Disease Severity and Exercise Testing Reduce Subcutaneous Implantable Cardioverter-Defibrillator Left Sternal ECG Screening Success in Hypertrophic Cardiomyopathy

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Background—The features of the hypertrophic cardiomyopathy (HCM) ECG make it a challenge for subcutaneous implantable cardioverter-defibrillator (S-ICD) screening. We aimed to investigate the causes of screening failure at rest and on exercise to inform optimal S-ICD ECG vector development.

Methods and Results—One hundred and thirty-one HCM patients (age, 50±16 years; 92 males and 39 females) with ≥1 HCM risk factor for sudden death underwent S-ICD ECG screening at rest and on exercise. Fifty patients (38%) were ineligible for S-ICD because of screening failure in every lead vector: 33 (66%) failed in the supine position, 12 (24%) failed in the standing position, and 5 (10%) failed on exercise. In patients who could exercise and passed screening at rest, 31 (44%) had 1 vector safety, 16 (23%) had 2 vector safety, and 24 (33%) had 3 vector safety. Increased R:T wave ratio in the S-ICD screening ECG (odds ratio, 4.0; confidence interval, 3.0–5.3; P<0.001) was associated with screening failure, while R:T ratio <3 in aVF (odds ratio, 0.3; confidence interval, 0.12–0.69; P=0.006) and increasing age (odds ratio, 0.97; confidence interval, 0.95–0.99; P=0.03) was associated with reduced screening failure. European Society of Cardiology risk score was higher in those failing screening (risk score 5.5% [interquartile range, 3.2–8.7] in failed versus 4.5% [interquartile range, 2.9–7.4] in passed; P=0.04).

Conclusions—HCM patients have a significant incidence of screening failure, which is determined primarily by the increased R:T wave ratio on the screening ECG and lead aVF. High-risk patients have an increased screening failure rate. Optimization of sensing algorithms is required to ensure that the highest risk HCM patients can benefit from S-ICD implantation. (Circ Arrhythm Electrophysiol. 2017;10:e004801. DOI: 10.1161/CIRCEP.117.004801.)

Key Words: arrhythmia ▪ hypertrophic cardiomyopathy ▪ S-ICD ▪ S-ICD screening ▪ sudden cardiac death

The implantable cardioverter-defibrillator (ICD) has been a groundbreaking advance in the prevention of sudden cardiac death (SCD). However, the complications of current transvenous implantable devices, such as infection and lead failure, are a significant and expanding problem, particularly with the improved survival of younger recipients. In patients with hypertrophic cardiomyopathy (HCM), where devices are frequently implanted for primary prevention in young individuals, complication rates are often unacceptably high. The advent of the subcutaneous ICD (S-ICD) represents an important alternative avoiding intravascular leads as reflected in the IDE study and EFFORTLESS registries where young patients with inherited channelopathies or nonischemic cardiomyopathy including HCM were implanted. 

The S-ICD continuously senses the surface ECG from 3 bipolar vectors derived from its subcutaneous poles and ICD generator positions (Figure 1A). The QRS and T wave morphology are templated within the device, and this is used in combination with internal algorithms to differentiate between ventricular and supraventricular arrhythmias. Thus, the quality of the ECG recorded from the surface and the amplitude and ratio of the T wave and QRS complexes are critical elements in the screening process of eligibility for the device. Previous studies have suggested that ≤7.4% of patients fail screening and that HCM may increase the odds of screening failure because of large-amplitude T wave and QRS complexes in these patients. However, either limited numbers of patients with HCM have been recruited in previous studies or high-risk HCM patients likely to represent those clinically considered for ICD have been underrepresented. Additionaly, systematic screening on exercise, when QRS and T-wave morphology frequently change, has not been performed. This study aimed to assess the proportion of HCM patients without pacing indications and ≥1

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of the American Heart Association guideline\textsuperscript{21,22} risk factors for SCD were eligible for the S-ICD on the basis of screening at rest and on exercise.

**Methods**

**Study Population**

One hundred and thirty-one consecutive patients with HCM and \geq 1 risk factor for SCD were screened for eligibility for S-ICD, during their outpatient clinic visit, between July 2014 and September 2015.

**Screening Protocol**

ECG screening was undertaken by placing ECG electrodes on the xiphoid, sterno-manubrium junction, normal lead position V6, and the right lower abdomen (ground electrode) to simulate the 3 sensing vectors of the S-ICD (Figure 1A). A 30-second ECG was recorded in the supine and standing positions, as well as standing step exercise to a heart rate of 120 beats per minute. The 3-lead ECGs were recorded on the Boston Scientific Zoom programmer (Boston Scientific Inc) at a paper speed of 25 mm/s, with the ECG gain set to 5, 10, and 20 mm/mV. The ECG template screening tool (Figure 1B and 1C), as provided by Boston Scientific, was used to assess whether each of the 3 vectors was suitable for the S-ICD. A patient was considered suitable if at least 1 vector passed in all 3 screening positions (supine, standing, and exercise). Screening analysis was performed by Drs Patel and Srinivasan. There were disparities in 3 cases, where Prof Lambiase was the adjudicator. Alternative screening positions were not assessed as part of the protocol because the study was designed as a prospective assessment of standard screening methodology, and there were time constraints for patients in clinic.

**Data Collection**

Patient demographic data were collected from the medical records. Left ventricular ejection fraction was estimated using either visual methods or Simpsons biplane method by the hospital echocardiography department. Twelve-lead ECG parameters were collected from the most recent supine surface ECG. All 12-lead ECG data are expressed with the machine calibrated to 10 mm/mV, while 3-lead ECG parameters are expressed in relation to a calibration of 5 mm/mV.

**Statistical Analysis**

Parametric data are expressed as mean and standard deviation and analyzed using a Student’s \( t \) test. Nonparametric data are expressed...
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>92 (70%)</td>
</tr>
<tr>
<td>Age, y (mean)</td>
<td>51±16</td>
</tr>
<tr>
<td>Weight, kg, median (IQR)</td>
<td>82 (70–93)</td>
</tr>
<tr>
<td>ICD</td>
<td></td>
</tr>
<tr>
<td>Primary prevention, n (%)</td>
<td>45 (34%)</td>
</tr>
<tr>
<td>Secondary prevention, n (%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>LVEF, median (IQR)</td>
<td>65 (60–70)</td>
</tr>
<tr>
<td>LA size, mm, median (IQR)</td>
<td>45 (41–51)</td>
</tr>
<tr>
<td>Max wall thickness, mm, median (IQR)</td>
<td>17 (15–20)</td>
</tr>
<tr>
<td>Posterior wall thickness, mm, median (IQR)</td>
<td>10 (9–11)</td>
</tr>
<tr>
<td>Peak LVOT gradient, mmHg, median (IQR)</td>
<td>16 (5–61)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>LVOT obstruction, n (%)</td>
<td>52 (40%)</td>
</tr>
<tr>
<td>Family history SD, n (%)</td>
<td>56 (43%)</td>
</tr>
<tr>
<td>Syncope, n (%)</td>
<td>44 (34%)</td>
</tr>
<tr>
<td>NSVT, n (%)</td>
<td>74 (56%)</td>
</tr>
<tr>
<td>Max wall thickness ≥30 mm, n (%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Altered BP response to exercise, n(%)</td>
<td>61 (47%)</td>
</tr>
<tr>
<td>12-Lead ECG characteristics</td>
<td></td>
</tr>
<tr>
<td>PR interval, ms, median (IQR)</td>
<td>172 (155–192)</td>
</tr>
<tr>
<td>QRS duration, ms, median (IQR)</td>
<td>108 (100–129)</td>
</tr>
<tr>
<td>QT interval, ms, median (IQR)</td>
<td>447 (427–477)</td>
</tr>
<tr>
<td>ESC 5-y risk</td>
<td></td>
</tr>
<tr>
<td>High risk, n (%)</td>
<td>53 (41%)</td>
</tr>
<tr>
<td>Intermediate risk, n (%)</td>
<td>24 (18%)</td>
</tr>
<tr>
<td>Low risk, n (%)</td>
<td>54 (41%)</td>
</tr>
<tr>
<td>Conventional risk factors ≥2</td>
<td>81 (62%)</td>
</tr>
<tr>
<td>Antiarrhythmic medications, n (%)</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>46 (35%)</td>
</tr>
<tr>
<td>Calcium-channel antagonist</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>Beta-blocker+calcium-channel antagonist</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Beta-blocker+disopyramide</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Beta-blocker+amiodarone</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Calcium-channel antagonist+amiodarone</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>1 (0.8%)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; ESC, European Society of Cardiology; ICD, implantable cardiac-defibrillator; IQR, interquartile range; LA, left atrium; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; and NSVT, nonsustained ventricular tachycardia.

as median and interquartile range and analyzed using Mann–Whitney U test. Categorical data are expressed as percentages and analyzed using chi-square test. Clinical predictors of failure of screening protocol were analyzed using multivariable analysis. Factors associated with increased screening failure or success at a P value of <0.05 were input into the model. Where there was significant pairwise correlation between factors, correlation of >0.8, these were eliminated and all remaining variables put into a manual backwards elimination model. P values <0.05 were considered significant. Postural variations between vectors associated with passing or failing screening were assessed using logistic regression. Three-lead ECG factors associated with screening failure were analyzed by logistic regression. Statistical analysis was performed using R statistical computing software (Version 3.2.2).

Results

Baseline Characteristics

One hundred and thirty-one consecutive patients with HCM and ≥1 risk factor for sudden death were screened in our outpatient department. Clinical characteristics of the patients (70% male, mean age, 50±16 years) are shown in Table 1. Eleven patients were in atrial fibrillation at the time of screening. In total, 51 patients (39%) had a preexisting ICD, 45 (34%) for primary prevention and 6 (5%) for secondary prevention. Ten patients were unable to exercise, either because of their clinical condition or because of their request not to exercise. Fourteen patients (11%) had a previous myomectomy and 4 patients (3%) had a previous alcohol septal ablation. Forty-six patients (35%) were on no medication (Table 1).

Eighty-one patients (62%) had ≥2 conventional risk factors for SCD. Based on the European Society of Cardiology (ESC) risk assessment score, 53 patients (41%) were high risk (5-year risk ≥6%), 24 patients (18%) were intermediate risk (5-year risk of ≥4% and ≤6%), and 54 patients (41%) were low risk (5-year risk <4%).

Eligibility for S-ICD Based on 3-Lead ECG Vector Screening

In total, 50 patients (38%) were ineligible for S-ICD because of screening failure on the basis of failure in every S-ICD lead vector (Table 2). Figure 2A shows the percentage of all patients passing or failing S-ICD screening in the supine position, with additional failures during standing and exercise (Figure 2B and 2C) as a percentage of total patients screened. Of the 50 patients who failed screening, 33 (66%) failed screening in the supine position, a further 12 (24%) failed screening in the standing position, and 5 (10%) failed on exercise.

Of the patients who passed screening in the supine position (Figure 2D), 47 (48%) had 1 vector safety, 28 (29%) had 2 vector safety, and 23 (23%) had 3 vector safety. In patients who passed screening in the standing position (Figure 2E), 39 (45%) had 1 vector safety, 29 (34%) had 2 vector safety, and 18 (21%) had 3 vector safety. Finally, 10 patients who passed screening in the supine and standing positions were unable to exercise because of mobility issues. Thus, in the 71 patients who were able to exercise and passed all screening (Figure 2F), 31 (44%) had 1 vector safety, 16 (22%) had 2 vector safety, and 24 (34%) had 3 vector safety.

Figure 2G through 2I shows the number of patients passing or failing in the supine, standing, and exercise positions, in relation to their screening vector. Logistic regression suggested that the primary vector was statistically more likely to fail screening in the supine (fail 62% and pass 38%; odds...
ratio [OR], 1.6; confidence interval [CI], 1.1–2.6; \( P = 0.03 \)) and standing positions (fail 59% and pass 41%; OR, 2.2; CI, 1.2–4.0; \( P = 0.007 \)), while the alternate vector was more likely to pass in the standing (fail 39% and pass 61%; OR, 1.5; CI, 1.05–2.4; \( P = 0.03 \)) and during exercise (fail 21% and pass 79%; OR, 1.9; CI, 1.2–8; \( P < 0.001 \)).

Twenty-two patients (44%) failed because of a large-amplitude QRS complex for the template, 17 (34%) because...
of a T wave morphology not fitting the template, 10 (20%) failed because of a broad QRS for the template, and 1 (2%) had frequent ectopy as a cause for screening failure. The differences in maximal QRS deflection, QRS width, T wave amplitude, and R/T ratio between passing and failing screening on the 3-lead ECG calibrated to 5 mm/mV are shown in Figure 3. Logistic regression demonstrated an increased R/T wave ratio in patients who failed screening (OR, 4.0; CI, 3.0–5.3; \( P < 0.001 \)), while patients who passed vector screening in HCM had a broader QRS (OR, 1.02; CI, 1.01–1.03; \( P < 0.001 \)) and larger-amplitude T waves (OR, 1.6; CI, 1.5–1.8; \( P < 0.001 \)). Patients who failed screening showed no significant difference in QRS amplitude at the chosen significance level, with a median maximal deflection 9 mm (interquartile range, 6–12) versus 7 mm (interquartile range, 4–14; OR, 1.01; CI, 0.98–1.03; \( P = 0.326 \)).

Clinical and 12-Lead ECG Factors Influencing Screening Pass or Failure

Clinical

Factors associated with screening success or failures are shown in Table 2. There was no sex difference in screening failure rate, 34 males (36% of all males) and 16 females (41% of all females) failed screening; \( P = 0.81 \). Younger patients were more likely to fail than older patients. The mean age of patients passing was 54 years versus 46 years for patients failing \( P = 0.006 \). Patient weight (n=127) was not associated with an increased screening failure rate (\( P = 0.35 \)). Conventional risk factors were not associated with a failure of screening; however, patients with a family history of SCD appeared to show an increased rate of screening failure versus success (62% versus 31%, respectively; \( P < 0.001 \)). Posterior wall thickness was not associated with an increased failure rate (\( P = 0.11 \)). Patients

Figure 2. Percentage and number of patients passing or failing screening in the supine, standing, and exercise positions (A–C) as a proportion of total screened. Percentage of patients with 1, 2, or 3 qualifying vectors in those who passed, in each of the screening positions shown below (D–F). G–I. The number of patients passing or failing in the alternate, secondary, and primary vectors in each of the screening positions, with statistical significance between passing and failing shown above the bars. NS indicates nonsignificant.
with preexisting ICDs were not more likely to fail screening ($P=0.7$). Of the patients who were intermittently paced, 16 (84%) passed screening. Maximal left ventricular outflow tract velocity was greater in patients who passed versus those who failed screening (22 versus 10 mm\(\text{Hg}\), respectively; $P=0.009$).

**Surface 12-Lead ECG**

Surface ECG characteristics that were significantly different between patients who passed and failed screening are shown in Table 2. QRS duration (114 versus 100 ms; $P=0.004$) and QTc interval (455 versus 438 ms; $P=0.02$) were found to be significantly different between patients passing and failing, respectively. T wave factors associated with a screening pass or fail were maximal T wave amplitude (6 versus 5 mm; $P=0.03$) in any lead, maximal T wave amplitude in lead I (2 versus 1.5 mm; $P=0.005$), and maximal T wave amplitude in lead aVF (2 versus 1.5 mm; $P=0.03$). An increased ratio of the R wave to T wave in lead aVF (2.5 versus 5; $P=0.003$) was associated with a risk of screening failure, while a low ratio of R/T in aVF was associated with an increased likelihood of passing screening (53% versus 22%; $P<0.001$).

**Patient Risk**

ESC 5-year risk was significantly higher in patients who failed screening (5.5%/5 year versus 4.5%/5 year; $P=0.04$). Patients

![Boxplots of differences in QRS amplitude (A), QRS width (B), T-wave amplitude (C), and R/T ratio (D) in the 3-lead screening ECG, between patients who passed and failed screening. Statistical significance based on logistic regression is shown above each boxplot. NS indicates nonsignificant.](image)

**Table 3. Predictors of Screening Failure**

<table>
<thead>
<tr>
<th>Multivariable Analysis</th>
<th>OR</th>
<th>95% CI</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per year</td>
<td>0.97</td>
<td>0.95–0.99</td>
<td>0.03</td>
</tr>
<tr>
<td>Maximal T-wave amplitude any lead per millimeter</td>
<td>0.90</td>
<td>0.76–1.04</td>
<td>0.18</td>
</tr>
<tr>
<td>T wave amplitude in lead I</td>
<td>0.77</td>
<td>0.55–1.03</td>
<td>0.1</td>
</tr>
<tr>
<td>R/T &lt;3 in aVF</td>
<td>0.30</td>
<td>0.12–0.69</td>
<td>0.006</td>
</tr>
<tr>
<td>Max LVOT velocity per mm Hg</td>
<td>0.99</td>
<td>0.98–1.00</td>
<td>0.07</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; LVOT, left ventricular outflow tract; and OR, odds ratio.
deemed high risk by the ESC 5-year risk score accounted for a greater proportion of screening failures (27 of 50 patients (54%); P=0.02), as shown in Table 2. There was also a trend toward patients with ≥2 conventional risk factors failing screening (P=0.08). Patients at low risk showed a trend toward increased screening success (P=0.06).

**Screening Failure**
Variables that differed significantly (P<0.05) between screening pass or failure were assessed for pairwise correlation between each other. Variables without correlation to each other were then all input into a manual backwards elimination multivariable logistic regression mode. The final model variables are seen in Table 3. Multivariable logistic regression analysis demonstrated that R/T <3 in lead aVF was associated with lower odds of screening failure (OR, 0.3; 95% CI, 0.12–0.69; P=0.006), and increasing age per year made screening failure less likely (OR, 0.3; 95% CI, 0.95–0.99; P=0.03).

**Screening Vector Screening Safety in Relation to ESC Risk Profile**
As shown in Table 2, 50 patients (38%) failed ECG screening using the 1-vector safety rule. Using the more stringent 2-vector safety rule, 93 patients (71%) failed screening for the device. Figure I in the Data Supplement shows that the screening failure rate with 1-vector and 2-vector safety. Using 1-vector safety, screening failure increased with increasing ESC-Risk score, from low (28%) to intermediate (33%) and high risk (51%). Using the recommended 2-vector safety, 67% of low-risk patients failed, 71% of intermediate-risk patients failed, and 76% of high-risk patients failed screening.

**Discussion**
The S-ICD is a groundbreaking and important clinical tool in the management of patients at risk of ventricular arrhythmia. Its use has now become standard practice particularly in young patients with inherited cardiac syndromes. This is the first systematic study to look specifically at S-ICD eligibility of HCM patients with one or more conventional American Heart Association risk factors for SCD at rest and on exercise in the limited standard screening positions. Although the majority of patients (62%) with HCM passed screening assessment for the device, 38% of patients failed screening. ESC 5-year risk was associated with increased screening failure rate (5.5%/5 year versus 4.5%/5 year; P=0.04), and patients deemed higher risk were more likely to fail screening, accounting for 54% of failed screenings (P=0.02). On multivariate analysis, an R/T ratio of <3 in aVF (OR, 0.3; P=0.006) and increasing age per year (OR, 0.97; P=0.03) were associated with lower occurrence of screening failure. Of the patients who passed screening for the device, 55% had >1 vector safety, while 45% of patients passed with 1-vector safety using conventional supine and standing screening, with similar findings (41%) on exercising the patients. Though the majority of failures occurred in the supine (66%) and standing positions (24%), 10% of total screening failures occurred on exercise. The primary vector was the most likely to fail screening (Figure 2).

**Eligibility For S-ICD**
Eligibility for S-ICD based on preimplant ECG screening is reported to be in the range of 80% to 95%. Previous studies in a mixed SCD risk cohort have suggested that HCM is an independent risk factor for S-ICD screening failure. Two previous studies have specifically assessed screening failure in patients with HCM. Francia et al investigated screening failure in 47 patients and found a failure rate of 7% using the standard supine and standing screening method and 15% in patients who were exercised. Recently, Maurizi et al screened a cohort of 165 patients with HCM and found a 16% screening failure rate; however, they did not screen these patients on exercise, where T wave oversensing may be a particular problem. Our study shows the highest screening failure rate (38%) in a cohort of higher risk HCM patients (41% high risk and 18% intermediate ESC score risk), who are more representative of patients being considered for ICD implantation in standard clinical practice. It is interesting to note in the study of Maurizi et al that in their small cohort (n=22, 13% of total cohort) of high-risk patients, 36% of patients failed screening with at least 1-vector safety. Thus, our study shows comparable results of screening failure in patients who are most likely to be clinically considered for an ICD.

**Underlying Reasons for HCM ECG Screening Failure**
Patients with HCM exhibit progressive remodeling of the ventricles over time with dynamic changes on surface ECG. These changes are critical to the applicability of S-ICD technology because the device is currently entirely dependent on the surface ECG to determine eligibility. It has previously been described that the severity of 12-lead ECG abnormalities, particularly T wave abnormalities, QRS duration, and LV hypertrophy, correlate with the severity and evolution of the structural phenotype in HCM. Additionally, the severity of the ECG phenotype correlates with outcome, in those patients with a phenotypically normal ECG seem to have a low mortality compared with those with significant ECG abnormalities. This may explain the higher screening template failure rate in our higher risk cohort because they may have been more likely to present with an abnormal ECG that is outside the bounds of the current screening template. Our study, therefore, has major implications regarding the need for careful screening of patients who are at higher risk of SCD and require an ICD according to current clinical guidelines to ensure they have adequate sensing safety. Additionally, it highlights the importance of careful monitoring of the patients to ensure that the evolution in ECG morphology with disease progression does not alter device sensing. This is particularly relevant in lower-risk HCM cohorts where screening failure may be as low as the 13% reported by Maurizi et al and clinicians may be more inclined to implant an S-ICD, given the lower risk of long-term complications. Such patients will benefit from the avoidance of transvenous lead implantation by monitoring the ECG on follow-up, and if significant changes develop, the S-ICD can be optimized to avoid any inappropriate therapies.
3-Lead S-ICD Vector Template Screening

Our study shows that using standard recommended supine and standing screening in only the left sternal position, 45% of the total patients screened passed with 1-vector safety. Current ESC guidelines\(^3\) recommend ≥2-vector safety on screening before implanting the S-ICD in HCM. Applying this more stringent cutoff would increase the failure rate of screening to 71% (n=93), which is similar to that described by Maurizi et al., where 44% of the entire cohort of patients and 72% of the high-risk cohort of patients were ineligible based on these criteria. Additionally, 10% of total screening failures occurred during exercise, which reflects the importance of screening patients on exercise where T-wave oversensing is a known problem.\(^20,30\)

We noted that the primary vector was statistically more likely to fail screening while the alternate vector was more likely to pass (Figure 2). Francia et al.\(^20\) also recently reported that the alternate sensing vector was the most compatible in their cohort of HCM patients with a preexisting ICD. This is contrary to the findings in general population screening,\(^18\) where the alternate vector is the most likely to fail screening. In the S-ICD, the alternate vector is orientated at 90° to the frontal plane of the chest, while the primary vector is at 0°, with the secondary vector in between the 2. In HCM, the cardiac frontal axis is progressively shifted leftward because of left ventricular hypertrophy.\(^32,33\) This potentially shifts the major depolarizing and repolarizing vectors parallel to the primary screening vector in HCM patients, making large QRS and T wave complexes more likely to cause screening failure. This is particularly notable during standing and exercise where the alternate vector was statistically more likely to pass; perhaps because of the effect of changing position of the heart with posture in realigning the major depolarizing and repolarizing vectors more perpendicular to the alternate screening vector, making T wave oversensing and problems with large amplitude QRS complexes less likely. It also explains the finding that in patients with HCM patients, right sternal lead placement seems to have no significant effect in improving screening failure rate\(^20\) because this alters the alternate vector but does little to influence the primary vector, which appears to be the predominant sensing vector in screening failure.

The S-ICD is designed for optimal lead and generator position to achieve the lowest possible defibrillation threshold and appropriate sensing vectors.\(^3,13\) The sternal position of the lead and lateral siting of the can mean that only the primary vector is deployed maximally orthogonal to the cardiac axis, with the alternate vector being the least orthogonal in patients with structurally normal hearts. In HCM, there is a leftward shift of the cardiac axis,\(^32,33\) and the opposite is true. This is evident in the screening ECG as demonstrated in this study and others.\(^18,19\)

The major cause for screening failure was large-amplitude QRS complexes. This is reflected in the finding of larger maximal QRS amplitude in patients who failed and a larger R/T ratio (Figure 3). The finding of T waves not fitting the screening template as a second major cause for screening failure, despite such patients having smaller maximal T wave amplitude, suggests that the morphology of the T wave and not amplitude alone determine screening failure. It is interesting to note that in the study of Maurizi et al., T wave inversion in the 12-lead ECG was associated with screening failure. This warrants further investigation, particularly in relation to the design of the screening template.

Clinical Characteristics of Failure

The major clinical factor associated with an increased risk of screening failure was the presence of an increased ESC 5-year risk score (median 5.5%/5 year in failed patients versus 4.5%/5 year in pass patients; P=0.04). High-risk patients accounted for 54% of failed screening patients (P=0.02). Using the 1-vector and 2-vector safety rule, the majority of patients who passed S-ICD screening were from the low-risk cohort, with screening failure increasing with ESC risk score. This has important implications because 45% of patients who would be considered for an ICD based on the American Heart Association guidelines\(^22\) would potentially be ineligible for the device using a 1-vector safety rule. It is well known that lower risk patients seem to display a more normal phenotypic ECG,\(^36\) while increasing phenotypic expression of HCM on cardiac magnetic resonance imaging has been associated with progressive severity of ECG abnormalities.\(^34\)

It is interesting to note that patients that passed screening were older, and this is reflected in the multivariable analysis where increasing age was associated with lower screening failure rate. This may reflect the natural history of the ECG in HCM, where R wave amplitude in aVL and septal leads have been reported to decline over time,\(^31,32\) thus, making potential screening failure because of large-voltage QRS complexes less likely. An R/T ratio <3 in aVF was associated with a lower screening failure rate, highlighting this lead as a potential surrogate marker of screening template ECG failure because of tall R waves. This is in keeping with our finding of R/T ratio being associated with screening failure in the 3-lead screening ECG.

Future Directions

Screening failure could be improved by filtering of R wave and T wave amplitude in the device to account for features of the HCM ECG, such that the current ECG template used can be modified to increase the ECG screening success rate. Identical band pass filtering as used by the implanted S-ICD is due to be introduced in an automated screening tool as opposed to the current manual template, which coupled with the SMARTPASS algorithm to prevent T wave oversensing may help reduce screening failure. This will need to be formally addressed in future studies. Alternatively, using a tailored floating bipole away from the heart implanted at a site of optimal R wave sensing or integrating signals from the 3 vectors to achieve an optimal R/T wave ratio as a summation of sensed surface ECG data could be considered. This would enable the minimization of large-amplitude R waves and the subtraction of large T waves, avoiding the need to implant additional hardware that has to communicate with the generator. A move toward bespoke and remote-sensing electrode positions, which are patient specific and allow the sensing field to be independent of the shock field, could prove an advantage in such patients. Ultimately, potential...
screening/sensing problems could be solved with leadless sensors/pacing electrodes that would ensure endocardial R-wave sensing in combination with the S-ICD. An additional atrial sensor could further optimize the discrimination between supraventricular tachycardia and ventricular tachycardia.

Limitations
Screening was performed at rest and exercise, with no assessment of right-sided lead positioning, central sternal, or posterior S-ICD generator placement. This may have resulted in the higher screening failure rate reported in this study. However, a recent study reported that right-sided lead placement did not significantly increase screening success rate in HCM patients. We were also limited to exercising the patients to a maximal heart rate of 120 beats per minute (for ethical safety reasons), whereas standard treadmill testing with exercise to maximal heart rate of 120 beats per minute (for ethical safety reasons), whereas standard treadmill testing with exercise to maximal heart rate as is routinely performed in our institution may have further altered failure rate of patients on exercise. Additionally, we only report failure of screening patients for the S-ICD; no published data exist regarding the correlation between the screening ECG template and sensing within the implanted S-ICD itself where there are differences in the S-ICD sensing algorithms which the manual ECG template alone does not account for.

Conclusions
The S-ICD is a groundbreaking and important leap forward in the management of patients with risk of ventricular arrhythmia, and its applicability is ever expanding. Although the majority of patients in our cohort of patients with HCM and ≥1 indication for ICD passed based on >1-vector safety on surface ECG screening, 38% of patients were ineligible for the S-ICD with 1-vector safety and 71% were ineligible with ≥2-vector safety as recommended in the ESC guidelines based only on standard screening methodology with left parasternal sensing. The median ESC risk score was higher in patients who failed screening, while 10% of total failures occurred on exercise. This highlights the need for careful screening and selection of S-ICD candidates with HCM, including consideration of alternative screening positions. This should not deter from implanting devices in HCM patients as in HCM patients who pass screening for S-ICD as the device has an excellent safety and efficacy profile. New and more advanced screening algorithms are required to make this important device available to a wider population with unusual ECG morphologies.

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Disease Severity and Exercise Testing Reduce Subcutaneous Implantable Cardioverter-Defibrillator Left Sternal ECG Screening Success in Hypertrophic Cardiomyopathy

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Supplemental Figure 1. Number and percentage of patients passing or failing screening based on their ESC risk category from low to high. Pie charts show the number and percentage of patients who would pass or fail in each risk category based on having 1-vector (A-C) or 2-vector (D-E) screening safety. Screening failure rate increases with increasing ECG risk severity, and when applying 2-vector safety.