3	Pocket 12:00 o'clock	1.8	0.5	1.8
Coil Proximal	1.5	1.3	Pocket 3:00 o'clock	1.3	2.0	1.8
			Pocket 6:00 o'clock	1.8	1.2	2.3
			Pocket 9:00 o'clock	2.0	1.5	1.8
<i>Average</i>	<i>1.6</i>	<i>1.3</i>		<i>1.7</i>	<i>1.3</i>	<i>1.8</i>

Scoring could range from 0 (no change) to 3 (severe). Numbers represent the average score for a given site across the 4 control or S-ICD animals.
 S-ICD = subcutaneous implantable cardioverter-defibrillator; TV = transvenous