Implantable cardioverter-defibrillators (ICDs) represent a very effective therapy for primary and secondary prevention of sudden cardiac death (SCD). However, implantation of endocardial leads using a transvenous approach is associated with significant procedural and long-term complications. An entirely subcutaneous ICD (S-ICD) has been developed, potentially eliminating many of the complications associated with traditional transvenous ICDs. This novel approach has been demonstrated to be a reliable and effective system for detection and termination of ventricular arrhythmias. The available therapeutic interventions are a result of the unique characteristics of a high energy subcutaneous delivery system, and therefore require appropriate patient selection to optimize therapeutic benefit and minimize the limitations of the first generation S-ICD. By maintaining the effectiveness of conventional ICDs while limiting the associated complications, the S-ICD provides an alternative therapy for clinicians treating many patients at risk for SCD. This review will examine the development of the subcutaneous ICD, its advantages, limitations, and potential clinical role in the treatment of ventricular tachyarrhythmias and prevention of SCD.

Background

Despite advances in cardiovascular care, SCD remains a significant public health issue. A variety of nonpharmacologic therapies for primary and secondary prevention of SCD exist, including ICDs by endovascular lead implantation or placement of epicardial defibrillation patches. Nonimplantable strategies for SCD protection in high-risk patients have also been attempted, including a wearable defibrillator vest, as well as automated external defibrillator use at home in selected cohorts. The subcutaneous ICD provides an alternative device for treatment of SCD.

The development of an entirely subcutaneous ICD was motivated initially by special circumstances where a traditional endovascular system was not practical. It was first applied in the pediatric population, where congenital anatomic variation often precludes safe endocardial lead placement; the technique was extended to other patient populations in whom venous access may be obstructed, may need to be preserved, or in which chronic endovascular leads may have a very high risk of secondary infection, as in the case of patients with chronic indwelling catheters. These systems often required an epicardial or transvenous lead for sensing, similar to the initial ICD systems developed more than 25 years ago. As a consequence of the inability or desire not to place endovascular leads in such patients, a subcutaneous approach emerged as case reports, primarily in the pediatric population. However, these early hybrid systems were traditional transvenous ICDs with leads placed in the subcutaneous space, and only later incorporated dedicated subcutaneous leads. As the feasibility of a dedicated S-ICD became apparent, so did greater recognition of the increasing long-term risks of endovascular lead placement, including intravascular infection, pneumothorax, vein thrombosis, and lead fracture. Similarly, the morbidity and mortality associated with revision and extraction of chronic endocardial leads highlighted potential long-term benefits of a subcutaneous device. The clinical requirement to avoid a transvenous approach, as well as the apparent benefits, including risk avoidance, ultimately resulted in more formal attempts to develop an entirely subcutaneous ICD. As a novel approach for prevention of sudden cardiac death, the development of an S-ICD required demonstration of a highly sensitive arrhythmia detection algorithm as well as reliable defibrillation.

Arrhythmia Detection

A subcutaneous ICD presents unique challenges for identification of life-threatening ventricular tachyarrhythmias. Because of the subcutaneous electrode location, myopotentials, noise, and low voltage electrograms make diagnostic discriminators fundamentally different than that of transvenous ICDs. This raises concern of the ability to detect ventricular tachyarrhythmias accurately, and in particular ventricular fibrillation (VF). In contrast, the ultra far field signal recorded with subcutaneous leads more closely mimics the surface ECG, and theoretically may improve arrhythmia discrimination.

Subcutaneous versus Transvenous Arrhythmia Recognition Testing (START) was designed as a prospective study to compare arrhythmia detection with transvenous and subcutaneous signals. A library of induced arrhythmias was constructed at the time of ICD implantation, with simultaneous recording of transvenous and cutaneous signals. These recordings were then played back into the header of each device offline to assess the comparative efficacy of the sensing algorithms to discriminate ventricular and supraventricular tachyarrhythmias. The sensitivity for the detection of ventricular
Table 1. Primary Results From START Comparing Transvenous and Subcutaneous Discrimination for Induced Ventricular and Supraventricular Arrhythmias

<table>
<thead>
<tr>
<th></th>
<th>Transvenous*</th>
<th>Dual Chamber</th>
<th>S-ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriately withheld therapy</td>
<td>115</td>
<td>100</td>
<td>49</td>
</tr>
<tr>
<td>Inappropriate defibrillation</td>
<td>35</td>
<td>47</td>
<td>1</td>
</tr>
<tr>
<td>Specificity</td>
<td>76.7%</td>
<td>68%</td>
<td>98%</td>
</tr>
</tbody>
</table>

*Pooled results from 3 manufacturers with devices programmed in single chamber or dual chamber mode.

S-ICD indicates subcutaneous implantable cardioverter-defibrillator; START, Subcutaneous versus Transvenous Arrhythmia Recognition Testing.


Arrhythmia Termination

Because of the subcutaneous placement of the shocking electrode, the energy required for successful defibrillation is higher than for transvenous ICDs (Figure 1). In a comparative study performed at the time of ICD implantation, the average defibrillation threshold for transvenous and S-ICDs was 11.1±8.5 J and 36.6±19.8 J, respectively (P<0.001), using a binary search algorithm. The electrodes used in this study were placed to mimic the location of the present commercially developed S-ICD system. The larger energy requirement for subcutaneous defibrillation places technological constraints on the S-ICD system, including larger pulse generator size, shorter battery life, and limited provision of nonshock therapies such as temporary pacing. Therefore, any subcutaneous ICD system must optimize energy output by using a lead configuration that promotes efficient and effective defibrillation that is technologically and biologically achievable.

The efficiency of subcutaneous defibrillation has been shown by finite element modeling to be improved by longer electrode coil length as well as using configurations that place the shock vector close to the center of ventricular myocardial mass. As such, other shock vectors have been assessed for defibrillation using various combinations of electrode lead length, lead placement, and pulse generator location. Grace et al evaluated an anterolateral shock vector using an 8 cm left parasternal electrode and a left lateral thoracic patch electrode. In 7 of 9 patients (78%), successful defibrillation was achieved using 50 J, whereas 2 patients required 100 J to terminate VF. Lieberman et al evaluated an anterior-anterior vector by placing the can in a clavicular pocket and an anterior cutaneous defibrillation patch electrode. In 7 of 9 patients (78%), successful defibrillation was achieved using 50 J, whereas 2 patients required 100 J to terminate VF. Lieberman et al evaluated an anterior-posterior shock vector placing the can in a low medial pectoral position and a 25 cm coil electrode tunneled posteriorly between the 6th and 10th intercostal spaces. Using this shock configuration, 26 out of 32 patients (81%) were defibrillated using 35 J or less. Of those, 18 patients were defibrillated with 17 J or less.

These pivotal studies demonstrated the ability to terminate ventricular arrhythmias using a variety of shock vectors and with variable energy requirements, thus leading to development of the fully implantable S-ICD. Prior to permanent implantation and long term testing of the present S-ICD system, 4 lead configurations were tested using specific anatomic landmarks. The configuration with the lowest mean defibrillation threshold at 32.5±17 J used a left lateral pulse...
generator and an 8 cm coil electrode positioned along the left parasternal margin. Other configurations tested (defibrillation threshold) included a left pectoral pulse generator with a left parasternal 4 cm coil electrode at the inferior sternum (40.4±13.7 J), a left pectoral pulse generator with an 8 cm coil electrode curving from the left inferior parasternal line across to the inferior margin of the left sixth rib (40.1±14.9 J), and a left lateral pulse generator with a left parasternal 5 cm oval disk (34.3±12.1 J).

Following selection of the optimal S-ICD configuration, the system then was evaluated in 59 patients who each had 2 episodes of VF induced at the time of implantation. Of these, 58 patients (98%) were successfully converted with 65 J on both occasions. The 59th patient was defibrillated successfully during the first but not second attempt. Following permanent implantation of the S-ICD, the device was set to deliver only 80 J shocks to ensure an adequate safety margin. During a mean 10 months of follow-up there were 12 episodes of spontaneous ventricular tachycardia occurring in 3 patients that were treated successfully. The successful termination of VF and sustained ventricular tachycardia (VT) also had been balanced with appropriately withheld therapies in patients with detected but nonsustained episodes. In a single center experience reporting on 31 S-ICD implants, 52 sustained episodes of VF induced at the time of implant were detected appropriately and treated in all episodes. Four patients had spontaneous ventricular tachyarrhythmias in an average of 286 days of follow-up, which were all treated successfully.

**The Subcutaneous Implantable Cardioverter-Defibrillator**

An entirely subcutaneous ICD (Cameron Health Incorporated) has been developed and is the first subcutaneous ICD permanently implanted with long term follow-up. As noted previously, acute studies at the time of transvenous ICD implantation demonstrated effective rhythm detection and defibrillation. The S-ICD can be implanted by use of anatomic landmarks, obviating the need for fluoroscopy, thereby reducing radiation exposure for both the patient and physician. With this system the pulse generator is placed in a left lateral position between the midaxillary and the anterior axillary lines. The pulse generator is connected to a 3 mm tripolar parasternal electrode (polycarbonate urethane) that is tunneled 1 to 2 cm to the left of and parallel with the sternal midline via 2 parasternal incisions. The electrode has a distal sensing electrode next to the xiphoid process, with an 8 cm shocking coil separating the 2 sensing electrodes.

Rhythm detection is performed using 1 of the 3 vectors formed between available combinations of either sensing electrode and pulse generator (proximal-to-canister (CAN), distal-to-CAN, and distal to proximal; Figure 2). Three different algorithms are applied to each cardiac signal to prevent double counting and T-wave oversensing. After the optimal sensing vector is automatically selected by the S-ICD, the heart rate then is calculated as the average of the last 4 intervals. When the optional discrimination zone is programmed “on”, tachyarrhythmias occurring between 170 and 240 bpm initiate arrhythmia discrimination analysis. This stepwise approach to arrhythmia discrimination incorporates template matching that is conceptually similar to that found in transvenous devices. However, transvenous ICDs typically use a limited number of analysis points for morphological comparison, whereas the S-ICD evaluates up to 41 points of the ventricular complex in an effort to improve signal resolution. Rhythm analysis is performed using an 18 of 24 beats duration criteria.

During device implantation arrhythmia termination is tested using 65 J shocks to establish an adequate safety margin. However, following implantation the device output is nonprogrammable and will only deliver 80 J shocks. The average capacitor charge time is 14±2 seconds, which is significantly longer than that of transvenous ICDs. After capacitor charging and prior to shock delivery, the arrhythmia is reconfirmed to ensure the presence of a sustained ventricular arrhythmia. If initial therapy is unsuccessful the device can reverse shock polarity automatically. Postshock asystole occurring for more than 3.5 seconds triggers demand pacing at 50 bpm using a 200 mA biphasic transthoracic pulse, and is available for 30 seconds. Up to 24 treated events can be stored with 120 seconds of recorded electrogram per event from arrhythmia onset to termination.

Complications of S-ICD implantation include lead migration, pocket infection, and parasternal lead dislodgement in the absence of adequate anchoring at the distal electrode. Long term data regarding lead durability is not yet available. Inappropriate shock therapy has been described resulting from myopotentials, oversensing, and double counting. In 1 report these issues were primarily resolved with software updates and alternative vector selection, though 1 patient required lead repositioning.
fact, with approximately 10% of delivered energy reaching the heart, cardiac myocytes are exposed to a relatively low voltage gradient. By contrast, endocardial defibrillation results in uneven energy delivery, with potentially high voltage gradients that can damage myocytes through the process of electroporation, leading to transient myocardial stunning. In animal models using serum troponin levels as a measure of myocardial injury following defibrillation, endocardial defibrillation resulted in significant troponin release at 35 J, while subcutaneous defibrillation with 80 J did not cause troponin release. Several studies have identified a relationship between ICD shocks and mortality, though it is unknown whether ICD shocks are a risk factor for mortality or a risk marker for disease severity, a defibrillation technique that minimizes myocyte damage theoretically may mitigate any potential hazard. This may be of particular importance in patients with already reduced left ventricular systolic function whose limited reserve may not withstand endocardial defibrillation associated myocardial injury.

Subcutaneous Implantable Cardioverter-Defibrillator Advantages

The subcutaneous ICD was initially developed for patients who were not candidates for transvenous ICDs, such as those with some congenital heart abnormalities or no venous access. However, there are several advantages of the subcutaneous approach that may make it a preferred approach for prevention of SCD rather than simply an alternative to transvenous ICDs in select patient populations (Table 2).

Without requiring venous access there is no risk of vascular injury and presumably a very low risk of systemic infection. Such an intravascular sparing procedure can be important when infectious risks are high or venous access must be preserved for other needs, such as hemodialysis. Patients with artificial valves or those receiving chronic immunosuppression may be excellent candidates for a subcutaneous ICD, as the consequences of systemic infection are more serious in these populations.

In addition to a simplified implantation procedure, the subcutaneous approach also avoids the risks associated with endovascular lead extraction. With the failure rate of transvenous leads variably reported as 28% to 40% at 8 years, a subcutaneous approach could substantially reduce risks associated with lead extraction and is particularly suited to young patients with a long life expectancy and higher lead failure rates due to active lifestyles. This includes patients with several genetic disorders where the risk of bradycardia and monomorphic VT is low, such as Brugada syndrome, long QT syndrome, and hypertrophic cardiomyopathy. Additionally, the S-ICD may prove beneficial in patients anticipating cardiac transplantation by avoiding significant endovascular fibrosis that may complicate surgical lead extraction at the time of transplant.

Paradoxically, the S-ICD may have some cosmetic advantages despite its larger size. The anatomic location in the lateral axilla is preferred anecdotally, particularly by women, to the prepectoral location of ICDs in some patients.

There may also be an inherent benefit to subcutaneous versus transvenous defibrillation. While S-ICDs have higher energy requirements for effective defibrillation, the energy is distributed more evenly throughout the myocardium. In fact, with approximately 10% of delivered energy reaching the heart, cardiac myocytes are exposed to a relatively low voltage gradient. By contrast, endocardial defibrillation results in uneven energy delivery, with potentially high voltage gradients that can damage myocytes through the process of electroporation, leading to transient myocardial stunning.

<table>
<thead>
<tr>
<th>Patient Selection</th>
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<tr>
<td>Favorable Factors</td>
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<tr>
<td>Young and active</td>
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<tr>
<td>CHD that limits lead placement</td>
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<tr>
<td>Indwelling catheters</td>
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<tr>
<td>Immunocompromised</td>
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<td>Inherited channelopathies</td>
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S-ICD indicates subcutaneous implantable cardioverter–defibrillator; VT, ventricular tachycardia; CHD, congenital heart disease; CRT, cardiac resynchronization therapy; ARVD, arrhythmogenic right ventricular dysplasia.

Subcutaneous Implantable Cardioverter-Defibrillator Limitations

In its current iteration there are several limitations of S-ICDs that may make the approach unsuitable for certain patient populations. The device is designed to deliver high energy shocks for termination of lethal arrhythmias but, with the exception of 30 s of backup pacing for postshock asystole, does not have backup pacing ability for bradyarrhythmias. Even in the absence of a clear bradycardia indication for pacing, a small percentage of patients who require ICDs go on to require pacing at a later time. Additionally, biventricular pacing in addition to an ICD (CRT-D) has been demonstrated to reduce heart failure hospitalizations and mortality in patients with heart failure, QRS prolongation, and reduced left ventricular systolic function. Cardiac resynchronization therapy remains an important therapeutic intervention not available with an S-ICD. In fact, patients with any pacing indication are best served with a transvenous ICD. Whereas the S-ICD is not intended for treatment of bradyarrhythmias, the treatment available for ventricular tachyarrhythmias is limited to high energy shocks without the ability to first attempt pace termination. Antitachycardia pacing (ATP) has been shown to be a safe and effective therapy for initial treatment of spontaneous fast VT, thereby limiting the number of shocks delivered. Though the association of both appropriate and inappropriate shocks with mortality is not fully understood, optimal ICD programming frequently incorporates initial attempts at ATP in an effort to avoid high energy shocks. This programming is supported by data suggesting that the potentially deleterious effect of ICD shocks can be mitigated in part by use of ATP. Therefore, the S-ICD should be avoided in patients with known monomorphic VT and potentially those at high risk for VT, such as sarcoidosis or right ventricular dysplasia.

In general, the clinical results with the use of dual chamber ICDs have been disappointing. Dual chamber pacing has been associated with worse clinical outcomes compared with backup single chamber pacing. Moreover, the addition of an atrial lead has not improved arrhythmia discrimination.

Table 2. Subcutaneous Implantable Cardioverter-Defibrillator Candidate Selection

<table>
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<th>S-ICD Candidate Selection</th>
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<tr>
<td>CHD that limits lead placement</td>
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However, recent data suggest that monitoring of atrial tachyarrhythmias has important prognostic significance,\textsuperscript{37-39} though such information is not available with the S-ICD. In patients requiring a primary or secondary prevention device who also have atrial arrhythmias, the ability to monitor atrial activity provides the opportunity to manage electrophysiological comorbidities more comprehensively. Whether judicious use of atrial detection offsets any deleterious effects of an additional lead and the often observed increased ventricular pacing remains to be determined.

Most transvenous ICDs are also capable of being monitored remotely, which simplifies follow-up, reduces office visits, and is associated with better patient outcomes. At present, the S-ICD has no remote monitoring capabilities.

Because of the higher energy requirements for subcutaneous defibrillation the pulse generator is larger compared with contemporary transvenous ICDs. Despite its larger size the anticipated battery life of the S-ICD is approximately 5 years, which is somewhat shorter than transvenous defibrillators, and may impact the cost effectiveness of this device.

In the absence of a previously standardized S-ICD system, long term safety and efficacy data are not currently available. While several European centers have presented their follow-up data for the S-ICD, the research and clinical cardiology community have significantly greater data and experience with transvenous systems. An improved long term understanding of battery life, lead durability, appropriate and inappropriate shocks, effective shocks, requirement for addition of a transvenous pacing lead, pain associated with subcutaneous defibrillation, and patient preference will help tailor patient selection.

Discussion

The development of an entirely subcutaneous ICD represents one of the most significant changes in implantable ICD technology in the last 10 years and may change the approach to many subjects at increased risk of SCD. There are several important implications of the subcutaneous approach. First, it provides a clinically proven ICD system for patients who are either not eligible for a traditional endovascular ICD or are at high risk for endovascular lead placement. Such patients may now be able to receive clinically proven protection from SCD without the risks associated with endovascular leads. Second, by standardizing a subcutaneous system, important clinical outcomes can be compared more directly with other available traditional ICDs, thereby further tailoring each system to patient populations that are likely to benefit most from each therapy. Third, the improved specificity of arrhythmia discrimination provides additional insight into successful sensing vectors and arrhythmia algorithms. Finally, ICD technology can be disseminated more widely as fluoroscopy, and training in electrophysiology is not needed for the implant procedure. The need for defibrillation efficacy testing will be determined by ongoing studies, but the potential exists eventually for this system to be implantable in any facility with sterile procedure rooms and a physician with basic surgical skills. This would widely expand implant centers, not only in North America and Europe, but even more so in other geographies with fewer electrophysiologists.

Interestingly, the S-ICD does not separately evaluate atrial activity, though it had the highest specificity for ventricular arrhythmias when compared with both single chamber and dual chamber transvenous systems in START. There are several possible explanations for this finding, including the earlier use of morphology discriminators in the S-ICD compared with late stage morphology discriminators used by most transvenous ICD systems, the number of data points obtained for morphology template comparison, or the ultra far field electrograms that are used for interpretation. The improved specificity may lead to further analysis of current ICDs and ultimately result in improved arrhythmia discrimination. Long term data are still needed to insure that this improved detection with induced rhythms translates into better discrimination of spontaneous arrhythmias as well as extracardiac signals, both biological (eg, pectoral and diaphragmatic myopotentials) and extrinsic noise.

Although the S-ICD has been demonstrated to identify and treat ventricular arrhythmias accurately and effectively, there are several technical limitations that will limit its more widespread use. The absence of any pacing ability, other than postshock, eliminates several important clinical therapies, including back up pacing for bradyarrhythmias, resynchronization therapy for heart failure, and antitachycardia pacing. Whereas patients who develop a pacing indication after placement of an S-ICD can still have endovascular pacing leads placed, this eliminates significantly reduces the more favorable risk profile of the S-ICD and is a very costly strategy. Furthermore, additional diagnostic information and the simplicity of follow-up associated with remote monitoring capabilities is a technical limitation of the S-ICD at this time.

There are many patients in whom the limitations of the S-ICD appear less than the long term complications and risks of transvenous devices. Therefore, the S-ICD may be a preferred approach for primary prevention in young patients, dialysis patients, those with previous infected systems, and those with inherited diseases such as Brugada syndrome, long QT syndrome, or idiopathic VF where the risk of VT is very low. The role of subcutaneous ICDs in other populations will evolve over time as long term data become available comparing outcomes with transvenous ICDs.

Clearly some patients will not be candidates for an S-ICD and others will be excellent candidates; the majority of patients requiring an ICD, however, will likely be candidates for either a subcutaneous or transvenous device. The largest determinate of device selection is likely to be clinician preference and experience. With relatively few clinicians currently trained in the S-ICD implant technique, it is likely that the transvenous approach will continue to be preferred, especially as long term efficacy and safety data continue to be acquired. However, with increased physician training in implant technique as well as patient selection, the S-ICD is likely to gain in popularity.

Conclusion

The subcutaneous approach to ICD implantation was developed initially for patients in whom a transvenous approach
was not feasible. Having demonstrated effective arrhythmia detection, discrimination, and termination, the first purpose built entirely subcutaneous ICD was developed. With appropriate patient selection, the S-ICD is emerging as an effective alternative to transvenous systems for primary and secondary prevention of sudden cardiac death.

Disclosures
Dr Gold is a consultant, is involved in clinical trials, and receives honoraria from Boston Scientific, Cameron Health, Medtronic, St. Jude, and Sorin.

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Christopher P. Rowley and Michael R. Gold

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