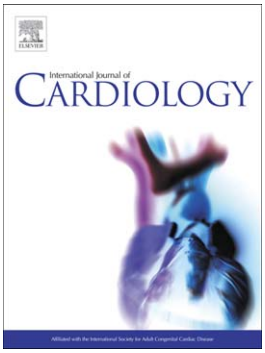

Sensitivity and Specificity of the Subcutaneous Implantable Cardioverter Defibrillator Pre-implant Screening Tool

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Sensitivity and Specificity of the Subcutaneous Implantable Cardioverter Defibrillator Pre-implant Screening Tool.

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Short Title: Sensitivity and Specificity of the S-ICD Pre-implant Screening Tool.

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ABSTRACT

Background

The sensitivity and specificity of the subcutaneous implantable cardioverter defibrillator (S-ICD) pre-implant screening tool required clinical evaluation.

Methods

Bipolar vectors were derived from electrodes positioned at locations similar to those employed for S-ICD sensing and pre-implant screening electrodes, and recordings collected through 80-electrode PRIME®-ECGs, in six different postures, from 40 subjects (10 healthy controls, and 30 patients with complex congenital heart disease (CCHD); 10 with Tetralogy of Fallot (TOF), 10 with single ventricle physiology (SVP), and 10 with transposition of great arteries (TGA). The resulting vectors were analysed using the S-ICD pre-implant screening tool (Boston Scientific) and processed through the sensing algorithm of S-ICD (Boston Scientific). The data were then evaluated using 2x2 contingency tables. Fisher exact and McNemar tests were used for a comparison of the different categories of CCHD, and $\rho<0.05$ vs. controls considered to be statistically significant.

Results

57% of patients were male, mean age 36.3 years. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the S-ICD screening tool were 95%, 79%, 59% and 98%, respectively, for controls, and 84%, 79%, 76% and 86%, respectively, in patients with CCHD ($\rho=0.0001$).

Conclusion

The S-ICD screening tool was comparatively more sensitive in normal controls but less specific in both CCHD patients and controls; a possible explanation for the reported high incidence of inappropriate S-ICD shocks. Thus, we propose a pre-

implant screening device using the S-ICD sensing algorithm to minimise false exclusion and selection, and hence minimise potentially inappropriate shocks.

Keywords: Sudden Cardiac death, congenital heart disease, subcutaneous implantable Cardioverter, sensing algorithm.

Word Count: 4848 **Figures: 2** **Table: 1**

INTRODUCTION

Implantable cardioverter defibrillators (ICD) are considered to be the most effective treatment for primary and secondary prevention of sudden cardiac death (SCD) [1-5]. The main function of ICD is to sense and terminate potentially fatal ventricular arrhythmias. However, the conventional transvenous ICDs carry risks of a variety of complications [6-8]. These complications include procedural (bleeding, pneumothorax, vascular damage and myocardial perforation), short-term (infection, thrombosis) and long-term (lead failure, inappropriate shocks) factors [8].

The use of transvenous ICD is conservative in patients with congenital heart diseases (CHD) because of the anatomical challenges and higher risk of life long complications; despite the fact that these people experience a high rate of SCD at young age and would benefit most from ICD [9, 10]. The totally subcutaneous implantable cardioverter defibrillator (S-ICD) has been developed, and used in a selected number of patients because of the limitations of transvenous ICD. S-ICDs are entirely subcutaneous, and aim to reduce complications through avoidance of the use of intracardiac leads [11-13]. However, despite these advantages, the S-ICD is limited by inability to provide anti-tachy pacing (ATP) and can provide post shock brady pacing for 30 seconds only [11]. Additionally, selection for S-ICD implant is based on pre-implant electrographic body surface mapping [14].

The S-ICD consists of a pulse generator (SQ-RX® pulse generator Boston Scientific) [14], implanted subcutaneously in the left mid-axillary line at the level of the fifth and sixth intercostal spaces [14]. The L-shaped S-ICD lead (Q-TRAK® lead, Boston Scientific) is inserted subcutaneously and has two segments, (i) a horizontal segment which is attached to the S-ICD pulse generator and continues as a (ii) a vertical segment parallel to the left sternum edge [14]. This configuration offers three sensing

vectors (Figure 1) [11, 15]. Pre-implant screening identifies the most appropriate sensing vector, which is then confirmed by post implant device interrogation. However, the current generation of S-ICD do not automatically select the sensing vector. The S-ICD uses subcutaneous electrocardiogram (ECG) signals to monitor cardiac output and discriminate between shockable and non-shockable rhythms [15]. Early trials of S-ICD defibrillation ability have demonstrated effective termination of VT and VF similar to transvenous ICDs [11, 15]. However, recent clinical studies have reported inappropriate shocks in at least 7-13% cases within one year of implant suggesting that the sensing algorithm requires further evaluation [11, 12, 15-21]. Bellardine et al. have demonstrated a good correlation between subcutaneous and the corresponding transcutaneous body surface ECGs [22], suggesting that it is feasible to study the sensing algorithm of S-ICD through surface ECG measurements. Additionally, patient selection for S-ICD implant is based on pre-implant screening; carried out using a three-lead surface ECG, acquired in both supine and standing postures. The ECG tracings are then mapped out using the Boston Scientific screening tool; intended to identify patients with acceptable sensing characteristics [14, 15]. However the diagnostic and discriminatory ability (sensitivity and specificity) of the pre-implant screening tool against the sensing algorithm of S-ICD is not known.

In this study we have tested the sensitivity and specificity of the pre-implant screening tool against the sensing algorithm of the S-ICD in six postures (standing, sitting, supine, left lateral, right lateral, prone) for three vectors. Four subgroups were considered; including normal adults and adults with complex congenital heart diseases (Tetralogy of Fallot (TOF), transposition of great arteries (TGA) and single ventricle physiology (SVP).

METHOD

This observational study was conducted at the tertiary care cardiology centre of our university teaching hospital. Patients were identified from their records upon presentation to the inpatient and outpatient departments and anonymised by assignment of a unique ID number.

This study received approval from an independent review board of the Southampton University Hospital & South West Hampshire Research Ethics Committee B (REC 08/H0504/55).

Study Population

All the subjects were aged 18 years or over and had the ability to give informed consent.

Forty patients were recruited into the following subgroups.

1. Ten adults with morphologically normal heart on cardiac magnetic resonance imaging (half of these patients had assessment with late gadolinium enhancement at the discretion of the attending radiologist and showed no abnormality).
2. Ten adults with TOF.
3. Ten adults with TGA.
4. Ten adults with SVP.

Patients in arrhythmias and paced rhythm were excluded from the study.

Electrocardiographic Data collection

Electrocardiographic body surface mapping was performed through 80-electrode ECG (PRIME®-ECG Verathon Inc); consisting of an on-board computer and flexible plastic anterior and posterior electrode vests, as described previously [23, 24]. The

anterior vest contains 64 electrodes and the posterior vest contains 16 electrodes, thus enabling the recording of 80 simultaneous ECG signals [23, 24]. The vests are arranged in vertical strips referenced to their anatomical landmarks. In each subject, 80-electrode ECGs were recorded in six postures (standing, sitting, supine, left lateral, right lateral, prone), for 10 seconds, at a sweep speed of 25 mm/s, and a sampling rate of 1kHz. Adequate adhesion of individual ECG skin electrodes and good quality signal collection were ensured through prior skin preparation, shaving hair where necessary and using alcohol wipes. Three bipolar vectors were created from electrodes at locations mimicking the placement of the S-ICD sensing electrodes as recommended by the manufacturers (Boston Scientific) for pre-implant screening (Figure 1) [14]. The bipolar vectors Lead I, Lead II and Lead III were derived, representing surface ECG equivalent of Boston Scientific sense vectors (Primary = Lead III, Secondary = Lead II, Alternate = Lead I). Each vector was created at gain 5, 10, 15 and 20 mm/mV.

Screening tool and bipolar vectors analysis

The manufacturer of the currently available S-ICD (Boston Scientific) recommends pre-implant screening through surface ECG in all patients considered for S-ICD. A pre-implant screening tool is used to identify patients with acceptable sensing characteristics, prior to the implant of S-ICD. This is a printed chart, containing six profiles of varying morphology, with a horizontal line passing through all the colour profiles to adjust with the baseline. Each colour profile has an identical window above and below the baseline; to account for positive or negative amplitude of the R-wave and T-wave. Each window is subdivided by dotted lines and the peak of the R-wave has to lie within this sub-window for of one of the six profiles to be appropriate for

sensing. Additionally, the trailing T-wave has to be contained within the same colour profile as the R-wave for the vector to be appropriate for sensing (Figure 2) [14]. This screening tool was used to evaluate each vector. A coloured map from the screening tool that best matched the amplitude and duration of the QRS complex and the T-wave was determined. For biphasic signals, the larger peak was used. The left-hand edge of the selected coloured map was aligned with the onset of the QRS complex. The horizontal line on the coloured template was used as a guide for isoelectric baseline alignment. The QRS peak had to be within the window bounded by the dotted line and the peak of the coloured profile (Figure 2). If, when printed at the maximum 20mm/mV gain, the QRS peak did not reach the minimum boundary (dotted line) of the smallest coloured profile, the vector was considered unacceptable. If the entire QRS complex and trailing T-wave were contained within the coloured profile, the vector/posture combination was considered suitable. If any portion of the QRS complex or trailing T-wave extended outside the coloured profile, the sense vector was considered unacceptable. All vectors were examined individually at four gain settings (5, 10, 15 and 20 mm/mV); mimicking the automatic gain adjustment of the sensing algorithm. A vector acceptable at any of these gains was considered suitable.

Analysis of the bipolar vectors by S-ICD sensing algorithm

The data from the three bipolar vectors was exported in Matlab® readable format. The three bipolar vectors were then presented to the S-ICD sensing algorithm (built in Matlab® by Boston Scientific) and this algorithm identified the vectors suitable or unsuitable for rhythm discrimination, based on the current sensing algorithm of the S-ICD. The sensing algorithm has an automatic gain adjustment function, therefore no

external manipulation of gain for the vectors is required before assessment using the sensing algorithm.

Statistical analysis

Statistical analyses were performed using the SPSS 19.0 software package (IBM SPSS limited). Continuous variables were expressed as mean ±1 SD and were compared using Student's *t* test. Sensitivity and specificity were determined using 2x2 contingency tables and comparison of dichotomous categorical variables was made by x^2 test. Fisher's exact test and McNemar chi square test were used to determined significant differences between different groups on the basis of cardiac morphology, lead position and postures. A $\rho < 0.05$ was considered significant.

RESULTS

A total of 2880 vectors collected from 40 subjects (10 normal control and 30 complex congenital heart disease (CCHD) patients (10 Tetralogy of Fallot (TOF), 10 single ventricle physiology (SVP), 10 transposition of great arteries (TGA)) were generated and analysed in groups of three bipolar vectors for each of the 6 postures, at gain 5, 10, 15 and 20 mm/mV from 240 BSM (80-electrode PRIME®-ECGs). The mean age was 36.3±14.4, and 57% (23/40) were male.

Table 1 summarises the results of screening tool sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR) and 95% confidence interval (95% CI) for all subjects, normal controls, CCHD patients (TOF, TGA, SVP), three vectors (Lead III,

Lead II, Lead I) and six postures (standing, sitting, supine, left lateral, right lateral, prone).

The screening tool displayed high sensitivity and lower specificity in normal controls. The sensitivity and specificity of the screening tool were significantly lower in individuals with CCHD compared with individuals with normal heart morphology ($\rho < 0.05$) (all CCHD $\pi=0.001$, TOF $\rho=0.001$, TGA $\rho=0.001$, SVP $\rho=0.001$), and in Lead III in comparison to primary Lead I ($\rho=0.004$). However, there was no significant difference in Lead II compared with Lead III or in the six postures compared with supine (all $\rho>0.05$).

DISCUSSION

The sensing algorithm of the S-ICD depends on the surface (subcutaneous) ECG morphology, specifically the R-wave amplitude, T-wave amplitude, R/T ratio, QRS duration and QT interval. A pre-implant screening tool has been developed by the manufacturers (Boston Scientific) taking into account these ECG parameters [14]. The screening tool is used in all patients under consideration for S-ICD implantation; to select individuals with ECG morphology that offering appropriate signal configuration to satisfy the requirements of the S-ICD sensing algorithm critical for appropriate delivery of ICD therapy [14] . In this study the performance of the screening tool was compared against a gold standard (sensing algorithm prepared by the manufacturers (Boston Scientific) in Matlab®.

Our study demonstrated sensitivity and specificity of the S-ICD pre-implant screening tool in individuals with normal cardiac morphologies that is compatible with patient selection for subcutaneous ICD therapy and an expectation of delivery of appropriate

therapy. However, the sensitivity and specificity of the screening tool were significantly lower in individuals with CHD (p=0.001) compared with normal controls. The screening tool was developed using data from adults with normal cardiac morphologies, accounting for the higher sensitivity in this group. The sensitivity and specificity of the screening tool was highest in Lead I, followed by Lead III; there was no statistically significant difference between Lead II and Lead III. There were no statistically significant differences in sensitivity and specificity of the screening tool between the six postures.

This study showed a high sensitivity but relatively lower specificity of the S-ICD screening tool across all the groups, leads and postures. In clinical terms, most suitable patients for S-ICD implantation (true positives) are identified by the screening tool but there are many false positives (unsuitable patients, likely to have poor performance of the detection algorithm due to subcutaneous ECG features). In this study, the screening tool had a high probability of selecting individuals inappropriate for S-ICD.

The current criteria of patient selection for S-ICD is less well defined and the clinicians are left with the dilemma that whether to accept a patient with just one suitable vector, or multiple suitable vectors for S-ICD implant. It is possible that more than one suitable vectors would enable more stable sensing configurations; however, the current generation of S-ICD is limited in its ability of automatic mode switching between sensing vectors, and requires the use of device programmer for manual reconfiguration, thus in current settings the suitability of multiple vectors have limited role.

There are limited published data regarding the performance of the pre-implantation screening tool; especially in patients with structural abnormality due to congenital

heart disease. However, for appropriate S-ICD sensing, it is vital to identify suitable candidates. The START study directly compared transvenous and subcutaneous devices, by assessing their respective abilities to discriminate between arrhythmias [15]. This study showed that all ICDs tested had >99 % appropriate detection for ventricular tachyarrhythmias, but the specificity of supraventricular arrhythmias discrimination was markedly higher for S-ICDs (98%) than for two of three transvenous devices tested (76.7% and 68%) [15]. Similarly, further clinical studies demonstrated the excellent ability of the S-ICD for rhythm discrimination [16, 17, 19, 25]. However, most of these studies on the rhythm discrimination were performed immediately after implantation of S-ICD with patients in a supine posture and this poses questions regarding "real life" performance of S-ICD sensing. Additionally, recent clinical studies have reported inappropriate therapies in as many as 13% of therapy deliveries at one-year follow-up in patients having had S-ICD implantation [12, 20, 26]. In the majority of these cases, the inappropriate therapies were due to sensing algorithm failure rather than mechanical factors, such as subcutaneous lead displacement [20]. The recently published EFFORTLESS S-ICD registry of 472 patients with follow-up at 558 days, reported a 360-day inappropriate shock rate of 7% with the vast majority occurring due to T-wave oversensing of cardiac signals [27]. We speculate that the relatively low specificity of the screening tool may have allowed patients with ECGs that were not appropriate for the S-ICD to have received the device; resulting in inappropriate sensing and therapies.

We suggest that the sensitivity and specificity of the screening method can be improved by using a device with a "live virtual" sensing algorithm for the pre-implant screening purpose. This device would allow testing of the potential sense vector by a fully-featured sensing algorithm in all patients considered for S-ICD implantation and specificity of selection should be improved.

LIMITATIONS

Our study has several limitations. Firstly, the sample sizes are small, due to limited resources, time constraints, and the relative difficulty of finding appropriate patients, having the relevant structural cardiac defects, for inclusion in the four categories. However, all data were collected by a single investigator to reduce variation, and furthermore, the sample size for the current study was selected to mimic preclinical drug safety studies [28]. Secondly, since ECGs were collected from individuals in sinus rhythm at rest, there is the possibility of variation in the morphologies of ECGs during exercise and arrhythmia. However, in this study the Boston Scientific S-ICD pre-implant screening method was followed and this method recommends collection and analysis of resting surface ECGs. More recently, screening is also performed on ECGs acquired during exercise [14]. Considering the patient population who are likely to receive an ICD, the congenital heart disease cohort sampled was limited to three groups – Tetralogy of Fallot, transposition of the great arteries and single ventricle physiology. However, these conditions represent the most complex congenital structural abnormalities [29]. Although such defects are rare, they do represent patients who have a high burden of ventricular arrhythmias and the risk of sudden death [29]. Also, the number of complex CCHD patients attached to any single centre is small and therefore difficult to recruit. Compounding factors were

reduced by recruiting 10 near age and sex matched subjects from normal control, TOF, TGA and SVP patients.

CONCLUSION

The screening tool plays a vital role in the selection of appropriate candidates for S-ICD implantation. In this study the screening tool itself proved to be highly sensitive in identifying S-ICD patients without CHD and would satisfy the requirements of the detection algorithms but it was too non-specific in that it also selected patients who would not. Additionally, the screening tool is significantly less sensitive in patients with CHD. We propose the use of a device with a real-time sensing algorithm for screening purposes, that would allow testing of the potential sense vector through that algorithm in patients considered for S-ICD and so permit a more rigorous assessment of patient suitability; with the aim of reducing inappropriate shock therapies.

Authors contribution

Zeb M was involved in concept/design, data collection, data analysis/interpretation, drafting article, and approval of article. Curzen N, Allavatam V, Yue A, Roberts P, and Wilson D are responsible for interpretation of data, and for critical revision and approval of the article. Morgan J has carried out concept/design, interpretation of data, critical revision and approval of the article, and has secured funding.

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Figure 1

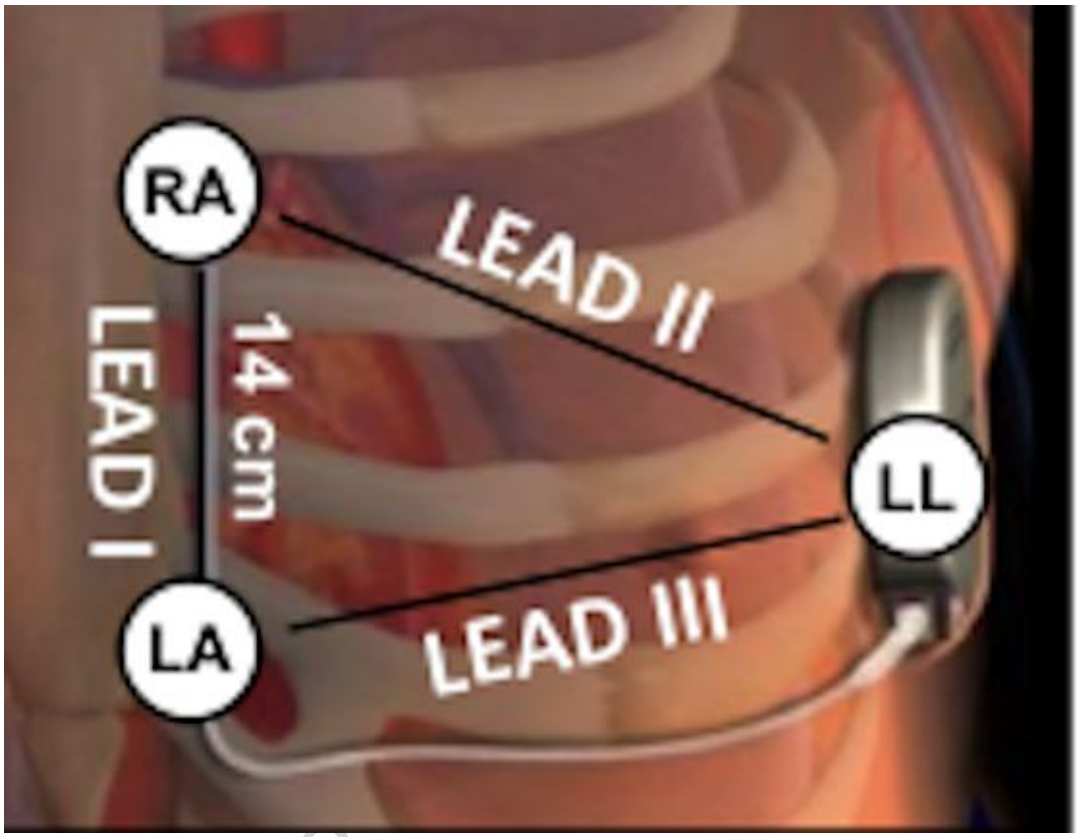

Figure 1: S-ICD generator and lead position. This figure shows the position of subcutaneous sensing arrays and location of bipolar three lead ECG leads placement to generate Lead I, Lead II and Lead III for S-ICD pre-implant screening. [ECG= Electrocardiology, S-ICD= subcutaneous implantable cardioverter defibrillator]

Figure 2

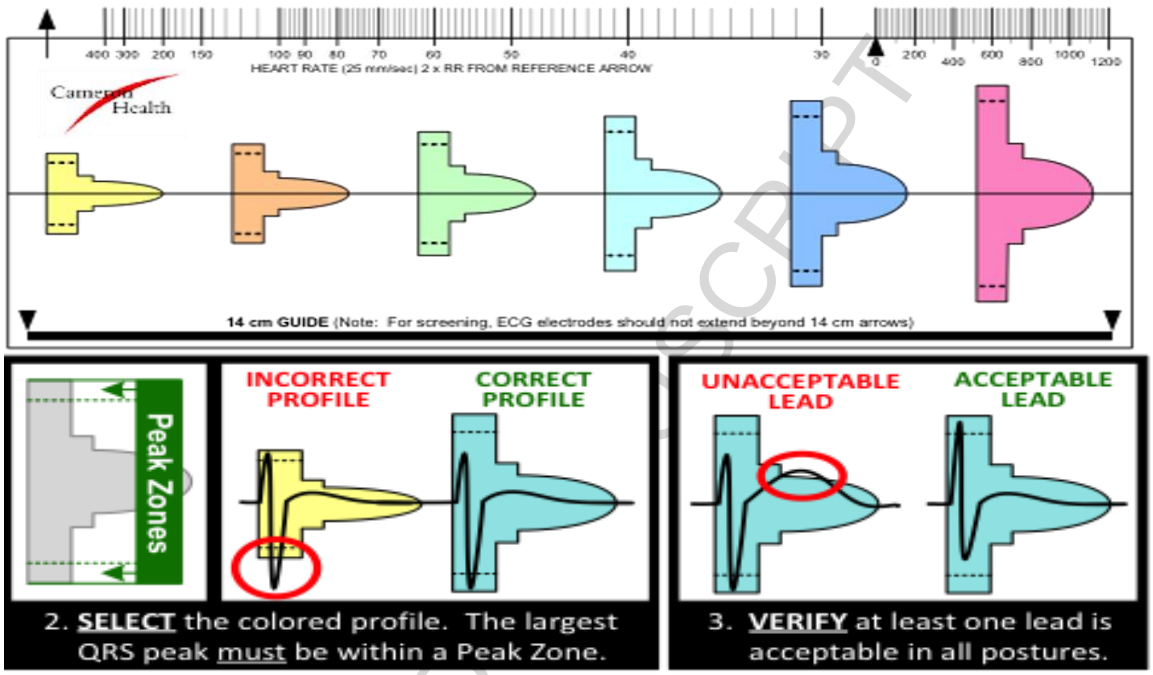

Figure 2: Pre-implant (Boston Scientific) screening tool to identify patients with acceptable sensing characteristics prior to the implant of S-ICD. If the entire QRS complex and trailing T-wave is contained within the coloured profile, the vector/posture combination is deemed acceptable. If any portion of the QRS complex or trailing T-wave extends outside of the coloured profile, the sense vector is deemed unacceptable.

Table 1: Subcutaneous ICD screening tool sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, Fisher exact and McNemar p value for comparison of different categories. [95% CI= 95% confidence interval, TOF=tetralogy of Fallot, TGA=transposition of great arteries, SVP=single ventricle physiology].

	Sensitivity % (95% CI %)	**Specificity % (95% CI)**	**Positive predictive value % (95% CI)**	**Negative predictive value % (95% CI)**	**Positive likelihood ratio (95% CI)**	**Negative likelihood ratio (95% CI)**	**p value**
All	86 (81, 90)	79 (74, 82)	73 (68, 77)	89 (86, 92)	4 (3, 5)	0.2 (0.1, 0.2)	
Normal	95 (83, 99)	79 (70, 85)	59 (47, 70)	98 (93, 99)	4 (4, 6)	0.06 (0.01, 2)	
C-CHD	84 (79, 89)	79 (74, 83)	76 (71, 81)	86 (81, 90)	4 (3, 5)	0.2 (0.1, 0.2)	0.001‡
TOF	77 (64, 87)	76 (68, 83)	60 (48, 71)	88 (80, 93)	3 (2, 4)	0.3 (0.2, 0.5)	0.001‡
TGA	83 (73, 90)	76 (66, 84)	75 (65, 83)	84 (74, 91)	3 (2, 5)	0.2 (0.1, 0.3)	0.001‡
SVP	90 (82, 95)	86 (76, 93)	89 (81, 94)	87 (77, 93)	6 (4, 11)	0.1 (0.06, 0.2)	0.001‡
Lead III	88 (80, 93)	72 (63, 80)	79 (72, 85)	83 (74, 90)	3 (2, 4)	0.2 (0.1, 0.3)	
Lead II	83 (73, 90)	78 (72, 85)	68 (58, 77)	90 (83, 94)	4 (3, 6)	0.2 (0.3, 0.6)	1†
Lead I	89 (78, 95)	83 (76, 88)	68 (58, 77)	94 (89, 97)	5 (4, 7)	0.1 (0.07, 0.3)	0.004††
Supine	79 (64, 89)	83 (72, 89)	76 (61, 86)	86 (75, 92)	5 (2, 8)	0.2 (0.1, 0.4)	
Standing	86 (73, 94)	84 (73, 91)	80 (67, 89)	89 (78, 95)	5 (3,9)	0.2 (0.1, 0.3)	0.1§
Sitting	85 (71, 93)	80 (69, 89)	74 (60, 85)	89 (79, 95)	4 (3, 7)	0.2 (0.1, 0.4)	1§
Left lateral	92 (79, 97)	73 (61, 83)	70 (57, 80)	93 (82, 98)	3 (2, 5)	0.1 (0.04, 0.3)	1§
Right lateral	88 (74, 96)	71 (60, 80)	63 (50, 75)	92 (80, 97)	3 (2, 4)	0.2 (0.1, 0.4)	0.6§
Prone	89 (76, 96)	82 (71, 90)	76 (62, 96)	92 (82, 97)	5 (3, 8)	0.1 (0.05, 0.3)	0.1§

‡Fisher exact p value derived in comparison to individual with normal heart morphology.

†McNemar p value derived in comparison to primary vector (Lead III).

§McNemar p value derived in comparison to supine posture.