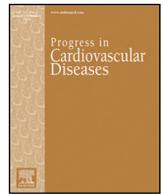




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Evolution of extravascular implantable defibrillator technologies[☆]

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ABSTRACT

The implantable cardioverter-defibrillator (ICD) has been successfully treating patients with lethal ventricular arrhythmias for decades. The main acute and chronic complications of this therapy modality are related to the use of a transvenous lead. An entirely extravascular ICD concept was developed over the last 20 years, with emergence of the subcutaneous ICD (S-ICD). This device was approved for clinical use seven years ago, and accumulating real-life experience confirms its safety and efficacy. The main limitations related to this system include the lack of pacing capabilities for bradycardia, tachycardia or resynchronization therapy, a large size, and relatively high energy requirements for effective defibrillation. This review article summarizes current knowledge and potential future developments of the extravascular ICD technologies.

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The implantable cardioverter-defibrillator (ICD) is the cornerstone therapy for primary and secondary prevention of sudden cardiac death (SCD).^{1–4} However, conventional transvenous (TV) ICD systems have been associated with significant acute and chronic complications, the majority of which are related to the use of TV leads.^{5–7} Acutely, lead insertion can cause a pneumothorax, hemothorax or perforation of cardiac or vascular structures. Over the long term, lead failure and

infection can require TV lead extraction, which by itself can cause significant morbidity and mortality.^{8–10} Insertion of TV leads can also be challenging in patients with venous occlusions or congenital heart disease. To eliminate the need for a TV lead, an entirely subcutaneous ICD (S-ICD) was introduced.¹¹ In this review article, current knowledge about the S-ICD, the limitations that are inherent to its design, and different current and future strategies to overcome these limitations are summarized.

S-ICD: development, current applications and limitations

The S-ICD was developed to provide reliable detection and treatment of life-threatening ventricular arrhythmias while preventing complications related to TV leads. Although animal models were used early during the development of the ICD with extrathoracic electrodes,¹² animal models cannot sufficiently replicate the human conditions needed to test various cardiac sensing and defibrillation vectors during the development of an extravascular defibrillator. The first human feasibility

Abbreviations and acronyms: AF, atrial fibrillation; ATP, anti-tachycardia pacing; CRT, cardiac resynchronization therapy; DFT, defibrillation thresholds; FDA, Federal Drug Administration; ICD, implantable cardioverter defibrillator; IDE, implantable device exemption; LV, left ventricle or ventricular; MRI, magnetic resonance imaging; SCD, sudden cardiac death; S-ICD, subcutaneous-implantable cardioverter defibrillator; SVT, supraventricular tachycardia; TV, transvenous; TV-ICD, transvenous-implantable cardioverter defibrillator; US, United States; VF, ventricular fibrillation; VT, ventricular tachycardia.

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trial was presented in 2002, using an electrode in the precordial left thorax.¹³ Following this study, regulatory approval clinical trials were conducted between 2001 and 2009, and reported by Bardy et al.¹¹ The initial short-term trials identified the best electrode configuration for a S-ICD, and compared that configuration to a TV-ICD. A left lateral pulse generator implant location with an 8-cm left parasternal shocking coil had the lowest mean defibrillation threshold (DFT). A PA and lateral chest X-ray of a patient after successful implantation of a S-ICD is shown in Fig. 1. In the Bardy study, it appeared that failed defibrillation was frequently related to incorrect position of the parasternal coil. In the patient whose S-ICD failed defibrillation testing, the parasternal electrode had been incorrectly positioned approximately 6 cm to the left of the sternum, beyond the left lateral margin of the heart. However, even when appropriately positioned, this configuration still had significantly higher defibrillation energy requirements compared to a TV-ICD (mean DFT 11.1 ± 8.5 J for TV-ICD vs 36.6 ± 19.8 J for S-ICD, $p < 0.001$).

After a pilot study involving 6 patients who underwent S-ICD implantation with successful DFT testing, a single-group clinical trial was conducted in European centers.¹¹ A total of 55 patients with an indication for ICD implantation, but without a need for antibradycardia pacing or a presumed need for antitachycardia pacing (ATP) [i.e., a history of ventricular tachycardia (VT) at rates slower than 170 beats/min or documented termination of VT with ATP] were enrolled. They received a 3-mm tripolar parasternal lead connected to a pulse generator implanted over the 6th rib between the anterior and midaxillary lines. Ventricular fibrillation (VF) induced at the time of device implantation was successfully detected in all patients and appropriately converted in 98% of patients with 65-J shocks. The average follow up was 10 months. A pocket infection developed in two patients: pocket revision was performed in one patient, and the other elected to discontinue defibrillator therapy. Lead dislodgement occurred in four patients: in three patients, lead repositioning was required within a week after surgery; in the fourth patient, lead dislodgement occurred at 6 months, during vigorous physical activity.

Following the pilot study, a prospective, non-randomized investigational device exemption (IDE) trial enrolled 330 patients in 33 sites across the United States (US), New Zealand, the Netherlands and the United Kingdom.¹⁴ Patients who had an indication for ICD implantation without need for pacing or documented pace-terminable VT were selected. 314 patients who underwent successful implantation were followed for 180 days, with the primary safety endpoint being the S-ICD complication-free rate, and the primary effectiveness endpoint being the acute conversion rate of induced VF at the time of implantation. The primary effectiveness endpoint was achieved in 100% of patients who underwent the full testing protocol. In terms of safety, the 180-day device and procedure-related complication-free rate was 92.1%. This exceeded the performance goal of 79%. Notably, the incidence of inappropriate shocks was 13.1% over an average follow-up period of 11 months. This was mostly secondary to cardiac oversensing (usually of T waves), or supraventricular tachycardia (SVT) at rates above the discrimination zone. It was noted that the use of an SVT discrimination zone was associated with a lower risk of inappropriate shocks for SVT. Consequently, the use of dual-zone programming with an SVT discrimination zone was more frequent in the latter two-thirds of the patients enrolled. The results of this trial led to approval of the S-ICD by the United States (US) Federal Drug Administration (FDA) in 2012.

In an effort to obtain real-world data, the EFFORTLESS registry (Evaluation of FACTORs Impacting Clinical Outcome and Cost Effectiveness of the S-ICD) collected outcomes in 985 patients at 42 clinical centers in 10 countries during a 5-year period.¹⁵ Pre-specified endpoints were the perioperative complication rate (30 days post-implant), 360-day complication rate, and rate of inappropriate shocks for atrial fibrillation (AF) or SVT. For the purpose of this study, complications for the primary endpoint were defined as adverse events that resulted in an invasive intervention. The overall 30-day complication rate was 4.1%, and the 360-day complication rate was 8.4%, with 11.7% of patients having suffered a complication over the average 3.1-year follow-up. The most common reported complication was infection requiring device removal (2.4%).

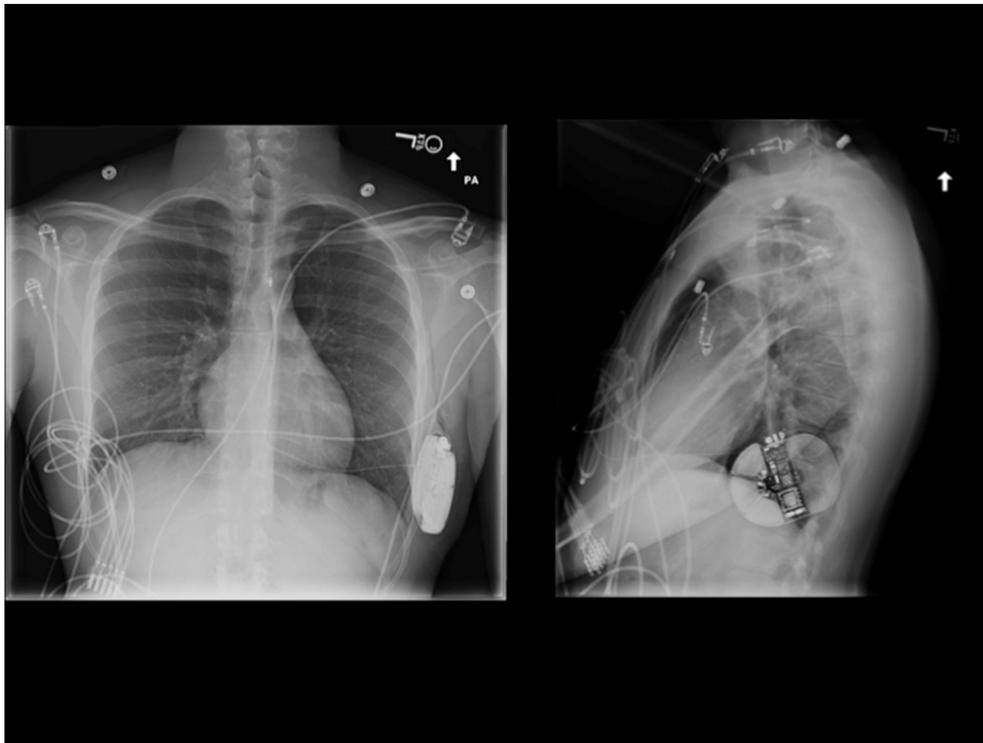


Fig. 1. Postoperative chest X-ray postero-anterior (left) and lateral views (right) of a patient after S-ICD implantation. The generator is located over the left ventricular apex in the midaxillary line and the sensing and defibrillation lead with an 8-cm coil is implanted on the fascia along the left parasternal space. Note that in the lateral view, the device is located posteriorly projecting over the retrocardiac space, to lower defibrillation energy requirements.

Notably, the overall 1-year complication rate improved over time, suggesting a learning curve. Whereas the rate of inappropriate shocks for AF or SVT was relatively low (2.3% at 3.1 years), the overall rate of inappropriate shocks was much higher (11.7%) with the majority being secondary to T-wave oversensing or low amplitude signals (63% of all inappropriate shocks). Importantly, 10.6% of patients received an appropriate shock for ventricular arrhythmias over the follow-up period. The overall conversion success for discrete spontaneous episodes was 97.4%. Interestingly, almost half of these patients were treated for monomorphic VT. Examples of appropriate shocks for VT/VF are shown in Fig. 2.

The currently available, second-generation, subcutaneous defibrillator is a 59 cc device and can deliver an 80-J shock as well as post shock pacing for up to 30 s. It is capable of remote monitoring, is magnetic resonance imaging (MRI) compatible, and has an estimated battery longevity of 7.3 years. However, relative to TV ICDs, the S-ICD continues to have limitations that include the inability to pace, a longer time to therapy, larger size, more incisions/tunneling/sedation required at implant, shorter battery longevity, problems with oversensing/need for pre- and postprocedure screening, continued need for defibrillation testing at implant, and overall less clinical experience.

To determine how significant the limitations of the S-ICD are in clinical practice, including the potential need for atrial or ventricular pacing, development of an indication for cardiac resynchronization therapy (CRT), or termination of a ventricular arrhythmia by ATP, Melles et al. studied their prospectively collected registry of all patients who received an ICD at their institution between 1998 and 2017.¹⁶ They retrospectively focused on patients who would have been candidates for a S-ICD (i.e., excluding patients with indications for antibradycardia pacing, or who had known monomorphic VT), and assessed their inappropriateness for a S-ICD over time. Among 254 patients, 31% became ineligible for S-ICD during the follow-up period. Noneligibility was caused more often by appropriate ATP (4.9 per 100-patient-years) than by development of need for antibradycardia pacing or CRT. There was no

clear baseline determinant that could predict future unsuitability in this study. Despite these findings, the explanation rate for a change in indication in the EFFORTLESS S-ICD registry was very low (1.3% over 3.1-year follow-up).¹⁵

With the approval of the S-ICD system by the FDA, a post-approval follow-up study was mandated. This prospective registry was started in 2013 and included all patients deemed appropriate for an S-ICD in the US, and with predicted life expectancy >1 year. The primary safety endpoint was S-ICD system-related complications at 60 months. 1637 patients were included in the registry over 3 years.¹⁷ Overall, patients in this registry had more comorbidities than in the prior studies, with a higher prevalence of end-stage renal disease requiring dialysis (13.4%) and more patients with reduced left ventricular (LV) systolic function (mean LV ejection fraction was 32.0 ± 14.6%). Despite the higher rate of comorbidities, acute and 30-day safety was comparable to prior studies. Among patients with complete data, acute defibrillation testing was successful in 98.7% of cases. 7 patients required explantation due to failed VT/VF conversion testing. Prior TV-ICD extraction was the most significant predictor of failed defibrillation testing in a multivariate analysis, with OR 2.61 (95% confidence interval 1.25–5.45). Freedom from device- and procedure-related complications at 30 days was 96.2%, with the highest complication rates being related to infection and hematoma (1.2% and 0.4%, respectively). In a multivariate analysis, diabetes, younger age and higher BMI were positive predictors of complications within 30 days.

While the IDE trial and registries detailed above provided crucial information regarding efficacy and safety of the S-ICD platform, a randomized trial comparing S-ICD to TV-ICD for patients without need for bradypacing or tachypacing remains unavailable at this time. This has limited the level of indication for the S-ICD in the latest “2017 AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death”,¹⁸ with S-ICD receiving a Class IIa recommendation for patients without need for

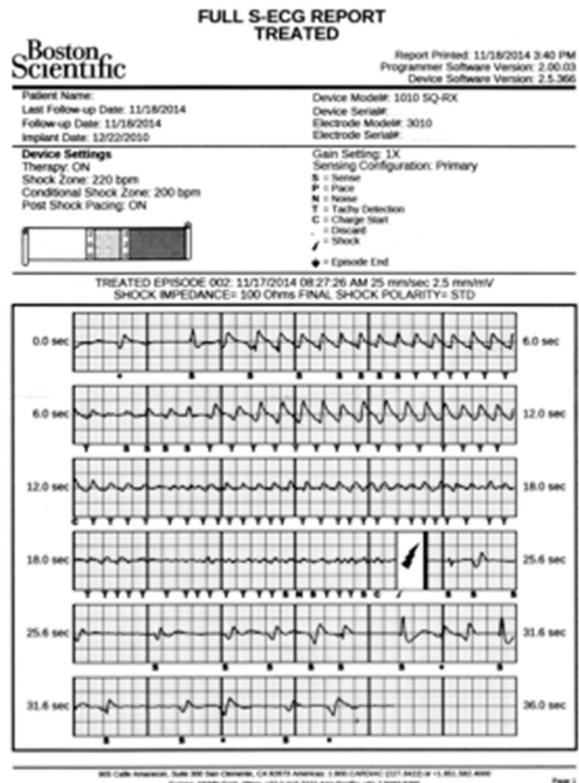
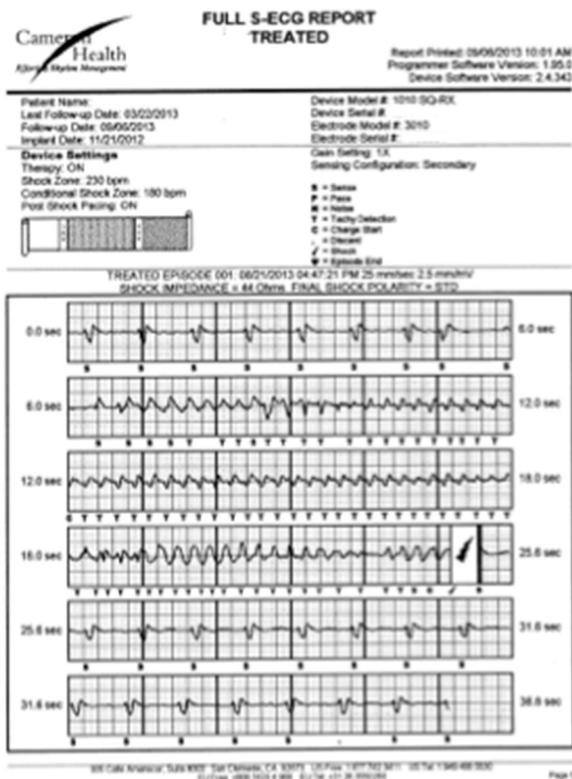


Fig. 2. S-ICD stored electrograms showing two appropriately detected and treated episodes of polymorphic VT (left) and VT progressing to VF (right).

bradypacing, ATP or CRT, and a Class Ia recommendation limited to patients who have inadequate vascular access or are at high risk for infection. The PRAETORIAN trial, a randomized, controlled, multicenter, prospective 2-arm trial comparing S-ICD and TV-ICD,¹⁹ was designed to answer this question. This study is expected to be completed at the end of 2019, and its results will likely inform future guidelines.

The significant limitations related to the S-ICD drove further innovation to try to address the need for better sensing, lower DFTs, and ability to deliver antibradycardia pacing or ATP without a transvenous lead. Recent refinements in the sensing algorithm and implant position, and two other concepts that are currently being investigated, are discussed next.

Improved sensing algorithms

To refine detection of arrhythmias and minimize oversensing, several algorithms were developed over time. First, as described in the IDE trial, a conditional zone was added at rates below the shock zone to help discriminate SVT from VT.²⁰ When the heart rate falls within the conditional zone, the morphology of the QRS complex and T wave are compared to a template obtained while in normal rhythm. If it matches the template, it is sensed as supraventricular in origin. If the tachycardia does not match the template, it is analyzed for uniformity and QRS width (with a cutoff of 20 ms above template duration). When compared to a single zone, dual zone programming led to a significant reduction in inappropriate shocks in the IDE cohort (hazard ratio 0.38).

Patients with small R waves and large T waves in all three of the S-ICD sensing vectors are at increased risk of T-wave oversensing. During the initial stages of development and availability of the S-ICD, patients were screened prior to implant to identify individuals at risk of oversensing. Prior to all implants, a screening 3-lead surface electrocardiogram must be recorded in the supine and upright positions, and electrocardiographic R waves, T waves, and ratio of R to T wave amplitudes are assessed. The cutaneous electrodes are placed in the same position as the planned subcutaneous electrodes would be to confirm that the signals are sufficient for the S-ICD to adequately sense cardiac potentials and not double count the T-wave in at least two of the three available sensing vectors, with the patient in both a supine and upright position. Although there are limited data related to the value of repeating this testing with exercise, it is reasonable to do so in young and active patients as an extra precaution. If these signals are insufficient, the patient is deemed not to be a candidate for S-ICD implant for concern of inappropriate sensing. Some studies found that certain standard electrocardiographic findings such as T-wave inversion in the inferior leads predicted screening failure.²¹ This tedious manual process was an obstacle to adoption of the S-ICD. A new automatic version is currently available using the programmer and has made screening patients more objective and simpler.²² Despite successful screening, some patients still receive inappropriate shocks for T-wave oversensing due to the dynamic nature of the QRS:T-wave ratio with body position, heart rate, etc. However, with more troubleshooting experience, patients with T-wave oversensing, caused by changes in body position for example, can be successfully managed with device reprogramming and use of a different sensing vector (Fig. 3).

T-wave oversensing was further addressed with a new algorithm developed with a database of recorded episodes containing both T-wave oversensing and appropriate therapies.²³ This algorithm involves comparison of 3 consecutive deflections, such as when two similar QRS complexes are separated by a dissimilar complex (QRS – T – QRS). In addition to a direct comparison of complexes to each other, the algorithm also integrates the width of each complex and the intervals between complexes to enhance its performance. This algorithm was validated using a second electrogram dataset and led to a 30.7% reduction in T wave oversensing.

Refinement in implantation

Currently, defibrillation testing is recommended for all patients receiving a S-ICD. In the EFFORTLESS registry, 17 patients required repositioning of either the generator or electrode for defibrillation failure.¹⁵ A computer modeling study investigated the possible causes for high DFTs.²⁴ The model was based on MRI imaging and was used to test different generator and coil positions. The generator was virtually moved from the standard position (at the level of the 6th rib in the midaxillary line) by 4 cm posteriorly, anteriorly, cranially or caudally. The coil was placed at the left parasternal border, with variable thickness of modeled fat between the fascia and the coil. The heart size was also changed to emulate dilated cardiomyopathy. With each of these changes, the authors modeled DFTs and shock impedances. Location of the generator 4 cm posterior to the midaxillary line generated the lowest DFT, and the most anterior location increased DFT significantly. Cranial and caudal displacements were slightly less favorable. Fat under the coil caused a direct increase in DFT, with fat under the generator causing a less pronounced increase in DFT than fat under the coil. Modeled dilated cardiomyopathy showed similar results, with slightly reduced DFTs in all positions when compared to a normal heart. Overall, this study suggests that a more posterior location of the generator and placement of the coil directly on the sternal fascia might be preferable to prevent unacceptably high DFTs. Even if this has not yet been validated in patient cohorts with more variable anatomy, these results should encourage a deeper insertion of the S-ICD system, and consideration of a more posterior technique. Fig. 4 shows a very posterior S-ICD generator position after the device was implanted using an intermuscular approach between the serratus anterior and latissimus dorsi muscles.

The important effect of generator location and adiposity on DFT led to the development of a score to help distinguish patients at high risk of failed defibrillation testing.²⁵ This score is being evaluated in an ongoing prospective randomized trial comparing conventional acute defibrillation testing with the use of the score without defibrillation.

Much has been learned since introduction of the S-ICD. With more experience implanting the device and managing new issues that have arisen, physicians implanting the S-ICD are now able to successfully implant the device in patients with varying anatomical challenges that include very small patients, young patients, obese patients (Fig. 5), patients with a LV assist device²⁶ and in those with congenital heart disease or dextrocardia. A two-incision approach is commonly used now to avoid the superior sternal incision by using a tunneling tool and peel-away sheath. In addition, there are more data available now that demonstrate safety and efficacy in certain subsets of patients including patients with primary electrical disorders such as long QT syndrome and hypertrophic cardiomyopathy. There is also experience now showing that the parasternal lead can be safely salvaged during a sternotomy. Fig. 6 shows a woman undergoing sternotomy during which the lead was preserved by moving it out of the field and then reimplanting it to the left of the sternum after sternal closure.²⁷

Substernal lead placement

Chan et al. first reported the use of the substernal space for lead placement instead of the left parasternal location used for the S-ICD system.²⁸ The rationale was that closer proximity to the heart would allow effective defibrillation with a lower shock energy, as well as painless pacing at a lower output than with the conventional S-ICD. Sixteen subjects who were scheduled to undergo a sternotomy or ICD implantation were enrolled in the feasibility study. Prior to their scheduled procedure, they received a left substernal lead with an 8-cm defibrillation coil via a subxiphoid approach and under fluoroscopic guidance. The lead was placed in close proximity to the right ventricle. A skin patch electrode was positioned along the left midaxillary line and both were connected to an external pulse generator. Among the 14 subjects with successfully induced VF, 13 (93%) had a successful defibrillation at

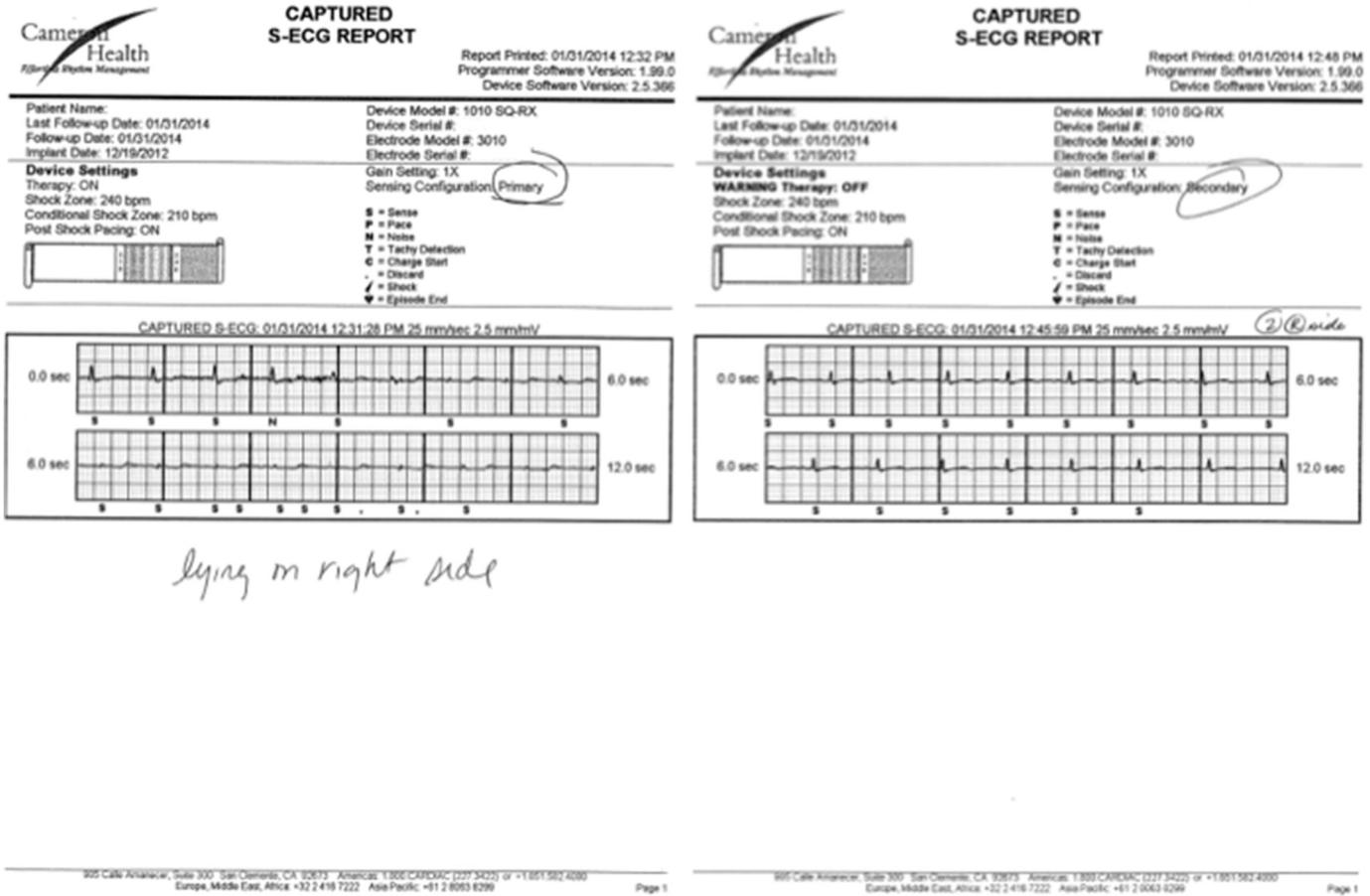


Fig. 3. S-ICD stored electrograms of a patient lying on his right side showing undersensing of the QRS when the using primary sensing vector (left). After changing settings to the secondary sensing vector, appropriate sensing was restored (right).

35 J. For comparison, the S-ICD system requires 65 to 80 J for defibrillation. The one failure to defibrillate was associated with a more left lateral placement of the lead with the tip protruding above the heart border. Following this small feasibility study, a larger prospective multicenter acute study was performed using a lead specifically designed for the substernal space.²⁹ In this study, Boersma et al. enrolled 87 patients across 16 sites who, as previously, were scheduled for a surgical

procedure requiring a sternotomy or an ICD (TV-ICD or S-ICD). 79 patients underwent substernal lead placement, using a commercially available tunneling tool or an investigational tool. The lead used in this study was investigational, with 2 ring electrodes used for pacing and sensing, and 2 coil electrodes for pacing, sensing and defibrillation. When coupled together, both coils are equivalent to an 8-cm defibrillation coil. This lead and a patch electrode placed on the left mid-axillary

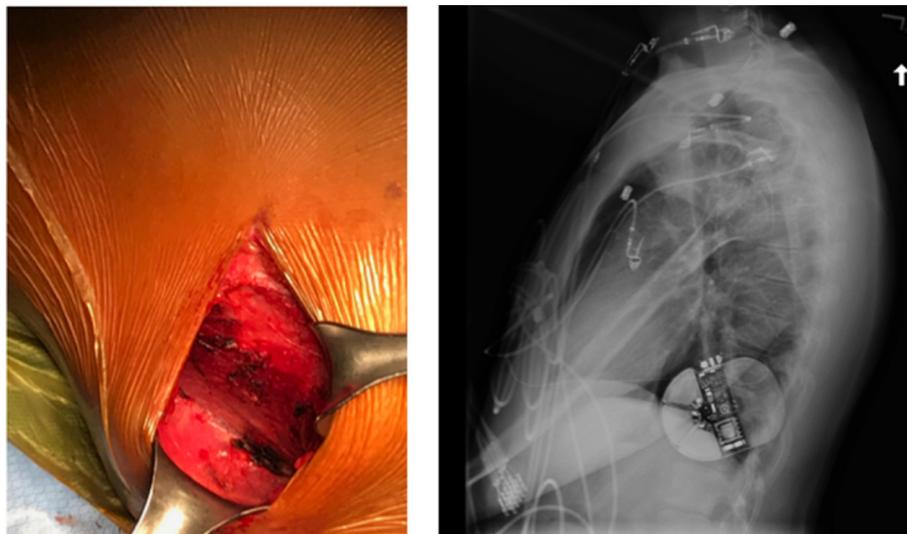


Fig. 4. Intraoperative photograph (left) and lateral chest X-ray (right) of a patient also shown in Fig. 1, who underwent S-ICD implantation using an intermuscular approach (between the serratus anterior and latissimus dorsi muscles), allowing for a more posterior location and a more favorable shocking vector.

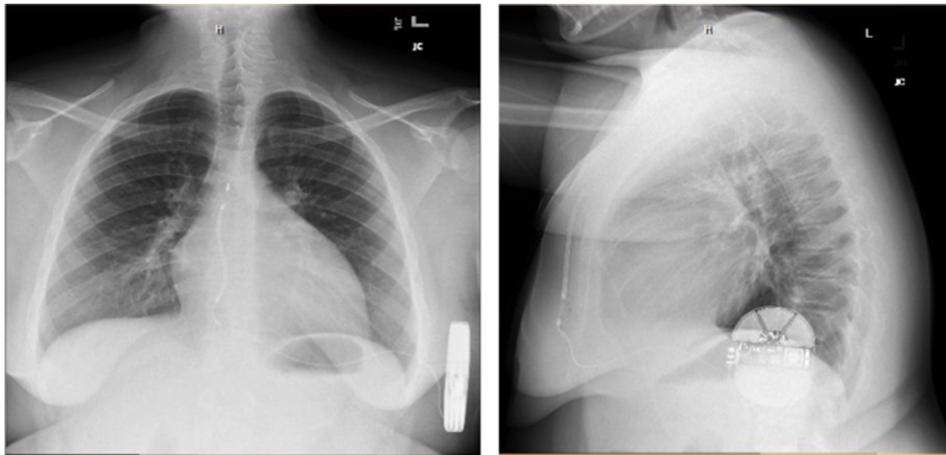


Fig. 5. Postero-anterior (left) and lateral (right) chest X-rays of an obese 15-year-old patient with a severe dilated cardiomyopathy and heart failure who underwent S-ICD implantation for primary prevention of sudden death.

line or a subcutaneous active can emulator were connected to an external defibrillator. Ventricular pacing capture was successful in at least one vector for 97.4% of patients. Capture was most successful using the high-voltage coils 1 and 2. Low-voltage vectors (ring 1 to ring 2, or ring 1 to coil 2) were less successful (82.1% of tested patients). Of note, mean capture voltage was fairly high (around 10 V for the high-voltage vector, around 5 V for the low voltage vectors). Up to two episodes of VF were induced in each patient. A single 30 J shock was delivered between the patch or active can emulator and both coils coupled together. The shock successfully terminated 81.3% of induced VF episodes. Notably, all failures occurred in patients in whom a defibrillation

patch electrode was used. Overall, this rate of first-shock defibrillation efficacy is similar to the observed efficacy of 77% to 93% in TV-ICDs.^{30,31} Expectations for first-shock efficacy have increased over time, however.

Seven adverse events occurred in 6 of the 79 patients enrolled in this study (5 adjudicated as causally related, 2 as possibly related). Only one of the 5 causally related events was serious, with the patient developing pericardial tamponade from the substernal tunneling procedure. However, the study sample was small, and further investigation will be required to determine the safety of substernal lead implantation. Overall, the substernal approach proves to be a promising evolution of the S-ICD, with possibility to deliver effective defibrillation with a lower energy and mostly, with the possibility to adequately sense the RV and deliver pacing as well. Future studies are needed outside of the acute setting and to appropriately assess how effective this system will be, particularly in regards to antibradycardia pacing and ATP. Patients are currently being enrolled in a pilot trial outside of the US of permanent implantation of an extravascular ICD with a substernal lead, and there are plans for a large pivotal international trial to be conducted soon.

The modular cardiac rhythm management system

Tjong et al. proposed another approach to circumvent the pacing limitations of the S-ICD: by combining existing S-ICD technology with a leadless pacemaker, pacing capabilities could be added to the subcutaneous system in a modular fashion.³² Both devices have shown clinical efficacy and safety.^{11,33–36} The authors propose the use of the currently available EMBLEM™ S-ICD platform (Boston Scientific Corporation) that would require only a firmware update for unidirectional communication with a leadless pacemaker via the conductive properties of the human body. This would allow ATP capabilities in patients who already have a S-ICD in place. A pre-clinical study with large animals (sheep, pigs and dogs) tested acute and 3-month performance of this configuration. All animals received a S-ICD and a leadless pacemaker. ATP is requested via a series of short electrical pulses transmitted using a vector from the shocking coil to the can. The authors showed successful unidirectional communication from the S-ICD to the leadless pacemaker in 99% of communication attempts at baseline, and in 100% of communication attempts in the animals that were followed for 3 months. The authors note that all unsuccessful communication attempts occurred in the same animal, in which a suboptimal S-ICD position was noted. When communication was successful, all ATP requests triggered by the S-ICD resulted in ATP delivery. Importantly, right ventricular pacing with the leadless pacemaker did not result in oversensing by the S-ICD in this study. A subset of animals was evaluated for post-shock

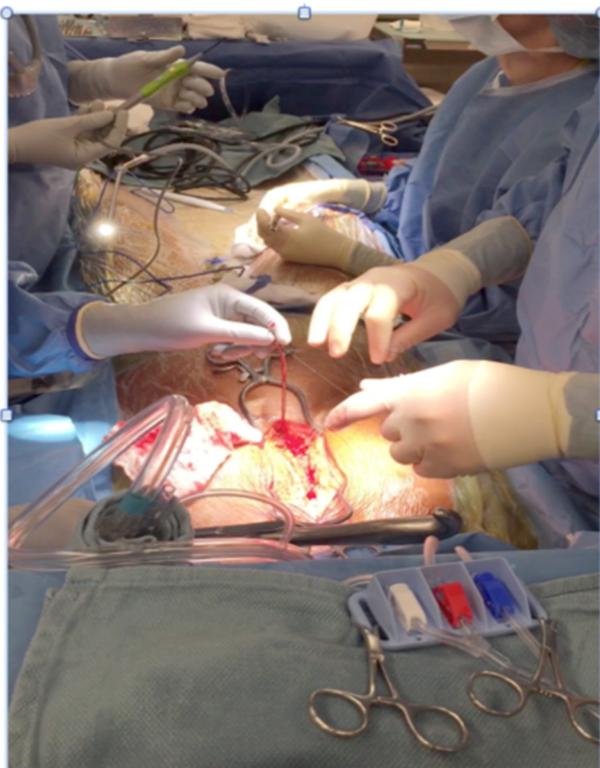


Fig. 6. Intraoperative photograph of a 63-year-old woman with an ischemic cardiomyopathy and prior S-ICD implanted in standard position for primary prevention of sudden death who required a sternotomy for coronary artery bypass grafting (CABG). Her defibrillation coil was preserved by dissecting out the lead and moving it out of the field prior to sternotomy, and then reimplanting it to the left of the sternum after sternal closure.

performance of the leadless pacemaker, and showed no alterations. Overall, this is a very promising solution for patients who develop the need for ATP after implantation of a S-ICD. However, the inherent limitations of the leadless pacemaker (limited longevity, difficulty retrieving and replacing the device at this time) remain applicable to this combination. Future developments of the leadless pacemaker platform, and possible use in other heart chambers as well (right atrium, LV) will allow a more widespread use of this technology. In addition, several specific issues will need to be addressed in future pre-clinical or clinical trials: although ventricular pacing did not result in oversensing by the S-ICD in this study, it is conceivable that this may occur in humans with more variable paced electrocardiograms. Bidirectional communication could overcome this expected risk. Electromagnetic interference is also of potential concern in this system. The investigators added two safety features to limit this risk (specific signal sequence and prevention of ATP below a certain threshold), but the efficacy of these safety features in real-life scenarios remains to be demonstrated.

Conclusions

The S-ICD has reduced the complications related to traditional ICDs, largely by the elimination of the TV lead, while providing effective primary and secondary prevention of SCD. While the rate of significant complications has remained low, the current S-ICD technology is limited by an inability to provide antibradycardia pacing or ATP, and by a fairly high rate of inappropriate shocks and high DFTs. Recent improvements in algorithms have minimized the rate of inappropriate shocks. Two approaches to circumvent pacing limitations are currently under investigation: a substernal lead, whose proximity to the right ventricle allows pacing; and a modular system integrating current S-ICD technology with a leadless pacemaker. Both technologies are predicted to continue to evolve over the next few years, with great potential for improvement in clinical practice.

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