UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

Human Development and Health

Subcutaneous and transvenous implantable cardioverter defibrillators:

Developing an individualised approach to assessment and treatment

by

David G Wilson

Thesis for the degree of Doctor of Medicine

August 2017

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF MEDICINE

Human Development and Health

Thesis for the degree of Doctor of Medicine

SUBCUTANEOUS AND TRANSVENOUS IMPLANTABLE CARDIOVERTER DEFIBRILLATORS:

DEVELOPING AN INDIVIDUALISED APPROACH TO ASSESSMENT AND TREATMENT

By David Graham Wilson

In recent years the subcutaneous implantable cardioverter-defibrillator (S-ICD) has emerged as a novel technology which offers an alternative choice to the traditional transvenous implantable cardioverter-defibrillator (TV-ICD) in treatment and prevention of sudden cardiac death. Early experience with the S-ICD however has highlighted that its capacity to accurately sense the cardiac signal can be challenged, in particular with regard to the risk of varying amplitude of signals and risk of T wave oversensing. S-ICD sensing is therefore an important weakness of this technology which this thesis addresses.

Initially only a relatively small group of patients were thought to be suitable for S-ICD, in particular patients with difficult venous anatomy or young patients. Therefore I explored how the important ECG parameters in S-ICD sensing, the R wave, the T wave and the R:T ratio, vary when measured from a right compared to a left parasternal lead position in a population of patients with complex congenital heart disease and normal controls. I go on to explore how the R wave, T wave and R:T ratio in the same patient population vary with posture and discuss how this relates to potentially clinically important in relation to S-ICD sensing. As the sensed S-ICD signal resembles the signal measured with a standard 12 lead ECG, I go on to evaluate what are the ECG predictors of T-wave oversensing are. Lastly, I explore how application of mathematical vector transformation techniques can help reconstruct an 8 lead ECG from 2 S-ICD vectors, and from then create a 12-lead ECG, and I discuss how this technique may potentially help solve some sensing problems related to the S-ICD.

Within this thesis, I demonstrate that much could be done at an individual level (optimise lead position, identify patients at risk of T wave oversensing and using vector transformation to reduce

the likelihood of inappropriate therapy) in order to maximise the potential benefit (and reduce the unwanted consequences) of S-ICDs. This thesis has advanced the understanding of how to improve therapy to treat SCD by reducing the unwanted events of S-ICD therapy by developing a concept of a tailored assessment of patient's suitability for ICD therapy.

Table of Contents

DECLARATION OF AUTHORSHIP

I, DAVID WILSON ..... [please print name]

declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

Subcutaneous and transvenous implantable cardioverter defibrillators: Developing an individualised approach to assessment and treatment

I confirm that:

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;

2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

3. Where I have consulted the published work of others, this is always clearly attributed;

4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

5. I have acknowledged all main sources of help;

6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

7. Parts of this work have been published as: [please list references below

Signed: .....

Date: .....

List of peer reviewed publications

1. Chapter 3
   Left and right parasternal sensing for the S-ICD in adult congenital heart disease patients and normal controls
   Wilson D, Zeb M, Veltman G, Dimitrov D, Morgan J.
   Pacing Clin Electrophysiol. 2016 Mar;39(3):282-90.
2. Chapter 5
   ECG predictors of T wave oversensing in S-ICD recipients.
   Wilson DG, Leventgianis G, Barr C, Morgan JM International Journal of Cardiology 2016 1;220:27-31.
3. Chapter 6
   Reconstruction of an 8-lead surface ECG from two subcutaneous ICD vectors.
   Wilson DG, Cronbach PL, Panfilo D, Greenhut SE, Stegemann BP, Morgan JM
   Int J Cardiol. 2017 Jan 27
4. Chapter 6
   Electrode positions, transformation coordinates for ECG reconstruction from S-ICD vectors.
   Wilson DG, Cronbach PL, Panfilo D, Greenhut SE, Stegemann BP, Morgan JM
   Data Brief. 2017 Feb 22;11:611-616

Presented abstracts

Oral presentation

1. Reconstruction of 12 – lead ECG from TWO S-ICD vectors: generation and validation of transformation coefficients.
   Wilson DG, Cronbach PL, Panfilo D, Greenhut SE, Stegemann B, Morgan JM
   Heart Rhythm Congress, Birmingham 2015

Poster Presentation

1. Reconstruction of 12 – lead ECG from TWO S-ICD vectors: generation and validation of transformation coefficients
   Cronbach PL, Wilson DG, Panfilo D, Greenhut SE, Stegemann B, Morgan JM.
   American Heart Association, Miami November 2015
   Circulation 2015;132:A13578

2. ECG predictors of T-wave oversensing in subcutaneous implantable cardioverters.
   Wilson DG, Leventigiannis G, Barr C, Morgan JM
   Heart Rhythm Congress 2015

List of Tables

List of Figures

List of Accompanying Materials

1. Appendix A – Primary prevention ICD programming from University Hospital of Southampton NHS Foundation Trust and The Bristol Heart Institute
2. Appendix B – Details of therapy delivered for heart rates > 200bpm and for rates <200bpm

Acknowledgements

I would like to thank Professor John Morgan for his constant guidance, support and encouragement, Professor Paul Roderick who gave invaluable advice and supervision and Associate Professor Borislav Dimitrov who provided expert statistical advice and guidance. It is particularly poignant that Borislav Dimitrov died tragically six months ago following a short illness. I remember him to be a rigorous academic, who would generously dedicate time and effort to assisting me in my research. We had many conversations about his childhood in Bulgaria and his subsequent medical training and I was always impressed by the number of languages he spoke fluently. Without him I would not have been able to produce this piece of work.

I would like to thank Dr Mehmood Zeb. The work I carried out of subcutaneous lead sensing during postural change and parasternal lead position change (Chapters 3 and 4) is built upon work that he had set up. He had collected the data using the Prime ECG and was kind enough to allow me to analyse the data separately and provided advice during the writing up process.

I thank Dr Barr, Consultant Cardiologist at Russells Hall Hospital for agreeing to collaborate with him and for his generosity in providing funding for the study on ECG predictors of T wave oversensing in S-ICD recipients. I also thank Dr Leventogiannis who helped in the data collection for this study and to for all the research team who helped me feel welcome and supported.

I would like to thank Medtronic for providing the financial support that made this work possible. Berthold Stegemann and to Saul Greenhut who provided expert advice and assistance in the collaborative work on ECG reconstruction. (Chapter 7). Peter Cronbach a medical student was extremely helpful for his work collected the ECGs for this study.

I am indebted to the research team at Southampton for all their help and support and with whom I spent many happy moments discussing the surprising disadvantages of being long-legged and left eye dominant but right-handed in the sporting arena, amongst other discussions!

Finally, I owe a tremendous amount of gratitude to my wife Sarah for her eternal love and support. Sarah, Albert, Annie and Charlie provided me with an escape during the research and also gave me the space to complete this thesis.

Definitions and Abbreviations

ACEi	angiotensin converting enzyme
ACHD	Adult congenital heart disease
AICD	Automated implantable cardioverter-defibrillator
BSM	Body surface mapping
CABG	Coronary artery bypass graft
CABG-PATCH	Coronary artery bypass Patch trial
CCU	Coronary care unit
CKD	Chronic kidney disease
DER	defibrillation energy requirements
DINAMIT	Defibrillator in acute myocardial infarction trial
ECG	Electrocardiogram
EF	Ejection fraction
EFFORTLESS	Evaluation of factors impacting clinical outcome and cost effectiveness of the S-ICD – International S-ICD registry
ICD	Implantable cardioverter-defibrillator
HIV	Human immunodeficiency virus
HCM	Hypertrophic cardiomyopathy
MADIT II	Multicenter Automatic Defibrillator Implantation Trial II
MADIT-RIT	Multicenter Automatic Defibrillator Implantation reduction in inappropriate therapy trial
NOAC	Novel oral anticoagulant
NNT	Number needed to treat

NICM	Non-ischaemic cardiomyopathy
OR	Odds ratio
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PEA	Pulseless electrical activity
PVD	Peripheral vascular disease
PTSD	Post-traumatic stress disorder
QOL	Quality of life
S-ICD	Subcutaneous implantable cardioverter-defibrillator

SVT	Supraventricular tachycardia
TV-ICD	Transvenous implantable cardioverter-defibrillator
TWOS	T-wave oversensing
SCD	Sudden cardiac death
SVP	Single Ventricle Physiology
TB	Tuberculosis
TOF	Tetralogy of Fallot
TGA	Transposition of the Great Arteries
VT	Ventricular tachycardia
VF	Ventricular fibrillation

Chapter 1: Introduction

1.1 Personalised medicine

The completion of the human genome project in 2003 has resulted in a greater understanding of molecular medicine and has the led to a burgeoning interest in personalised medicine as evidenced by the increase in the publications of scientific and medical journals on the subject. (Figure 1) Personalised medicine can be defined in the following way [1]:

1. The use of combined knowledge (genetics, or otherwise) about a person to predict *treatment response* and thereby improve that person's health
2. The use of combined knowledge (genetics, or otherwise) about a person to predict *disease prognosis or treatment response* and thereby improve that person's health
3. The use of combined knowledge (genetics, or otherwise) about a person to predict *disease susceptibility, disease prognosis or treatment response* and thereby improve that person's health

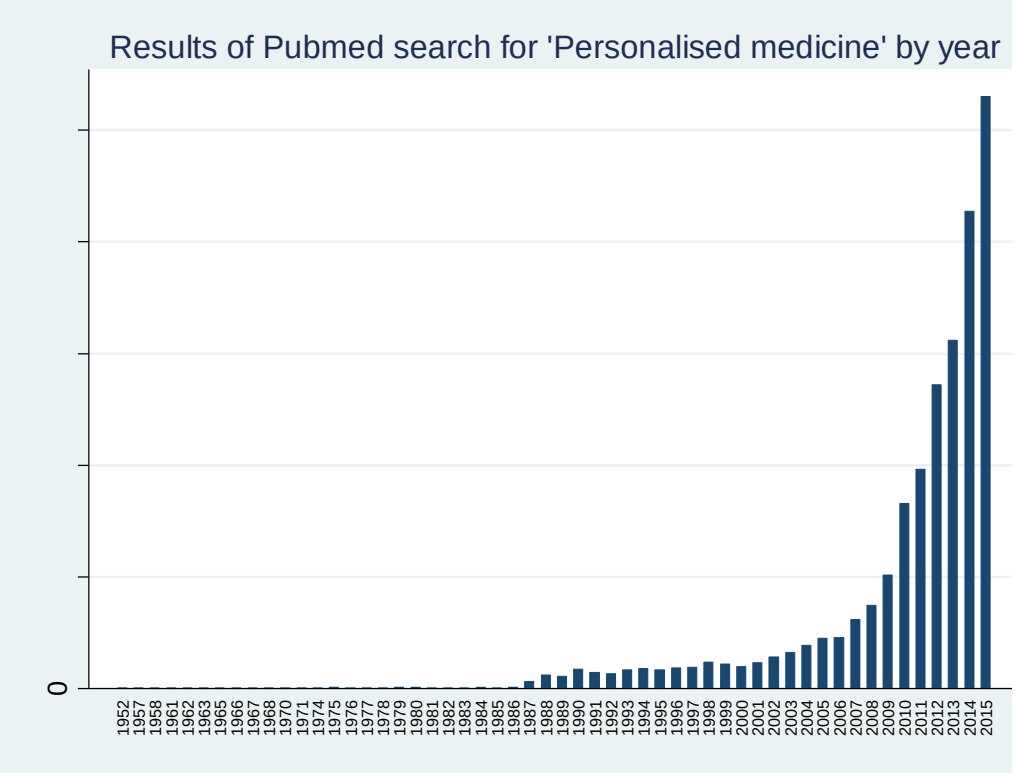


Figure 1 Results of Pubmed search for 'Personalised medicine'

Schleigden et al. sought to quantitatively refine and render the definition of personalised medicine more precise:

> Personalised medicine seeks to improve stratification and timing of health care by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics. [2]

The terms personalised medicine is used interchangeably [3] with precision medicine [4] or individualised medicine (imedicine) and occasionally the term P4 is used (personalized, predictive, preventive, and participatory).[5] For the purpose of this thesis, the term personalised medicine will be used hereafter.

Medical practitioners have always sought to treat the patient as an individual, and thus one might argue that personalised medicine has existed for hundreds of years. However, practitioners have been bound in their ability to treat each individual in a unique way by their limited understanding of disease process and relatively narrow array of therapeutic options. Increasingly though, thanks largely to progress in the understanding of the genetics underpinning diseases and pharmaco-therapy , medical specialities [4, 6-12] have embraced personalised medicine.

Such is the promise of personalised medicine that NHS England have recently published a 'Personal Medicine Strategy'[13] in which '*emergent approaches in areas such as diagnostic tests, functional genomic technologies, molecular pathway, data analytics and real time monitoring of conditions to better manage patients' health and to target therapies to achieve the best outcomes in the management of a patient's disease or predisposition to disease'.*

Thus the vision for the future of the NHS requires the implementation of targeted and personalised interventions in order to improve outcomes.

1.2 The global burden of cardiovascular disease

Cardiovascular disease (CVD) is a leading cause of global mortality, accounting for approximately 30% of deaths worldwide. [14] In high income countries, cardiovascular disease (excluding cerebrovascular disease) accounts for more deaths that all pulmonary and gastrointestinal malignancies combined and in low and middle incomes countries, cardiovascular disease causes more deaths than HIV/AIDs, malaria and TB combined. [15]

1.2.1 Mortality associated with CVD

Approximately 40-50% of cardiovascular deaths are sudden cardiac deaths (SCD) and about 80% of these are caused by ventricular tachyarrhythmia. [14] SCD is an unexpected death due to cardiac causes that occurs in a short time period (generally within one hour of symptom onset) in a person with known or unknown cardiac disease. [14]

In the UK, it is estimated that 60,000 out of hospital cardiac arrests occur each year. [16, 17 18] An out of hospital cardiac arrest can be defined as a sudden disturbance of the cardiac rhythm caused by ventricular fibrillation or ventricular tachycardia that can occur either in the context of an acute myocardial infarction or of a structural or electrical abnormality of the heart and will usually result in SCD unless promptly treated by cardiopulmonary resuscitation and cardiac defibrillation.

Approximately 1 person every day aged <35 years suffers a cardiac death in the UK. [19] Survival rates following an out of hospital cardiac arrest in the UK remain poor ranging from 2% to 12%. [20,21] Despite using the best appropriate medical treatment, arrhythmia recurrence rates in survivors of cardiac arrests are still 40-50% at five years. [22]

1.2.2 Implantable cardioverter-defibrillators to treat and prevent sudden cardiac death

To combat this, implantable cardioverter-defibrillators (ICD) have been developed and are implanted in those considered to have an elevated risk of SCD. ICD technology is over 30 years old and have traditionally consisted of an active can (battery and computing power) and transvenous leads which are implanted into the right ventricle in order to sense the cardiac signal. If a pathological ventricular arrhythmia is sensed the ICD will attempt to abort the rhythm by delivering overdrive pacing or by delivering a high voltage shock. Unfortunately, the presence of a transvenous lead with the heart can be problematic not only in terms of implanting the lead and the potential trauma the can result (pneumothorax and cardiac tamponade secondary to localised perforation of the heart due to the ICD lead), but the lead can serve both as a conduit for infection descending from the pocket and as a nidus for infection seeding on the intra-cardiac lead. Given these limitations a novel technology has emerged that offers an alternative solution to treating a preventing sudden cardiac death, the subcutaneous ICD (S-ICD).

1.2.3 The S-ICD

The S-ICD consists of an active can (battery and computing power) and single defibrillation electrode which is tunnelled subcutaneously across from the left axilla to an area left of the xiphisternum and upwards, to be left in a left parasternal position. The can is buried in a pocket between the serratus anterior and the trapezius muscle. Thus the lead forms a large ‘L’ shape on the torso, see Figure 2.

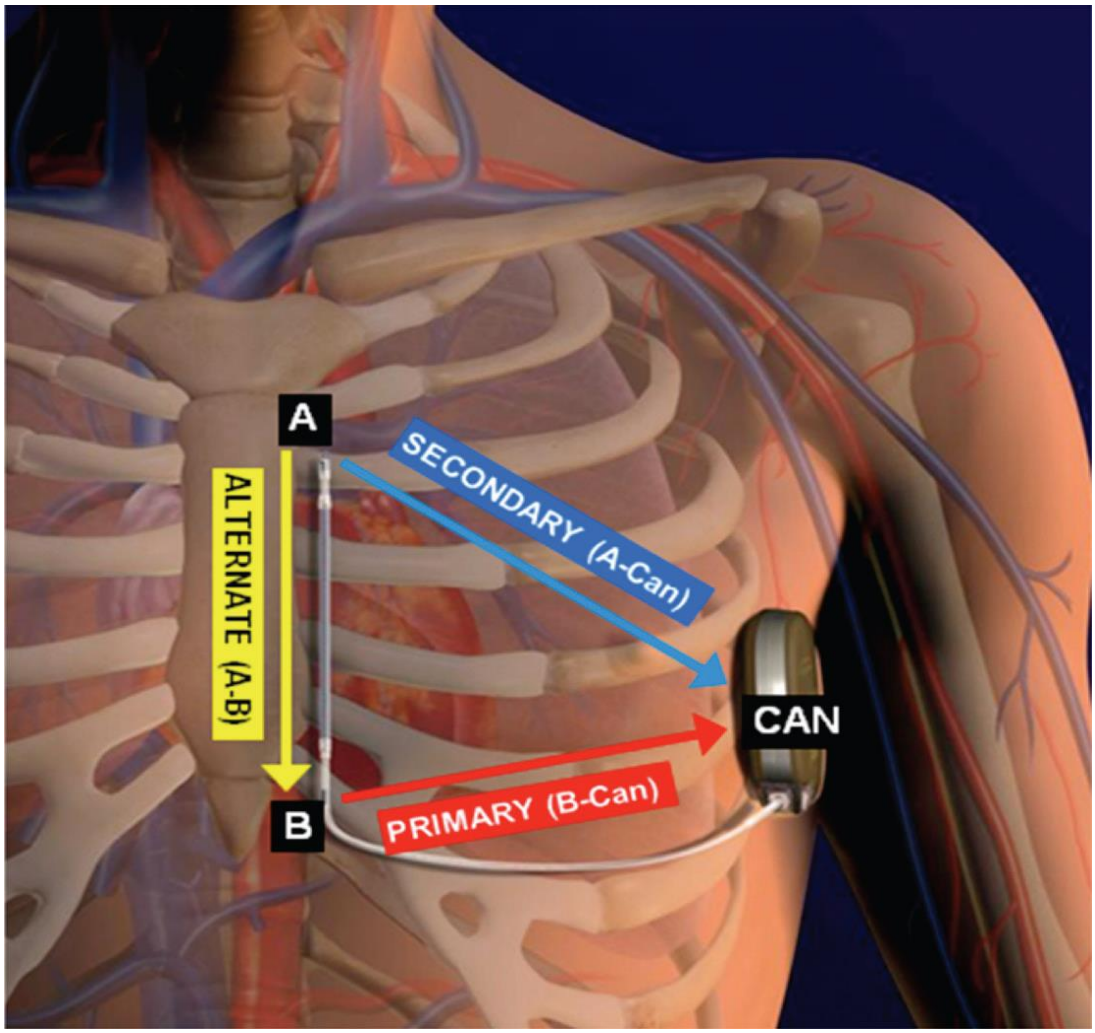


Figure 2 Illustration of the S-ICD with the anatomical location of the sensing components. The sensing vector can be selected from the proximal electrode B-CAN (primary), the distal electrode A-CAN (secondary), or the distal to proximal electrode A-B (alternate). Image reused with permission from Wolters Kluwer Health, Inc. (Rowley CP, Gold MR Subcutaneous Implantable Cardioverter Defibrillator 2012; Circ Arrhythm Electrophysiol. 5:587-593).

1.3 Research problem defined

1.3.1 Early signal of sensing difficulties associated with the S-ICD

In 2009 the S-ICD received Conformité Européene (CE) mark approval and in the autumn of 2012, the U.S. Food and Drug Administration (FDA) granted Boston Scientific Corporation regulatory approval for its S-ICD System. From the outset of clinical experience with the S-ICD it became apparent that the ability of the S-ICD to accurately sense the cardiac signal all the time may be challenged.

In 2012 a Dutch group reported on their initial experience with the S-ICD implanted in 118 patients in four centres and followed up over 18 months. [23] The rate of inappropriate shocks was 13%, much higher than conventional TV-ICDs, and were mainly due to T wave oversensing. However, authors did comment that a lot of these sensing problems were resolved by a software update and changing the sensing vector. The following year, a report summarised the United Kingdom experience in S-ICD and reported an inappropriate shock rate that remained above what many clinicians would consider acceptable, occurring in 15% in 111 patients. [24] T-wave oversensing was the most common cause of inappropriate shock delivery.

The same year, a landmark Investigation Device Exemption (IDE) study was published and this led to the FDA approval being granted for the S-ICD. [25] This study was prospective, nonrandomized, multicentre trial included adult patients with a standard indication for an ICD with an aim of evaluating the safety and efficacy of the S-ICD. In total, 330 patients were recruited (314 devices implanted) in 33 sites in United States, New Zealand, the Netherlands and the United Kingdom. The rate of inappropriate shock remained high at 13.1% and inappropriate sensing of the cardiac signal was the most common cause, occurring in 7% of the 314 patients.

1.3.2 Motivation to carry out research

It is in this context that the motivation for carrying out this research must be viewed. The S-ICD is a novel technology that appeared to offer a useful alternative to the transvenous-ICD. However with approximately one in eight persons implanted with an S-ICD receiving an inappropriate shock caused mainly by T wave oversensing, this technology, in particular the sensing component appeared to be somewhat flawed.

This thesis investigates the sensing difficulties related to the S-ICD. In order to understand more about the sensing characteristics that may be important or relevant to the S-ICD, a number of studies were carried out. The first two studies evaluated how varying posture and the location of where the sensed ECG signal recorded from cutaneous electrodes recorded over where a S-ICD sensing electrode would lie, would impact on– the R wave, the T wave and the R:T ratio. These parameters are considered to be the most important components of the ECG signal for S-ICD sensing. These studies were carried out using participants with complex congenital heart disease as these patients were originally considered to be ideal recipients of S-ICDs due to their difficult venous anatomy, young age and relative high risk of endocardial lead complications with TV-ICDs. The population of patients consisted of 3 groups, Transposition of the Great Arteries, single ventricle physiology and Tetralogy of Fallot. These groups were compared to a control group of participants with structurally normal hearts. It must be noted that since this study was performed,

implanting physicians have become more accustomed to the S-ICD and the population into whom the device is implanted has broadened to include patients with LV systolic dysfunction.

The third study was designed to evaluate the hypothesis that as the sensed S-ICD signal resembles the cardiac signal measured with a standard 12 lead ECG, it should be possible to identify ECG characteristics that are more prevalent in patients who have received an inappropriate shock due to T wave oversensing. In order to test this, I conducted a logistic regression analysis to identify ECG predictors of T wave oversensing.

In my final study, I tested the hypothesis of whether it is feasible to apply techniques used in reconstructing 12 lead ECGs from reduced lead sets and generate reconstructed 8-lead ECG from 2 S-ICD vectors. An 8-lead ECG contains all the necessary information to create a 12-lead ECG (augmented leads are generated from the measured leads I and II). This study has particular relevance for clinical practice and I discuss how this technique may potentially help solve some sensing problems related to the S-ICD.

1.3.3 Difficulties evaluating S-ICD sensing without access to the commercially available S-ICD sensing algorithm

This thesis was carried out in part as a results of a research grant from Medtronic Inc. who do not have a commercially available S-ICD at present. However, their market competitors, Boston Scientific purchased the original company who developed the S-ICD (Cameron Health) and therefore I was never given privileged access to the S-ICD sensing algorithm in order to perform my data analysis and studies. My understanding of how the commercially available S-ICD functions from a sensing perspective is derived from information available in the public domain, mainly in scientific journals and a medical conferences. I have not knowledge or understanding of what signal processing and filtering of the recorded signal is performed by the S-ICD, both of which are important in cardiac signal sensing performance. It is important for the reader to understand this whilst reviewing this thesis.

1.3.4 Novel contribution

This thesis has generated a number of novel contributions in understanding issues surrounding S-ICD sensing.

Firstly, I have demonstrated that sensing the cardiac signal from electrodes located over where a right parasternal S-ICD may lie may potentially offer some useful beneficial sensing characteristics

compared to a left parasternal sensing location in particular with patients with structurally normal hearts.

Secondly, I have demonstrated that varying posture can have a significant impact on the sensed ECG signal when it is measured from skin electrodes located over where a conventional S-ICD may lie. In particular, the left lateral, the right lateral and the prone postures accounted for the greatest extremes (maximal and minimal R wave, T wave amplitude and R:T ratio). Again, this effect appeared to be more important in those with structurally normal hearts rather than those with complex congenital heart disease.

The statistical methods employed to analyse the data for these paired studies are novel and were purposely written by a statistician (Dr Borislav Dimitrov, Associate Professor of Medical Statistics). The data were particularly challenging to analyse given the large number of variables (4 subgroups, 3 vectors and 6 postures) and therefore a bespoke statistical analysis was required. The graphical presentation of the data are also novel, namely the summary boxes. This method of presenting the data succinctly summarise the data from over 400 pages of statistical results.

Thirdly I have demonstrated that in a retrospective analysis of the resting 12 lead ECGs recorded at the time of the patient's S-ICD implant that it is possible to identify ECG predictors of inappropriate shock due to T wave oversensing. However, given the small numbers of patients who went on to receive inappropriate shocks due to T wave oversensing, these results must be viewed as exploratory and hypothesis generating.

Lastly, the concept of generating an 8-lead ECG from 2 S-ICD vectors is entirely novel and has the potential for application in future generators of S-ICD. The results from this study are again exploratory and would need to be replicated in a larger dataset including patients with structurally normal hearts, congenital heart disease and arrhythmias and also exploring whether increasing the number of recording electrodes on the S-ICD would improve the results of the transformation.

Chapter 2: Background and general methods

2.1 Overview of the history of ICDs

The importance and scale of problem posed by SCD became apparent in the 1960s. The advent of electrocardiographic monitoring resulted in the observation that ventricular arrhythmias occurring in patients with acute myocardial infarction in a hospital setting was directly associated with a high mortality. Coronary care units (CCU) were therefore developed. These were specialist wards in which patients admitted with myocardial infarction were clustered. CCUs were staffed with personnel who were in constant attendance, observing patients for the onset of lethal arrhythmias so that they could treat them with the necessary drugs, cardiopulmonary resuscitation and electrical defibrillation. Patients with acute myocardial infarction treated on coronary care ward had significantly improved survival compared to those who were treated elsewhere.[26] There continued to be however a high incidence of sudden cardiac death occurring predominately in the community.

Epidemiological studies in men and women in the 1970s and 1990s suggested that 88% to 91% of deaths that occur within 1 hour of symptom onset are arrhythmic in nature. [27, 28] Pharmacological treatments were proving to be relatively ineffective in preventing SCD. A more robust approach was required.

Dr Michael Mirowski, is credited for developing the first implantable cardioverter defibrillator (ICD). Mirowski was born in Poland in 1924 but escaped to Russia to avoid the invading Germans in 1939. [29] At the age of 15, Mirowski first considered how a defibrillator could be developed, remarkable considering, cardiopulmonary resuscitation and even pacemakers had yet to be developed.[30] He went to medical school in Lyon, France and subsequently moved to Baltimore, USA to work as a cardiologist. It was only after his mentor, Professor Harold Heller died following several episodes of ventricular tachycardia that he focused on developing away to tackle the problem of treating ventricular arrhythmias more seriously. [31] Mirowski had the vision of applying external defibrillator technology that had been successful used in the coronary care units to pacemaker technology and so be implanted in humans. This idea was met with considerable criticism.

Mirowski first described a device capable of sensing and appropriately treating ventricular fibrillation (the most lethal ventricular arrhythmia) forty-six years ago in 1970. [32] A sensor placed in the right ventricle of a dog sensed ventricular fibrillation and a 30-50 wattsecond (*SIC* joule) shock was delivered between a cutaneous electrode and the intra-cardiac electrode (

Figure 3). It was hypothesised that this technology could be refined and introduced into man in order to provide protection from sudden cardiac death.

Three years later an article was published on the efficacy of low energy intraventricular catheter defibrillation in human patients in ventricular fibrillation at the time of coronary artery bypass grafting. [33] One electrode was introduced to the right ventricle via an atriotomy and the second electrode, a saline-soaked sponge was placed on the superior vena cava. Eight of the 11 patients were successfully defibrillated in this manner. This study laid the scene for the technological development that would result in the development of a totally automated version.

In 1976 the first implant of an automated implantable cardioverter defibrillator (AICD) was made in a dog [34] and the first implant in a human was made in February 1980. Outcomes from three patients suffering from recurrent malignant arrhythmias (arrhythmia likely to be lethal unless treated appropriately) underwent AICD implantation were published shortly afterwards. [35] Seven episodes of ventricular tachycardia and flutter/fibrillation were documented in the following weeks and six were automatically reverted to normal sinus rhythm by the device. One episode was treated with conventional external defibrillation before the implantable device could recharge.

These early iterations of the ICD (Figure 3) were rudimentary compared to contemporary transvenous ICD (TV-ICD) technology. [36] Implantation of the device required a thoracotomy or a sub-xiphoid approach. The potential implantees were all cardiac arrest survivors, and needed to have survived two episodes of cardiac arrest due to VA outside the context of a myocardial infarction. These must have been resistant to conventional and investigational pharmacotherapy. The response to sensed ventricular fibrillation or ventricular tachycardia at rates above a pre-specified threshold was to deliver a 25 joule pulse. The device could re-charge 3 times. Battery longevity was estimated at 3 year of monitoring or ability to deliver 100 shocks. One year mortality in those implanted with these devices was 22.9%, half that than in an equivalent population without the device (52% one-year mortality).[36]

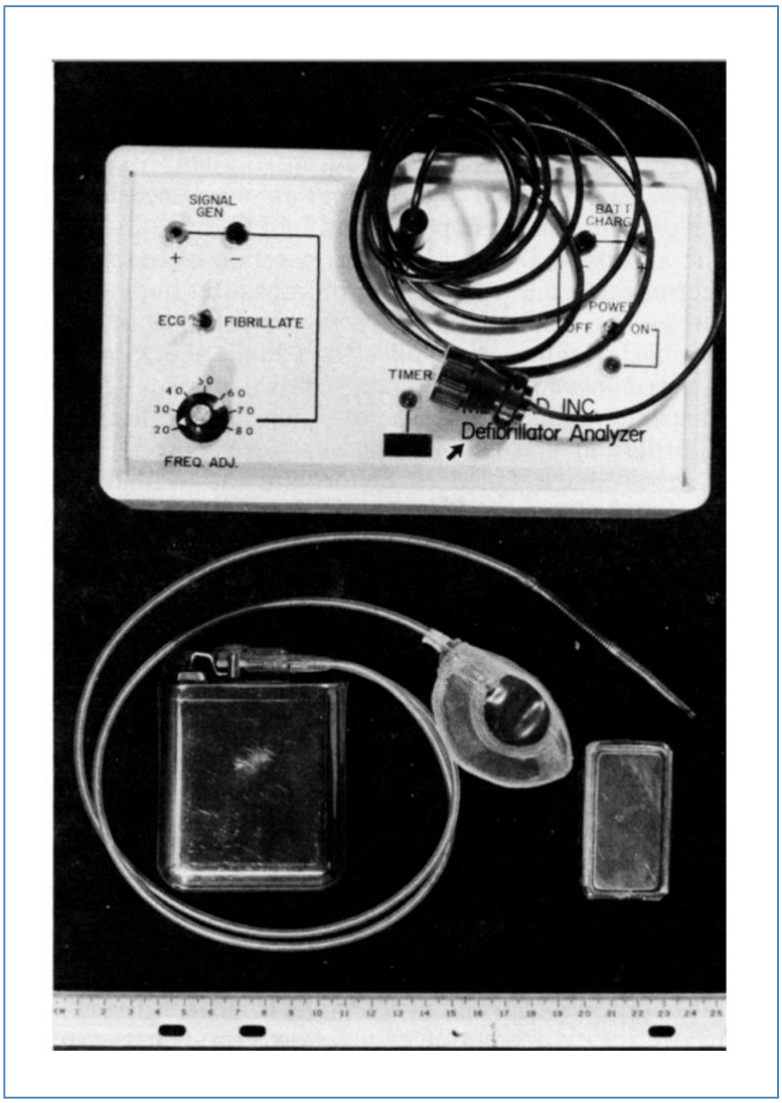


Figure 3 The original defibrillator

The implantable defibrillator with apex and superior vena cava electrodes appears at the bottom left of the image and the fibrillator at the bottom right. This was used to induce ventricular fibrillation in animal studies. The defibrillator analyser in the upper half of the photograph. The arrow points toward the electromagnetic transducer. Reused with permission from Wolters Kluwer Health, Inc. (Circulation 1978 Mirowski Defibrillation in dogs [34]).

2.2 ICD trials

The early clinical trials involving ICDs compared ICD therapy to medical drug treatment for the prevention of death in survivors of ventricular fibrillation or ventricular tachycardia where no reversible cause was found, in other words, for secondary prevention of SCD [37-40] Table 1 provides an overview of the secondary prevention ICD trials**.** These trials consistently found that the ICD reduced the risk of SCD death due to a 50% reduction in malignant ventricular arrhythmias. [41]

Subsequently, a series of clinical trials tested the hypothesis that ICD may prevent death in patients at elevated risk of ventricular arrhythmias, primary prevention trials. Elevated risk of ventricular arrhythmia can be defined variously as reduced left ventricular ejection fraction, evidence of non-sustained ventricular tachycardia, positive electrophysiology stimulation test, depressed heart rate variability, elevated 24-hour heart rate on holter monitoring or abnormalities on signal averaged ECG). [42-48] Five of these seven trials demonstrated the superiority of ICD therapy of medical therapy in improving survival in this primary prevention population. [44, 46-48] The majority of these trials evaluated patients with established coronary artery disease, though Kadish and Bardy demonstrated the superiority of ICD over medical therapy in non-ischaemic cardiomyopathy, [42, 46] however the recently published Danish trial challenges this viewpoint, and will be discussed in more detail below.

Table 2 provides an overview of the important primary prevention ICD trials. [49] MADIT II was the largest of these trials and established reduced ejection fraction (<30%) as the principal predictor of SCD. [48] Not all the trials demonstrated a mortality benefit from the ICD. Two trials CABG-PATCH and DINAMIT had negative results. [43, 45] The CABG-PATCH trial evaluated the effect on survival of a prophylactic ICD on patients at the time of coronary bypass grafting (CABG). No evidence of improved survival in the ICD group was found, a finding that is explained by the positive remodelling that occurred post CABG and the limited role of a tool used to risk stratify patients which has not been found to be useful in identifying high risk patients, the signal averaged ECG. The DINAMIT trial was an open label comparison of ICD therapy versus no ICD therapy in the early (day 6 to day 40) post myocardial infarction stage. The results demonstrated a reduction in the rate of death due to arrhythmia, this was offset by an increase in the rate of non-arrhythmic death, which were reportedly cardiovascular in nature.

The effectiveness of ICDs without cardiac resynchronisation therapy in patients with ischaemic and non-ischaemic cardiomyopathy was evaluated in a systematic review and meta-analysis and ICDs were found to reduce arrhythmic mortality [relative risk (RR): 0.40; 95% confidence interval (CI): 0.27-0.67] and all-cause mortality (RR: 0.73; 95% CI: 0.64-0.82) regardless of aetiology. [50]

Trial	Year	No. of patients	Enrolment criteria	Aim	Results
DUTCH [39]	1995	60	Survived cardiac arrest due to VF/VT and old MI (<4 weeks) and inducible VT at EPS	ICD as first choice therapy vs conventional therapeutic strategy (antiarrhythmic drugs and then eventual ICD)	73% reduction in primary end points of death, recurrent cardiac arrest and cardiac transplantation at 24 months (95% C.I., 0.09 - 0.85; P=0.02)
AVID [37]	1997	1016	Survived VT/VF cardiac arrest or VT with Survived VT/VF cardiac arrest or VT with syncope or VT with LVEF <40%	Antiarrhythmic treatment vs ICD	31% reduction of mortality with ICD at 3 years (95% C.I. 0.10-0.52; p<0.02)
CASH [37]	2000	288	Cardiac arrest due to VF or VT	ICD vs antiarrhythmic agents	Non-significant reduction in all-cause mortality at mean follow up of 57 months. 28% reduction of all-cause mortality at 3 years with ICD (97.5% C.I. upper bound 1.112; P=0.08)
CIDS [40]	2000	659	Cardiac syncope due to VF or sustained V and syncope or poorly tolerate VT and LVEF <40% or syncope and inducible or monitored VT	ICD vs amiodarone	Non-significant 19.7% reduction of all-cause mortality with ICD (95% C.I. 0.077 – 0.4) p= 0.142

AVID, Antiarrhythmic Versus Implantable Defibrillators; CASH, Cardiac Arrest Study Hamburg; CIDS, Canadian Implantable Defibrillator Study; EPS, electrophysiological study; ventricular fibrillation; VT, ventricular tachycardia; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; VF, ventricular fibrillation; C.I., confidence interval.

Table 1 Summary of secondary prevention ICD trials adapted from Santini et al. Heart 2007 [49]

Trial (year)	Patients enrolled	Enrolment criteria	Aim	Results
MADIT (1995) [47]	196	LVEF 35%; prior MI; asymptomatic NSVT; NYHA I–III; inducible VT refractory to iv procainamide on EP study	ICD vs standard medical treatment	54% reduction in total mortality with ICD therapy (95% C.I 0.26–0.82) P=0.009
CABG-Patch (1997) [43]	900	LVEF (35%; patients scheduled for CABG; positive SAECG results	ICD vs. no ICD	Non-significant 7% increase in mortality (95% C.I 0.81 to 1.42) p=0.64
MUSST (1999) [58]	704	LVEF (40%; CAD; NSVT; inducible VT on EP study	EP guided therapy (antiarrhythmic or ICD) therapy vs no antiarrhythmic	23% reduction of total mortality with ICD therapy or antiarrhythmic at 5 years (95% C.I. 0.64-0.92) p=0.005
MADIT II (2002) [48]	1232	EF<30% & prior MI	Conventional therapy vs ICD	31% reduction of all-cause mortality with ICD (95% C.I. 0.51–0.93) P= 0.016
DEFINITE (2004) [46]	229	EF <36%; NICM; NSVT or PVCS at Holter monitoring	Conventional therapy vs conventional therapy and ICD	35% reduction in mortality in ICD group at 2years (95% C.I. 0.40 - 1.06) P=0.08
DINAMIT (2004) [45]	674	EF <35%, recent MI (within 4–40 days); impaired cardiac autonomic modulation (HR variability)	Conventional therapy vs ICD	No reduction in mortality in ICD therapy (HR for death in the ICD group, 1.08; 95% C.I., 0.76 to 1.55; P=0.66); reduction of arrhythmic deaths with ICD p <0.01
COMPANION (2004) [59]	1520	NYHA class III–IV due to ischaemic and non-ischaemic cardiomyopathy, QRS <120ms	Conventional therapy vs conventional therapy and CRT-P or CRT-D	40% reduction in all-cause mortality with CRT-D (95% C.I. 0.49 to 0.75) P<0.001
SCD-HeFT (2005) [42]	2521	EF <35%, NHYA class II–III (ischaemic and non-ischaemic)	OMT + placebo vs OMT + amiodarone vs OMT vs ICD	23% reduction of overall mortality with ICD (97.5% C.I. 0.62 - 0.96; P=0.007)
DANISH (2016) [60]	1116	NICM EF ≤35%, NYHA II-IV	OMT including CRT-P if indicated vs. OMT + ICD or CRT-D if indicated	No reduction in mortality in ICD group (HR, 0.87; 95% C.I. 0.68 - 1.12 ;) P=0.28

CABG-Patch, Coronary Artery Bypass Graft Patch; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT, cardiac resynchronisation therapy; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; EF, ejection fraction; EPS, electrophysiological study; HR, heart rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MI, myocardial infarction; MUSTT, Multicenter Unsustained Tachycardia Trial; NSVT, electrocardiogram; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2 An overview of the important primary prevention ICD trials

2.2.1 Danish trial

Investigators in Denmark published the results of a contemporary trial of ICD therapy in patients with non-ischaemic cardiomyopathy the results of which have challenged current thinking in ICD therapy in patients with non-ischaemic cardiomyopathy. This trial, named Danish (Defibrillator implantation in patients with non-ischaemic systolic heart failure), sought to evaluate the benefit of ICD therapy in non-ischaemic cardiomyopathy as until then, the data for benefit in this patient population had been derived from subgroup analysis of trials, principally, SCD-Heft.[42] The study was a randomised controlled trial and 556 patients with non-ischaemic cardiomyopathy were assigned to the ICD arm and 560 patient were assigned to the usual care. There was a high uptake of cardiac resynchronisation therapy (CRT) in both arms (58%). Primary outcome of the trial was death from any cause and the secondary outcome were sudden cardiac death and cardiovascular death.

ICD therapy did not result in a mortality benefit after a median follow up of 67.6 months. The primary outcome occurred in 21.6% in the ICD group and 23.4% in the control group (hazard ratio, 0.87; 95% confidence interval, 0.68 to 1.12; P=0.28). There was a significant reduction in sudden cardiac death in the ICD compared to the control group 4.3% vs 8.2% (hazard ratio, 0.50; 95% confidence interval, 0.31 to 0.82; P=0.005). In a subgroup analysis the only group to derive a mortality benefit from ICD therapy was the younger than 68 years old (hazard ratio, 0.64; 95% confidence interval, 0.45 to 0.90; P=0.01), presumably as they survived long enough to derive benefit from the device and did not die of other causes during the follow up period.

There may be several explanations for the lack of mortality benefit in this trial. Firstly, patients with non-ischaemic cardiomyopathy may be less vulnerable to ventricular arrhythmias compared to patients with ischaemic cardiomyopathy who often have demonstrable scar which can service of a focus for re-entrant ventricular tachycardias, the most frequent mode of ventricular arrhythmia in ischaemic cardiomyopathy. Both arms had very good pharmacological therapy with high rates of angiotensin converting enzyme inhibitor, β-blocker and mineralocorticoid receptor antagonist use and high rates of CRT may have reduced the likelihood of an arrhythmic death. The event rate in this study was lower compared to other studies and this reflects excellent medical management of their heart failure, an effective method of preventing sudden cardiac death.

Secondly, it is possible that the DANISH trial was underpowered to detect a significant difference in all-cause mortality. When the DANISH trial is combined in a meta-analysis of ICDs for primary prevention of death a patients with left ventricular dysfunction with other randomised controlled

trials which recruiting patients with non-ischaemic cardiomyopathy there continues to be a clear 24% reduction in all-cause mortality in patients treated with ICDs. [51]

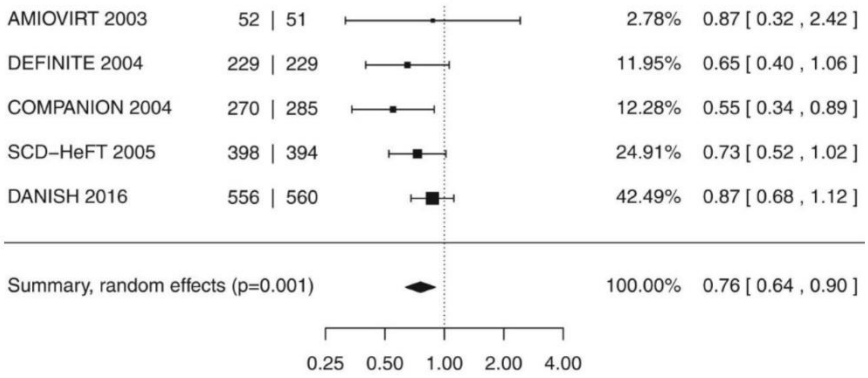


Figure 4 Left ventricular dysfunction without ischaemic heart disease: impact of primary prevention ICD on all-cause mortality. Data from Shun-Shin MJ, Zheng SL, Cole GD, Howard JP, Whinnett ZI, Francis DP. Implantable cardioverter defibrillators for primary prevention of death in left ventricular dysfunction with and without ischaemic heart disease: a meta-analysis of 8567 patients in the 11 trials. [51]

This result remained stable for the removal of any one trial. The fact that the addition of DANISH to a meta-analysis would not reduce the benefit of ICD therapy over medical therapy in non-ischaemic cardiomyopathy has been acknowledged by the authors of DANISH prior to the publication of this meta-analysis. [52] The authors also acknowledge that the DANISH trial has the longest follow-up of any of the ICD trials and this may have contributed to the reduced effect of the ICD. As can be observed in the Kaplan-Meier curves, there is early separation between the ICD and control groups which later re-join (Figure 5). Any trial, if follow-up is long enough will ultimately have re-joining of survival curves as eventually all patients reach the primary end-point, death.

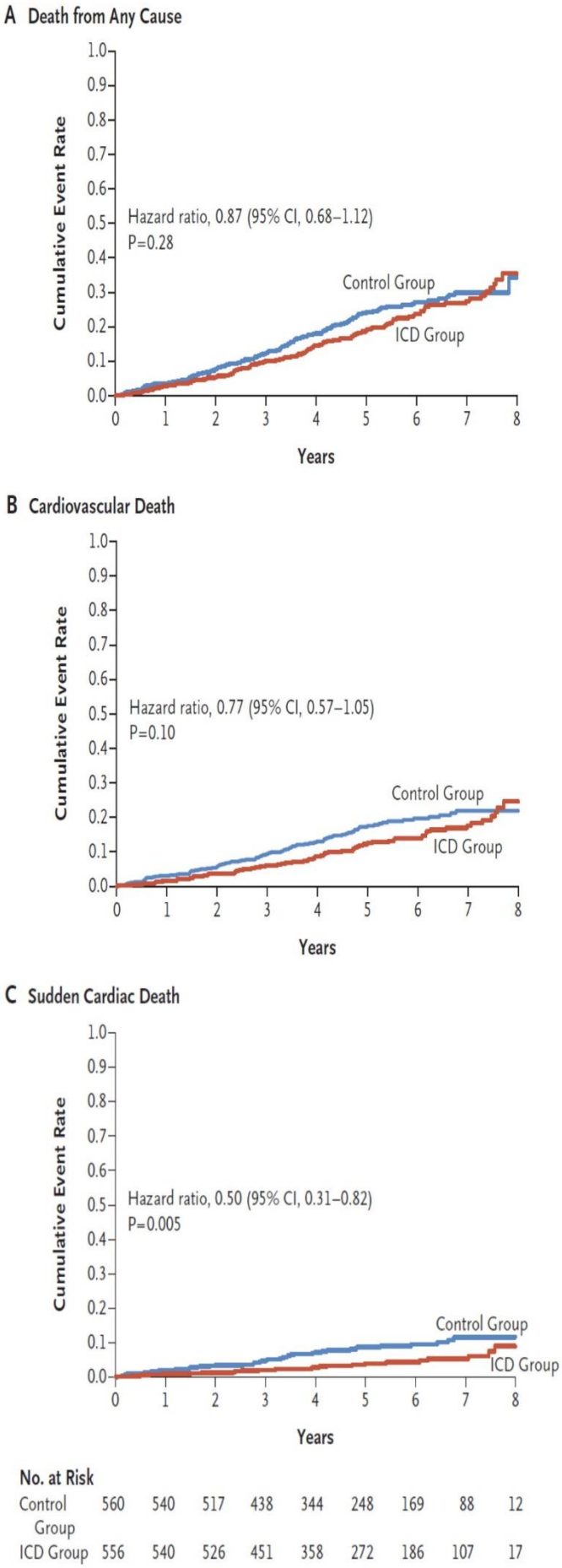


Figure 5 Time-to-event curves for death from any cause (A), cardiovascular death (B), and sudden cardiac death(C) from the DANISH trial.

Whilst the results of Danish have stimulated discussion amongst cardiologists, it has yet to influence policy but impacting on national and international guidelines.

2.3 Impact on policy and practice

Following the publication of these data, there were a number of international guidelines detailing the indications for primary and secondary prevention ICD implantation. [53, 54] This led to a rapid expansion in the rates of ICD implantation[55] particularly in the United States and in some European countries, though even within nations there existed significant geographical variation in implantation, explained by a variation physicians with a particular interest in ICD therapy driving services forward and variability in local referral pathways. [56 57]

2.3.1 United Kingdom guidelines

The National Institute of Health and Clinical Excellence (NICE) issued updated guidelines on the implantation of ICD in the technology appraisal guidance in 2014 (TA314) [58] and this replaced the earlier guidelines which were published in NICE technology appraisal guidance95 (published January 2006) and NICE technology appraisal guidance 120 (published May 2007).

2.3.2 The National Institute for Health and Care (clinical) Excellence guidelines for the implantation of ICDs

2.3.3 Secondary prevention of sudden cardiac death

1. ICDs are recommended for treating people with previous serious ventricular arrhythmia without a treatable cause if they

- have survived a cardiac arrest caused by either ventricular tachycardia (VT) or ventricular fibrillation **or**

- have spontaneous sustained VT causing syncope or significant haemodynamic compromise **or**

- have sustained VT without syncope or cardiac arrest, and also have an associated reduction in left ventricular ejection fraction (LVEF) of 35% or less but their symptoms are no worse than class III of the New York Heart Association (NYHA) functional classification of heart failure.

2. Treating people who:

- have a familial cardiac condition with a high risk of sudden death, such as long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia **or**
- have undergone surgical repair of congenital heart disease.

2.3.4 Primary prevention of sudden cardiac death

Implantable cardioverter-defibrillators and cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P) are recommended as treatment options for people with heart failure who have left ventricular dysfunction with a left ventricular ejection fraction (LVEF) of 35% or less as specified in Table 3.

	NYHA class			
QRS interval	**I**	**II**	**III**	**IV**
<120 milliseconds	ICD if there is a high risk of sudden cardiac death			ICD and CRT not clinically indicated
120–149 milliseconds without LBBB	ICD	ICD	ICD	CRT-P
120–149 milliseconds with LBBB	ICB	CRT-D	CRT-P or CRT-D	CRT-P
≥150 milliseconds with or without LBBB	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P
LBBB, left bundle branch block; NYHA, New York Heart Association				

Table 3 Treatment options with ICD or CRT for people with heart failure who have left ventricular dysfunction with an LVEF of 35% or less (according to NYHA class, QRS duration and presence of LBBB)

2.3.5 European Society of Cardiology guidelines for the implantation of ICDs

In 2015, the European Society of Cardiology (ESC) published their updated guidelines on the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. [59]

Recommendation	Class	Level
ICD implantation is recommended in patients with documented VF or haemodynamically not tolerated VT in the absence of reversible causes or within 48 h after myocardial infarction who are receiving chronic optimal medical therapy and have a reasonable expectation of survival with a good functional status >1 year.	I	A
ICD implantation should be considered in patients with recurrent sustained VT (not within 48 h after myocardial infarction) who are receiving chronic optimal medical therapy, have a normal LVEF and have a reasonable expectation of survival with good functional status for >1 year.	IIa	C
In patients with VF/VT and an indication for ICD, amiodarone may be considered when an ICD is not available, contraindicated for concurrent medical reasons or refused by the patient	IIb	C

Table 4 Summary of ICD implantation guidelines for the secondary prevention of sudden cardiac death issued by the European Society of Cardiology in 2015. [59] (LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; VT, ventricular tachycardia).

Recommendation	Class	Level
ICD therapy is recommended to reduce SCD in patients with symptomatic HF (NYHA class II–III) and LVEF ≤35% after ≥3 months of optimal medical therapy who are expected to survive for at least 1 year with good functional status.	I	A

Table 5 Summary of ICD implantation guidelines for the primary prevention of sudden cardiac death issued by the European Society of Cardiology in 2015. [59] (LVEF, left ventricular ejection fraction).

2.4 Effectiveness of ICDs

In well selected patient populations, the ICD has been repeatedly shown to be effective in reducing arrhythmic deaths. In an analysis of the pivotal primary and secondary prevention trials, Betts et al. expressed efficacy in terms of absolute rather than relative risk reduction and number needed to treat to prevent one death (NNT). [60] For secondary prevention trials (AVID, CIDS and CASH) the absolute risk reduction (ARR) at 3 year follow up ranges from 3.7% (NNT = 27) to 11.3% (NNT=8.8). For primary prevention trials (MADIT, MUSTT, MADIT II, DINAMIT and SCD-HeFT) the ARR at 3 years ranged from 0 (no benefit) to 24.6% (NNT=4). These initial trials had relatively few patients followed up beyond 2 years with the exception of the MADIT II trial. This trial reported outcomes up to eight years with ARR of 13% (NNT=7.7) [61]

Many of the patients enrolled in these trials were under the age of 65 years and thus the outcomes may not reflect current clinical practice. The largest international registry of ICDs reported that of the 150 264 primary prevention patients who received ICDs from January 2006 to December 2008, 61% were aged over 65 years.[62] In an analysis of over 65 000 Medicare patients with ICDs over the age of 65 mean age was 75 years, and nearly one-third had died within 3 years, reflecting a population with more advanced age and disease than seen in trial populations for primary prevention ICD. [63]

In spite of the overall net benefit in terms of improved survival, clinical experience showed that there were important limitations associated with ICDs which may have limited the uptake of the technology to a degree.

2.5 Limitations of the ICD

ICD leads were introduced in 1993. This simplified the task of implanting an ICD as a thoracotomy was no longer required. However, the implantation of a ICD is associated with a small but significant risk of serious complication [64]which is likely to be underreported in clinical trials. [65] These can be classified as early and late complications and are listed in Table 6 and Table 7 below. Many of these complications relate to the presence of transvenous leads.

Complication	Clinical consequence	Incidence	Reference
Pocket haematoma	Surgical evacuation	2.2-4.7%	66
Pneumothorax	Intercostal drain	0.4-1.3%	66 67-69
Lead displacement	Lead reposition	1.80%	66
Lead related trauma	Cardiac perforation / cardiac tamponade	0.1-0.5%	-67-69
	Haemothorax or mediastinal haemorrhage	Rare case reports	70-74
Defibrillation related	Delayed or failed cardioversion of VF	0.14%	75
	Left atrial thrombus-related thromboembolism	0.03%	75
	Post shock PEA	Rare	
Thrombo-embolic	Subclavian thrombosis / venous occlusion	9-28%*	76
	Pulmonary embolism related to subclavian thrombosis	16-36%**	76, 77
	Paradoxical embolism	Rare case report	77, 78
	Coronary or systemic embolism	Rare case reports	79, 80
Any mechanical complication		3.7-6.6%	67-69 77
In hospital death		0.20%	66

Table 6 Summary of early complications related to transvenous-ICD implantation.

PEA (pulseless electrical activation); * the incidence of subclavian thrombus or venous occlusion is based on data from three studies in which bilateral venography was performed prior to ICD generator exchange. The incidence of abnormal venography and total venous occlusion have been presented; ** incidence of PE quoted only if subclavian thrombosis present.

	Clinical consequence	Incidence	Reference
Infection	System extraction	1.61%	79
Inappropriate shocks	Psychological distress and mortality association	6-10% †	78, 80-82
		2%‡	83
Tricuspid valve injury	Worsening tricuspid regurgitation by at least one grade	34.20%	84
Lead failure	Inappropriate shocks, repeat procedures	10.7-15%* at 5 years	85-87
Can failure	Generator malfunction requiring early replacement	26.5/1000 patient years	88
Psychological distress	PTSD* , reduced QOL, depression and anxiety related to ICD shocks	14-66%	89, 90
Attendant complication rate at generator exchange	Most commonly lead fracture, infection, lead dislodgement.	4-15%‖	91

Table 7 Summary of late complications related to the ICD.

PTSD*, post-traumatic stress disorder, QOL, quality of life

†Annual incidence of inappropriate shocks from retrospective analysis of two prospective multicentre studies, one retrospective analysis of manufacture registry and one retrospective single centre study.

‡ Incidence of inappropriate shock at mean follow up time of 1.4 years from the high-rate programming arm of MADIT-RIT trial which represents current standard for ICD programming.

*Single centre longitudinal follow up of over 5000 ICD leads. Survival curves for recalled versus non-recalled leads separated at 2 years.

‖Data from the REPLACE registry [91]. Rates of complication at pacemaker and ICD generator replacement vary from 4% with no additional lead requirement to 15% with additional lead requirement. Major complications were higher in ICD compared to pacemaker generator replacements (Odds Ratio (OR), 2.38; 95% CI 1.30 to 4.38; P<0.004).

2.5.1 Lead and generator failure

The average life of an ICD lead is approximately 10 years and 6 years for the generator. Lead failure rates have been suggested to be approximately 1% per annum and progresses over time. [87, 92] As patients live longer with ICD implant, the ICD hardware has longer exposure to mechanical stresses. Lead design innovation led to smaller diameter leads being developed for ease of use, this has been at the cost of reduced lead insulation with resultant lead fracture and erosion occurring in some leads. [93] ICD leads are therefore considered to be the weak-link in conventional ICDs. [85] The five year failure-free survival of ICD leads from three manufacturers is presented in Figure 6.

Two ICD leads, the Sprint Fidelis (Medtronic Inc. Minneapolis, Minnesota) and the Riata (St Jude Medical, Sylmar, California) have been recalled by the US Food and Drug Administration in 2007 and 2011 respectively. ICD lead failure are associated with inappropriate shock in 76% of cases. [94] Serious complications can result from a failing lead as evidenced by the high frequency of inappropriate shocks seen with the Sprint Fidelis and Riata leads. [95-97] Rates of psychological distress are higher amongst patients who have received shocks of any kind. [83, 89] The young and woman have been reported to be the most affected by Riata lead failures. [97] It is recommended to extract fractured leads and to replace recalled leads with no signs of fracture at the time of generator exchange. Whilst the extraction of a transvenous endocardial lead has improved significantly, [98] it is still associated with occasional serious complications and a small risk of death. [99]

Patients with ICDs can also experience inappropriate shocks due to inappropriate identification and classification of non-lethal arrhythmias as potentially lethal. This occurs in about 10-20% of ICD recipients and is associated with pro-arrhythmia, anxiety, depression, poor quality of life and increased mortality. [83, 100-102] The data are conflicting on whether the inappropriate shocks increase mortality directly or whether they occur more frequently in a sicker population (increased incidence of atrial fibrillation etc.).[103] Optimising the programming of the ICD can reduce the likelihood of inappropriate shocks due to incorrect identification and classification of arrhythmias.[104] Improved rhythm discrimination algorithms can also reduce inappropriate shocks and thus provide direct benefit to the patient.

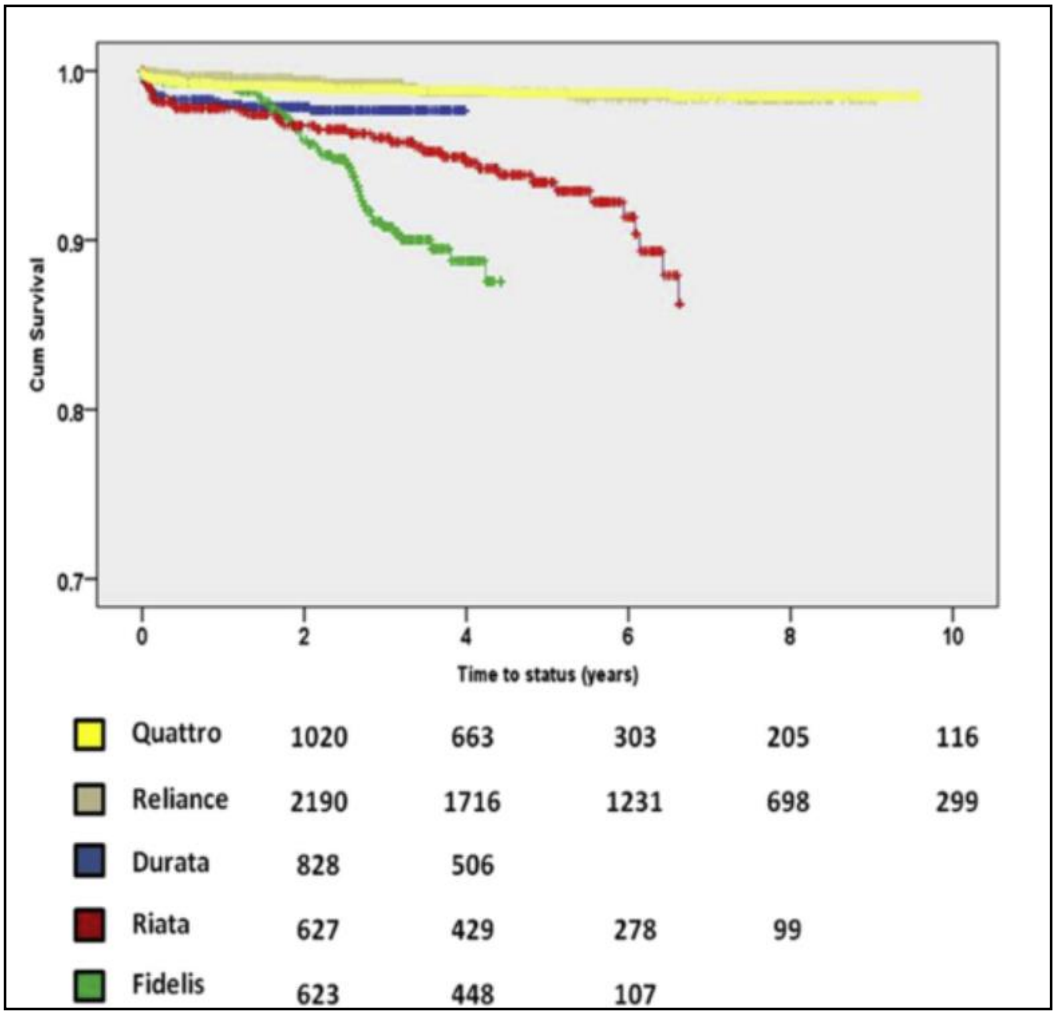


Figure 6 Five year failure-free survival of ICD leads from 3 manufactures.
Survival curves for the 2 leads with advisories diverged from the other ICD leads at 2 years. This occurred due to deficiencies in lead design Re-used with permission Elsevier, from Liu et al. Longitudinal follow-up of implantable cardioverter defibrillator leads. *The American journal of cardiology* 2014; **113**: 103-106. [85]

2.6 Evolution of the S-ICD

The landmark primary prevention ICD trials using TV-ICD described above [42, 47, 48] meant that a large number of patients with a history of previous myocardial infarction or heart failure could be eligible for ICD therapy. However, due to the limitations of the TV-ICD, the perceived cost of the devices and other factors, there rates of implantation did not meet this increased need. [105-110] There were also cases of patients with a need for ICD but in whom TV-ICD leads were not suitable due to the young age of the patient or the presence of complex venous anatomy. [111] In order to address some of the limitations the subcutaneous ICD (S-ICD) was developed.[112, 113] However, there were several problems that needed to be overcome such elevated defibrillation

requirements, lack of safety and efficacy data of shock efficacy and issues surrounding appropriate sensing in S-ICD. These shall be considered in next sections.

2.6.1 Defibrillation energy requirements

Defibrillation requires the generation of a sufficient voltage gradient over the myocardium to terminate fibrillation. [114] It is hypothesised that a voltage gradient of ≃ 5V per cm over ≃ 90% of the myocardium is required for efficient defibrillation. [115, 116] TV-ICD s are easily able to achieve this threshold, however, due to the close proximity of the shock coil within the heart, much greater gradients of over 30V per cm are achieved near the shock coil. [117] Defibrillation with such high voltages has been shown to damage myocytes,[118] a term known as electroporation. [119] This can result in transient reduction in contractility and troponin release and a voltage gradients greater than 50 V per cm electrical stunning and post-shock ventricular arrhythmias. [120-124]

Early S-ICD trials focused on the defibrillation energy requirements (DER) for the S-ICD, as unlike the TV-ICD, an S-ICD lacked a defibrillation electrode within the heart, and therefore the potential energy requirements were likely to be much greater. This has resulted in reduced battery longevity and larger generator size in S-ICDs compared to TV-ICDs.

A study designed to estimate the subcutaneous DER using a subcutaneous to cutaneous (SQ to Q) electrode configuration in the left upper anterior chest region in patients undergoing TV-ICD implantation using additional two VF inductions was performed. [113] Twenty patients were recruited and were entered into either a high (70 joule) or low (50 joule) stage with an energy step up or down for the second shock dependent of the success of the first shock. The results were as follows: Q-SQ defibrillation at 50 J was successful in 17/18 patients (94%); Q-SQ defibrillation at 30 J was successful in 7/9 patients (78%), and two patients (10%) required 100 J for successful SQ defibrillation. This suggested that there was considerable variability in the DER between patients and was considerably more than the latest iterations of TV-ICDs. Therefore a change in the device size, components and possible SQ vectors was considered.

In a subsequent study evaluating the efficacy of a novel anteroposterior defibrillation shock pathway using a long time-constant shock waveform found that over 80% of patients were successfully defibrillated using 35J or less. [125]

Finite element computer modelling was then used in a study designed to determine factors affecting optimal lead positions for S-ICD. [126] This technique is able to explore the electric fields generated by electrodes placed in arbitrary locations and orientations in the human torso as a way of estimating the relative defibrillation efficacies on S-ICD orientations. Pseudo-DFTs were

generated. In total 122 single-electrode/array configurations and 28 dual-electrode configurations were tested. This study concluded that the choice of electrode configuration which maximises shock vector alignment with the centre of the myocardial mass and the use of longer leads is more likely to result in lower DFT.

Whilst the DER of the S-ICD are nearly three times greater compared to the TV-ICD, the energy is dissipated in a more uniform manner through the thorax, with only approximately 10% reaching the myocardium. This resembles the ideal model of defibrillation and is evidenced by significantly lower troponin I release from pigs hearts following 80J S-ICD shocks compared to 35J transvenous shocks. [118] The cost however, is increased skeletal muscle damage with the S-ICD shocks. No pulmonary damage was reported in pigs either type of shock.

In summary the elevated DER in S-ICDs was overcome by developing S-ICD with a capacity to deliver 80J rather than the 35-40J seen with TV-ICDs.

2.7 Shock efficacy and safety

2.7.1 Preclinical

Cappato et al. described the process that led to the development of the S-ICD to be used in humans. They tested the combination of an anterior electrode adjacent to the left edge of the sternum and a lateral electrode at the site along the axillary line between the 4th and 6th intercostal space in two acute defibrillation studies, the first to test the DFT and the second to test the S-ICD's ability to induce, detect and shock VF in canines. Shock energies of less than 80J terminated all induced VFs as well as providing effecting detection of activation of shock therapy in all cases. [127]

2.7.2 Clinical

Two short-term small, non-randomised clinical trials were then conducted to identify suitable device configuration and assess energy requirements. [128] The results were published in the New England Journal of Medicine and has become the seminal paper for S-ICDs. Four S-ICD configurations were evaluated in 78 patients and subsequently tested in 49 patients to determine the S-ICD DFT in comparison with that of the standard TV-ICD. (Figure 7) The optimal configuration consisted of a left parasternal electrode and a left thoracic pulse generator located in the 5th and 6th intercostal space in the mid axillary line. This configuration was as effective for terminating induced ventricular fibrillation as a TV-ICD albeit with significantly higher energy requirements (36.6±19.8J vs. 11.1±8.5J).

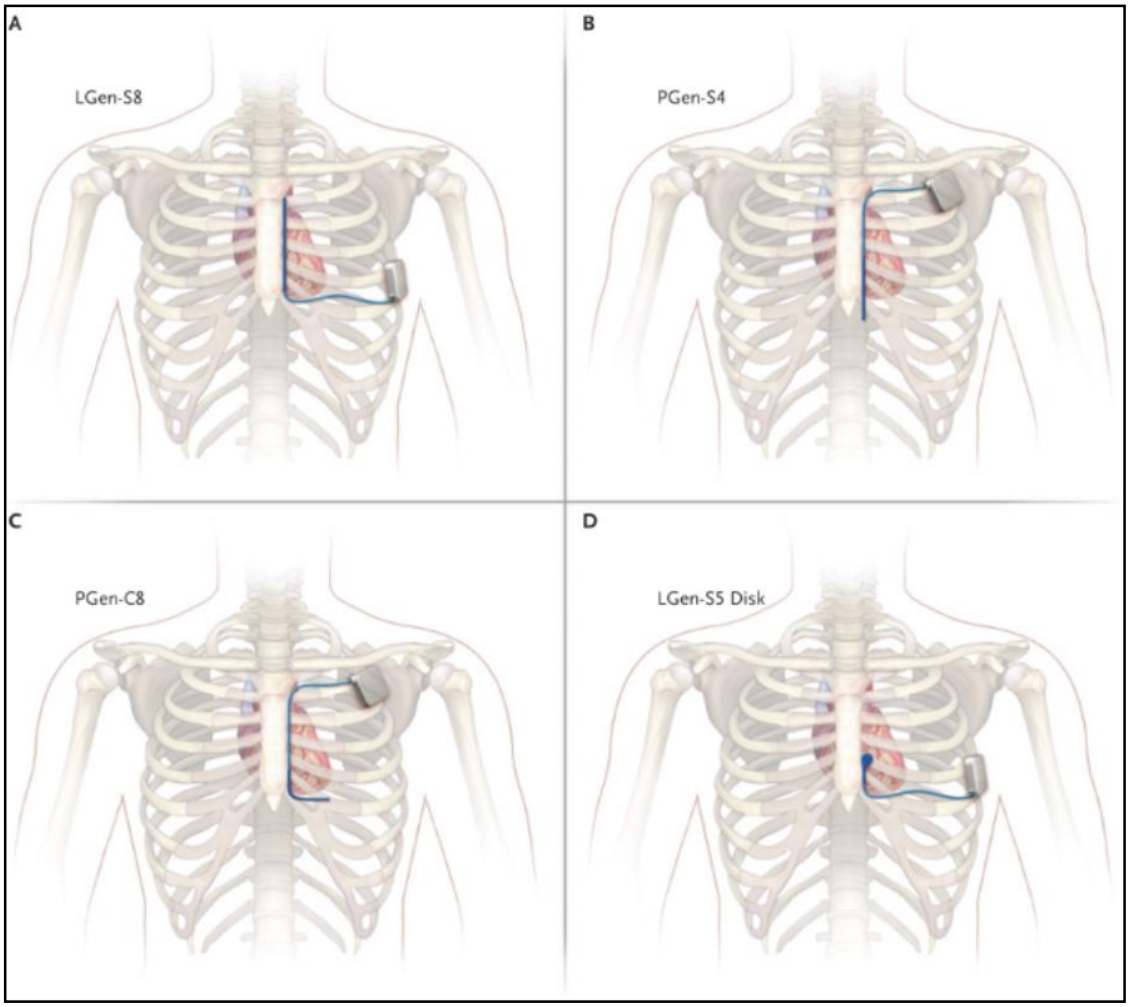


Figure 7 S-ICD experimental configurations

Four configurations of an S-ICD as tested by Bardy et al. Panel A (top left) ultimately became the preferred configuration for lead and generator placement. Reproduced with permission from (Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, et al. An entirely subcutaneous implantable cardioverter-defibrillator. NEJM 2010; **363**: 36-44.), Copyright Massachusetts Medical Society [128]

Induced ventricular fibrillation was successfully converted twice in 58/59 patients (98%) with a 65J shock. In a longer follow up (mean 10±1 months) the device successfully detected and treated all 12 episodes of spontaneous sustained ventricular tachyarrhythmia. [128]

A prospective nonrandomised, multicentre trial confirmed the safety and efficacy of the S-ICD. The acute conversion rate for ventricular fibrillation was >90% for the 330 patients with a 180 day system complication-free rate of 99%. [25]

2.8 S-ICD screening

In contrast to patients receiving a TV-ICD, potential S-ICD recipients must have an ECG with an appropriate morphology as the sensing occurs form the subcutaneous electrodes (resembling a surface ECG) and not an endocardial lead). Pre-implant screening is therefore mandated prior to implantation of an S-ICD. This is achieved by recording a three-lead electrocardiogram with surface electrodes placed over the 5th intercostal space in the mid-axillary line, 1cm lateral to the xiphoid midline, on the patient's left and 14 cm superior to this. This configuration replicates the S-ICD sensing vectors. The ECG is acquired in the supine and standing postures. The acquired electrograms are then analysed using a proprietary ECG screening tool prior to device implantation. (Figure 8) As the morphology analysis is crucial to S-ICD rhythm detection and discrimination, this screening process is to ensure reliable sensing.[129] Patients need to have an ECG that suitably matches the template in at least one vector in both postures to pass the screening process. Patients who fail this screening process are not suitable for S-ICD implantation.

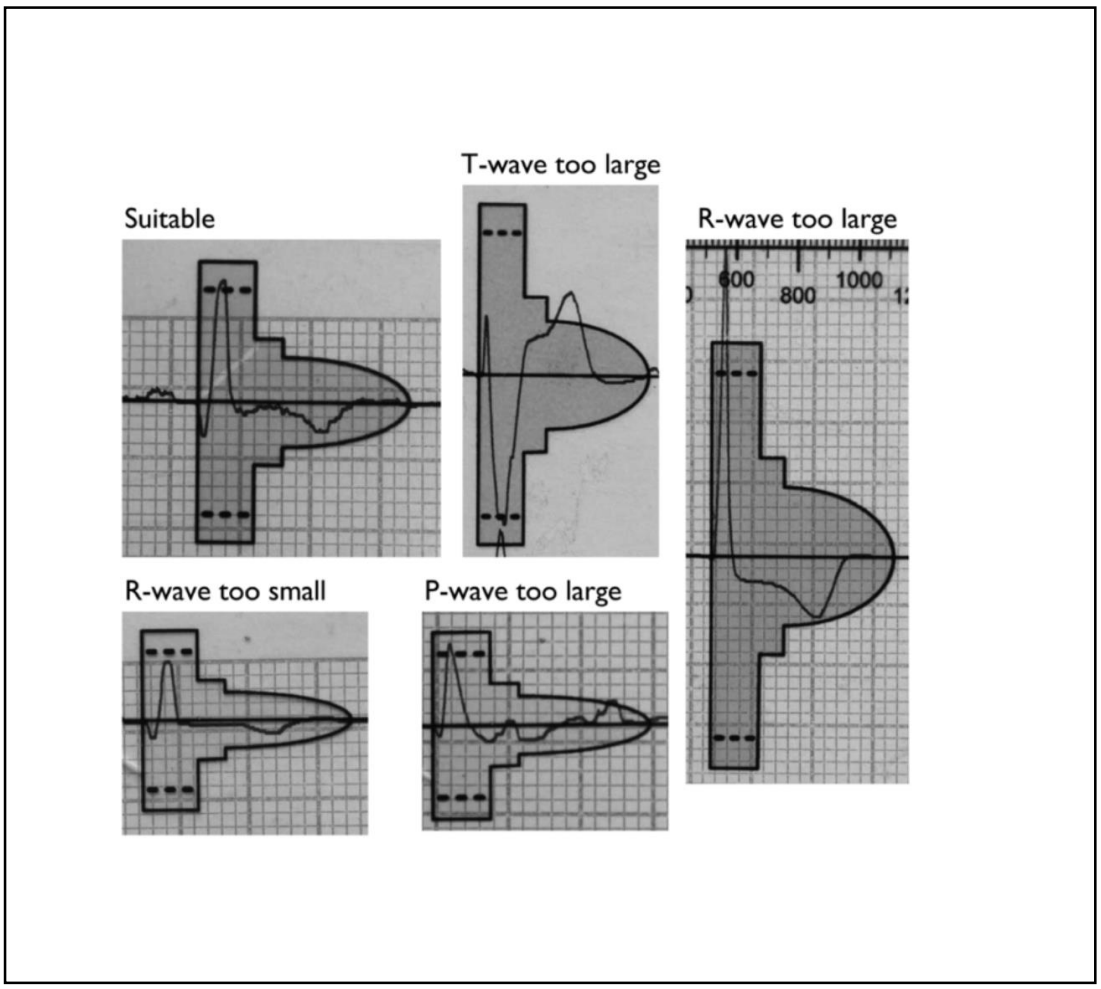


Figure 8 Pre-implant screening tool.

Appropriate and inappropriate pre S-ICD ECG screening. Only one of the ECGs fits the ECG template (top right) all others failed as part of the P-QRS-T complex fell outside or below the pre-

specified zone. Reused with permission from Wiley (Olde Nordkamp LRA, Warnaars JLF, Kooiman KM, de Groot JR, Rosenmöller BRAM, Wilde AAM, et al. Which patients are not suitable for a subcutaneous ICD: incidence and predictors of failed QRS-T-wave morphology screening. Journal of cardiovascular electrophysiology 2014; 25: 494-499. [129]

2.9 Sensing with the subcutaneous implantable cardioverter

The S-ICD senses cardiac signals very differently from a TV-ICD. This is because electrocardiograms derived subcutaneously resemble a surface ECG rather than the unique signal obtained from an intracardiac electrode. [130] The morphology of normal sensed beats differs significantly from ventricular tachycardia sensed beats in the surface ECG and the S-ICD ECG. (Figure 9) This is one of the strengths of the S-ICD as it uses morphology based discrimination to accurately distinguish SVTs from ventricular arrhythmias. [131]

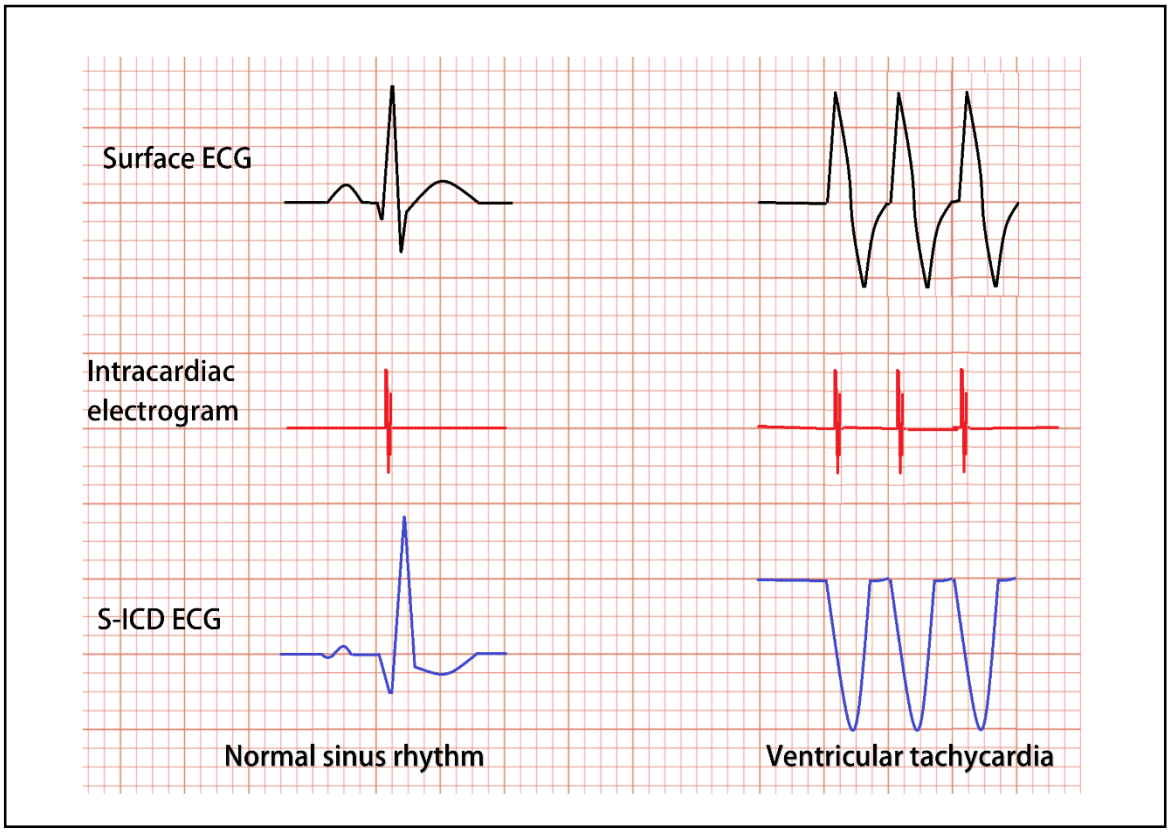


Figure 9 Surface ECG, IEGM and S-ICD electrograms.
A comparison of the sensed signal with the surface ECG, the intracardiac electrogram and the S-ICD ECG in normal rhythm and in ventricular tachycardia. Adapted from slide in presentation by Dr Boersma, St Antonius Hospital, Nieuwegein, The Netherlands available at http://events.medtelligence.net/2012/may9/Boersma/index.htm

The S-ICD uses 3 sensing electrodes to generate 3 sensing vectors. Two electrodes, distal and proximal, flank the parasternal defibrillation coil. The distal electrode is located at the level of the manubriosternal joint and the proximal electrode is located adjacent to the xiphoid. The third sensing electrode is the active can. (S-ICD generator) This configuration generates three sensing vectors, primary vector (between the distal electrode and the can), secondary vector (between the distal electrode and the can) and the alternative vector (between the distal and proximal electrode). (Figure 2).

The S-ICD automatically selects the sensing vector with the best signal for rhythm detection and in clinical practice, this is usually the primary vector. The QRS template is sampled in 41 locations along the QRS contour and are compared with subsequently sensed signals. This is conceptually similar to the TV-ICD morphology based comparison algorithm but the resolution is considerably higher with the S-ICD.

Recent work has identified that approximately 85% of patients with an indication for an ICD on primary or secondary prevention grounds have an ECG that meets the S-ICD screening criteria. [132] Hypertrophic cardiomyopathy, a heavy weight, prolonged QRS duration and an R:T ratio <3 in the ECG lead with the largest T wave were independently associated with failure to pass the screening test. [129]

2.10 Overview of S-ICD sensing algorithms

The S-ICD sensing the cardiac signal very differently from TV-ICDs. The S-ICD utilises a morphology based sensing algorithm that uses the rich signal of the QRS-T complex which resembles the surface ECG. This signal is analysed by the S-ICD in a similar manner to how a clinician would analyse an ECG, by assessing the rate and the morphology of the QRS-T complexes. The main advantage of this method is that discrimination between supraventricular tachycardia (narrow and regular) and ventricular arrhythmias (broad and regular) is as good as if not better with S-ICDs than TV-ICD. This was demonstrated in a head-to-head comparison of the S-ICD and TV-ICDs form three manufactures[131] and well as in clinical practice. [25, 133] However, the advantages of morphology based sensing are off-set by the disadvantages caused by the presence of T-waves which can lead to T-wave oversensing and inappropriate shocks. This is one of the most common causes of inappropriate shocks in patients with S-ICD at the current incidence is approximately 5-7% per annum.

To prevent this, commercially available S-ICD system employ several strategies to risk the likelihood of T wave oversensing:

1. The pre-implant screening tool to exclude patients with large T waves who may be prone to T wave oversensing
2. Automatic setup whereby the S-ICD selects the optimal vector out of the three available for sensing
3. Variable threshold detection profiles to avoid T wave detection
    a. This a relatively commonly employed technique in implantable cardiac electronic devices the 'window' or threshold for detecting cardiac signal decays rapidly after a sensed R wave but not too rapidly in order to avoid the T wave. The threshold for detection needs to be lowered so that the device can detect low amplitude ventricular fibrillation waves should they arise. An example of a profile of a variable threshold detection taken from a patent submitted by the S-ICD engineers is shown in Figure 10. [134]

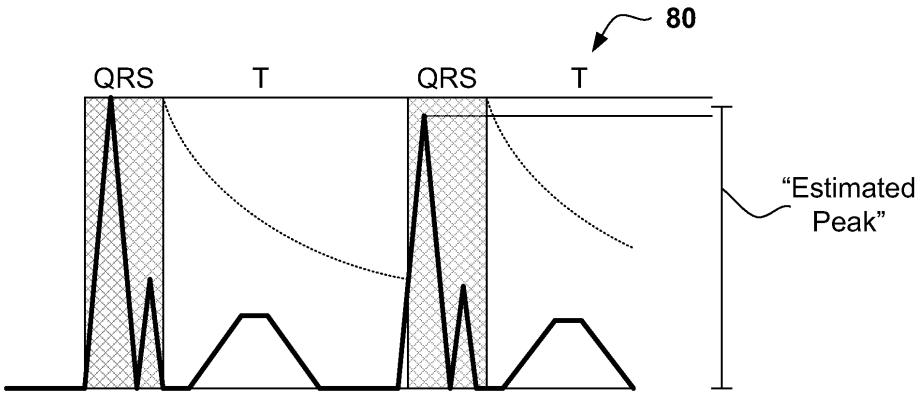


Figure 10 Illustration of the use of a variable threshold detection profile to avoid the unnecessary detection of the T wave after having detected the preceding QRS complex.
Taken from patent application 'Accurate cardiac event detection in an implantable cardiac stimulus device 'US 20140046394 A1[134]

    b. These algorithms employ S-ICD hardware features that measure the minimum and maximum amplitudes of each potential QRS complex, time intervals between detections, widths of each detected complex, and morphologic comparison of the currently detected complex to both the previous complex and to a stored normal sinus rhythm, known as the Reference ECG. Software algorithms then look for patterns in either the morphologic comparison to the Reference ECG (Figure 11A) or the intervals (Figure 11B) to recognize and discard the inappropriate detections and correct the time interval between the appropriate detections. [135]

   c. The most recent of these compares the morphology of 3 successive detections to identify when 2 similar QRS complexes (N vs. N-2) are separated by a dissimilar T-wave complex (N vs. N-1; see Figure 11C). In addition to comparing complexes N to N-1 and N to N-2, the width of each complex and the intervals between detections were used to enhance algorithm performance. When 3 successive detections fit the rules of the algorithm, detection N-1 is deemed to be a T-wave and is discarded.[135] The authors of the article that describes this algorithm claim that it will reduce the incidence of T-wave oversensing by 40% and that it is hoped that this will translate into a meaningful reduction in inappropriate shocks.

4. SMARTPASS filter
   a. This is a high-pass filter designed to reduce oversensing while maintaining an appropriate sensing margin, though the details of this a commercially sensitive and have not been released into the public domain.
5. The use of a conditional zone for the detection of tachycardias (see below).

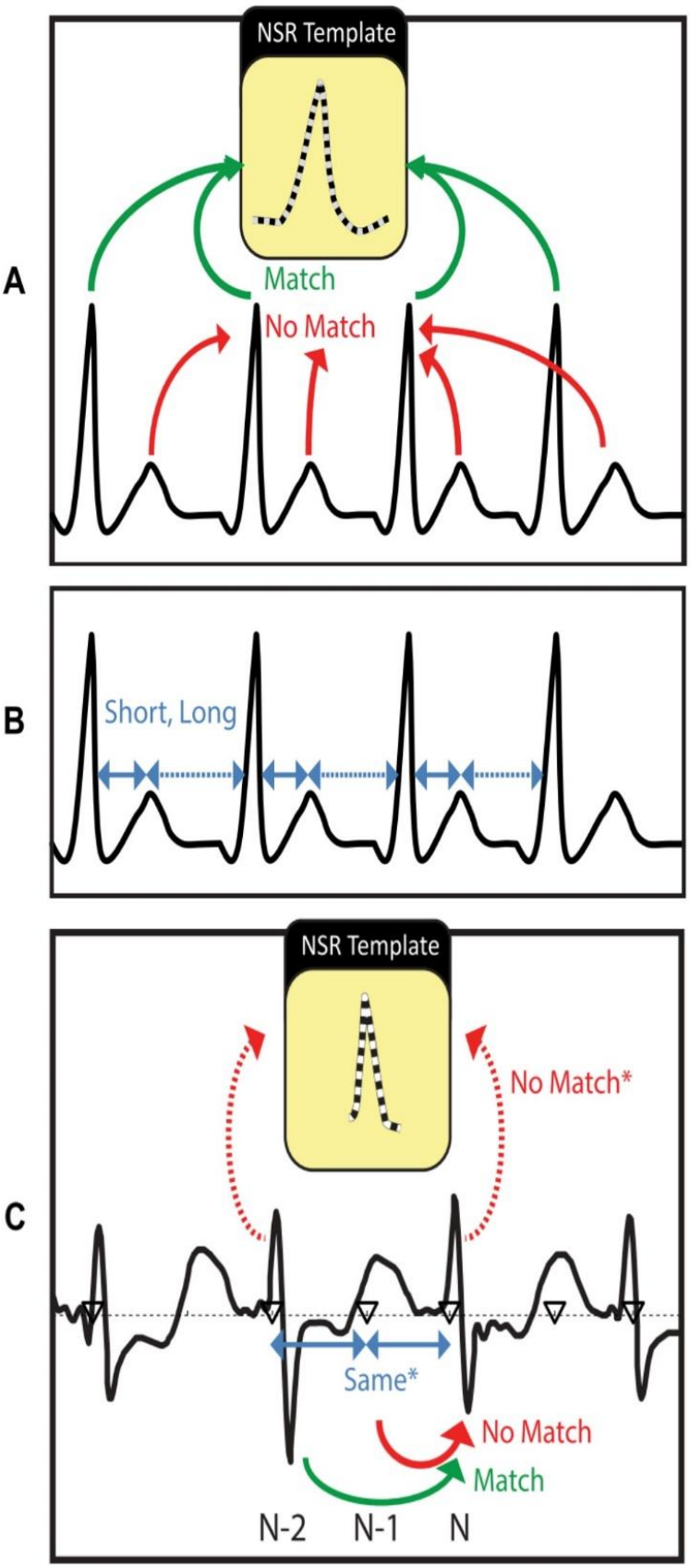


Figure 11 Novel sensing algorithm to reduce T wave oversensing

A: An S-ICD sensing algorithm that compares detected complexes to a normal sinus rhythm reference and identifies repeated patterns of match–no match to discard over-detections. Panel B: An S-ICD sensing algorithm that identifies repeated patterns of short to long intervals to discard over-detections. Panel C: This algorithm was developed to reduce T wave oversensing. The most recently detected complex (N) is compared to both the previous (N-1) and the 2nd previous complex (N-2). Patterns where N matches N-2 but not N-1 could be used to remove T-waves. *Dashed red lines and solid blue lines indicate that the algorithms depicted in Panels A and B, respectively, would not detect the T-wave in this example.

2.11 Rhythm discrimination in S-ICD

2.11.1 The Insight™ algorithm

The Insight™ algorithm is used by the current version of the S-ICD (Boston Scientific, 1 Boston Scientific Pl, Natick, MA 01760, United States) to discriminate between different arrhythmias to prevent inappropriate shocks.

There are 3 tiers of rhythm analysis that it runs simultaneously once the rate falls within the tachycardia zone.

2.11.2 Static morphology analysis

A sensed tachycardia beat morphology is compared with a stored template. If there is a good match between the sensed beat and the stored template it is considered to be supraventricular in origin and labelled a sensed beat 'S', otherwise it is considered to be ventricular and the algorithm continues.

2.11.3 Dynamic morphology analysis

A sensed tachycardia beat morphology is compared with the preceding beat. This assesses for a polymorphic relationship between beats. If there is polymorphic relationship, the beat is labelled a tachycardia beat 'T' and if it is a good match the algorithm continues. If not the device assumes the rhythm is ventricular fibrillation and commences capacity charging for preparation of shock delivery.

2.11.4 QRS width analysis

The QRS width of the sensed tachycardia beat is compared with the stored template (recorded at the time of implant and representing a 'normal beat'). If the QRS width is narrow, the beat is considered supraventricular and is labelled a sensed beat 'S' otherwise it is considered ventricular and it is labelled as a tachycardia beat 'T'.

Table 8 summarises the interventions that have been shown to reduce the incidence of inappropriate shock or T wave oversensing.

Intervention	Reduction in incidence of inappropriate shock[1] / TWOS[2]
Appropriate use of screening tool	Unknown
Use of dual zone programming	15.9% (1)
Use of 3 successive complexes algorithm	39.8 +/- 11.4% (2)

Table 8 Interventions that have been shown to reduce the incidence of inappropriate shock or T wave oversensing.

2.12 Calculation of heart rate

The S-ICD uses a mean of four sensed QRS complexes to determine heart rate. Once the heart rate falls within the tachycardia zone the Insight™ algorithm is triggered.

2.12.1 The importance of accurate heart rate detection

An alternative method to reduce oversensing would be to find an alternative method of calculating the heart rate by detecting the QRS in a way that oversensing of the cardiac signal is avoided completely. The importance of accurate heart rate detection is illustrated in the following clinical case that I reported. [136]

2.12.2 Five shocks two mechanisms

A 69 year-old male was recommended to have an implantable cardioverter-defibrillator for secondary prevention of sudden cardiac death. The patient had a relative contraindication to a transvenous ICD by having a large right atrial thrombus despite being on warfarin with a therapeutic INR. The patient was assessed for suitability for an S-ICD and successfully passed the ECG screening process. An S-ICD (Model number 1010, Boston Scientific, 1 Boston Scientific Pl, Natick, MA 01760, United States) was implanted without complication prior to the patient's discharge home. The device was programmed with a conditional zone between 190-230 bpm and a shock zone for rates greater than 230 bpm. Sensing was from the secondary vector.

The patient subsequently presented on four occasions having received a total of five inappropriate shocks from the S-ICD. The first four episodes were from the same mechanism. The patient underwent VT ablation which was successful at preventing VT recurrence. The patient then had a fifth episode of inappropriate therapy. The S-ICD was replaced with a TV-ICD. No further inappropriate shocks have occurred since.

Inspection of stored subcutaneous ECGs (S-ECGs) for the first four inappropriate shocks reveals an identical mechanism of onset. (Figure 12 and 13)

2.12.2.1 Explanation of the electrograms

The heart rate is between 140-150 bpm and the complexes are broad and the rhythm is regular. Monomorphic ventricular tachycardia is the most likely cause (Figure 12). The S-ICD ascribed the largest positive or negative wave as an R wave. There are sensing markers throughout the recording. Some of these complexes are sensed on the R-wave (positive wave) and some on the T-wave (negative wave). We speculate that this occurred because rhythm had positive and negative wave of equivalent amplitudes. At a critical moment (Figure 12 and Figure 13; red circles) sensing of both the R-wave and the T-wave occurs within a single VT complex (T-wave oversensing) resulted in the calculated heart rate falling into the shock zone.

The S-ICD calculates heart rate by measuring the mean of 4 consecutive RR intervals. The initial rate 140 bpm (Figure 12), which is well below the tachycardia zones (conditional zone rate 190-230 bpm and shock zone >230 bpm). At the point the duration of 4 sequential sensed beats is 920ms and the calculated heart rate is therefore 920ms/4 = 230ms or 260 bpm, thus falling into the shock zone. It is important to note that the S-ICD initially employs rate criteria alone to trigger tachycardia detection (unlike TV-ICD which variously employ onset, stability, duration etc.). In summary, a single double counted beat during monomorphic VT resulted in the first four inappropriate shocks.

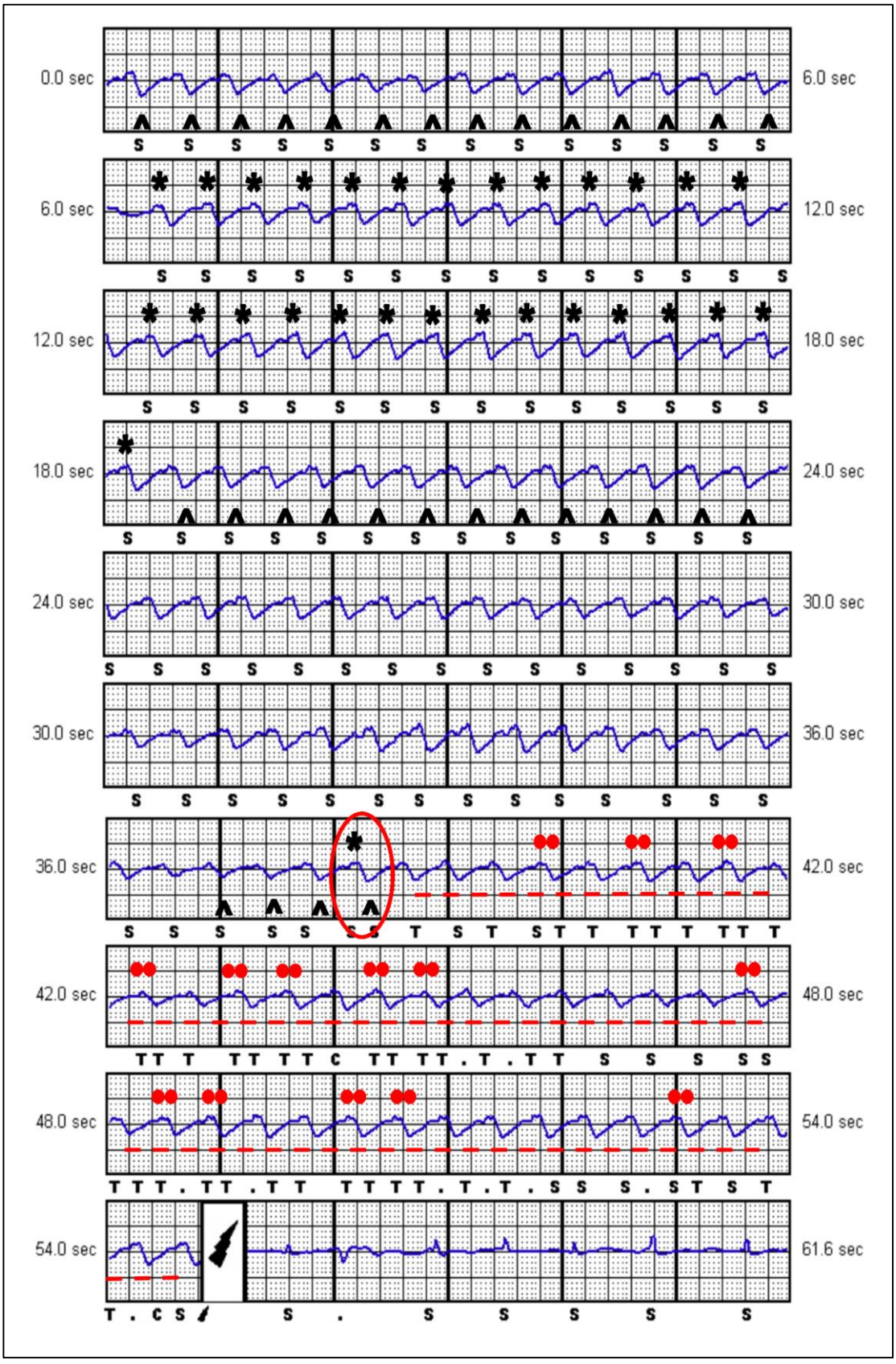

0.0 sec
6.0 sec
6.0 sec
12.0 sec
12.0 sec
18.0 sec
18.0 sec
24.0 sec
24.0 sec
30.0 sec
30.0 sec
36.0 sec
36.0 sec
42.0 sec
42.0 sec
48.0 sec
48.0 sec
54.0 sec
54.0 sec
61.6 sec

Figure 12 Stored S-ICD ECG from the alternate vector taken from treated episode in November 2013.

The rhythm is monomorphic VT rate 140 bpm. This image illustrates the variation in where the S-ICD senses each complex (S): * R-wave sensed and ^ T –wave sensed (0-24 seconds). However each complex is only counted once. The red circle (38 seconds) highlights single complex that has been double counted (T-wave oversensing). This marks the point where the calculated heart rate falls within the shock zone. Dashed red arrow indicates increased sensitivity within conditional zone with multiple complexes double counting ( ) resulting in tachycardia confirmation, device charging (C) and shock delivery ( ) and termination of the tachycardia.

.

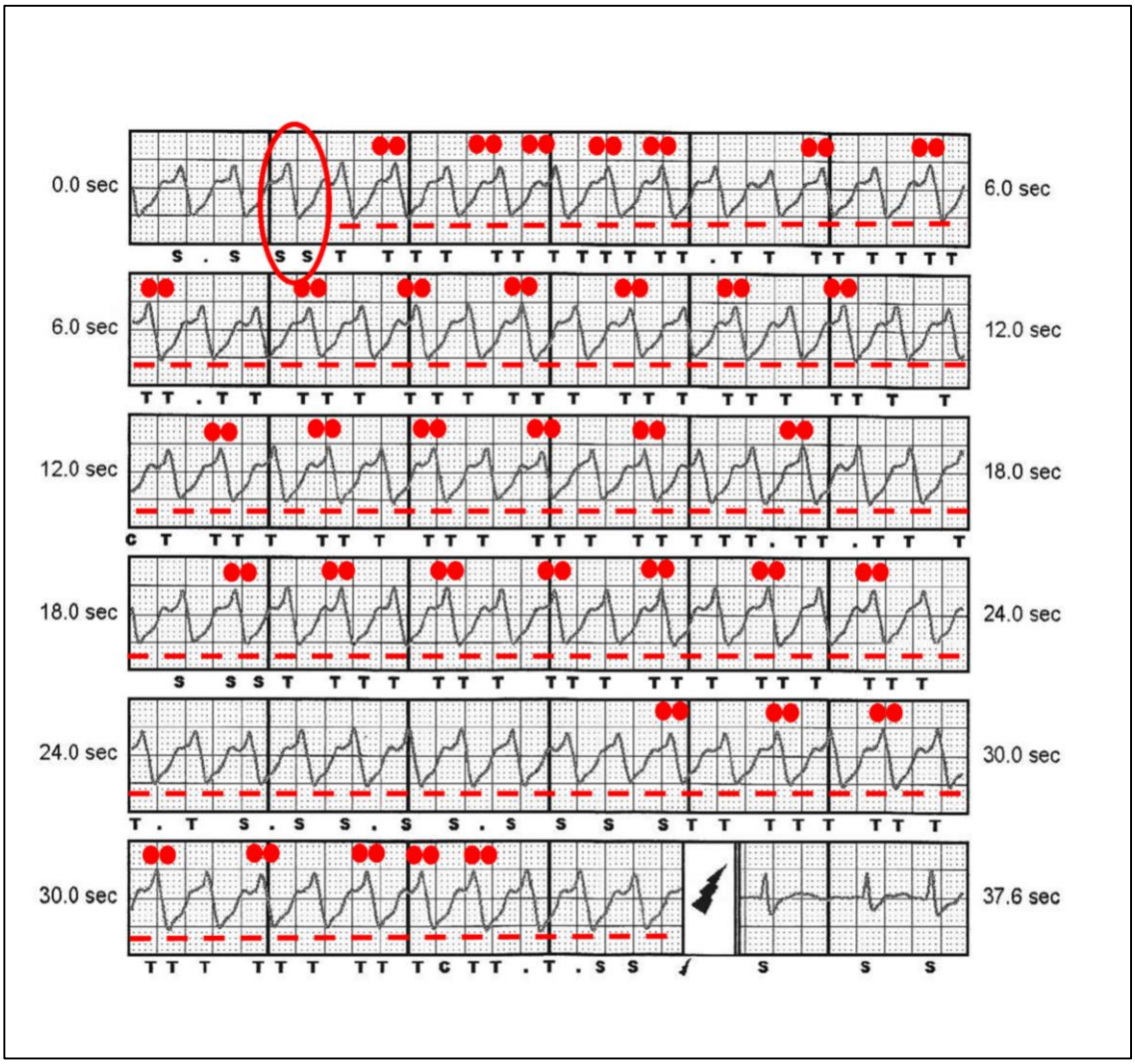


Figure 13 Subcutaneous ECG from the secondary vector taken from treated episode in October 2013.

The rhythm is monomorphic VT rate 150 bpm. Red circle highlights single complex that has been double counted. This marks the point where the calculated heart rate falls within the conditional zone. The dashed red arrow indicates increased sensitivity within conditional zone with multiple complexes double counting resulting in tachycardia confirmation, device charging(C) and shock delivery ( ) and termination of the tachycardia.

Once in the shock zone the sensing characteristics within the S-ICD become much more aggressive. However, in this case, there is clear evidence of frequent T-wave oversensing that was not apparent prior to triggering the shock zone (Figure 12 and Figure 13). Ultimately, sufficient number complexes were labelled as tachycardia beats to fulfil the predetermined criteria for device charging and subsequent shock delivery.

2.12.3 How does sensing influence tachycardia therapy?

The principal function of any defibrillator is to sense the cardiac signal. Once this is achieved then the heart rate can be determined and detection of ventricular arrhythmias can occur. Accurate sensing is likely to influence the tachycardia therapy appropriately and inaccurate sensing is likely to misinform the tachycardia therapy.

In a study comparing the sensing and discrimination performances of the S-ICD and three commercial available TV-ICD devices, the S-ICD performed better than two of the three TV-ICD devices in SVT discrimination. [131] Ventricular arrhythmia detection was comparable between the technologies and was >99% accurate in all 4.

The aim of all ICDs is to achieve 100% sensitivity in detecting potentially lethal arrhythmias. However, this is often achieved at the expense of reduced specificity, in other words inappropriate detections and potentially shock delivery for non-lethal arrhythmias such as supraventricular tachycardia (SVT).

Registry data suggests that the S-ICD is effective in sensing and then terminating ventricular arrhythmias, but with nearly 1 in 8 patients receiving inappropriate shocks, mainly due to T-wave over sensing. [23] This is relatively high rate of inappropriate therapy and one of the main drawbacks of this technology as discussed in the section on complications above.

T-wave oversensing occurs when the S-ICD misinterprets the T wave as an R wave, and therefore double counts each beat. Thus an episode of oversensing occurring whilst an individual is exercising with a heart rate of 125bpm will result in the ‘inaccurate’ sensed heart rate to be 250bpm. This falls in the S-ICD tachycardia window (maximum programmed rate is 240bpm) and therefore if the oversensing is sustained it would probably result in the delivery of an inappropriate shock.

Inappropriate shocks due to T wave oversensing can be significantly reduced by reprogramming the sensing vector and / or the therapy zones of the device using a template acquired during exercise. [137] Inappropriate shocks were also significantly reduced when dual zone versus single

zone programming was used (two-year inappropriate shock free rate 89.7% vs 73.6%; respectively (hazard ratio 0.38, P < .001).[138]

2.12.4 Previous experience analysing sensing vectors

Burke et al. identified variances in QRS and T wave signal amplitudes that were due to changes in body posture. [139] This was the stimulus to introduce two postures into the ECG screening process for the S-ICD.

2.13 Clinical experience with S-ICD

Early experience supported the efficacy and safety the S-ICD [25] though there were concerns regarding the rate of inappropriate therapy and other adverse events. [23, 24] This was thought partly to represent the learning curve associated with new technologies. However, the EFFORTLESS S-ICD registry has reported appropriate system performance with clinical events equivalent to conventional TV- ICDs. [133] Rates of inappropriate shock were 7% per annum which is equivalent to rates of inappropriate therapy with TV-ICD prior to the MADIT RIT trial. The principal cause of the inappropriate therapy in the EFFORTLESS registry was due to oversensing (85%) most frequently of the cardiac signal (94% of oversensed episodes). T waves or low amplitude signals (31 and 53% respectively) were the principal cause of such signal oversensing.

2.14 Comparison of S-ICD and TV-ICDs

There are a number of important differences between TV-ICDs and S-ICDs. (Table 9) Some of these differences are clear advantages for the S-ICD over the TV-ICD such as the reduced risk of pulmonary and cardiac complications at the time of device implantation whereas some are clear disadvantages such as the absence of long term outcome data and lack of bradycardia pacing. Other potential disadvantages such as the elevated shock strength with S-ICD are offset by a reduced myocardial voltage gradient. The results of a prospective randomised comparison of TV-ICDs and S-ICDs are awaited when the outcomes from the PRETORIAN trial are published. [140]

	TV-ICD	S-ICD
Pre-implant screening ECG	Not required	Mandated
Implant Technique	Need for transvenous puncture and endocardial lead with attendant risk of pneumothorax and cardiac tamponade	No transvenous lead with no risk of pneumothorax or cardiac tamponade
Venous anatomy	Requires venous and right ventricular access	Can be implanted in patients without venous access or with complex cardiac anatomy
Shock efficacy	Effectively detects and terminates ventricular fibrillation	Effectively detects and terminates ventricular fibrillation
Shock strength	Lower shock strength (35-40J)	High shock strength (80 J)
Myocardial voltage gradients	High myocardial voltage gradients	Lower myocardial voltage gradients
Bradycardia pacing	Provides pacing for bradycardia, resynchronization, and tachycardia termination	Does not pace, apart from limited postshock pacing
Lead reliabilty	Dependent on transvenous lead with documented reliability issues	Subcutaneous lead with potential but not proven long-term reliability
Lead explantation	Device and lead explantation moderately risky	Explantation easy and low risk (initial experience only)
Programability	Highly programmable	Limited programmability
Size of generator	Small device (30cm3)	Larger device (60cm3)
Track record	Established technology with proven benefits	Novel technology with limited experience and follow-up

Table 9 A comparison of transvenous-ICDs and subcutaneous-ICDs.

Adapted from Crozier et al. How the Subcutaneous Implantable Cardioverter Defibrillator Works: Indications/Limitations and Special Groups to Consider Cardiac Electrophysiology Clinics 2014 6; 2: 285-295 [119]

2.15 S-ICDs in patients with complex anatomy

The advent of new surgical techniques in the 1970s and 1980s has led to an increase in the survival of patients with congenital heart disease who would have otherwise died in childhood. The majority of these patients now survive into adulthood and there are now more adults with congenital heart disease (ACHD) alive than there are children with congenital heart disease. Historically there has been a paucity of data on the clinical features that predicted risk of SCD. This is because ACHD is relatively rare compared to acquired heart disease, though recently there has been much interest in the occurrence of late onset arrhythmia in this population group. Often arrhythmias in ACHD do not become manifest until the third decade, suggesting that a period of negative remodelling is important in the development of these arrhythmias.[141] This is a good reason why it is important to understand the mechanism effective treatment of potentially lethal arrhythmias in this population.

2.15.1 Causes of arrhythmias in ACHD

There are two main reasons that arrhythmias arise in ACHD.[141] The first is due to the abnormal physiology (pressure and volume loads) and certain anatomical features associated with the various congenital lesions. The second is as a consequence of previous surgery as the surgical scars form an anatomic barrier to normal electrical impulse thereby promoting macro re-entrant circuits as a mechanism for both atrial and ventricular arrhythmias.

Longitudinal follow-up of these patients has demonstrated that a) approximately 1% of all patients with some form of ACHD will develop a malignant arrhythmia over a mean follow-up of 10 years, b) these events will usually occur in patients with more complex haemodynamic and anatomical lesions (Transposition of the Great Arteries (TGA) Single Ventricular Physiology (SVP), Tetralogy of Fallot (ToF) and patients with LV outflow obstruction) and in these patients the SCD may reach 10% over a 10 year period c) abnormal systemic ventricular function is one of the strongest predictors of malignant arrhythmia.[141-144]

2.15.2 Causes of SCD in ACHD

In a study of 25 790 adults with a broad spectrum of CHD, 1189 deaths (5%) were identified, of whom 213 patients (19%) died suddenly. Arrhythmic death occurred in 171 of 25790 patients. The underlying cardiac lesions were mild, moderate, and severe CHD in 12%, 33%, and 55% of the SCD cases, respectively. [143] Clinical variables associated with SCD were supraventricular tachycardia (odds ratio [OR], 3.5; 95% confidence interval [C.I.], 1.5–7.9; P<0.004), moderate to severe

systemic ventricular dysfunction (OR, 3.4; 95% CI, 1.1–10.4; P<0.034), moderate to severe subpulmonary ventricular dysfunction (OR, 3.4; 95% CI, 1.1–10.2; P<0.030), increased QRS duration (OR, 1.34 [per 10-ms increase]; 95% CI, 1.10–1.34; P<0.008), and QT dispersion (OR, 1.22 [per 10-ms increase]; 95% CI, 1.22–1.48; P<0.008).

With respect to specific ACHD lesions, there are the most data on ToF as it one of the most common complex ACHD lesions, with a long follow-up into adulthood. A summary of the commonly accepted risk factors for the development of malignant arrhythmias after surgical repair in TGA, ToF, SVP and LV outflow obstruction are presented in Table 10 Risk factors for SCD in complex ACHD.

…

After repair of tetralogy of Fallot	After atrial switch for transposition	Repair for Single Ventricle Physiology	LV outflow obstruction
Older age at the time of complete repair	Longer duration of follow-up	Longer duration of follow-up	Longer duration of follow-up
Longer duration of follow-up since complete repair	History of syncope or rapid palpitation	History of syncope or rapid palpitation	History of ≥2 episodes of syncope
History of syncope	Atrial tachycardia	Atrial tachycardia	Outflow gradient of >50mmHg
Severe pulmonary incompetence	Depressed systemic RV function	Depressed systemic ventricular function	Aortic regurgitation
Severe RV enlargement		Older Fontan technique (atriopulmonary connection)	Elevated LV end-diastolic pressure
Moderate to severe RV systolic dysfunction			Depressed LV systolic function
Extensive RV fibrosis			Severe LV hypertrophy
Moderate to severe LV systolic dysfunction			
Elevated LV end-diastolic pressure			
QRS duration ≥180ms			
Nonsustained VT on ambulatory monitoring			
History of atrial tachycardia			
Inducible VT at EPS			

EPS, electrophysiology study; RV, right ventricle; LV, left ventricle

Table 10 Risk factors for SCD in complex ACHD

Table adapted from Walsh Review in Sudden death in adult congenital heart disease: risk stratification in 2014 Heart Rhythm 11; 12: 1735-42 [141]

2.15.3 Outcomes of patients with ACHD and ICDs

Data on outcomes of patients with ACHD with ICDs has historically been based largely on single centre studies. However, a recent systematic review meta-analysis of 24 studies involving over 2000 patients (50% ToF) with ACHD and ICDs with a mean follow-up of 3.6 ± 0.9 years has demonstrated that overall 24% (18.6-31.3) of patients received one of more appropriate ICD therapies (ATP or shock), 25% of patients received inappropriate shocks in 25% (20.1 -31.0) and lead-related complications occurred in 26% (18.9-33.6) of patients.[145] This study included any type of ICD (epicardial, TV and S-ICD) though the majority of patients received TV-ICDs (96.1%).

The S-ICD is an ideal tool to treat the elevated risk of SCD in patients with complex ACHD as no transvenous leads are required to negotiate the often challenging venous anatomy and the risk of pneumothorax and endocarditis are markedly reduced. There is however a limited amount of data available on outcomes of patients with ACHD treated with S-ICDs. Initial reports have been mixed [146, 147] with critics citing problems relating to T wave oversensing and delays to therapy. Alternative strategies such as improved screening and non-standard leads positions may help reduce some of these problems.

2.16 Need for research and development

A number of questions arise from the preceding discussion. Firstly, there is a need to understand whether any change in the location of the parasternal sensing electrode would improve the S-ICD sensing characteristics in patients with ACHD. Secondly, there is a need to understand there is a need to understand whether increasing the number of postures during the screening process would improve the S-ICD sensing characteristics in patients with ACHD. Thirdly, there is a need to understand what the electrocardiographic features are that predispose to T wave oversensing. Lastly, as S-ICD technology is new, there is scope for research and development that may the potential of the device, in particular with reference to personalised medicine in order to improve outcome that remain hitherto unexplored.

Given this, in this thesis I will explore the following areas relating to this:

1. The impact of right parasternal versus left parasternal sensing electrode position on the amplitude and ratio of ECG waves in controls and adults with complex congenital heart disease.
2. The impact of postural change on the amplitude and ratio of ECG waves in controls and adults with complex congenital heart disease.
3. Clinical and electrocardiographic predictors of T-wave oversensing in patients with S-ICDs. A multicentre study.
4. Calculation of the transformational coordinates to generate an 8-lead ECG from the two S-ICD sensing electrode positions.

2.17 Outline of thesis

This thesis contains four separate studies corresponding to the research question and aims outlined in the introduction, each detailed in individual chapters. Each study is presented in full, including the methodology, results and discussion pertinent to the specific work.

2.18 Setting

All original research was conducted at University Hospital Southampton NHS Foundation Trust. This hospital serves 1.3 million people living in Southampton and South Hampshire, in addition to tertiary cardiac services to around 3 million people in central southern England and the Channel Islands. Two studies involved collaboration with other UK centres. Bristol Heart Institute, University Hospitals Bristol NHS Foundation Trust for the impact of age on ICD outcomes (Chapter 3) and the Dudley Group NHS Foundation trust for the T wave oversensing study (Chapter 6).

2.19 Ethical considerations

All work was undertaken in accordance with the Declaration of Helsinki and according to the principles of Good Clinical Practice. Ethical approval for prospective study was granted by the Southampton University Hospital and South West Hampshire Research Ethics Committee B (REC 08/H0503/55) (Chapters 3 and 4), the NRES Committee for the East of England – Norfolk (REC 14/EE/0197) (Chapter 5) and the Proportionate Review Sub-committee of the NRES Committee London-Brent (REC 13/LO/1800) (Chapter 6).

2.20 Data handling and record keeping

Data was collected and retained in accordance with the Data Protection Act 1998.Study documents (paper and electronic) were retained in a secure location during and after the relevant trial had finished. All essential documents and source data, including any medical records where entries related to the research have been made, will be retained for a minimum period of 5 years following the end of the study. A ‘DO NOT DESTROY’ label stating the time after which the documents can be destroyed was placed on the outer cover of relevant medical records.

..

Chapter 3: Evaluating the use of right parasternal versus left parasternal ECG parameters using surface electrodes as surrogates for sensed ECG signal from subcutaneous implantable cardioverter defibrillator in adult congenital heart disease patients and normal controls

3.1 Abstract

3.1.1 Aim

This study investigated the impact of a right parasternal sensing electrode position on the R and T wave amplitudes and the R:T ratio using surface electrodes a surrogates for the S-ICD vectors in patients with adult congenital heart disease (ACHD) and normal controls.

3.1.2 Methods

Conventional left parasternal sensing electrode position and right parasternal sensing electrode positions were used to collect 10-second electrograms, recorded through an 80-electrode body surface mapping technology (Prime ECG ™ system). Recordings were made in the supine, prone, left lateral, right lateral, sitting and standing positions in using both the standard electrode vector position and the right parasternal positions.

3.1.3 Results

Forty patients were recruited and 37 patients were used for analysis. Twenty-seven (73%) had complex ACHD, 10 patients had normal hearts and acted as controls. A total of 3708 data points were analysed. There were no significant differences in the R:T ratio when measured in ACHD patients in the right compared to the left parasternal lead position. In contrast there were important differences in the magnitude of the R:T ratio when measured in control patients in the right compared to the left parasternal lead position; in the primary vector, the R:T ratio was greater in right than left by 2.99 (p=0.0002 95% C.I. 1.48 to 4.50) and in the secondary vector, the R:T ratio was smaller in the right than in the left by 0.77 (p=0.004 95% C.I. -1.58 to 0.05).

3.1.4 Conclusion

In selected patients, a right parasternal lead position may provide a useful alternative sensing configuration for the S-ICD.

3.2 Introduction

The subcutaneous ICD (S-ICD) provides effective shock therapy for defibrillation/cardioversion in patients with potentially life threatening ventricular arrhythmias. [148] However, as the S-ICD relies on subcutaneous rather than endocardial electrogram sensing, its facility for arrhythmia sensing and discrimination requires specific scrutiny. Registry data has reported rates of inappropriate therapy of 7% per annum, [133] mostly due problems arising from algorithm driven interpretation of the sensed cardiac signal. This incidence of inappropriate shocks may exceed that for contemporary TV-ICD devices. [149] The S-ICD employs a morphology-based sensing algorithm and in its application a R:T signal ratio of <3 on the standard surface ECG has been identified as an important predictor of arrhythmia discrimination such that a potential S-ICD recipient would be identified as having failed S-ICD screening because of a high risk of inappropriate shock therapy. [129]

The S-ICD system comprises three sensing electrodes: the first is located on the can in the 5th intercostal space in the mid-axillary line; the second is a proximal electrode located 1cm lateral to the xiphoid midline, on the patient's left; the third is a distal electrode placed 14 cm superior. This configuration can produce three vectors: primary (horizontal, proximal electrode to can), secondary (diagonal, distal electrode to can) and alternate (vertical, distal to proximal electrode). The manufacturer of the only clinically released S-ICD recommends pre-implant ECG screening using three cutaneous sensing electrodes that are placed overlying the intended S-ICD sensing electrode locations, to demonstrate electrogram characteristics that will allow optimal operation of the device's sensing and arrhythmia discrimination algorithm.

The use of a right parasternal lead position has been shown to achieve satisfactory S-ICD electrogram sensing in selected patients with atypical cardiac morphology and ECG characteristics. [150-152]

However, to date the impact on sensing of a right parasternal lead position has not been systematically assessed and the differences between right and left parasternal sensing characteristics are not currently known. We speculated that a right parasternal lead position might offer particular sensing advantage in the ACHD population, particularly because of the associated abnormalities in cardiac morphology and topology.

Therefore, the aim of this study was to investigate impact of a right parasternal sensing electrode position on sensed R wave and T wave amplitudes, and the magnitude of the R:T ratio, in three S-ICD vectors in patients with ACHD and normal controls.

3.3 Methods

This was a non-randomised, observational study conducted in tertiary referral cardiac centre. Willing participants aged over 16 years were recruited. Patients were recruited into four groups: Tetralogy of Fallot (ToF), Transposition of the Great Arteries (TGA) and Single Ventricle Physiology (SVP) and controls with structurally normal hearts as defined by normal transthoracic echocardiography and magnetic resonance imaging. Exclusion criteria were inability to provide informed consent and participation in other studies and patients with paced ventricular rhythm.

3.3.1 Use of surface ECG data

We used ECG data collected from surface electrodes a surrogates for the S-ICD sensing vectors rather than implanting S-ICDs into participants as this was non-invasive, easier to recruit participants and considered to be a reasonable proxy for S-ICD sensing.

Ten-second electrograms were recorded (sampling rate 1000Hz) in using body surface mapping technology (Prime ECG ™ system, Heartscape Technologies Inc. now Verathon, Columbia, Maryland, United States). Recordings were made in the supine, prone, left lateral, right lateral, sitting and standing positions in using both the standard electrode vector position and the right parasternal positions. (Figure 14) The PRIME ECG ™ system is a validated form of body surface mapping (BSM) that can accurately detect cardiac electrical activity. [153-156] It consists of a flexible plastic anterior and posterior electrode vest and portable recording unit. The anterior vest contains 64 electrodes and the posterior vest 16 electrodes enabling the recording of 80 simultaneous unipolar ECG signals. The vests are arranged in vertical strips reference to their anatomical landmarks. Prior to recording, signal quality is checked in banks of 8 leads and any poor signal is identified and corrected. Previous studies have validated cutaneous-derived electrocardiography signals (e.g. body surface mapping) as reliable surrogates for subcutaneous sensing algorithm testing. [130] Sensing vectors were recreated using bipolar signals from one electrode position to another according to the standard S-ICD vector configuration described above with the alternate (vertical) vector being recreated using electrodes located on the left and right parasternal positions as necessary. (Figure 14) The amplitudes were analysed based on the beat-annotations by calculating the maximum rectified waveform within the P, QRS, T windows based on annotations at the raw sampling rate=1000Hz. The peak amplitudes of the R wave, T wave served as comparators for analysis, rather than the morphology of the of the recorded wave forms.

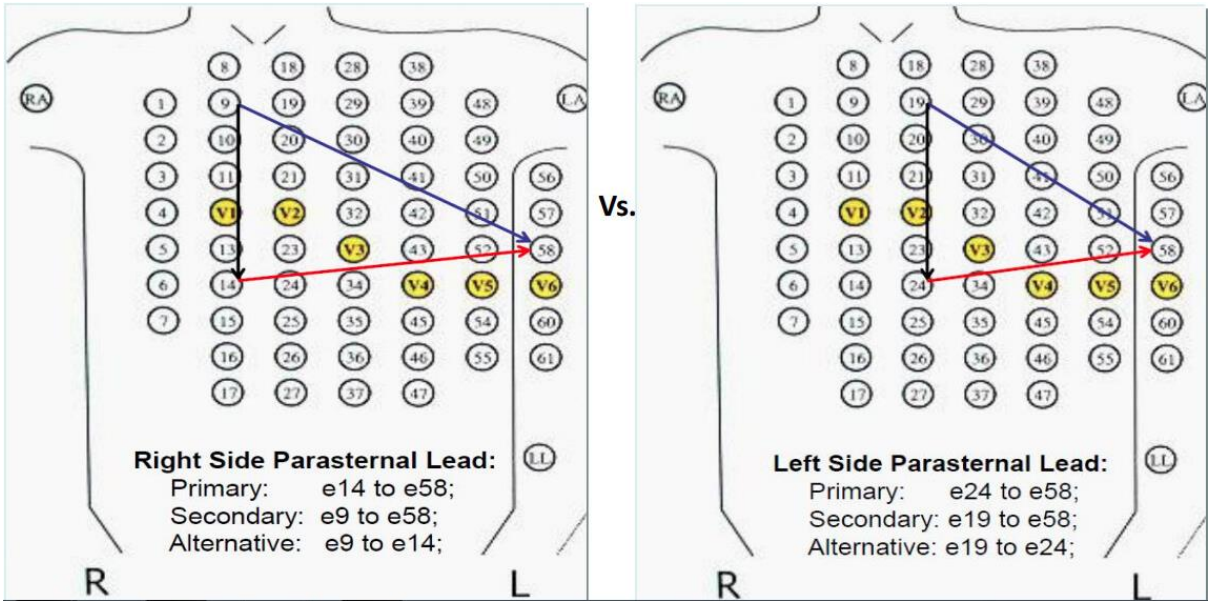


Figure 14 Illustration of the sensing electrodes used in the recording of the right parasternal and left parasternal lead position.

For generating the right parasternal lead set, the Primary vector equivalence was recreated from recording electrodes e14 to e58, the secondary vector was recreated from recording electrodes e9 to e58 and the alternate vector was recreated from recording electrodes e9 to e4. For generating the left parasternal lead set, the Primary vector equivalence was recreated from recording electrodes e24 to e58, the secondary vector was recreated from recording electrodes e19 to e58 and the alternate vector was recreated from recording electrodes e19 to e24.

3.3.2 Statistical methods

Continuous variables are reported as mean (range), mean (SD) or median and inter-quartile range (IQR) for data with distribution that deviated from the normal one, and categorical variables as frequency (%). The test of Shapiro-Wilk for normality of distributions was applied.

Descriptive statistics and univariate statistical comparisons of R wave amplitude, T wave amplitude and RT ratio magnitude between and within the groups were applied: for continuous variables: a two- sample t-test when relevant distributional assumptions were met and the Mann–Whitney U-test or Wilcoxon signed ranks test for paired data, otherwise. For categorical variables, $\chi 2$ test or Fisher's exact test were applied, as appropriate.

SPSS was the statistical software package used for the analysis (SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc. Released 2008.). Three dimensional charts were constructed to illustrate the amplitude of the R wave, T wave and RT ratios.

For the subgroup analysis, generalized linear mixed models ('proc glimmix') with random and repeated effects for the comparison between the paired measurements, were used to obtain

restricted maximum likelihood (REML) solutions with a diagonal type of the covariance matrices for all or selected measurements between or within the groups.

Least square means with 95% CIs were obtained. The value of $P<0.05$ was considered statistically significant. Three dimensional charts were constructed to illustrate the amplitude of the R wave, T wave and RT ratios. The sub-group analyses was performed with the statistical software SAS Ver.9.3 (SAS Institute Inc. Cary, NC, USA).

3.3.3 Explanation of statistical methods used

a. Shapiro-Wilk
    a. This test determines whether a population is normally distributed
b. :Two- sample t-test
    a. This tests evaluates the null hypothesis that two means from independent groups are equal. This test is used for data that follow a normal distribution.
c. Mann–Whitney U-test
    a. This is a non-parametric (does not require the data to be normally distributed) test comparing whether the means of paired observations from independent samples are equal. This test is the alternative to the independent T test.
d. Wilcoxon signed ranks test for paired data
    a. This is a non-parametric (does not require the data to be normally distributed) test comparing whether the means of paired observations from independent samples are equal.
e. $\chi 2$ test (Chi-square)
    a. This test is used on frequency data and to test differences in proportions using 2x2 table showing the distribution of one variable in rows and another in columns, (contingency) table.
f. Fisher's exact test
    a. This test is similar to the $\chi 2$ test in that is evaluates whether frequencies using a 2x2 contingency table, but it provides exact probabilities (rather than approximations used in the $\chi 2$ test) and is valid when the expected frequencies are small.
g. Generalised linear mixed models
    a. This is an advanced form of statistical analysis that is an extension of generalised linear model for example regression analysis. Regression analysis attempts to identify how a dependent variable (y axis) relates to independent data.[157] This

assumes a linear relationship between the independent and dependent variable and can be expressed mathematically as:

$$Y=a+bx$$

Y is the dependent variable, x is the independent variable, *a* is the intercept of the estimated line and *b* is the gradient of the estimated line.

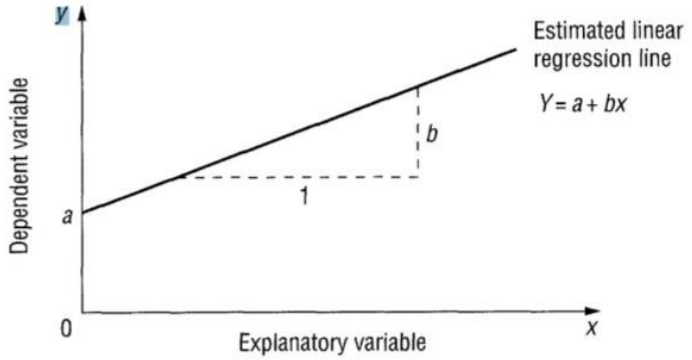


Figure 15 Estimated linear regression line showing the intercept *a* and the slope *b*, (the mean increase in Y for a unit increase in *x*). Taken with permission from *Medical Statistics at a Glance* Third Edition Petrie and Sabin Wiley & Blackwell.

In generalised linear mixed modelling, both fixed and random effects rather than just (fixed effects as in simple linear regression) hence the terms mixed. This this study, this test was selected due to the complexity of the data and the high number of variables. We wanted to compare the difference between ECG parameters when measured from the right versus the left parasternal side. However, within this, patients also had six changes in posture (repeated measures), three vectors (within group changes) and four subgroups (independent variables). The use of an ANOVA analysis (analysis of variance) was considered because of the repeated measures recorded in the postural change but this discounted a there were a small percentage of data points missing and therefore a mixed model was selected. Given the complexity and high number of interacting variables, the help of a statistician was sought who designed the generalised linear mixed model to address this question.

This method resulted in a highly detailed analysis of the interaction of posture on the ECG parameters such that each parameter in each posture was compared to each other rather than to a reference posture. Thus for example, the R wave recorded in the supine posture in the primary vector for the subgroup Tetralogy of Fallot for example, would be compared to all other R waves recorded in the

five other postures in that vector and subgroup. Each posture would in turn be compared to the other postures and between the left and right parasternal group. This would be repeated for all R wave, T wave and R:T ratios for all subgroups in all 3 vectors and parasternal groups

The high volume of data that was generated are succinctly presented in summary tables. Please see explanation below.

3.4 Results

Of 40 patients recruited, 37 were suitable for the analysis (3 were excluded due to poor quality signal in the right parasternal region). Twenty-seven (73%) had ACHD: 10 with Transposition of the Great Arteries (TGA); 10 with Tetralogy of Fallot (TOF) and 7 with single ventricle physiology (SVP). The remaining 10 patients had normal hearts, confirmed on transthoracic echocardiography and magnetic resonance imaging. The mean age of the patients was 36 years, 62% male. A total of 3708 valid data points were used for the analysis. A total of 3708 valid data points were used for the analysis.

The mean amplitude of the R wave and T wave in the left and right parasternal lead positions are summarised in Table 11.

			Right parasternal position		Left parasternal position		
Group	Vector		Mean	Std. Dev.	Mean	Std. Dev.	p value
ACHD							
	Primary	R wave	2.03	0.75	2.16	1.04	0.3898
	Primary	T wave	0.51	0.32	0.50	0.37	0.3165
	Primary	R:T ratio	5.88	5.38	5.39	2.90	0.1135
	Secondary	R wave	1.78	0.71	1.74	0.88	0.2369
	Secondary	T wave	0.45	0.26	0.44	0.26	0.0004
	Secondary	R:T ratio	5.51	4.97	5.03	3.77	0.6272
	Alternate	R wave	1.18	0.72	1.54	0.90	0.0002
	Alternate	T wave	0.29	0.29	0.38	0.37	0.0026
	Alternate	R:T ratio	5.78	3.61	6.20	4.75	0.8476
Control							
	Primary	R wave	1.85	0.74	1.82	0.76	0.6984
	Primary	T wave	0.26	0.13	0.37	0.16	0.0002
	Primary	R:T ratio	8.56	5.22	5.57	2.60	0.0002
	Secondary	R wave	2.03	0.59	1.89	0.66	0.2026
	Secondary	T wave	0.41	0.22	0.33	0.20	<0.0001
	Secondary	R:T ratio	6.60	4.22	7.36	4.00	0.0043
	Alternate	R wave	0.77	0.31	1.07	0.43	0.0004
	Alternate	T wave	0.29	0.19	0.48	0.28	<0.0001
	Alternate	R:T ratio	4.05	3.73	2.91	2.18	0.0679

Table 11 Mean amplitude of the R wave and T wave in millivolts and the R:T ratio.
Mean amplitude in millivolts of the R wave and T wave and the R:T ratio in all patients in primary, secondary and alternate vectors in right and left parasternal lead positions using Wilcoxon signed-rank test.

Overall, there were no significant differences in any vector in the magnitude of the R:T ratio when measured in ACHD patients in the right compared to the left parasternal lead position. The magnitude of the R:T ratio in the primary vector in controls was greater in right compared to the left by 2.99 (p=0.0002 95% C.I. 1.48 to 4.50). The magnitude of the R:T ratio in the secondary vector was smaller in the right than in the left by 0.77 (p=0.004 95% C.I. -1.58 to 0.05). The magnitude of the R:T ratio in the alternate vector tended to be greater in the right parasternal lead position (4.05) compared to the low R:T ratio in the left parasternal lead position (1.16) (95% C.I -0.03 to .31) but not with statistical significance (p=0.07).

Three-dimensional charts of the R and T wave amplitudes and R:T ratio magnitudes in the right and left parasternal sensing positions are presented in Figure 16 and Figure 17.

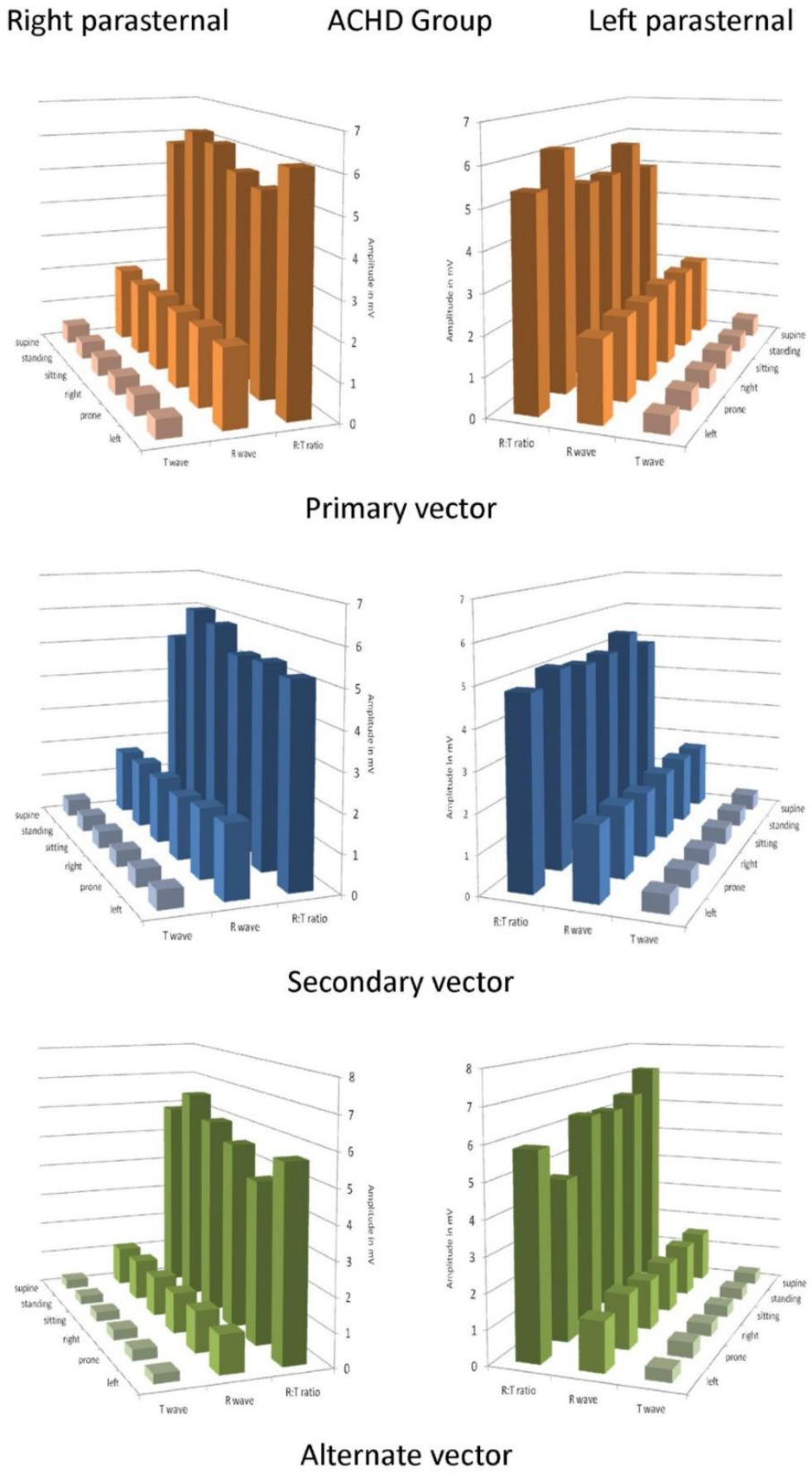


Figure 16 Three-dimensional charts of the R and T wave amplitudes and R:T ratio magnitudes in the right and left parasternal sensing positions in the ACHD group.

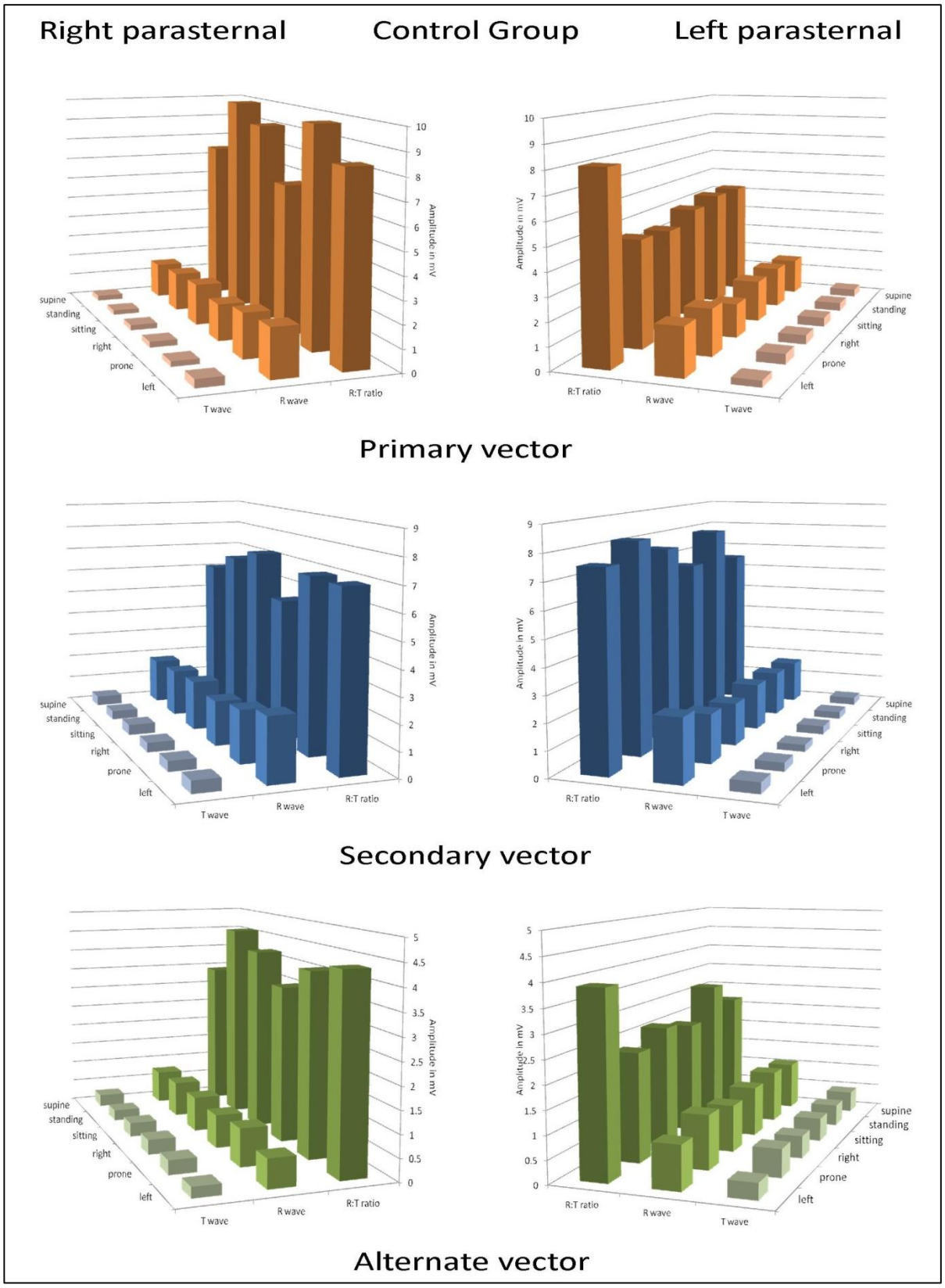


Figure 17 Three-dimensional charts of the R and T wave amplitudes and R:T ratio magnitudes in the right and left parasternal sensing positions in the control group.

3.4.1 Subgroup analysis

In order to determine whether pooling of the ACHD groups may mask differences between the amplitude of R and T waves recorded in the right and left parasternal lead position a subgroup analysis was performed using a generalised linear mixed model. The results are illustrated using summary boxes which indicate which results are statistically different ($p<0.05$). A detailed explanation of how to interpret the summary boxes is presented in Figure 18.

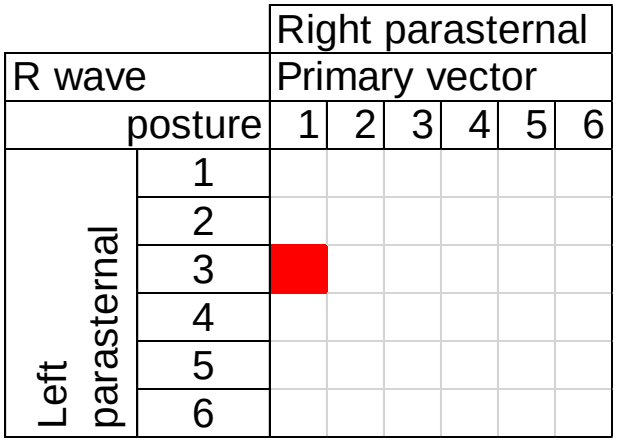


Figure 18 The panel is a representation of the results recorded in the R wave in the primary vector in all 6 postures.

3.4.2 Explanation of how to interpret sub-group summary boxes

Sub-group summary boxes were developed specifically for demonstration of the results of sub-group analyses of this study. The summary boxes provide a good overview of which parameter is significantly different from other parameters. In this study the mean amplitude of each R wave, T wave and R:T ratio in each sub-group recorded in one posture in the left parasternal lead position is compared to the mean amplitude of each R wave, T wave and R:T ratio in the same sub-group recorded in all postures in the right parasternal lead position.

The example in Figure 18 *uses the imaginary results of the analysis of the R wave amplitude result when measured in the primary vector. Results from posture 1 in the left parasternal lead position will be compared to results from posture 1-6 in the right parasternal lead position, results from posture 2 will be compared to results from posture 2-6 and so on and so forth. Results that are statistically significant within a parasternal group (adjusted p value <0.05) are coded red, in this example, only the posture 1 when measured from the left parasternal side is significantly different to posture 3 when measured from the right parasternal side. Thus for each sub-group a total of 324 comparisons were made (6x6 postures in 3 vectors for 3 ECG parameters – R wave T wave and*

R:T ratios).Posture 1 corresponds to the left posture, posture 2 corresponds to the prone posture, posture 3 corresponds to the right posture, posture 4 corresponds to the sitting posture, posture 5 corresponds to the standing posture and posture 6 corresponds to the supine posture.

The subgroup analysis (Figure 19) demonstrates that there is variation the differences between amplitude of the R and T waves and the R:T ratio when measured in the right and left parasternal lead position between the ACHD groups. The Transposition of the Great Arteries group has a greater number of statistically significant differences (27/324) in the amplitudes of the R and T waves and R:T ratio between left and right parasternal lead positions compared with the Tetralogy of Fallot (5/324) and Single Ventricle Physiology group (0/324). However, the control group has the largest number of statistically significant differences in the amplitudes of the R and T waves and R:T ratio between left and right parasternal lead positions (54/324). Most of the statistically significant differences occurred in the alternate (vertical) vector, with the R wave in the alternate vector accounting for most of the differences in the TGA group and the T wave in the alternate vector accounting for most of the differences in the control group.

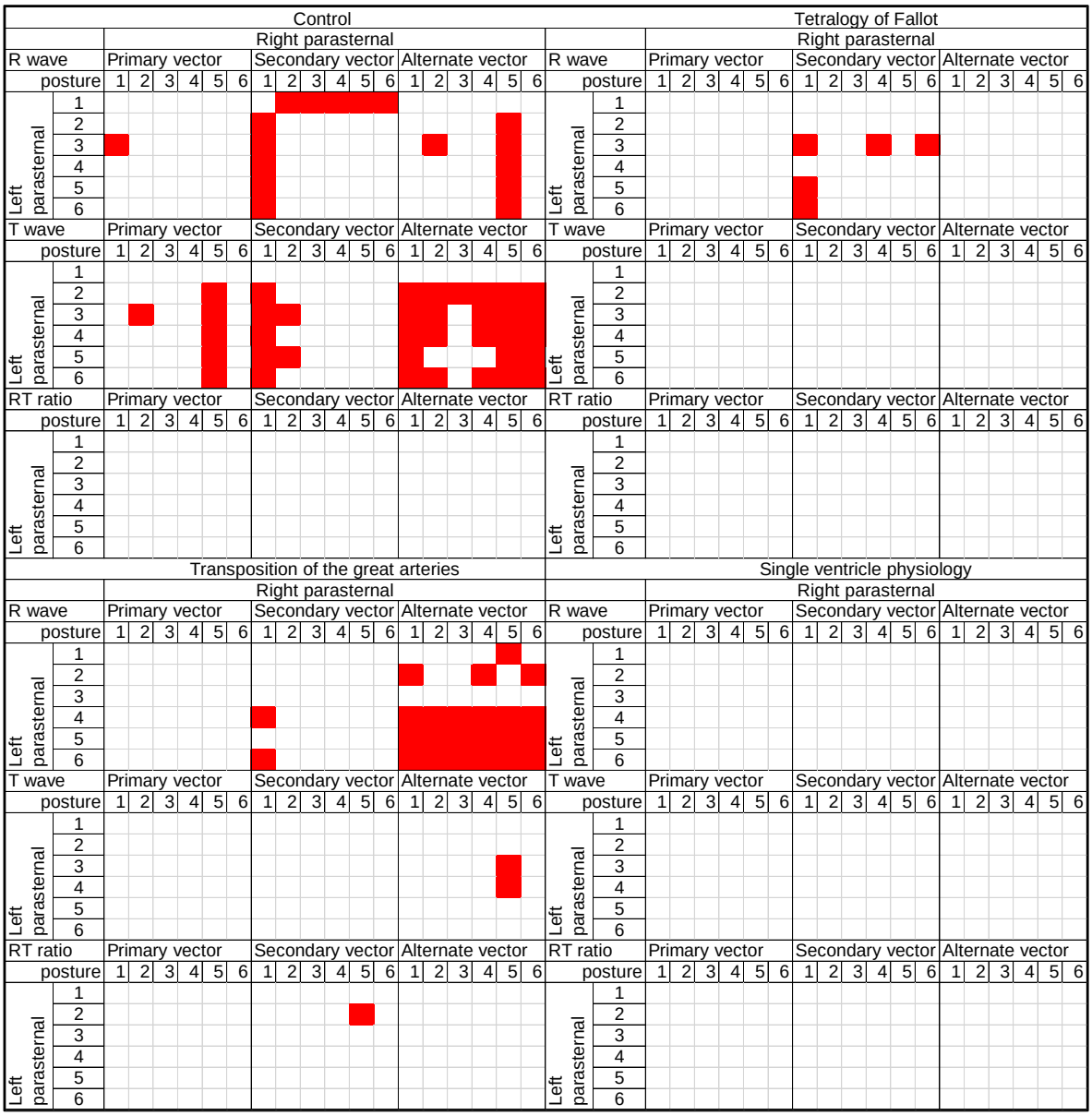


Figure 19 Subgroup analysis of impact of parasternal lead position on amplitude of the R wave, T wave and the R:T ratio.

1 = left posture, 2 =prone posture, 3 = right posture, 4 = sitting posture, 5 = standing posture and 6 = supine posture.

3.5 Discussion

In this prospective clinical study we investigated how using a right parasternal lead sensing electrode position would impact on the R wave and T wave amplitudes and R:T ratio compared to the left parasternal lead position in patients with ACHD and controls with structurally normal hearts.

We observed that overall, using a right parasternal lead position did not impact on the R:T ratio in patients with ACHD. In the control group by contrast, in two of the three vectors, there were statistically significant differences in the magnitude of the R:T ratio (greater in the primary and smaller in the secondary vector). In the alternate vector the magnitude of the R:T ratio tended to be greater in the right parasternal lead position but this did not achieve statistical significance.

In a detailed subgroup analysis of differences between left and right parasternal lead positions taking account of postural change, more significant differences were identified in the alternate vector than in the primary or secondary vectors. The TGA group and the control group accounted for most of the statistically significant differences whereas there were very few significant differences the ECG parameters when measured from the left and right parasternal lead position in the TOF and SVP groups.

The geometric position of the heart within the chest wall has been shown to be a large source of variation in body surface potentials and may help explain the differences observed between groups in this study. [158] Patients with ACHD tend to have a more centrally located heart in the thorax with larger right hearts and this is likely to explain the lack of variation in the R wave and T wave amplitude and the R:T ratio when measured from the right and left parasternal sensing positions. In contrast in normal controls, the right parasternal sensing electrode position is further away from the structurally normal heart, and therefore differences appear more marked compared to the left parasternal sensing position. We have not tested this using cross-sectional imaging. This may explain the larger variation in sensing parameters between the left and right parasternal positions in the control group.

The clinical uptake of S-ICDs, for the conventional ICD indication of primary prevention of sudden cardiac death in ischemic heart disease patients with severely impaired left ventricular ejection fraction, is rapidly increasing. These patients have leftward orientated hearts. We speculate that such patients are likely to exhibit similar sensed electrogram characteristics to the normal (control) group in this study. In fact, we observed improvements in the R:T ratio from R:T<3 in the left parasternal sensing position to R:T of approximately 4 in the right parasternal position. This

has clinical relevance. It is preferable to have more than one vector which satisfies implant S-ICD screening criteria, as this enhances the likelihood of later successful configuration of the S-ICD system for the avoidance of inappropriate shock therapy in the event of unexpected T wave over-sensing in the right parasternal lead position may provide this facility. However, the true clinical value needs to be tested in a larger cohort of patients with coronary artery disease and poor left ventricular function.

Non-standard lead positions are being increasingly employed as experience and confidence grows with implanting S-ICDs. This study supports the use of screening patients using a right parasternal sensing position in those patients where poor or borderline sensing parameters are identified at the pre-implant screen.

There are a number of potential disadvantages with use of a right parasternal sensing position. Firstly, a right parasternal sensing position may be advantageous in one or two vectors, but at the cost of potentially worsening sensing characteristics in the remaining third vector. At present we are not able to reliably predict specific patients who might benefit from a right parasternal position. Therefore, the approach needs to be individualised on a case by case basis.

Secondly, this study focused on how the sensing parameters might change by utilising a right parasternal lead position but not on the defibrillation effectiveness of the S-ICD system in this lead configuration. In the early clinical trial investigating the optimal electrode/can configuration for the S-ICD, four different positions were tested, all of which utilised a left parasternal defibrillation/sensing electrode. [128] We speculate however that a right parasternal lead position (with Can in the standard axillary position) is likely to offer similar defibrillation efficacy to that seen with a left parasternal lead position. Again, this needs to be tested prospectively.

Lastly, to implant an S-ICD with a right parasternal electrode, it is necessary for the defibrillation lead body to cross the midline at the level of the xiphisternum. This area has reduced amounts of subcutaneous tissue and the lead may be more vulnerable to erosion through the skin at this location.

3.5.1 Limitations

There are a number of limitations to this study. There is a modest number of participants. However, a total of 27 ACHD patients compares favourably to the number of such patients enrolled in the Effortless Registry [133] Furthermore, the number of data points generated is large and this goes some way to mitigating the effects of participants. The second limitation is that all

the data were collected at rest. Therefore there is the possibility of variability in ECG parameters with exercise and during arrhythmia.

3.6 Conclusion

This study has not demonstrated any significant differences in S-ICD sensing parameters using a right parasternal lead position compared to a left parasternal lead position in a broad range of adult patients with complex ACHD. However, a right parasternal lead position showed significant differences in the R:T ratio in the primary and secondary vector and a clinically important improvement in the R:T ratio in the alternate vector in participants with structurally normal hearts. In a subgroup analysis the alternate vector accounted for most of significant differences between the sensing parameters measured in the left and right parasternal leads position. In selected patients, a right parasternal lead position may provide a useful alternative for sensing in the S-ICD configuration.

Chapter 4: Evaluating the impact of postural change on ECG parameters using surface electrodes as surrogates for sensed ECG signal from subcutaneous implantable cardioverter defibrillator in adult congenital heart disease patients and normal controls

4.1 Abstract

4.1.1 Introduction

The aim of this study was to compare the R and T wave amplitudes and the R:T ratio magnitude in three S-ICD vectors in patients with ACHD and normal controls in 6 different postures.

4.1.2 Methods

A non-randomised, observational study was conducted. Patients were recruited into four groups: Tetralogy of Fallot (TOF), Transposition of the Great Arteries (TGA) and Single Ventricle Physiology (SVP) and controls with structurally normal hearts. 10-second electrograms were recorded using body surface mapping technology. Recordings were made in the supine, prone, left lateral, right lateral, sitting and standing positions in using both the standard electrode vector position

4.1.3 Results

Forty patients were recruited, 37 patients were suitable for the analysis. Overall, the R and T wave amplitudes and R:T ratio recorded in the right lateral posture was ranked the smallest in both the ACHD and control groups (mean rank 2.6 ± 1.3 and 2.3 ± 1.4) respectively, where rank 1 is the lowest and 6 the highest. The R and T wave amplitudes and R:T ratio in the prone posture was ranked the largest in both the ACHD and control groups (mean rank 4.7 ±1.6 and 4.7 ±1.9) respectively. In a subgroup analysis, posture had a more significant impact on the R and T wave amplitude and R:T ratio in controls than in the ACHD subgroups.

4.1.4 Conclusion

Postural change has a greater impact on the R and T wave amplitude and R:T ratio magnitude in patients with structurally normal hearts than in patients with complex ACHD. The left lateral, right lateral and prone postures account the extremes in R and T wave amplitude and R:T ratio magnitude. Introducing ECG screening in all 6 postures would make the process more robust.

4.2 Introduction

The subcutaneous implantable cardioverter-defibrillator S-ICD has a proven track record in delivering life safe and effective shock therapy for patients with lethal arrhythmias, [148] and has the advantage of not requiring intravenous lead placement. Patients with complex congenital heart disease tend to be younger and often have the combination of a high incidence of sudden cardiac death, accounting for nearly 1 in 5 deaths in the population, [159] and have more complex anatomy. [143] Given this, the S-ICD appears to be well suited to meet their requirements.

Registry data has reported rates of inappropriate therapy of up to 7% per annum, [133] mostly due to T-wave oversensing and undersensing of the cardiac signal. The S-ICD consists of three sensing electrodes, the first, the can is located in the 5th intercostal space in the mid-axillary line, the second, a proximal electrode located 1cm lateral to the xiphoid midline and the third is a distal electrode placed 14 cm superior. Three cutaneous sensing electrodes are placed overlying the intended S-ICD sensing electrode locations for the purposes of the pre-implant screen and recordings are made in two postures (supine and standing) at three gain settings.

The S-ICD appears more challenged in its ability to sense appropriately all of the time. Accurate sensing requires an adequate R wave with a minimal T wave amplitude to reduce the likelihood of T wave oversensing. An R:T of <3 on a surface ECG has been found to be a risk factor of inappropriate therapy in S-ICD patients. [129] Thus, changes in the R wave or T wave caused by postural change alone may result in changes to the R:T ratio. There are anecdotal reports of episodes of oversensing occurring whilst patients are in non-standard pre-implant screen postures e.g. prone and whilst in bed. Whilst the effect of changes in body posture on the electrocardiogram has been known about for over 70 years, [160] it is not known how postural change may impact upon the R wave, T wave and R:T in the S-ICD sensing vectors or in which postures is the signal sensed well (maximal amplitude) or less well (minimal amplitude) or indeed whether certain vectors are more vulnerable to postural change than others.

The aim of this study was to compare the R and T wave amplitudes and the R:T ratio magnitude in three S-ICD vectors in patients with ACHD and normal controls in 6 different postures.

4.3 Methods

This non-randomised, observational study was conducted in tertiary referral cardiac centre. Willing participants aged over 16 years were recruited. All the study subjects were adults and had the ability to give informed consent. Patients were recruited into four groups: Tetralogy of Fallot

(TOF), Transposition of the Great Arteries (TGA) and Single Ventricle Physiology (SVP) and controls with structurally normal hearts as defined by transthoracic echocardiography and magnetic resonance imaging. We used ECG data collected from surface electrodes a surrogates for the S-ICD sensing vectors rather than implanting S-ICDs into participants as this was non-invasive, easier to recruit participants and considered to be a reasonable proxy for S-ICD sensing Exclusion criteria were inability to provide informed consent and participation in other studies and patients with paced ventricular rhythm.

10-second electrograms were recorded (sampling rate 1000Hz) using body surface mapping technology (Prime ECG ™ system). Recordings were made in the supine, prone, left lateral, right lateral, sitting and standing positions in using both the standard electrode vector position. The PRIME ECG ™ system is a validated form of body surface mapping (BSM) that can accurately detect cardiac electrical activity. [153-156] It consists of a flexible plastic anterior and posterior electrode vest and portable recording unit. The anterior vest contains 64 electrodes and the posterior vest 16 electrodes enabling the recording of 80 simultaneous unipolar ECG signals. (Figure 20) The vests are arranged in vertical strips reference to their anatomical landmarks. Prior to recording, signal quality is checked in banks of 8 leads and any poor signal is identified and corrected. Previous studies have validated cutaneous-derived electrocardiography signals (i.e. body surface mapping) as reliable surrogates for subcutaneous sensing algorithm testing. [130]

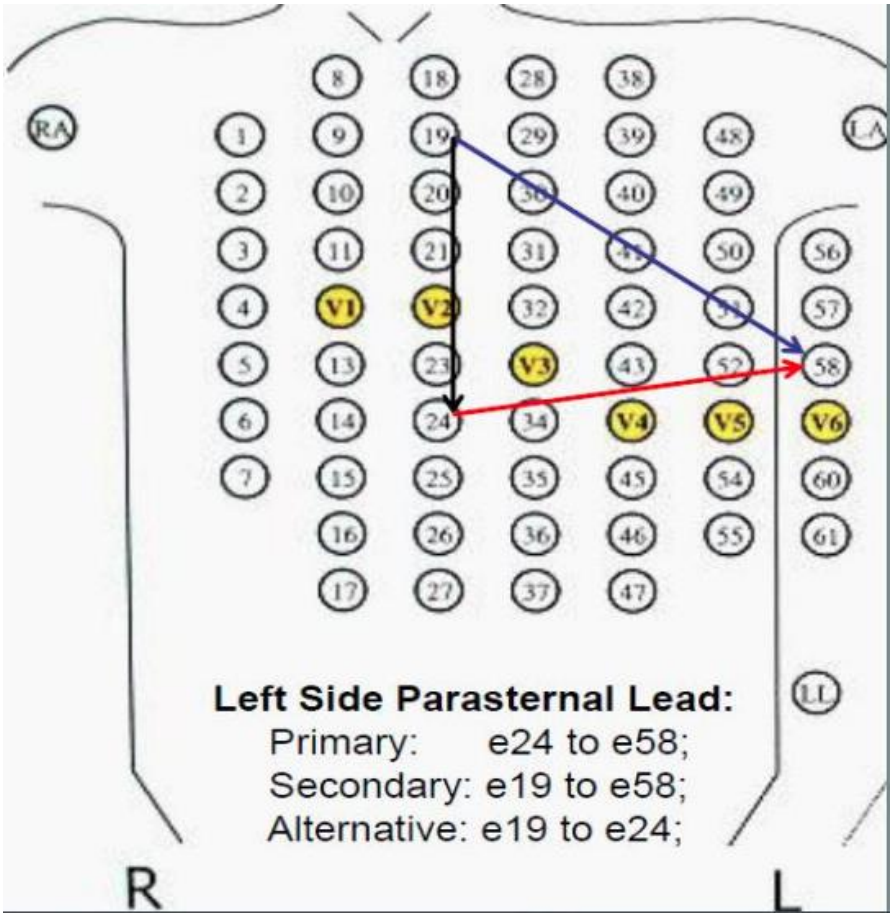


Figure 20 Illustration of the sensing electrodes used in the recording of the electrode lead positions utilising the Prime ECG™ system.
The Primary vector equivalence was recreated from recording electrodes e24 to e58, the secondary vector was recreated from recording electrodes e19 to e58 and the alternate vector was recreated from recording electrodes e19 to e24.

4.3.1 Statistical methods

Continuous variables are reported as mean (range), mean (SD) or median and inter-quartile range (IQR) for data with distribution that deviated from the normal one, and categorical variables as frequency (%).

Postural variation within each parameter was expressed as a percentage of the lowest value and categorised as low (<25% variation), medium (25-49% variation) and high (>50% variation).

Differences within groups caused by postural changed was assessed using a generalised linear model 'proc glimmix' model with random and repeated effects for the comparison between the paired measurements, used to obtain restricted maximum likelihood (REML) solutions with a diagonal type of the covariance matrices for all or selected measurements between or within the groups. Least square means with 95% CIs were obtained. The value of $P<0.05$ was considered

statistically significant. Three dimensional charts were constructed to illustrate the amplitude of the R wave, T wave and RT ratios. The sub-group analyses was performed with the statistical software SAS Ver.9.3 (SAS Institute Inc. Cary, NC, USA).

This sophisticated novel approach used to analyse complex, non-normally distributed data whilst adjusting for multiple comparisons and was devised entirely for the purposes of this analysis. The estimation technique used was the restricted maximum likelihood method. The least-squares means adjustment for multiple comparisons using Tukey-Kramer analysis was used. This resulted in each parameter being compared to all other parameters within that field (e.g. the R wave in a control patient in the primary vector in left lateral posture was compared to the five other postures in that vector in the left parasternal group and all six postures in the right parasternal group. This was repeated for all three vectors for the T wave and R wave in all four groups. A p value <0.05 was used to determine statistical significance.

Matrix comparison boxes were generated to illustrate the within and between parasternal group statistical differences (adjusted p<0.05). Three dimensional charts were constructed to illustrate the amplitude of the R wave, T wave and RT ratios.

4.3.2 Explanation of statistical methods used

a. Shapiro-Wilk
    a. This test determines whether a population is normally distributed.
b. :Two- sample t-test
    a. This tests evaluates the null hypothesis that two means from independent groups are equal. This test is used for data that follow a normal distribution.
c. Mann–Whitney U-test
    a. This is a non-parametric (does not require the data to be normally distributed) test comparing whether the means of paired observations from independent samples are equal. This test is the alternative to the independent T test.
d. Wilcoxon signed ranks test for paired data
    a. This is a non-parametric (does not require the data to be normally distributed) test comparing whether the means of paired observations from independent samples are equal.
e. $\chi 2$ test (Chi-square)
    a. This test is used on frequency data and to test differences in proportions using 2x2 table showing the distribution of one variable in rows and another in columns, (contingency) table.

f. Fisher's exact test

   a. This test is similar to the $\chi 2$ test in that is evaluates whether frequencies using a 2x2 contingency table, but it provides exact probabilities (rather than approximations used in the $\chi 2$ test) and is valid when the expected frequencies are small.

g. Generalised linear mixed models

   a. This is an advanced form of statistical analysis that is an extension of generalised linear model for example regression analysis. Regression analysis attempts to identify how a dependent variable (y axis) relates to independent data.[157] This assumes a linear relationship between the independent and dependent variable and can be expressed mathematically as:

$$Y=a+bx$$

Y is the dependent variable, x is the independent variable, *a* is the intercept of the estimated line and *b* is the gradient of the estimated line.

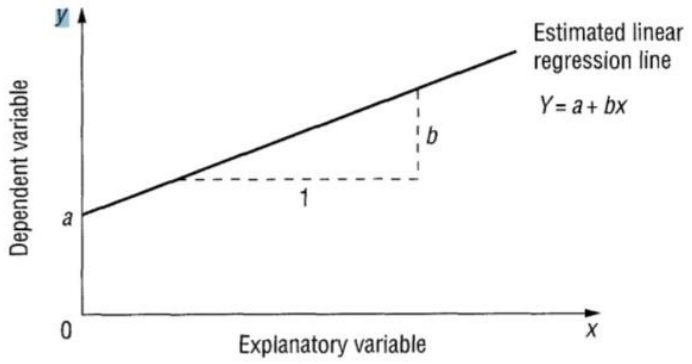


Figure 21 Estimated linear regression line showing the intercept *a* and the slope *b*, (the mean increase in Y for a unit increase in *x*). Taken with permission from *Medical Statistics at a Glance* Third Edition Petrie and Sabin Wiley & Blackwell.

In generalised linear mixed modelling, both fixed and random effects rather than just (fixed effects as in simple linear regression) hence the terms mixed. This this study, this test was selected due to the complexity of the data and the high number of variables. We wanted to compare the impact of postural change between ECG parameters when controlling for all the other variables. However, within this, patients also had six changes in posture (repeated measures), three vectors (within group changes) and four subgroups (independent variables). The use of an ANOVA analysis (analysis of variance) was considered because of the repeated measures recorded in the postural change but this discounted a there were a small percentage of data points missing and therefore a mixed model was

selected. Given the complexity and high number of interacting variables, the help of a statistician was sought who designed the generalised linear mixed model to address this question.

This method resulted in a highly detailed analysis of the interaction of posture on the ECG parameters such that each parameter in each posture was compared to each other rather than to a reference posture. Thus for example, the R wave recorded in the supine posture in the primary vector for the subgroup Tetralogy of Fallot for example, would be compared to all other R waves recorded in the five other postures in that vector and subgroup. Each posture would in turn be compared to the other postures. This would be repeated for all R wave, T wave and R:T ratios for all subgroups in all 3 vectors.

The high volume of data that was generated are succinctly presented in summary tables. Please see explanation below.

4.4 Results

Forty patients were recruited, 37 patients were suitable for the analysis (three excluded due to poor quality signal). Twenty-seven (73%) had ACHD: 11 with Transposition of the Great Arteries (TGA); 10 with Tetralogy of Fallot (TOF) and 6 with single ventricle physiology (SVP). The remaining 10 patients had normal hearts, confirmed on transthoracic echocardiography and magnetic resonance imaging. The mean age of the patients was 36 years, 62% male. A total of 1863 valid data points were used for the analysis.

The mean amplitude of the R wave and T wave in the left and right parasternal lead positions are summarised in Table 12. Three dimensional charts are shown in Figure 22 and Figure 23.

	Mean	s.d	Lower Bound 95%	Upper bound 95%	% difference between max and min.
ACHD					
R wave					
Primary vector	2.16	1.04	1.99	2.32	5.56
Secondary vector	1.74	0.88	1.60	1.88	10.32
Alternate vector	1.57	0.90	1.42	1.72	16.01
T wave					
Primary vector	0.50	0.37	0.45	0.56	12.65
Secondary vector	0.44	0.26	0.40	0.48	15.85
Alternate vector	0.37	0.38	0.31	0.43	28.56
R:T ratio					
Primary vector	5.39	2.90	4.92	5.85	24.86
Secondary vector	5.03	3.77	4.43	5.63	11.65
Alternate vector	6.40	4.74	5.63	7.17	50.94
Controls					
R wave					
Primary vector	1.82	0.76	1.61	2.02	39.42
Secondary vector	1.89	0.66	1.72	2.07	46.25
Alternate vector	1.07	0.43	0.96	1.19	24.27
T wave					
Primary vector	0.37	0.16	0.33	0.41	59.19
Secondary vector	0.33	0.20	0.28	0.38	53.77
Alternate vector	0.48	0.28	0.40	0.55	72.62
R:T ratio					
Primary vector	5.57	2.60	4.87	6.26	77.79
Secondary vector	7.36	4.00	6.30	8.43	25.65
Alternate vector	2.91	2.18	2.32	3.49	65.63

Table 12 Mean amplitude of the R wave and T wave in millivolts and the R:T ratio in all patients in primary, secondary and alternate vectors.
(Standard deviation and percent difference between maximal and minimal recording).

4.4.1 Ranking position

In order to determine which postures had the maximal and minimal recorded amplitudes, postures were ranked from 1-6 (smallest to largest) for the R and T wave amplitudes and R:T ratio in all vectors in the ACHD group and the control group. (Table 13) Overall, the R and T wave amplitudes and R:T ratio recorded in the right lateral posture was ranked the smallest in both the ACHD and control groups (mean rank 2.6 ± 1.3 and 2.3 ± 1.4) respectively. The R and T wave amplitudes and R:T ratio in the prone posture was ranked the largest in both the ACHD and control groups (mean rank 4.7 ±1.6 and 4.7 ±1.9) respectively.

The right lateral and left lateral and prone postures accounted for 17/18 (94.4%) of the postures that were ranked largest or smallest in the control group (p = 0.0027 for differences between groups) in the control group compared to 8/18 (44.4%) vector-postures that were ranked largest or smallest in the ACHD group.

ACHD Posture	Rank mean	S.D.	Control Posture	Rank mean	S.D.
Right	2.6	1.3	**Right**	2.3	1.4
Left	3.0	2.1	**Supine**	2.6	1.0
Supine	3.0	1.7	**Sitting**	3.7	1.1
Standing	3.8	1.7	**Standing**	3.8	1.2
Sitting	4.0	1.3	**Left**	4.0	2.4
Prone	4.7	1.6	**Prone**	4.7	1.9

Table 13 Posture ranking for the ACHD and control group

Average ranking position for the six postures in the ACHD and control groups for the R and T waves and R:T ratio in the primary, secondary and alternate vector where posture rank 1 = smallest and posture rank 6 = largest.

4.4.2 Magnitude of postural variation

Overall, there were 18 vector-postures (3 vectors x 6 postures). The left lateral posture exhibited the greatest variability in ranking of the R and T wave amplitudes and R:T ratio in both ACHD and control groups (standard deviation 2.1 in the ACHD group and 2.4 in the control group).

In order to determine the influence of postural change on the consistency in the measured ECG parameter, postural variation within each parameter was expressed as a percentage of the lowest value and categorised as low (<25% variation), medium (25-49% variation) and high (>50% variation). Overall, there were 9 outcomes, three ECG parameters (R wave, T wave and R:T ratio) measured in 3 vectors.

Overall, in the ACHD group, the influence of posture on the R wave, T wave and R:T ratio was classified as low or medium in 7/9 (77.8%, 95% C.I. 50.6 - 100) and high in 2/9 (22.2, 95% C.I. 0 - 49.4) possible outcomes. (Table 13) In the control group, the influence of posture on the R wave, T wave and R:T ratio was classified as high, with 8/9 (88.9% 95% C.I. 68.4 - 100) and low in 1/9 (11.1% 95% C.I. 0 – 31.6) possible outcomes.

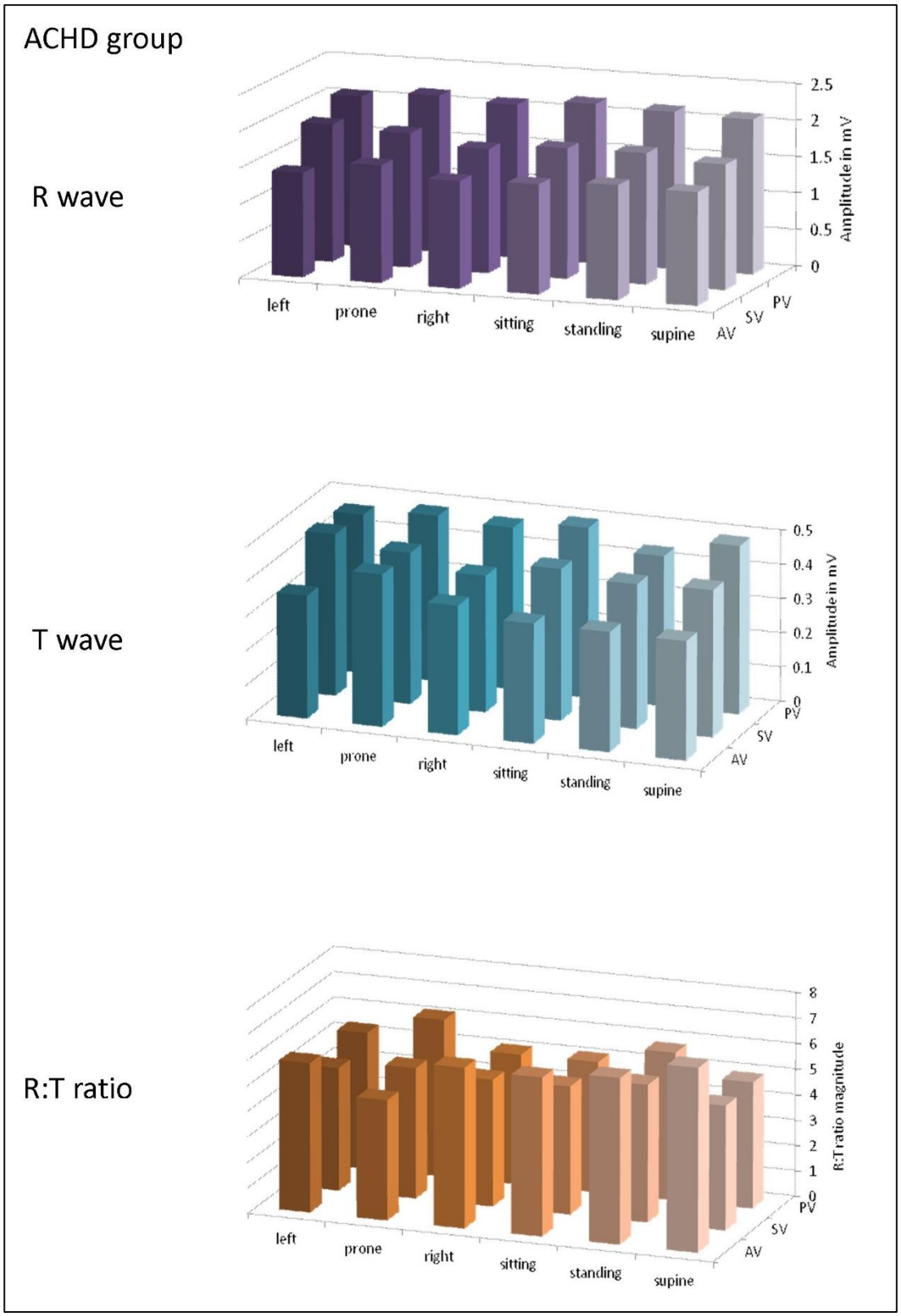


Figure 22 Three dimensional charts depicting the postural variation in amplitude of the R and T wave in millivolts (mV) and R:T ratio magnitude in all three vectors for the ACHD group.

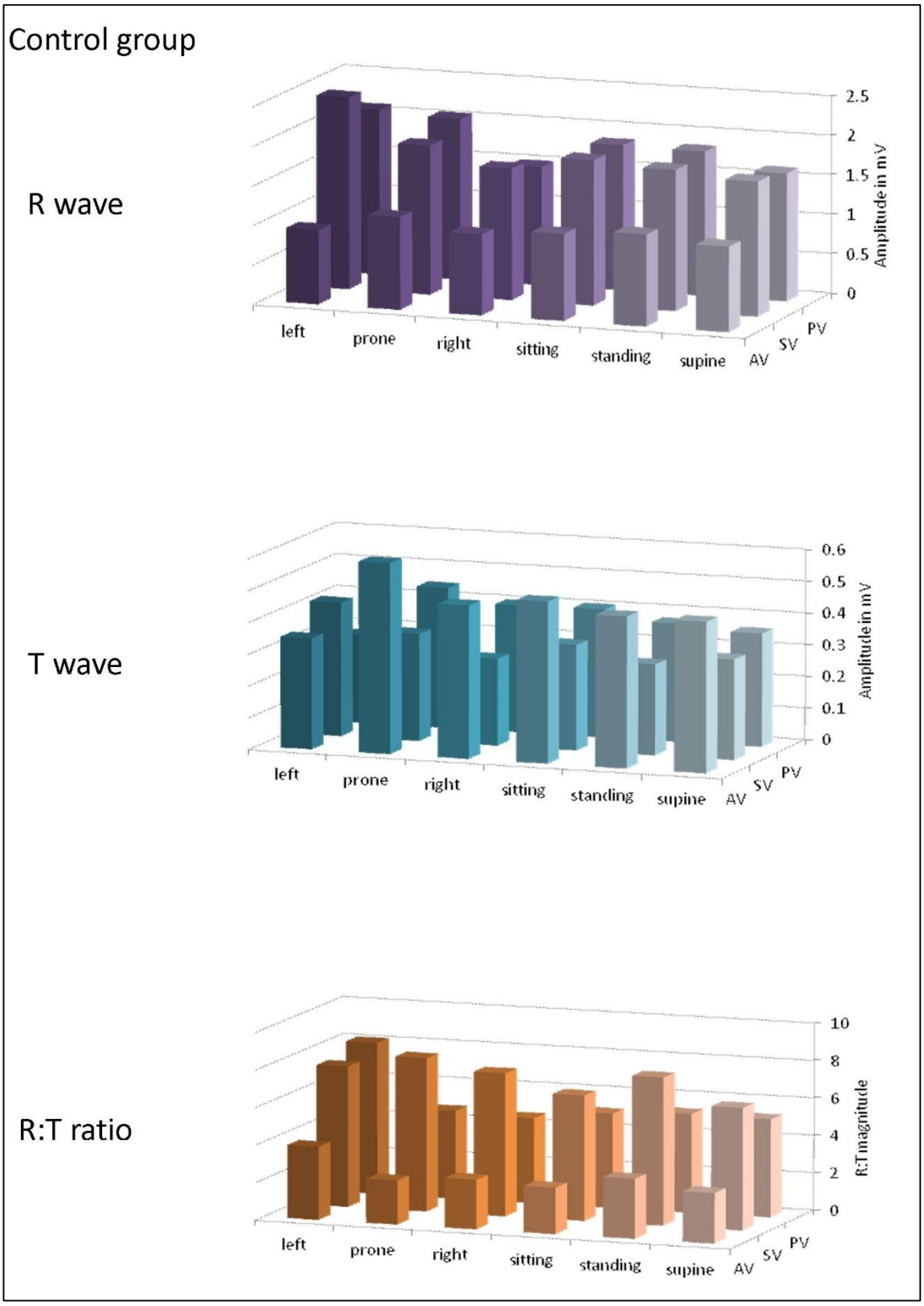


Figure 23 Three dimensional charts depicting the postural variation in amplitude of the R and T wave in millivolts (mV) and R:T ratio magnitude in all three vectors for the ACHD group.

4.4.3 Subgroup analysis

In order to determine whether pooling of the ACHD groups may mask differences between the amplitude of R and T waves recorded in the right and left parasternal lead position, a subgroup analysis was performed of the ACHD groups (Tetralogy of Fallot, single ventricular physiology and Transposition of the Great Arteries) and controls. The following tables summarise the statistically significant differences between R and T wave amplitude and the magnitude of the R:T ratio when all postures are compared to each other within each group using the Glimmix model.

4.4.4 Explanation of matrix comparison boxes

R wave primary vector						
lead	Left parasternal leads					
posture	Left	Prone	Right	Sitting	Standing	Supine
Left						
Prone						
Right						
Sitting						
Standing						
Supine						

Figure 24 Explanation of matrix comparison boxes

The panel in Figure 24 is a representation of the results recorded in the R wave in the primary vector in all 6 postures. Each result is compared to all other results. For example, results from the left posture will be compared to results from all the other five postures, results from the prone posture will be compared to results from the outstanding four postures and so on and so forth. Results that are statistically significant within a parasternal group (adjusted p value <0.05) are coded red, in this example, the left posture is significantly different to the right posture.

The matrix comparison boxes for the three ACHD subgroups and normal controls is presented in Figure 25.

Overall, the R wave in the right posture was significantly smaller than the R wave in the left posture in the TGA group ($p<0.05$). Otherwise there were no significant differences between any of the R or T wave amplitudes in any of the ACHD sub-groups.

In contrast in the control group, the R wave amplitude in the left posture was significantly larger than the R wave in all other postures in the control group in the secondary vector. The T wave was significantly smaller in the right and standing posture compared to the left posture in the

secondary vector (p<0.05). The T wave was significantly smaller in the prone and sitting posture compared to the left posture in the alternate vector (p<0.05) in the secondary vector.

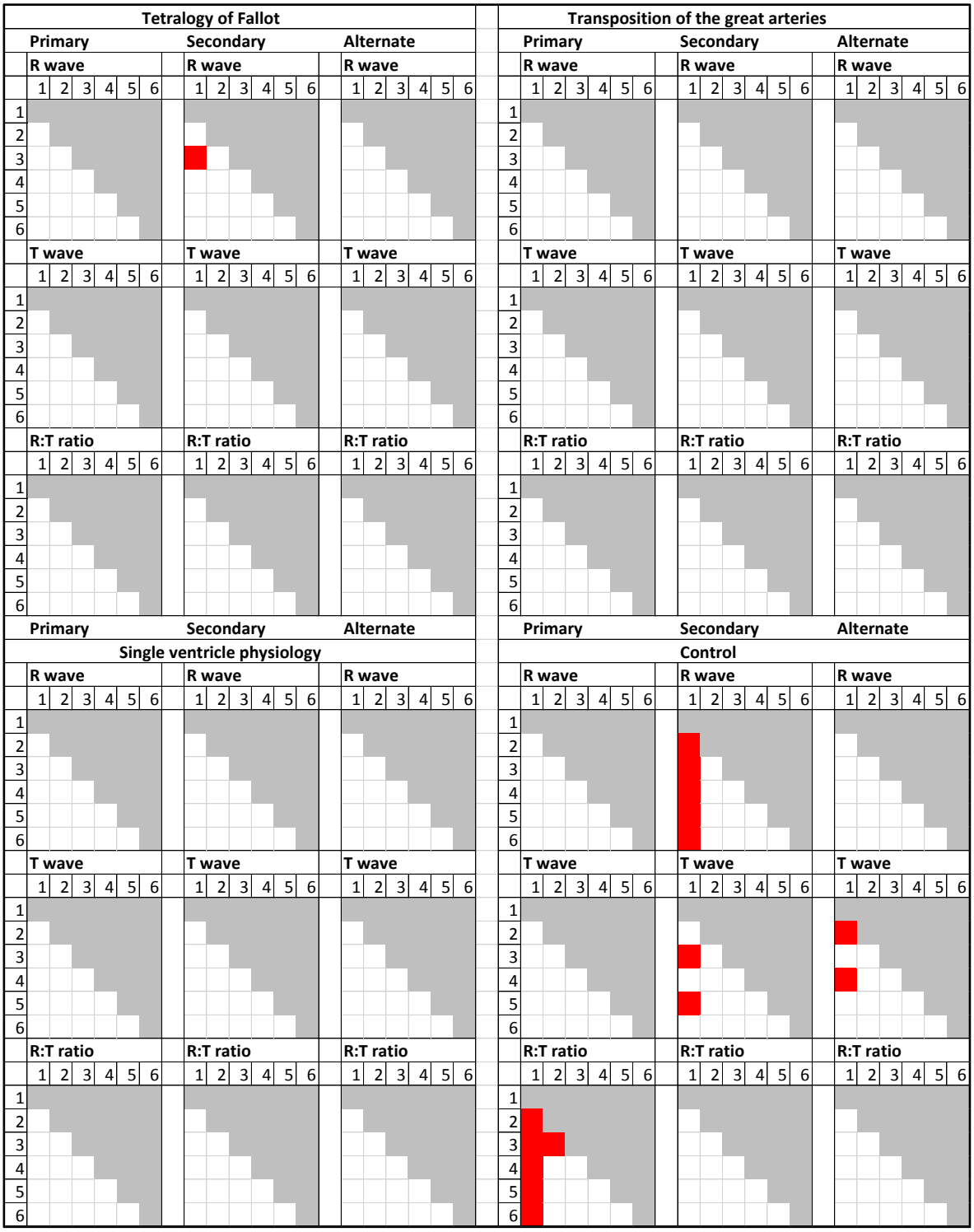


Figure 25 Subgroup analysis of impact of postural change on amplitude of the R wave, T wave and the R:T ratio.

1 = left posture, 2 =prone posture, 3 = right posture, 4 = sitting posture, 5 = standing posture and 6 = supine posture.

4.5 Discussion

4.5.1 Effect of postural change on signal variation in S-ICD

Postural change has been known to affect the electrocardiogram for over 70 years [160] and has been reported as a cause of T wave oversensing in a patient with a transvenous ICD. [161] In the context of S-ICDs, data published in abstract form compared QRS amplitude and QRS:T wave ratio made during multiple postures using standard S-ICD vectors. [162] Significant variance in QRS amplitude was observed, though the details of this variation remain unpublished.

In this prospective clinical study, we have identified that postural variation appears to have little impact on the R and T wave amplitude and R:T ratio magnitude in patients with complex ACHD. However in contrast, in patients with structurally normal hearts, posture has a large impact on the R and T wave amplitude and R:T ratio magnitude. Furthermore, we have identified that the right lateral, left lateral and prone postures account the extremes in R and T wave amplitude and R:T ratio magnitude in both patients with ACHD group and patients with structurally normal hearts.

It is unclear why patients with ACHD have less variation in R wave and T wave amplitude and R:T ratio compared to normal controls. We hypothesise that is may be due to a smaller relative change of the heart within the chest cavity with postural variation. This may be due to the larger size of the heart which may restrict movement within the mediastinum. Fibrous adhesion from previous surgical interventions may restrict movement caused by postural change. Alternatively, autonomic changes caused by postural change may modify the amplitude of the R wave, T wave and R:T ratio. It would be important to test these hypotheses prospectively. The finding of such a study would have potential implications in the screening procedure prior to S-ICD implantation.

Our finding that patients with structurally normal hearts exhibit significant variation in the R and T wave amplitude and R:T ratio magnitude has important clinical relevance. Firstly, approximately 21% of the patients enrolled in the Effortless registry could be considered to have a structurally normal heart (idiopathic VF (8%) and inherited channelopathies (13%)). [133] No data currently exist of which population of patients received inappropriate shock. Secondly, the S-ICD pre-implant screening template tool is designed to select patients who have a QRS-T complex for the morphology-based sensing algorithm employed by the device. The current recommendations mandate the use of only two postures, supine and standing. Patients who do not satisfy the screening tool and not recommended to proceed with S-ICD implantation. The potential consequence of a patient who does not satisfy the screening template is inappropriate sensing from the device, including T wave oversensing and inappropriate shock delivery. [163] We would therefore recommend the use of the left lateral, right lateral and prone postures at the pre-

implant screen in order to challenge the S-ICD screening tool with the extremes of the R and T wave and R:T ratio magnitude. We speculate that this may improve the negative predictive value of the pre-implant screen (i.e. better at excluding patients who will subsequently have poor S-ICD sensing) and help to reduce the number proportion of patients who receive inappropriate shock caused by T wave oversensing or undersensing of the cardiac signal.

4.5.2 Limitations

There are a number of limitations to this study. Firstly, in this study there are relatively modest number of participants. However, all 27 of patients with complex anatomical lesions and this number compares well to the number of patients enrolled in the Effortless registry [133] Furthermore, the number of data points generated is large and this goes in some way to mitigate the effects of a modest number of participants. Secondly, we have speculated that postural change may influence the success of the pre-implant ECG screen, though we have not tested this assumption.

4.6 Conclusion

Postural change appears to have a greater impact on the R and T wave amplitude and R:T ratio magnitude in patients with structurally normal hearts than in patients with complex ACHD. The left lateral, right lateral and prone postures account the extremes in R and T wave amplitude and R:T ratio magnitude. This may have implications at the time of screening patients for suitability for S-ICD implantation. Including postures that account for the extremes in R and T wave amplitude may identify patients at higher risk of T wave oversensing and therefore preventing these patients from having S-ICD implanted may help reduce the burden of inappropriate shock delivery in S-ICDs.

Chapter 5: ECG predictors of T wave oversensing in S-ICD recipients

5.1 Abstract

5.1.1 Introduction

T-wave over-sensing is the commonest cause of inappropriate shocks in subcutaneous implantable cardioverter defibrillators (S-ICDs). We hypothesise, that predictors of T-wave oversensing can be derived from surface ECG parameters.

5.1.2 Methods

In a cohort of SICD recipients in two UK centres, all patients who had T-wave oversensing (study group) were compared to all those who had not (control group). The pre-implant screen was scanned and the R wave, T wave amplitudes, QRS interval, time to peak T wave, QT interval and R:T ratio were measured using digital callipers. Logistic regression was performed to identify ECG predictors of T-wave oversensing.

5.1.3 Results

One hundred and one patients were studied. Six (5.9%) had T-wave oversensing. The mean age of the population was 58.6 years ± 18 years and the median follow-up from implantation was 19.5 months. By univariate analysis, the predictors of T-wave oversensing are QRS duration (140.7 ± 28.7 vs. 105.9 ± 24.6, *p*= 0.007), time to peak T wave (corrected for heart rate, pTc) (403.9 ± 22.6 vs. 347.8 ± 41.4, p =0.006), QTc interval (500.4 ± 41.2 vs. 446.8 ± 49.7, p=0.021) and R:T ratio (3.5 ± 1.1 vs. 9.5 ± 13.2, p=0.034). By multivariate analysis, time to pTc is the most predictive of T-wave oversensing. A time to pTc of 390ms cut-off point provided a sensitivity 38.5%, a specificity of 98.9%, a positive predictive value for T-wave oversensing of 83.3%, and a negative predictive value of 91.6%. For every 10ms increase in the pTc there is a 30% increase in the odds of an inappropriate shock from T wave oversensing.

5.1.4 Conclusion

In this pilot study, time to pTc was the most powerful ECG predictor of T-wave oversensing. This may have important implications in screening patients who may be at high risk of inappropriate

shocks from T-wave oversensing, however, the number of patients affected by T wave overssensing was small so need larger study is required with enough oversensing events to allow multivariate prediction score development and validation.

5.2 Introduction

The S-ICD has a proven track record in delivering life safe and effective shock therapy for patients with lethal arrhythmias. [164] The S-ICD performs well in a head-to-comparison with transvenous implantable cardioverter defibrillators in discriminating supraventricular tachyarrhythmia from ventricular tachyarrhythmia, [131] though results of a randomised trial comparing S-ICD to transvenous ICDs has yet to be published. Clinical experience has demonstrated that the S-ICD has limited sensing specificity due to failure to appropriately sense or discriminate electrical signals unrelated to supraventricular tachycardia. [133, 164] Indeed, registry data has reported rates of inappropriate therapy of approximately 7% per annum, mostly due to T-wave oversensing and undersensing of the cardiac signal. [131, 133, 165] This rate is considerably higher than rates of inappropriate shocks reported in contemporary TV-ICD device.[149]

The pre-implant ECG screen is an integral part of selecting potential S-ICD recipients and excluding patients whose QRS-T wave morphology does not satisfy the screening tool. As the S-ICD employs an ECG morphology-based sensing algorithm, we hypothesise that ECG markers may prove be useful predictors of T wave oversensing.

5.3 Methods

The pre-implant ECGs of patients who had successfully passed the pre-implant ECG screen and had an S-ICD implanted at two UK centres were studied. The study group comprised of patients who had experienced T-wave oversensing and had received an inappropriate shock due to T-wave oversensing. Patients with oversensing of the cardiac signal were excluded if they had experienced oversensing due to noise, a change in QRS morphology (e.g. monomorphic ventricular tachycardia or aberrantly conducted beats). Patients who had not received an inappropriate shock due to T-wave oversensing comprised the control group. The pre-implant ECG screen was scanned and the amplitude of the R/S wave and T wave was measured. The QRS interval, time to peak T wave (measured from the onset of the Q wave to the peak of the T wave), QT interval and R:T ratio was measured using digital callipers (Cardio callipers, On-screen electrocardiogram callipers, version 3.3, Iconico Inc.) with the ECG magnified to 500%. The amplitude of the R/S wave and the T wave was measured in all three vectors. The QRS duration, QT interval, time to peak interval were measured in the secondary vector where possible as this vector approximates the vector of lead II of a standard 12-lead ECG which tends to have a symmetrical positive T wave. When a T wave was of low amplitude or biphasic in the secondary vector, another vector with the maximal T wave amplitude was sought. The mean of four

consecutive complexes were used for each parameter to reduce measurement error. Patient clinical and demographic characteristics were recorded including heart failure aetiology, co-morbidities and medication at the time of S-ICD implant.

5.3.1 Statistical analysis

Continuous variables are expressed as the mean±1 standard error of measurement and were compared using Student's t test or nonparametric analysis where appropriate. A two-tailed p value of <0.05 indicated statistical significance. A univariate analysis was performed to determine factors that predicted T-wave oversensing (factors with univariable $P<0.1$). Binary logistic analysis was performed using a backward elimination method to determine the most fitted model for the parameters that influence the outcomeswith an adjusted $P<0.05$ needed for entry into the model and an adjusted $P>0.1$ for removal at any stage. Odds ratios were reported for those covariates that were significantly associated with T wave oversensing. Statistical analysis was performed using the STATA statistical package (Stata/IC 13.0 for Windows. StataCorp LP, USA).

5.3.2 Explanation of statistical analyses

1. Student's t test
    a. This tests evaluates the null hypothesis that two means from independent groups are equal. This test is used for data that follow a normal distribution.
2. Univariate analysis
    b. This is also known as a simple regression model and consists of one variable and one explanatory variable. Regression analysis attempts to identify how a dependent variable (y axis) relates to independent data.[157] This assumes a linear relationship between the independent and dependent variable and can be expressed mathematically as:

$$Y=a+bx$$

    Y is the dependent variable, x is the independent variable, a is the intercept of the estimated line and b is the gradient of the estimated line. See Figure 15
3. Logistic analysis
    a. Is a regression model, specifically a type of generalised linear model, which relates one or more explanatory variables to a categorical dependent (outcome) variable. [157] Thus, in this study, the binary outcome variable was the occurrence of T wave over sensing and the explanatory variables were the ECG predictors of this.
4. Odds

   a. The ratio of probabilities of two complementary events. In this study it would be the odds of T wave oversensing divided by the odds of no T wave oversensing.
5. Odds ratio
   a. The ratio of two odds (e.g. the odds of T wave oversensing). It can be considered to be an estimate of the relative risk in a case-control study.

5.4 Results

Complete datasets could be recorded in 101 patients, 10 (9.9%) of whom were not enrolled in the EFFORTLESS registry. The mean age of the population was 58.6 years ±18 years and the S-ICD was implanted for a primary prevention indication in 75 (75%). Mean follow-up was 19.5 months. In total 93% had dual zone programming, the most frequent setting being conditional zone 200 bpm and shock zone of 220 bpm in 54/94 (57.4%). The primary vector was programmed in 49 (48.5%), the secondary vector in 44 (43.6%) and the alternate vector in 8 (7.9%) of patients.

Fifteen (14.9%) patients were identified as having episodes of oversensing and 6 patients (5.9%) were identified as having received an inappropriate shock due to T wave oversensing that could not be explained by a change in morphology, noise or non-cardiac signal. (Table 14) These patients experienced 25 separate episodes of T-wave oversensing and received a total of 14 shocks (mean 0.56 shocks per episode). Their clinical history is summarised in Table 15 and baseline demographics are presented in Table 16. Given an oversensed signal, the odds ratio of a patient receiving a shock of the cause of the oversensed signal is due to T-wave oversensing is 3.27 (95% confidence interval 1.03 – 10.4). The T-wave oversensing group was compared with a control group of 95 patients who had not experienced T-wave oversensing. Baseline ECG characteristics are presented in Table 17.

Oversensing type	Number of patients	Number of episodes		Total
		Shock	No shock	
TWOS	6	14	11	**25**
Noise / ectopy	4	2	15	**17**
Morphology change - MMVT	3	4	1	**5**
Morphology change - other	2	1	2	**3**
Total	**15**	**21**	**29**	**50**

Table 14 Summary of the number of episodes of oversensed signal.

TWOS, T wave oversensing, MMVT, monomorphic ventricular tachycardia

ID	Age (yrs)	Gender	Implant date	Indication	Date of episode	time of episide	ECG characteristics at time of TWOS	Number of episodes	Number of shocks
1	75	Male	13/02/2009	PP	05/06/2009	14h13	Low amplitude signal. ST rate 110 bpm	7	3
2	63	Male	31/12/2009	SP	19/10/2011	19h05	Low amplitude signal. A flutter rate 140bpm	1	1
3	77	Male	29/11/2012	PP	12/02/2015	13h10	Low amplitude signal. ST rate 120 bpm	4	2
4	54	Male	28/11/2013	PP	21/04/2014	01h15	Low amplitude signal. SR rate 98 bpm	6	2
5	12	Male	07/08/2012	SP	26/09/2012	15h48	High amplitude T waves. ST rate 170 bpm	2	5
6	70	Male	09/07/2013	SP	04/02/2014	11h48	Low amplitude signal. AF rate 110 bpm	1	1

Table 15 Summary of baseline characteristics of patients who experienced T wave oversensing. Yrs, years, PP, primary prevention of sudden cardiac death, SP, secondary prevention of sudden cardiac death, ST, sinus tachycardia, A Flutter, atrial flutter, SR, sinus rhythm. .

Demographics	TWOS (n=6)	No TWOS (n=95)	*p* value
Male (%)	100.0	77.4	0.17
Age	55.8 ± 23.1	59.3 ± 17.9	0.65
Primary prevention (%)	50.0	75.8	0.16
Ischaemic (%)	50.0	56.8	0.70
NICM (%)	33.3	25.3	0.69
Valvular (%)	0.0	1.0	0.80
HCM (%)	0.0	5.3	0.56
EF	38.8 ± 15.4	32.9 ± 15.9	0.38
Hypertension (%)	16.7	52.2	0.16
Diabetes mellitus (%)	0.0	25.8	0.18
Atrial fibrillation (%)	16.7	28.4	0.53
Myocardial infarction (%)	40.0	54.0	0.54
CABG (%)	66.7	14.6	0.00
PCI (%)	16.7	21.6	0.78
Two zone programming	83.3	93.5	0.34
Conditional zone	202 ± 10.9	201.8 ± 8.7	0.96
Shock zone	231.7 ± 21.4	227.3 ± 12.7	0.43
Sensing vector			
Primary	50.0	48.4	0.75
Secondary	50.0	43.2	
Alternate	0.0	8.4	
R:T ratio	3.5 ± 1.1	9.5 ± 13.2	0.27
Aspirin (%)	50.0	48.4	0.61
Warfarin (%)	16.7	27.2	0.72
ACEi (%)	66.7	59.6	0.63
Angiotensin receptor blocker (%)	0.0	21.6	0.24
β blocker (%)	80.0	85.1	0.76
Aldosterone antagonist (%)	33.3	26.4	0.50
Loop diuretic (%)	50.0	55.9	0.86
Amiodarone (%)	33.3	11.4	0.06
Statin (%)	33.3	62.0	0.33

Table 16 Baseline clinical characteristics.

NICM, non-ischaemic cardiomyopathy, HCM, hypertrophic cardiomyopathy, EF, ejection fraction, CABG, coronary artery bypass graft, PCI, percutaneous coronary intervention, CKD, chronic kidney disease, PVD, peripheral vascular disease, NOAC, novel oral anticoagulant, ACEi, angiotensin converting enzyme.

ECG variable	TWOS (N=6)	No TWOS (N=95)	*p* value
Heart rate (bpm)	74.1 ± 25.3	71.6 ± 18.4	0.760
R/S wave amplitude (mV)	1.3 ± .4	1.9 ± .9	0.124
T wave amplitude (mV)	0.4 ± .1	0.3 ± .2	0.564
QRSd (ms)	140.7 ± 28.7	105.9 ± 24.6	0.001
Time to peak T wave (ms)	369.9 ± 52.2	322.7 ± 41.0	0.008
Corrected time to peak T wave (ms)	403.9 ± 22.6	347.2 ± 41.4	0.001
QT interval	462.5 ± 58.4	417.6 ± 51.9	0.040
QTc interval	500.4 ± 41.2	446.8 ± 49.7	0.011
R:T ratio	3.5 ± 1.1	9.5 ± 13.2	0.316
atrial fibrillation (%)	16.7	28.4	0.53

Table 17 Baseline ECG characteristics

Sample baseline screen ECGs, episodes of T-wave oversensing and clinic downloaded strips are shown in Figure 26.

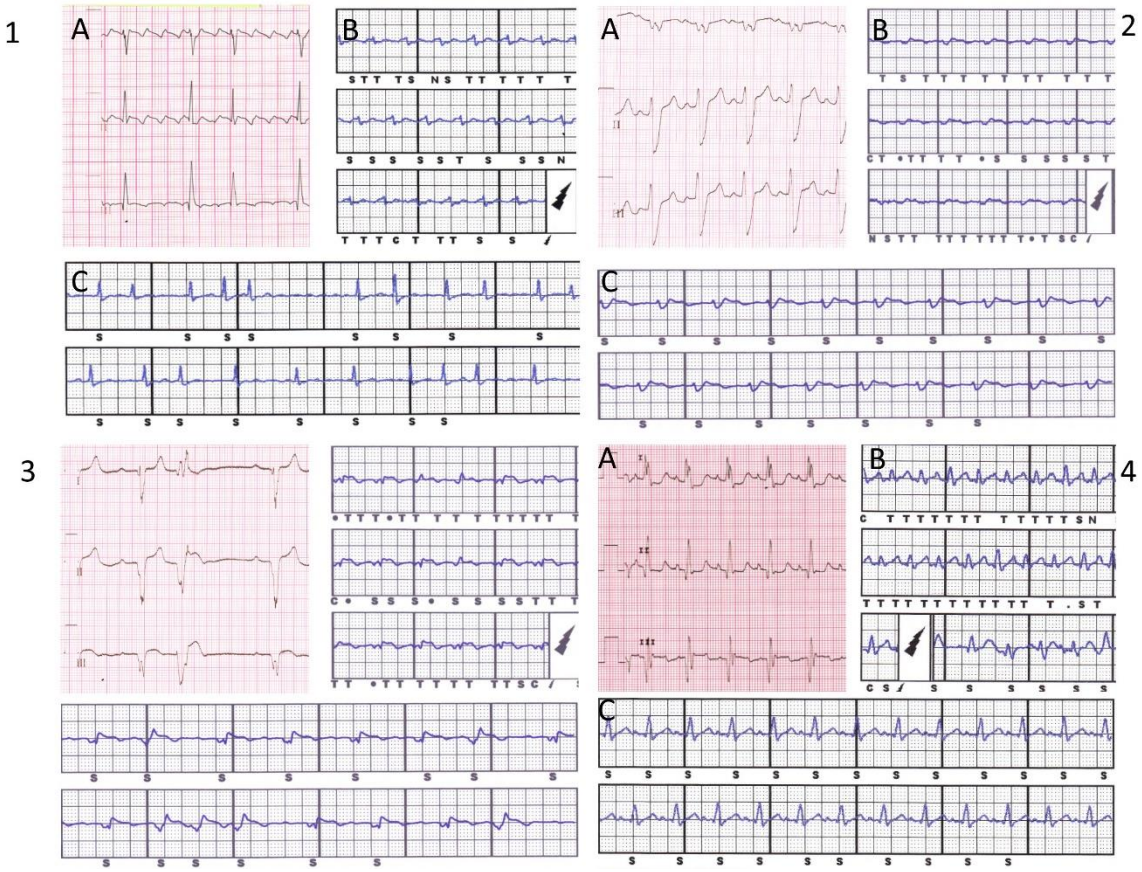


Figure 26 Montage of selection of four patients (1-4) who experienced T wave oversensing. Pre-implant screen is shown in image A, a screen shot of an episode of T-wave oversensing is shown in B, and a baseline electrogram at clinic prior to the episode is shown in C.

5.4.1 Clinical and electrocardiographic predictors of T-wave oversensing

By univariate analysis, the predictors of T-wave oversensing are QRS duration (140.7 ± 28.7 vs. 105.9 ± 24.6, *p*= 0.007), time to peak T wave (369.9 ± 52.2 vs. 322.7 ± 41.0, p=0.014) time to peak T wave (corrected for heart rate) (403.9 ± 22.6 vs. 347.8 ± 41.4, p =0.006), QT interval (462.5 ± 58.4 vs. 417.6 ± 51.9 p=0.021), QTc interval (500.4 ± 41.2 vs. 446.8 ± 49.7, p=0.021) and R:T ratio (3.5 ± 1.1 vs. 9.5 ± 13.2, p=0.034). By multivariate analysis, time to pTc is the most predictive of T-wave oversensing Table 18. For every 10ms increase in the tPc there is a 30% increase in the odds of an inappropriate shock from T wave oversensing.

Logistic regression	Coefficient (β)	Odds ratio	*p* value	95% Confidence interval
Univariate model				
QRSd (ms)	0.04	1.04	0.007	1.01 - 1.07
Time to pT (ms)	0.03	1.03	0.014	1.00 - 1.05
Time to pTc (ms)	0.03	1.03	0.006	1.01 - 1.05
QT interval	0.02	1.02	0.053	1.00 - 1.03
QTc interval	0.02	1.02	0.021	1.00 - 1.03
R:T ratio	-0.65	0.52	0.034	0.29 - 0.95
Multivariate model				
Time to pTc (ms)	0.03	1.03	0.011	1.00 - 1.05

Table 18 Results of univariate and multivariate analysis.

Results for all clinical and electrocardiographic variables that predicted T wave oversensing. QRSd, QRS duration, Time to pT, time to peak T wave, Time to pTc, time to peak T wave corrected for heart rate.

5.4.2 Predictive accuracy for determining T-wave oversensing.

Receiver operating characteristic (ROC) curves of time to pTc and CABG for T-wave oversensing were constructed. The area under the curve (AUC) were 0.88 and 0.76 respectively. The time to pTc of 390ms cut-off point provided a sensitivity 38.5% of a specificity of 98.9% a positive predictive value for T-wave oversensing of 83.3% and a negative predictive value of 91.6% (AUC = 0.687).

5.5 Discussion

In this study 5.9% of patients experienced T-wave oversensing over a median follow up of 19.5 months with a mean of 1.8 shocks per patient with T-wave oversensing. This incidence is similar to that for inappropriate shocks reported in the Effortless Registry. [133] Patients who experienced

T-wave oversensing had significantly broader QRS complexes, lower R:T ratios and greater time to peak T wave amplitude and QTc. On analysis using a univariate statistical model all these parameters were predictive of T-wave oversensing. With multivariate analysis, only time pTc was predictive.

Although T-wave oversensing and inappropriate shock occurred relatively infrequently in this study and in the literature, we believe that any inappropriate shock is too many and that all avenues should be explored in order to reduce the burden of inappropriate therapy to levels that approach those of transvenous ICDs. T-wave oversensing is an important cause of inappropriate shock therapy in S-ICD recipients, the adverse consequences of which are of major importance for patient wellbeing and acceptance of ICD therapy. We believe T-wave oversensing can be reduced with careful attention to pre-implantation ECG characteristics. T-wave oversensing arises due to double counting of the QRS-T complex, which is more likely to occur when the QRS-T complex falls outside of an algorithm-specific timing window. This concept is captured within the pre-implant ECG screening template area. The S-ICD utilises a morphology based sensing algorithm that uses the pre-implant screening ECG to exclude patients from S-ICD therapy because of possibility of inappropriate shock therapy and/or failed rhythm discrimination. Therefore, we hypothesised that refined analysis of the pre-implant ECG screen could better predict T-wave oversensing.

Whilst the number of patients in this study who experienced T-wave oversensing is small (5.9% over a median follow up of 19.5 months) the consequence is important with a mean of 1.8 shocks per patient with T-wave oversensing. This incidence is similar to that for inappropriate shocks reported in the Effortless registry. [133, 164-166]

In this study, patients who had T-wave oversensing had significantly broader QRS complexes, lower R:T ratios and greater time to peak T wave amplitude and QTc. On analysis using a univariate statistical model all these parameters were predictive of T-wave oversensing. With multivariate analysis, only time pTc was predictive.

All patients in the study had passed the pre-implant ECG screen in at least one vector in 2 postures using the patient screening template as recommended by the manufacturer. T-wave oversensing appears to occur early after S-ICD implantation (median time 4.2 months). Two cases required system extraction. One was in the context of recurrent shocks caused by T-wave oversensing and the second due to new RBBB developing which lead to vector change and failure to continue to satisfy and concomitant development of sustained monomorphic VT amenable to ATP. It is our observation that the pre-implant ECG screen, in its current form, is suboptimal in determining risk of T-wave oversensing. Using ECG parameters such as QRS duration and time to pTc may provide added value in the pre-implant ECG evaluation. On ROC analysis, the AUC is high

for pTc (0.88), demonstrating that time pTc could be a clinically reliable predictor of T-wave oversensing. At a cut-off of 390ms for pTc, there is a high sensitivity, acceptable specificity and excellent positive and negative predictive values.

Oversensing that may be predicted and oversensing that can't be predicted. In this study, we have been careful to distinguish between patients who have had T-wave oversensing during sinus rhythm and patients who have had oversensing and inappropriate shocks due to other causes. We have classified oversensing according to underlying rhythm and cause and distinguished whether the oversensing resulted in shock delivery or not. In a recent publication reported on the incidence, predictors and management of inappropriate shocks in the Effortless registry, patients with a history of atrial fibrillation (HR 2.4) and patients with hypertrophic cardiomyopathy (HR 4.6) had an increased risk for inappropriate shocks, while programming the primary vector for sensing (from xyphoid to V6) reduced this risk. [129]

In our study, one patient developed RBBB following VT ablation and subsequently received an inappropriate shock for T-wave oversensing. Nine other patients experienced oversensing, eight of which received inappropriate shocks for causes that would have been difficult to predict at the time of S-ICD implantation – noise, QRS morphology change due to monomorphic VT and other types of QRS morphology change (e.g. aberrant conduction).

5.5.1 Dynamic nature of electrocardiogram

Electrocardiographic parameters are dynamic in nature reflecting changes in transmembrane ionic gradients, ischaemia, parasympathetic tone, serum electrolyte levels to name but a few factors. There are four scenarios whereby changes in ECG parameters may render a patient with an S-ICD vulnerable to T-wave oversensing: attenuation of the R/S, an increase in the T wave amplitude, broadening of QRS complex and changes in the QT interval. In patients with oedematous states, the amplitude of the QRS complexes can be reduced, though they recover following treatment. [167] In heart failure patients the mean change in QRS duration is 1.36ms/year, though in some patients the rate of change is significantly more rapid at over 10ms/year.[168] T wave amplitude varies with exercise, ischaemia, haemodialysis, hypertension and medication [169-172] and the QT interval is affected by a wide range of drugs which include anti-arrhythmic medication, antibiotics and antipsychotics that have potassium channel blocking characteristics, predominantly affecting the rapidly activating current I(Kr). [173] Thus it may be prudent to re-evaluate the ECG of any patient who may be at risk of T-wave oversensing in light of a change in their heart failure status, ischaemic status or medication that may affect repolarisation or serum potassium levels.

Programming changes to reduce T-wave oversensing

The manufacturer of the currently available S-ICD has recently developed a refined sensing algorithm which has been shown to reduce T-wave oversensing by up to 51% in independent validation studies without impacting on tachycardia detection and discrimination. [135] Whether this results in an appreciable reduction in T-wave oversensing in clinical practice remains to be seen.

5.5.2 Limitations

This study only looked at T-wave oversensing. There is no process that predicts which patients will develop noise, aberrancy or MMVT at present. This study is a retrospective study, though the majority of the clinical data had been recorded prospectively as part of clinical trials or registries therefore we are confident that the data are accurate and reliable. The number of patients in this pilot study who have had T-wave oversensing is very small and therefore interpretation of the results must take this into account. In order to perform multivariate analyses, there must be a least 10 outcomes for each explanatory variable and this is something that was not present in this study. Therefore, the results of this study must be interpreted with a degree of caution.

We further conducted a calculation of a sample size that would be required to adequately power a study investigating the use of time to pTc in predicting T-wave oversensing. We used an information from the T-wave oversensing pilot study with an assumed T-wave oversensing incidence of 5% among a population of S-ICD patients and an odds ratio (OR) for “time to pTc” for predicting time to pTc of 1.03 per ms increase in time to pTc (95% confidence interval 1.00-1.05). At a power of 80%, a one-sided $p<0.05$ was assumed as only a prolonged time to pTc would be associated with an increase in probability for T-wave oversensing.

We estimated conservatively that a minimum of 756 patients would be required to be included in the analysis, with a minimal number of 38 T-wave oversensing cases, possibly increasing to 55. All calculations were performed on G*power 3.1.9 for Windows (1, 2)..

We determined that a conservative estimate would require 756 patients to be included in the study in which the minimal number of cases of T-wave oversensing would be 38, and increasing up to 55. All calculations were performed on G*power 3.1.9 for Windows (1, 2).

5.6 Conclusion

The ECG parameters that predict T-wave oversensing are QRS duration, time to peak T wave, QT interval and R:T ratio with time to pTc being the most powerful predictor of T-wave oversensing on multivariate analysis. However, the number of patients affected by T wave oversensing was

small so need larger study is required with enough oversensing events to allow multivariate prediction score development and validation.

Chapter 6: Reconstruction of an 8 –lead ECG from two S-ICD vectors

6.1 Abstract

6.1.1 Background

Techniques exists which allow surface ECGs to be reconstructed from reduced lead sets. We aimed to reconstruct an 8-lead ECG from two independent S-ICD sensing electrodes vectors as proof of this principle.

6.1.2 Methods

Participants with ICDs (N=61) underwent 3 minute ECGs using a TMSi Porti7 multi-channel signal recorder (TMS international, The Netherlands) with electrodes in the standard S-ICD and 12-lead positions. Participants were randomised to either a training (N=31) or validation (N=30) group. The transformation used was a linear combination of the 2 independent S-ICD vectors to each of the 8 independent leads of the 12-lead ECG, with coefficients selected that minimized the root mean square error (RMSE) between recorded and derived ECGs when applied to the training group. The transformation was then applied to the validation group and agreement between the recorded and derived lead pairs was measured by Pearson correlation coefficient (r) and normalised RMSE (NRMSE).

6.1.3 Results

In total 27 patients with complete data sets were included in the validation set consisting of 57 888 data points from 216 full lead sets. The distribution of the r and NRMSE were skewed. Mean r = 0.770 (SE 0.024), median r = 0.925. NRMSE mean = 0.233 (SE 0.015) median = 0.171.

6.1.4 Conclusions

We have demonstrated that the reconstruction of an 8-lead ECG from two S-ICD vectors is possible. The agreement between derived and measured signals was generally good to excellent though there were some negative correlations. If perfected, the ability to generate accurate multi-lead surface ECG data from an S-ICD would potentially allow recording and review of clinical arrhythmias at follow-up.

6.2 Introduction

The standard 12-lead electrocardiogram (ECG) represents the summed electrical forces of the heart as measured between limb lead electrodes (Einthoven leads, lead I, II and III), reconstructed combination of these directly recorded leads via simple mathematical formulae (Goldberger augmented leads, aVF, AVL and aVR), or directly recorded "unipolar" traces referenced to a fixed central dipole(precordial leads, V1-V6). Numerous studies have demonstrated the feasibility of generating and accuracy of using reconstructed 12-lead ECG from a reduced lead set. [174-178] Of these, the EASI ECG system has gained widespread appeal and is used derive continuous 12-lead ECG data for adult and paediatric patients. [178]

Reconstruction of a 12-lead ECG can be achieved by one of two methods [179, 180] Single stationary dipole reconstruction (exact solution, or deterministic approach) and linear and non-linear filtering methods (statistical approach). When the two methods are compared, the statistical approach is preferred as it is less affected by collinearity (when predictors are highly correlated). [176]

The underlying principle in limited lead systems is the transformation of information recorded from a 'source' lead system to another 'target' lead system. This idea relies on identifying a set of transformation coefficients that manipulate the signals in the source lead system to produce the signals in the target lead system. [178] The target lead can then be estimated using a weighted sum of the measured signals. Each new, or derived lead is defined as in equation (1):

Derived lead = (coef1 x lead1) + (coef2 x lead 2) + (coef3 x lead3)…
(1)

Where Derived lead is the estimated ECG signal, lead1, lead2 and lead3 are the measured signals and coef1, coef2 and coef3 are the coefficients that weight the measured signals.

Recent attempts have been made to generate 12-lead surface ECGs from endocardial electrograms recorded from cardiac implantable devices, such as implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy devices with and without a defibrillator (CRT-P/D). [181, 182] The ICD is limited by the use of intravascular leads which can compromise the venous circulation, can become infected or can fracture and result in inappropriate shocks. The subcutaneous implantable cardioverter-defibrillator (S-ICD) has developed as an alternative to transvenous implantable cardioverter-defibrillators. [128] The S-ICD system comprises three sensing electrodes: the first is located on the can in the 5th intercostal space in the mid-axillary line; the second is a proximal electrode located 1cm lateral to the xiphoid midline; the third is a distal

electrode placed 14 cm superior to the second electrode, 1cm lateral to the midline. Bellardine et al. have demonstrated good correlation between subcutaneous and corresponding transcutaneous body surface ECGs. [130]

To date, a surface ECG has not been transformed from S-ICD vectors. The objective of this proof of principle study is to reconstruct an 8-lead ECG from two independent S-ICD sensing vectors and to determine the accuracy of the reconstructed ECG.

6.3 Materials and methods

6.3.1 Study population

All patients with an ICD indication aged at 18 years and over attending the ICD clinic at Southampton General Hospital were eligible for this study. Informed, written consent was obtained before the participation in the study. The study was approved by the London and Surrey borders NHS research and ethics committee.

6.3.2 Study procedure

Simultaneous 12-lead ECG recording using the Mason-Likar 12-lead electrode arrangement and three study S-ICD surface electrodes placed in the conventional S-ICD electrode positions were recorded for three minutes. (Figure 27) ECGs were recorded with the participant in a supine position with the head and shoulders raised to approximately 45 degrees. The electrodes used were Ambu Blue Sensor SP single patient use ECG electrodes (Ambu, Denmark), connected to the Porti7 system with ExG shielded carbon cable (1.5m), microcoax to unipolar snap (TMS international, The Netherlands). ECGs were recorded using a TMSi Porti7 multi-channel signal recorder (TMS international, The Netherlands) attached to a laptop running TMSi polybench v1.30.3.3521 software (TMS international, The Netherlands). The sampling rate was set at 2000Hz. ECGs were stored in poly5 format.

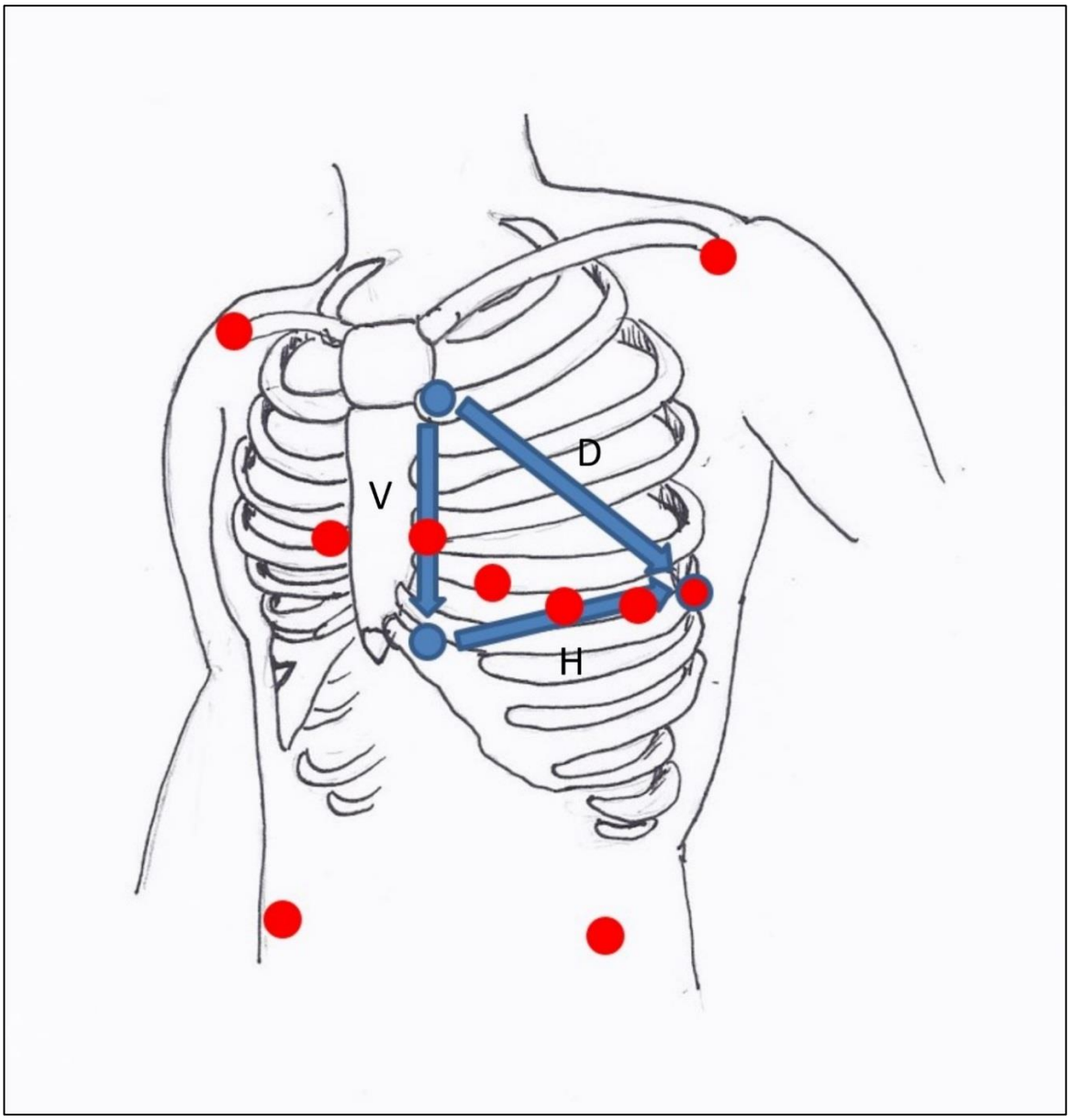
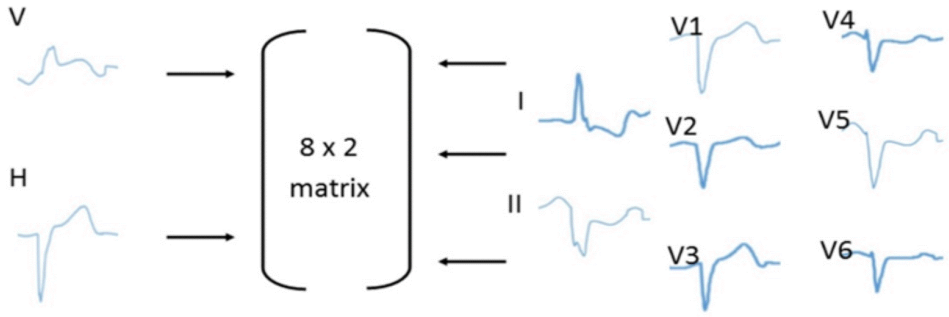


Figure 27 Illustration of the Mason-Likar 12-lead electrode arrangement

12-lead electrode arrangement (red dots) and three study S-ICD electrodes placed in the conventional S-ICD electrode positions, (blue dots) and the location of the horizontal (H), vertical (V) and diagonal (D) vectors.

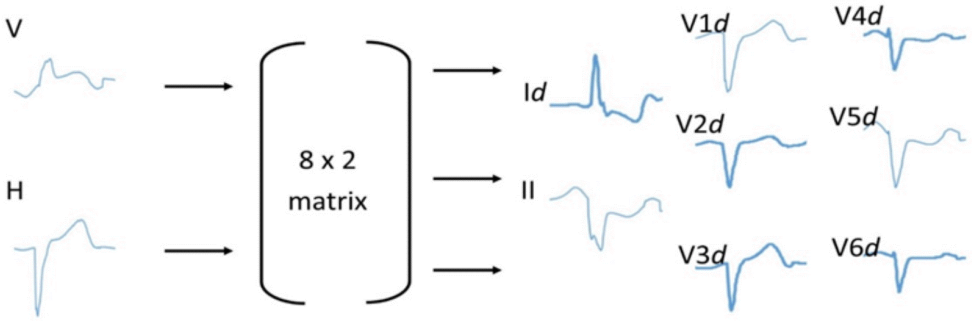
6.3.3 Randomisation

Participants were allocated to the 'training dataset' or to the 'validation dataset' using a random number generator. The training dataset was used to generate the transformation coefficients. The validation dataset was then used to test the coefficients, see Figure 28.



A

Representation of how the transformation matrix was derived from the training dataset. Electrograms recorded in the S-ICD vertical (V) and horizontal (H) lead electrode positions and the 8-lead ECG from the *same* patient were use to generate the transformation matrix using the least squared difference approach.



B

Representation of how the transformation matrix and transformed ECD was tested from the validation dataset. Electrograms recorded in the S-ICD vertical (V) and horizontal (H) lead electrode positions were transformed using the transformation matrix to generate the derived 8-lead ECG (I*d*, II*d*, V1*d*.....V6*d*). The signal from derived ECG was then compared to the measured -lead ECG using normalised root mean square error and pearson correlation coefficient. Augmented leads (aVL, aVF and aVR) were subsequently calculated using standard algebra.

Figure 28 Representation of how the transformation was created with the training dataset and used with the validation dataset.

Schematic illustrating how the transformation matrix was generated from the recordings from both the S-ICD vectors and the 12-lead ECGs (A) and how the transformation matrix containing the coefficients were combined with the S-ICD vectors to generate the reconstructed 12-lead ECGs (B).

6.3.4 Selection of representative beat for analysis

The representative QRST complexes that were compared were average beats over each of the recorded ECG leads generated in the following way: QRS complexes were sensed using an R-wave amplitude adaptively decaying sense threshold and any oversensed beats were manually removed. The QRS fiducial point for each patient was aligned for all leads by selecting the median QRS peak sample in time with the first beat in each lead used as the starting template beginning 100 milliseconds (ms) prior to sensed fiducial points and ending 450ms following sensed fiducial point.

6.3.5 Generation a signal averaged beat

The correlation coefficient of the template vs. each of the following beats was calculated. Initially, only beats with a correlation > 0.80 were included in the average. Then, the correlation coefficient was adjusted per lead between 0.5 and 0.9 to ensure the numbers of beats in each lead were similar. In addition, the difference in area between the template and the following beats were assessed for similarity and following beats were excluded if the area was not similar. The resulting signal averaged QRST complex from each patient and lead was used as the "representative" beat for which the transformation coefficients were computed.

6.3.6 Generation of coefficients, conversion matrix and derived ECGs

The following model was created for the matrix calculation from two independent S-ICD vectors to the 12-lead ECG:

$$
\begin{aligned}
lead\ I &= a1\ \times H + b1\ \times V \\
lead\ II &= a2\ \times H + b2\ \times V \\
lead\ V1 &= a3\ \times H + b3\ \times V \\
lead\ V2 &= a4\ \times H + b4\ \times V \\
lead\ V3 &= a5\ \times H + b5\ \times V \\
lead\ V4 &= a6\ \times H + b6\ \times V \\
lead\ V5 &= a7\ \times H + b7\ \times V \\
lead\ V6 &= a8\ \times H + b8\ \times V
\end{aligned}
$$

In which H is the horizontal vector, V is the vertical vector and a1...a8 and b1…b8 are the transformation coefficients. Leads III, aVR, aVL, and aVF are redundant (12) and are calculated from known geometries in the Einthoven triangle and therefore these leads were not included in the analysis.

The transformation coefficients were derived using the least squared difference approach, in which they are optimized for minimum root mean squared (RMS) difference between measured and derived vectors when applied to the training dataset. The optimization was performed in

MATLAB (MathWorks, 2014a, Natick, USA) using the optimization toolbox function '*fmincon*' which is a constrained nonlinear optimization method using the interior-point algorithm. This optimization algorithm is designed to efficiently determine the transformation matrix from the two subcutaneous leads to the 12-lead ECG that minimizes the RMSD between measured and computed 12-lead ECGs over all patients and leads.

6.3.7 Application of matrix to validation dataset

The measured ECG data for the validation dataset were imported into RashLab (a program for data processing, using the libRasch library (http://www.librasch.org/libRASCH-0.8.35)) where QRS complexes were automatically identified for all beats in the signal. The starting position of the P wave was stored into an array.

Each lead signal was then filtered in MATLAB using a 1st order high pass filter. For each starting position element in the array the next 520 samples were collected to ensure that the entire signal of interest was identified. Once all beats were acquired in this way for each lead, these were averaged for each lead, resampled from 1000 to 256 Hz and stored. This produced an averaged beat for each lead and each patient of 134 samples.

The averaged beats from study leads H and V were then combined with the transformation matrix to generate eight independent derived beats (lead I, II, V1-V6). Leads III, aVR, aVL, and aVF are redundant [183] and were not calculated in this study so as not over-estimate the value of the vectors in the frontal plane. The derived leads were compared to the measured leads for each patient in RAW format.

6.3.8 Statistical analysis

Continuous data were presented as mean and standard deviation and categorical variables were presented as frequencies and percentages. The quantitative measures of similarity between the original (measured) ECG and the corresponding derived (reconstructed) ECG were determined using Pearson r correlation [184, 185] and root mean square error (RMSE) analysis [175, 186] for each derived lead. The Pearson r was considered to show high positive correlation [187] at $r \geq 0.7$. The RMSE is a parameter that indicates the average voltage error (microvolts) across the ECG leads studied. These parameters have been used by other investigators who have recorded this type of data for derived ECG leads. [188] All analyses were performed in Stata 13 (StataCorp., College Station, TX: StataCorp LP.)

6.3.9 Explanation of statistical analyses

1. Peason's r correlation
    a. This is a quantative measure of the linear relationship between two variables with results ranging from -1 (total negative relationship, as one variable increase a unit, so does the other variable decrease by the same amount), 0 (no relationship) and 1 (perfect positive relationship). In this study pearson's r correlation was used to assess for how well the measured ECG correlated with the derived ECG.
2. Root mean square error
    a. This is a measure of the differences between two sets of values. The RMSE represents the sample standard deviation of the differences between predicted values and observed values. In this case it is the difference between the measured and derived ECGs.

6.4 Results

A total of 63 cases were recruited, mean age 66.5 ± 14.2 years and 76.4% male. A summary of the characteristics of participants assigned to each group are presented in Table 19. Four participants were excluded after enrolment (Figure 29).

Characteristic	Training dataset (n=31)	Validation dataset (n = 30)	*p* value
Age (years)	65.6 ± 15.9	67.1 ± 12.6	0.688
Male	23 (74.2)	24 (80)	0.59
Height (cm)	173.0 ± 4.5	174.0 ± 9.5	0.698
Weight (kg)	79.5 ± 11.2	83.4 ± 14.8	0.44
BMI (kg/m^2)	26.4 ± 3.3	27.5 ± 5.7	0.554
Primary prevention	15 (55.5)	11 (40.7)	0.519

Table 19 Summary of participants assigned to training and validation datasets

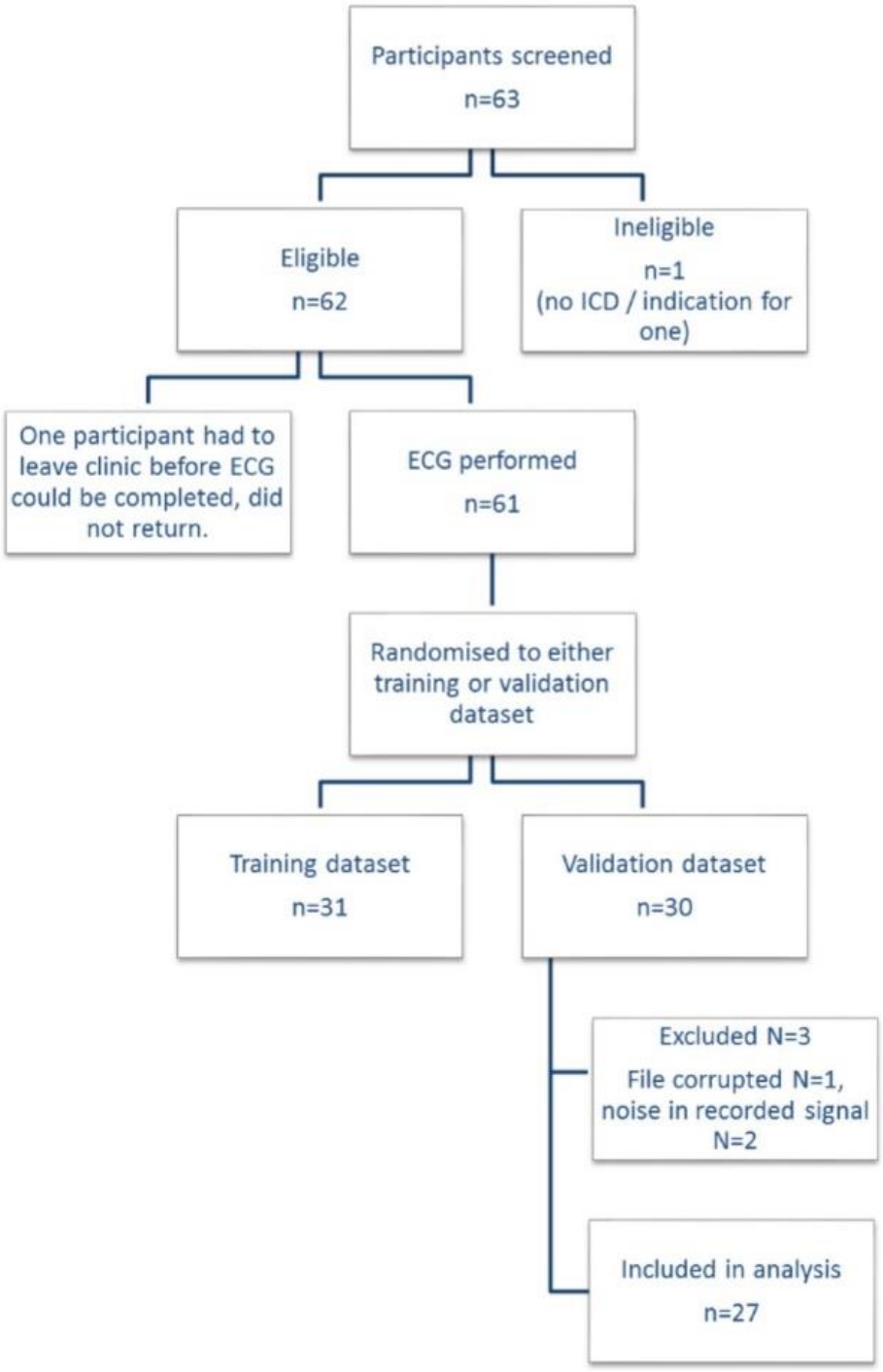


Figure 29 Flow chart for selection of participants

6.4.1 Transformation coefficients

The transformation coefficients optimised from the training dataset are shown in Table 20.

Lead	Horizontal vector	Vertical vector
I	-0.1615	-0.0692
II	-0.3746	-0.7210
V1	0.6175	0.1131
V2	0.7862	-0.0531
V3	0.3587	-0.4372
V4	-0.0152	-0.6531
V5	-0.3947	-0.6139
V6	-0.5059	-0.5118

Table 20 Transformation coefficients for all 8-leads

6.4.2 Reconstructed signal

Overall, 57 888 data points from 216 full lead sets over the 27-patient validation dataset were compared. Distribution of r and NRMSE were skewed. The distribution of the r and NRMSE were skewed. Mean r = 0.770 (SE 0.024), median r = 0.925 (interquartile range 0.76-0.97). NRMSE mean = 0.233 (SE 0.015) Median = 0.171 (interquartile range 0.10–0.29). The correlation coefficients and RMSE for each lead are summarised in Table 21. A scatter plot for each lead is presented in Figure 30.

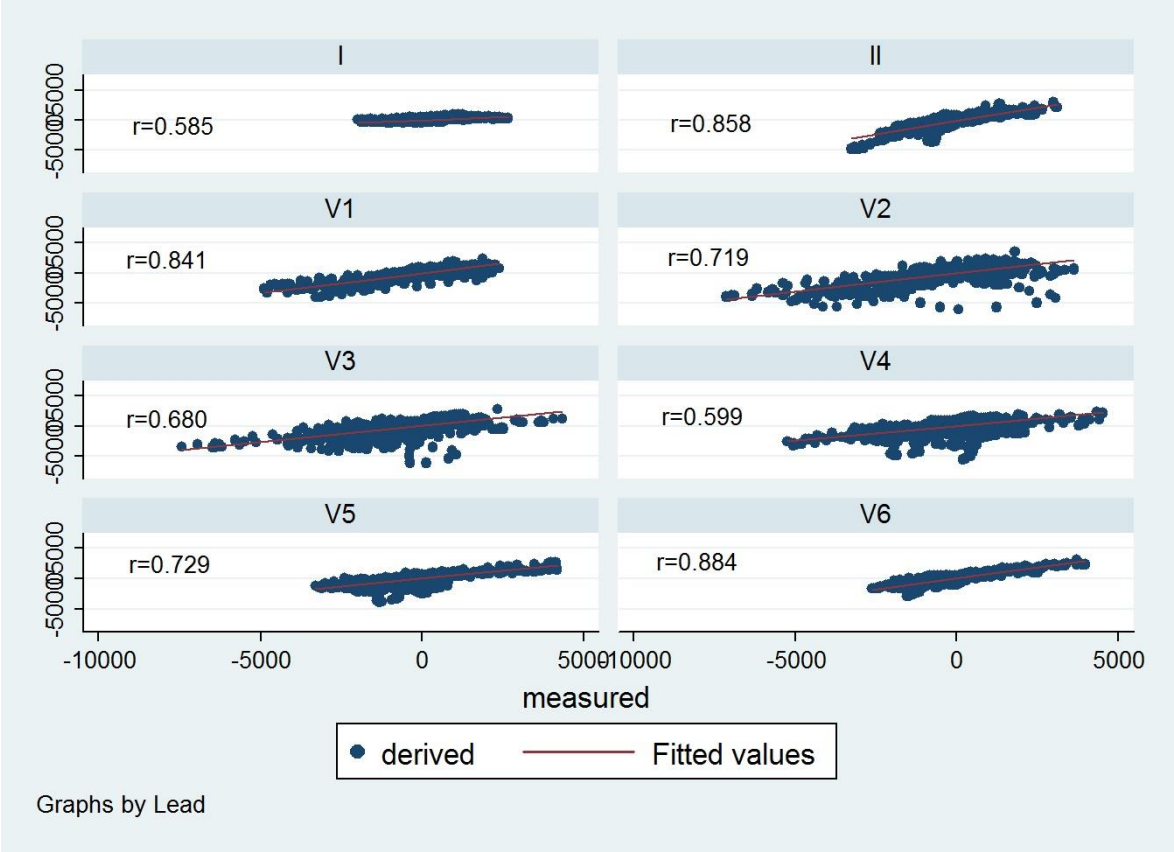


Figure 30 A scatter plot comparing the amplitude of the measured and derived signal for all leads.

6.4.3 Validation group

Lead-specific coefficients are summarised in Table 21. Table 22 describes Pearson correlation coefficient for all cases. From this, it can be observed that the data are skewed towards high correlation coefficients. Overall 123/216 (56.9%, 95% confidence interval 50.3 – 63.5) had an r value of >0.9 and 171/216 (79.2%, 95% confidence interval 73.8 - 84.6) had an r value >0.7. Reconstructed chest leads V3, V4 and lead I had significantly lower r values compared to the other leads (0.70 ± 0.40 vs 0.82 ± 0.32, p=0.0013). Examples of a case with a highly correlated reconstructed ECG and a case with a moderately correlated reconstructed ECG is shown in Figure 31.

Lead	RMSE	Pearson r in µV	*p* value
I	292.6	0.585	<0.00001
II	275.1	0.8579	<0.00001
V1	359.58	0.8413	<0.00001
V2	643.93	0.719	<0.00001
V3	638.76	0.6802	<0.00001
V4	618.2	0.5989	<0.00001
V5	455.88	0.7287	<0.00001
V6	242.99	0.8841	<0.00001

Table 21 Pearson correlation coefficients and RMSE for all leads

Case	I	II	V1	V2	V3	V4	V5	V6
1	0.463	0.945	0.984	0.664	0.738	0.817	0.903	0.944
2	0.661	0.985	-0.442	0.771	0.948	0.975	0.980	0.984
3	-0.440	0.847	0.981	0.949	0.949	0.930	0.859	0.554
4	0.966	0.774	0.989	0.992	0.924	0.574	0.692	0.707
5	0.738	0.947	0.960	0.837	0.768	0.597	0.960	0.967
6	0.970	0.988	0.217	-0.223	0.847	0.971	0.987	0.995
7	0.919	0.644	0.996	0.995	0.971	0.575	0.990	0.994
8	0.921	0.982	0.957	0.860	0.636	0.507	0.973	0.997
9	0.607	0.881	0.993	0.964	0.938	0.896	0.866	0.949
10	0.735	0.954	0.992	0.919	0.832	0.862	0.986	0.991
11	0.810	0.944	0.979	0.940	0.935	-0.230	0.975	0.994
12	-0.137	0.849	0.974	0.963	0.949	0.913	0.793	0.288
13	0.944	0.885	0.995	0.990	0.959	0.952	0.974	0.971
14	0.934	0.988	0.918	0.844	0.948	0.954	0.976	0.989
15	0.774	0.969	0.846	0.382	0.865	0.951	0.929	0.943
16	0.905	0.984	0.865	0.152	0.743	0.960	0.982	0.993
17	0.917	0.989	0.985	0.952	0.819	0.754	0.977	0.983
18	0.546	0.948	0.974	0.980	0.995	0.992	0.781	0.595
19	0.968	-0.280	0.969	0.969	0.942	0.866	0.755	0.932
20	0.815	0.885	0.768	0.427	0.637	0.849	0.891	0.924
21	0.809	0.723	0.960	0.962	0.961	0.710	0.779	0.973
22	0.598	0.939	0.922	0.510	0.168	0.507	0.909	0.967
23	0.626	0.963	0.777	0.105	0.347	-0.063	-0.094	0.348
24	0.846	0.977	0.985	0.851	0.721	0.946	0.935	0.966
25	-0.302	0.994	-0.092	-0.376	0.817	0.848	0.903	0.963
26	-0.598	0.991	0.924	0.319	-0.406	-0.617	-0.470	0.971
27	-0.073	0.935	0.926	0.973	0.981	0.973	0.901	0.949

Table 22 Pearson correlation coefficients (r) for all patients and leads

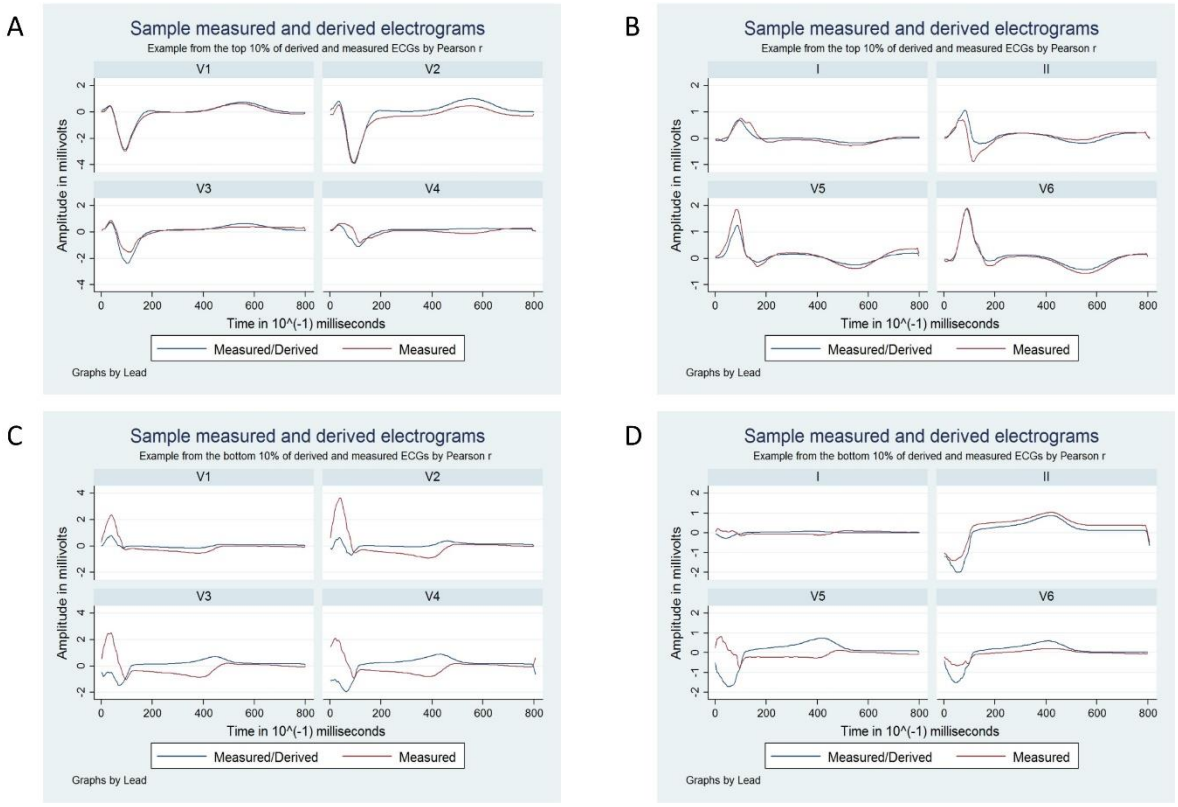


Figure 31 Sample reconstructed electrograms

Example from a case in the top 10% of derived and measured ECGs by Pearson r (case 7) image A, limb leads and image B, chest leads; example from a case in the lower 10% of derived and measured ECGs by Pearson r (case 26) image C, limb leads and image D.

6.5 Discussion and Conclusion

6.5.1 Feasibility and accuracy of S-ICD derived 12-lead ECGs

This study confirms the proof of concept that it is possible to create transformation coefficients and to reconstruct an 8-lead ECG using two independent S-ICD electrode vectors. Overall the accuracy has been good to excellent with a median r = 0.925 (interquartile range 0.76-0.97) for all reconstructed signals. Over 79% of reconstructed leads had an r value >0.7 and 50% of reconstructed leads had an r value >0.9. The coefficients we achieved are comparable to those published in other studies. [176, 181, 188-190] However, in some leads the reconstruction did not work well. In 27/216 (12.5%) of leads the r value was <0.5 with many examples of negative correlations. The reconstructed lateral limb leads Lead I and the chest leads V3 and V4 significantly lower r values compared to the other leads. In general leads II and V6 were most accurately predicted. We speculate that these differences are explained by differences in the heart and torso anatomy between patients resulting in variation in the spatial relationships between ECG electrodes.

We utilised a linear transformation model to reconstruct the 12-lead ECGs from two independent S-ICD vectors. It would have been feasible to utilise a fixed dipole method, though this would require a number of assumptions to be made regarding the conductively of the body tissues and fluid, would be more complex and time-consuming and thus would probably not have improved on these results.

The concept that all possible theoretical ECG vectors can be reconstructed using data from suitable measured independent vectors has been applied to create reduced lead ECG systems such as the EASI ECG system. In this study we have used only 2 measured vectors on a 2-dimensional plane to reconstruct the ECG. Traditionalists would argue that a larger part of the information that can be obtained from surface ECG recording is in three dimensions and therefore the results of this study represent a break from this traditionalist view. Adding a third dimension to the S-ICD sensing configuration is challenging given the generator and lead location on the chest wall, therefore our statistical solution is likely to remain the preferred option for this technology.

6.5.2 Clinical applications

At present the S-ICD will only store electrograms from the vector that has been selected as the sensing vector and only once a tachycardia has been detected. The ability to generate a 12-lead ECG from S-ICDs is novel and would provide the clinician with considerably more information than currently available. In particular, detailed information on the morphology, axis and origin of ventricular tachycardia which would inform future catheter ablation strategies.

6.5.3 Personalised coefficients

The accuracy of the derived ECGs for any given patient is dependent on the spatial arrangement of electrodes on that patient relative to each other and to the electric heart vector and the conductivity of the underlying tissue. A close match with those of the participants used to derive the conversion matrix will result in ECGs that are highly correlated with the patient's own measured ECG. Conversely, a poor match with those of the participants used to derive the conversion matrix will result in ECGs that are poorly correlated with the patient's own measured ECG. Therefore any factors that affect the size and shape of the thorax, the composition of the underlying tissue and position and pathology of the heart itself will affect the accuracy of the derived ECG. The accuracy of the derived ECGs could be improved if the coefficients were generated for specific sub-groups of patients stratified by these confounders. A more elegant solution may be to derive transformation coefficients on a patient by patient basis. Simultaneous

readings could be taken from a surface ECG and the S-ICD in-situ, and these used to generate coefficients which could then be uploaded to the S-ICD.

6.5.4 Limitations

The main limitation of this pilot study was the relatively small number of patients in the training and validation groups and the presence of a small but significance proportion of reconstructed leads having a low correlation with the measured signal. Notwithstanding this, we achieved our objective, to derive the transformation coefficients and to generate transformed ECGs most of which are highly correlated with the measured ECG. However, some of the derived ECGs would not be of sufficient quality to be used in a clinical setting and therefore repeating this study using a larger cohort, as was done with the original EASI coefficients would be necessary. [191] In order for this technology to be incorporated into subsequent versions of the S-ICD, future studies should also repeat this study whilst the patient is experiencing arrhythmias to test how precise the reconstructed ECGs are during arrhythmia. In addition to quantitative comparisons (Pearson correlation and RMSE), qualitative comparisons interpreted by 2 blinded physicians for adjudication and agreement may add clinical context.

6.6 Conclusions

We have demonstrated that the reconstruction of an 8-lead ECG from two S-ICD vectors is possible. The agreement between derived and measured signals was generally good to excellent though there were some negative correlations. If perfected, the ability to generate accurate multi-lead surface ECG data from an S-ICD would potentially allow recording and review of clinical arrhythmias at follow-up.

Chapter 7: Discussion and conclusion

Implantable cardioverter-defibrillator therapy can be life saving for an individual patient. In recent years the S-ICD has emerged as an alternative to the transvenous ICD though problems with S-ICD sensing of the cardiac signal has limited its uptake.

This thesis has covered a broad range of topics on the subject of S-ICD sensing: the impact of a right parasternal lead position and postural change on S-ICD sensing, ECG predictors of T-wave oversensing and reconstructing an 8-lead ECG from two S-ICD vectors. The theme that links these studies together is the concept of developing a tailored assessment of patient's suitability for S-ICD therapy. Most of the studies in this thesis are small and are exploratory in nature, due to the low incidence of T wave oversensing in the ECG predictors of T-wave oversensing, the relatively rarity of patient with complex congenital heart disease in the impact of right parasternal lead position and posture on S-ICD sensing studies demonstrate. As a consequence larger confirmatory studies would be required to corroborate my findings.

7.1 Summary of original findings

7.1.1 Assessment of a patient's suitability for an S-ICD and implications on S-ICD implantation

The impact of parasternal lead position and posture on sensing with the S-ICD.

In the linked studies of parasternal lead position and S-ICD sensing and postural change and S-ICD sensing, I have demonstrated that the current pre-implant screening process does not account for how the R wave and T wave amplitude vary with posture and placement of the sternal sensing electrode. I have demonstrated that by adopting an individualised approach at the time of the pre-implant ECG screen and prior to S-ICD implantation, S-ICD sensing parameters may be optimised and thus reduce some of the adverse events associated with S-ICD therapy, namely inappropriate shock due to T-wave oversensing. Changing the location of the parasternal lead position in an individual patient in response to results of pre-implant screen with more than two postures or using a right parasternal lead screening position may maximise the sensing capabilities of the S-ICD.

7.1.2 Assessment and follow-up of patients with S-ICDs

T-wave oversensing study

In this study I have demonstrated how the pre-implant ECG can be used to identify the ECG predictors of T-wave oversensing. I have identified the pTc as a marker for inappropriate shocks due to T wave oversensing and that there is a 30% increase in the odds of receiving an inappropriate shock due to T wave oversensing for every 10ms increase in this index. Thus, patient care can be individualised at the time of the assessment of the patient's suitability for the device and if they have ECG markers which places them at risk of T-wave oversensing then they may be advised that S-ICD treatment may not be in their interests. Alternative treatments include a cardiac resynchronisation therapy device with ICD (CRT-D) if there QRS is also broad. The incidence of T-wave oversensing in S-ICD is reducing due to improvements in discrimination algorithms and improved screening practices. This study was underpowered and the number of patients with T-wave oversensing was low thus reducing the value of the multivariable logistic analysis that was performed, therefore should be considered a pilot study. A post-hoc power calculation however has determined that over 750 patients would need to be recruited into a study in order for it to be powered adequately. Such a trial would be impractical to arrange given that the most recent published data on S-ICDs which pooled the original IDE trial and the international Effortless Registry has recruited a total of 882 patients implanted in 61 centres by 107 implanters in over 5 years. [192]

7.1.3 Follow up of S-ICDs

Reconstructing an 8-lead ECG from 2-independent S-ICD vectors

In this study, I have demonstrated the feasibility of reconstructing an 8-lead ECGs from 2 independent S-ICD vectors. The accuracy of the reconstructed ECGs was generally good, but in some individuals and in some leads, the accuracy was poor. However, I propose that if the transformation matrix was individualised at the time of the assessment of the patient's suitability for the device the resultant reconstructed would likely be highly correlated to the individual's ECG.

7.2 Contemporary challenges to defibrillator therapy and how findings from this thesis may influence these

The ICD has a clear benefit in preventing arrhythmic death in appropriately selected individuals, and this benefit is probably greatest in secondary prevention patients as they are at greater overall risk of SCD and have a higher incidence of appropriate therapy.[193] In an analysis by Betts et al.[60] of the absolute risk reduction (ARR) in total mortality with primary and secondary prevention ICDs, data from eight primary prevention (PP) trials, three secondary prevention (SP) trials and one SP meta-analyses were analysed. The ARR at 3-year follow-up ranged from 0 (no benefit) to 24.6% (NNT = 4) for PP. For SP the ARR at 3-year follow up ranged from 3.7% (NNT = 27) to 11.3% (NNT = 9). Absolute risk reduction increased with follow-up in PP trials, whereas there was considerable variation in SP trials. Data from extended follow up of the landmark trial in primary prevention of SCD with ICDs, [61] where the number needed to treat to prevent 1 death is six over an eight year time horizon.

From a technical perspective, the biggest challenge to the modern day defibrillator occurred approximately 7 years ago with the problems encountered with the transvenous lead failures associated with the Medtronic Sprint Fidelis leads and the St Jude Medical Riata lead failures. As discussed in the introduction, the perception was that the presence of a transvenous lead was the 'Achilles heel' of the ICD and this led to the development of the S-ICD. The S-ICD has become increasingly popular amongst physicians who implant defibrillators mainly due to the advantages of not having a transvenous lead in situ. However, there remain a number of important limitations of the S-ICD, mainly to do with accurate sensing of the cardiac signal and this will be the focus of the subsequent discussion.

7.2.1 Current challenges to S-ICD sensing

Many of the studies in this thesis have focused upon features that are specific to the sensing characteristics of the S-ICD (Chapters 3-6). In particular, the importance of how a small change in the location of where an electrogram is recorded (e.g. left versus right parasternal location), or how the change in the posture may influence the sensed electrogram by altering the amplitude of the R wave or the T wave, both fundamental to accurate sensing in the S-ICD. In addition the ECG predictors of T-wave oversensing highlights the importance of accurate S-ICD sensing capabilities.

The S-ICD is an evolving technology. Some critics were concerned that high rates of inappropriate therapy would limit the uptake of the device. [24] There is undoubtedly a learning curve for the implanters [192] but also for the manufacturers. As more data from international registries becomes

available, there is a greater understanding of the challenges that the S-ICD faces. One of the main challenges is improving the accuracy of the sensing function of the S-ICD and this follows on from the work carried out as part of this thesis.

7.2.2 Novel solutions

Whilst these new algorithms are welcomed they may be ineffective if the patient develops bundle branch block during SVT unless an ECG template recording aberrant beat morphology if it has been recognised during screening [194] or if there electromechanical noise.

In addition to continuously monitoring the heart rate, the S-ICD also compares the QRS-complex and T-wave morphology to a template registered and stored by the S-ICD immediately after implantation to discriminate between SVT and ventricular arrhythmias. For this reason also, QRS-T wave morphology screening and analysis is integral to assessing device eligibility and efficacy prior to implantation. [195]

It is in this context that the work done as part of this thesis must be viewed. In the studies investigating the impact of postural change and parasternal lead position I have demonstrated that the location of the sensing electrodes can alter the sensed amplitude of the R and T waves and R:T ratios. Thus adopting an individualised approach to pre-implant ECG screening in order to achieve the optimum R wave, T wave and R: T ratio to prevent complication such as oversensing appears to be a valid option. This method has been successfully used in clinical practice.[196, 197] However, adopting an individualised approach to where the sensing electrodes of an S-ICD are placed has yet to be proven as a strategy that translates into fewer oversensing episodes.

7.2.3 Difficulties of calculating heart rates

Given the ubiquity of the ECG, and the ease with which clinicians (and non-clinicians) are able to calculate accurate heart rates it is surprising that a robust 100% accurate computer-based method has yet to be developed. Indeed, if such a method were to be developed and integrated into S-ICD firmware, then that would become the ‘gold-standard’ heart rate monitor against which the other sensing processes which current sensing and analyse the a cardiac signal could be continuously compared. If the detected rate was found greater than the ‘gold-standard’ method, then it would mean oversensing was occurring, and inappropriate therapy could be withheld.

However, there are several reasons why creating a 100% accurate heart rate detector is challenging. The ECG is a non-stationary signal and is subject to a variety of corrupting sources of noise in a clinical environment, for example, power line interference, muscle contraction noise,

poor electrode contact, patient movement, and baseline wandering due to respiration any of which can degrade the quality of the ECG signal.

Since the advent of telemedicine, there has been increasing interest in the signal processing literature about developing accurate and efficient heart rate monitors. One of the more promising methods is the use of wavelet analysis which employs time-domain gradient based approach and spectral energy analysis to process the acquired ECG signal.

7.2.4 Overview of QRS detectors:

The algorithms for QRS detectors can be classified into three categories[198]

1) No syntactic, which are generally inefficient

2) Syntactic, which are used widely and

3) Hybrid.

Previously applied algorithms commonly use computing technique to detect QRS complexes using thresholding,[199] artificial intelligence using hidden Markov models,[200] and time recursive prediction techniques. [201] Normally the recorded signal is filtered to enhance the QRS complexes to suppress the P and T wave and noise and finally determining the presence of QRS complexes using a decision tool. The main drawbacks of these techniques is that frequency variation in QRS complexes adversely affects their performance.[198] The frequency band of QRS complexes generally overlaps the frequency band of noise, resulting in both false positives and false negatives. Methods using artificial intelligence are time consuming due to the use the necessary computational rules.

Wavelet analysis is a very promising mathematical tool that gives good estimation of time and frequency localization. Wavelet analysis has become a useful tool for characterizing ECG signal and some very efficient algorithms has been reported using wavelet transform as QRS detectors (Figure 32).

Table 23 provides a comparison of published ECG detection algorithms.

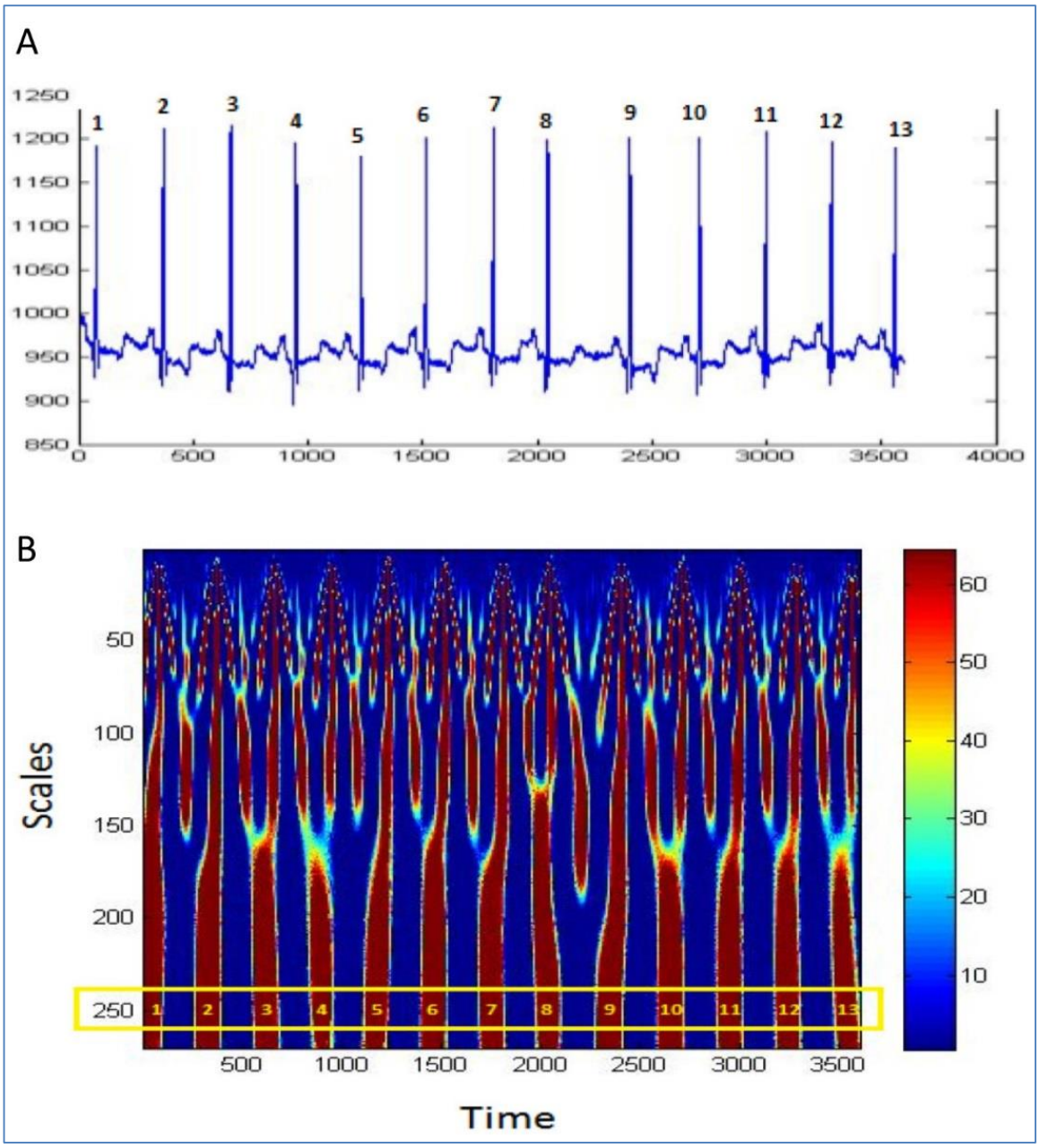


Figure 32 An example of wavelet based QRS identification.

A, ECG signal from a patient in normal sinus rhythm. Numbers denote cumulative number of detected R waves. B, Coefficient plot after application of wavelet transform with numbering indicating cumulative number of detected beats.

Characteristic	Algorithms	Complexity	Performance
Time domain[202]	Time domain analysis of ECG signals	Simple	96-98%
ECG morphology [203]	Neural network (based on ECG morphology)	Complex	99%
Time-frequency domain [204]	Time and frequency transforms; wavelet transform; non-linear transform	Medium	>99%
Combination [205]	Combined	Very complex	~99.9%

Table 23 Comparison of published ECG detection algorithms.

Comparison of published ECG detection algorithms. Adapted from Min YJ, Kim HK, Kang YR, Kim GS, Park J, Kim SW. Design of wavelet-based ECG detector for implantable cardiac pacemakers. *IEEE transactions on biomedical circuits and systems* 2013; 7: 426-436 [206]

Wavelet based heart rate technology has not to my knowledge been applied in S-ICD technology at present, but may do so in the future. An alternative method for improving the accuracy of QRS detection would be to use more than one S-ICD vector to determine the heart rate. At present, only the vector that is in use is capable to sensing all the time. Newer versions of the S-ICD may employ more than one of the S-ICD vectors to sense the cardiac signal and thus calculate the heart rate. An advantage of such a system would be a theoretically improved accuracy of the heart rate determination.

In summary, within this thesis, I have discussed some of the problems related to oversensing of the cardiac signal that can occur with the S-ICD and this has led me to hypothesise that by improving the mechanism by which the S-ICD counts the heart beat in a way that eliminates the T wave, any oversensing may be dramatically reduced. Whether this occurs remains to be seen in future studies in this area.

7.3 S-ICD sensing in the future

7.3.1 Automated screening

It is likely that in the future the manual screening process with the coloured ECG template will be replaced with an automated screening process whereby the patient's ECG will be recorded directly by the S-ICD manufacturer's pacing system analyser (PSA) which will have the up to date

sensing algorithms discussed in chapter 2 installed as software. This is likely to improve the proportion of patients who are appropriately selected for S-ICD therapy and could help identify patients who may go on to have inappropriate sensing with an S-ICD and recommend that these patients not receive an ICD.

7.3.2 Floating bipole away from the heart to provide optimal sensing and reducing the risk of inappropriate sensing

At present the S-ICD is limited to sensing via one of 3 vectors created from the lead/can interface. As this thesis has discussed, this paradigm has its limitations. The incorporation of an additional sensing electrode but separate from the S-ICD may offer alternative solutions for the problem of S-ICD sensing. This 'floating dipole' may potentially take the form an implantable loop recorder placed at the optimal location to provide useful additional information for accurate cardiac signal sensing. This floating bipole would communicate remotely (e.g. Bluetooth) with the S-ICD can to deliver this additional sensing information. [207]

7.3.3 Integrating the signals from more than 1 vector to achieve the best sensing vector

At present the majority of patients who are deemed suitable for S-ICD implantation on the basis of a successful template screening assessment have at least 2 vectors that passed the screen. In a study of 230 ICD patients with no pacing indication, 78% of the patients had ≥2 appropriate sensing vectors.[129] However, only one sensing vector will be used at any one time. It would therefore seem logical to attempt to incorporate the use of more than one vector in the assessment of the cardiac signal. This however may take up valuable computing power and jeopardise the duration of the battery, therefore these issues may need to be resolved before this incorporated into newer iterations of the S-ICD.

7.3.4 Combining transvenous, epicardial or leadless pacemakers with the S-ICD

One of the limitations of the S-ICD is the absence of durable bradycardia pacing capability. Physicians have overcome this by combining transvenous permanent pacemakers (PPM) or epicardial pacemakers (in cases where venous access is not feasible) with the S-ICD. In doing so, the PPM will provide the backup pacing and the S-ICD will provide the defibrillation capability should a ventricular arrhythmia occur. [208] [209] Prior to implanting the S-ICD in a patient with an incumbent PPM, both the intrinsic QRS complex and the paced QRS complex must satisfy the S-ICD screening template as described in Chapter 2.

The main risk of combining these two technologies is two-fold. Firstly, the S-ICD may over-sense the pacing spike and thus deliver inappropriate therapy. It is therefore important that the pacemaker be programmed in bipolar mode in order to minimise the amplitude of the pacing spike. It must be noted that after the delivery of a full output shock for ventricular tachycardia or ventricular fibrillation, the pacemaker would revert to unipolar pacing and therefore the is a risk of inadvertent oversensing and further, this time, inappropriate shock delivery. Secondly, during ventricular tachycardia or ventricular fibrillation, the PPM will continue to attempt to deliver paced beats (though these will not capture the myocardium and will be ineffectual). However, there is a risk that the S-ICD would sense these pacing spikes and therefore undersense the ventricular tachycardia/ventricular fibrillation and thus lifesaving therapy may not be delivered. It is therefore vital that intraoperative cross talk testing takes place to evaluate for the presence of either of the above scenarios.

As discussed in chapter 2, the presence of transvenous leads are a weak point of the TV-ICD. So are the presence the transvenous leads in PPM and therefore leadless pacemakers have been developed. These miniaturised pacing systems are implanted via the femoral vein and delivered to the right ventricular by means of a catheter delivery system. [210]To date, the data on the safety and efficacy of the Micra (Medtronic Minneapolis) device in particular appear very encouraging. One advantage that a leadless pacemaker would offer is the ability to deliver anti-tachycardia pacing in order to terminate ventricular tachycardia painlessly, which the S-ICD is unable to do at present. It seems logical therefore to explore the use of leadless pacemakers and the S-ICD.

Early experiments in sheep and humans have tested leadless pacemakers and S-ICD with evidence that this is feasible and safe, though more data are required. [211] Data from this study support using this combined therapy in clinic, aiming to benefit patients in whom transvenous access is not feasible or desired. This combined therapy is the next step in multi-component leadless cardiac rhythm management, with the objective to eliminate transvenous lead-related complications.

In conclusion, the combination of permanent (transvenous, epicardial and leadless) pacemakers is being tested. At present the pacemaker serves as a tool to deliver bradycardia pacing, however, it is entirely conceivable that they may also serve as an additional sensing tool to help eliminate the problems of oversensing with the S-ICD.

7.4 The future role of S-ICD in an ACHD population

In a subset of patients with ACHD there is a small but ongoing risk of SCD. As discussed in Chapters 3 and 4, the S-ICD is well suited to some patients with ACHD at high risk of SCD due in part due to the absence of a transvenous lead and also that postural change and parasternal lead positon do not affect the sensed ECG signal as much in patients with ACHD compared to normal controls. A recent systematic review and meta-analysis of ACHD patients with ICDs (transvenous ICD 96.1%) has reported remarkably high rates of appropriate ICD therapy (ATP and shocks) in both primary and secondary prevention (24% (18.6-31.3)) and that due to the younger age at implant and lower death rates from non-cardiac causes, the cumulative benefits are thought to be greater in ACHD patients compared to acquired heart disease patients. [145] However, the drawback is a high rate of inappropriate therapy (25% (18.9-33.6)) in 3.7 +/- 0.8 years. Supraventricular tachycardia (68%), sinus tachycardia (17%) and oversensing and lead failure (13%) were the most common reasons for the first occurrence of inappropriate shock. This highlights the importance of accurate sensing discussed in detail above (improve pre-implant screening protocol, minimising risk of T-wave oversensing by appropriately selecting patients with surface ECGs that are less likely to have oversensed signal). Importantly, the S-ICD has been shown to have an excellent capacity (better than two of the three commonly used transvenous ICDs) to discriminate ventricular from supraventricular rhythms [131] and therefore if S-ICDs were used from frequently in the ACHD population, one may speculate that the rate of inappropriate therapy may actually reduce, assuming no risk of T-wave oversensing from high amplitude T waves. Whether this is true remains to be seen in future studies.

7.4.1 Vector transformation

From the lead transformation study, I have demonstrated that it is feasible to reconstruct a 12 lead ECG from 2 independent S-ICD vectors with good overall accuracy. This entirely novel concept in the S-ICD does not resolve any specific sensing problems associated with S-ICD but rather provides insight into additional functionality associated with the S-ICD, which may eventually help resolve oversensing issues by optimising the sensing vector. The theory underlying this transformation is relatively simple. Any desired vector (lead) can be reconstructed if the known coefficients are multiple by the know vectors (leads).

Derived lead = (coef1 x lead1) + (coef2 x lead 2) + (coef3 x lead3)…

Applying this theory may help allow us to reconstruct sensing vectors that reduce the amplitude of the T wave, thus reducing the likelihood of T-wave oversensing.

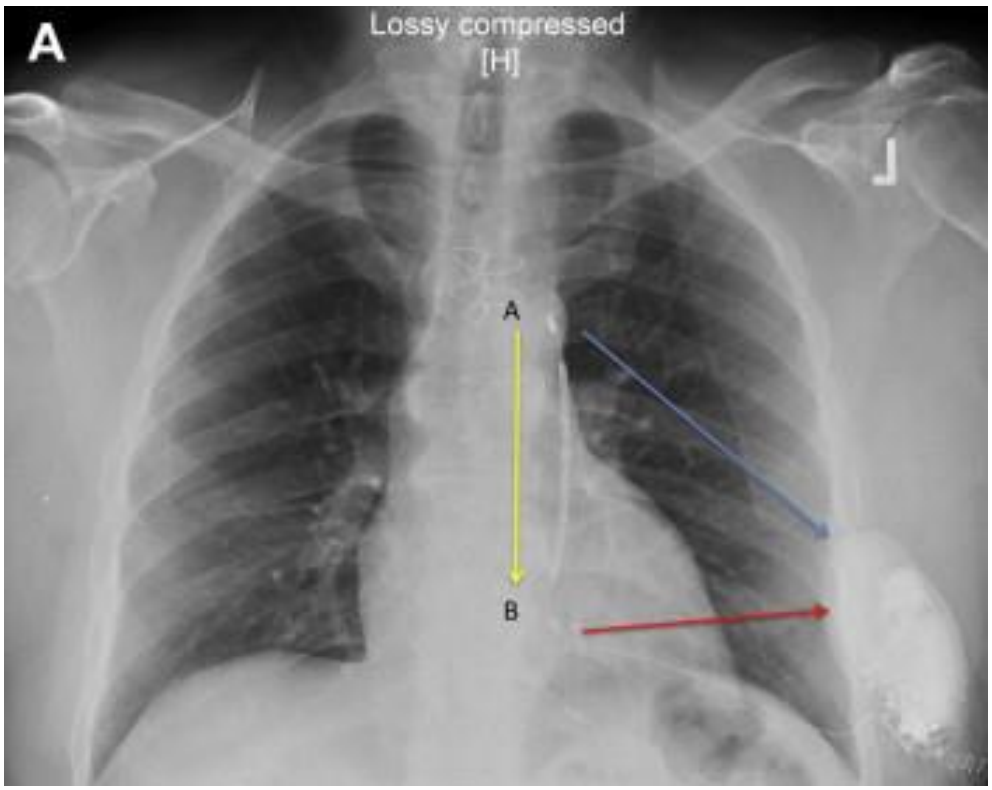


Figure 33 Right hand triangle formed from the three sensing vectors
Image reproduced with permission from Elsevier from Image from Aziz S et al. The Subcutaneous Defibrillator : A Review of the Literature Journal of the American College of Cardiology, Volume 63, Issue 15, 2014, 1473–1479

The S-ICD sensing configuration is in the shape of a right angle triangle. (Figure 33). This allows us to easily calculate the QRS and T wave axis. I have observed that the R wave axis and the T wave axis differ. (Figure 34). We know that ECG leads that record the cardiac signal in the same axis as that of the cardiac (QRS) axis have the maximal positive amplitude signal and those leads that are orthogonal to the cardiac axis have the lowest amplitude signal. Thus, if a sensing vector 90 degrees to the T wave axis then the resultant complex should have the smallest recordable T wave amplitude. The R wave would still be present assuming the QRS axis differs from the T wave axis. It is conceivable therefore that one could 'dial-up' the optimal sensing vector by transform the signal from the 3 S-ICD vectors to generate the new complex with the smallest T wave. This transformed complex would act as the principle sensing vector. This would be another step towards personalisation of the ICD therapy.

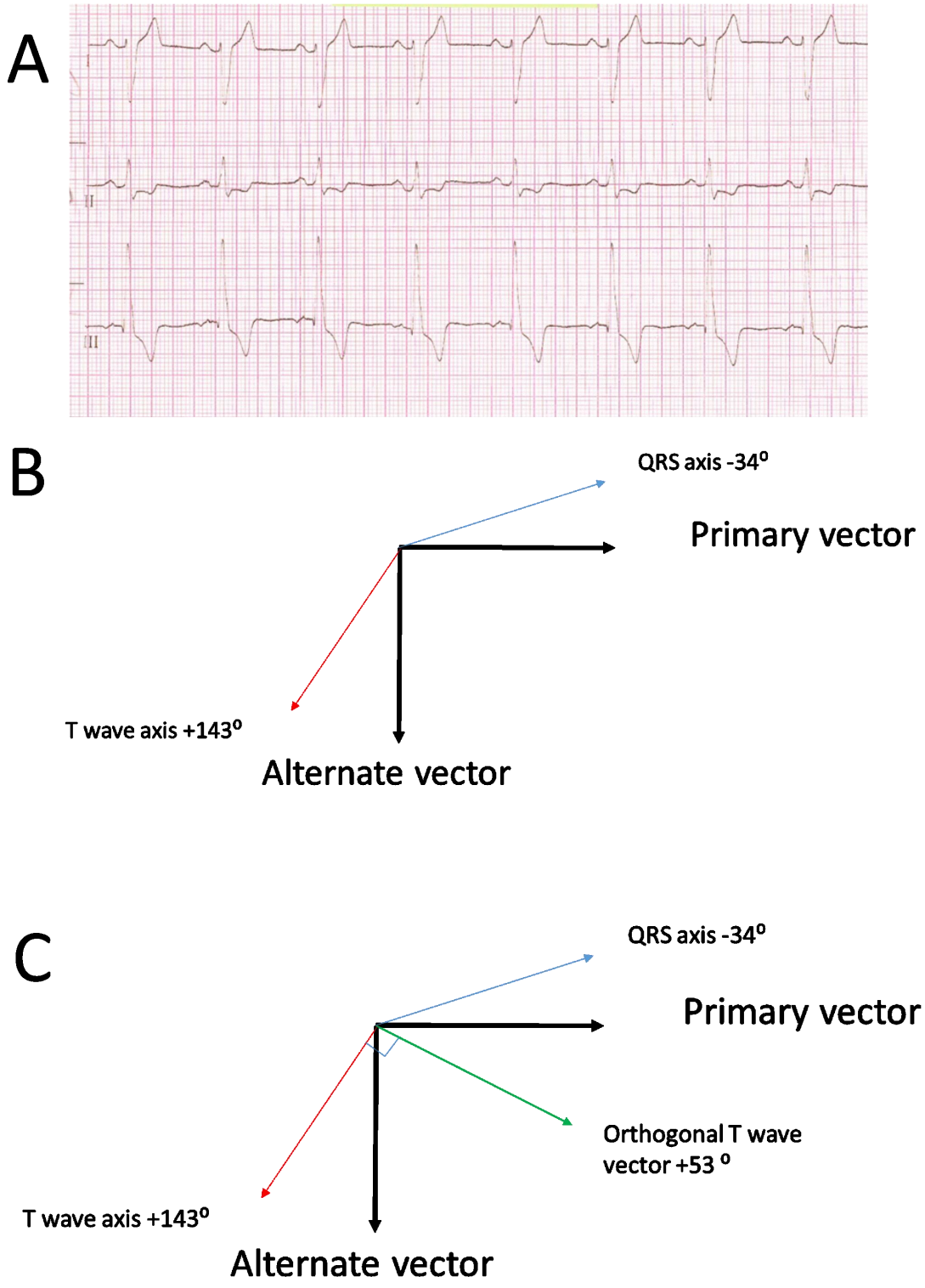


Figure 34 Transforming vectors to reduce the amplitude of the T wave

A: A pre-implant ECG screen taken from a patient who went on to receive an inappropriate shock due to T wave oversensing. B: A schematic to illustrate the QRS and T wave vectors. C: An illustration of where an orthogonal angle to the T wave axis would lie. This new vector would theoretically have the lowest amplitude T wave.

This hypothesis would need to be tested to prove that 1) It is possible to create the necessary coefficients required to transform the signal to the desired vector and 2) The transformed signal is superior to the native S-ICD signals in terms of sensing accuracy, discrimination and reduction in rates of T wave oversensing.

7.4.2 Identification of patients at risk of T-wave oversensing prior to inappropriate therapy

One of the limitations of the current iteration of the S-ICD is its ability to store electrograms only once the capacitors start charging. This contrasts with transvenous ICDs which are capable of storing considerably more data (episodes of atrial tachyarrhythmia, non-sustained ventricular tachycardia in the monitor zones etc.). At present, we are therefore unable to identify episodes of T-wave oversensing that do not result in inappropriate therapy. It is possible that there are patients who are experiencing T-wave oversensing but that these are occurring at rates below the tachycardia detection window even accounting for the double counted beat. It would be important to identify this cohort of patients as they may be at higher risk of subsequent inappropriate shock from T-wave oversensing.

7.4.2.1 Research implications

A study to identify episodes of subclinical T-wave oversensing is being designed in order to test this hypothesis. Holter monitors with electrodes placed over the S-ICD sensing electrodes will be attached to patients with S-ICDs who have a prolonged pTc. Data from the holter monitors will be sent to Boston Scientific (S-ICD manufacturer) for further analysis. The data will be run through their proprietary sensing algorithm to detect episodes of T-wave oversensing that would not have been identified previously. This might have important implications as it may lead to better identification and of patients at risk of T-wave oversensing. Interventions that may reduce their risk of subsequent clinical T-wave oversensing and inappropriate shock include S-ICD reprogramming (using different vectors, modifying tachycardia therapy zones, updating discrimination algorithms), medication changes (stopping medication that prolong the QT intervals), lead re-positioning or even device explantation if the risks of T-wave oversensing are thought to be too great.

7.4.3 Does device therapy for prevention of sudden cardiac death need to be tailored to the individual?

At present clinicians only have relatively crude tools to guide them in the decision to implant a defibrillator the clinical history the surface ECG and the ejection fraction. There are several novel risk markers that have been used for the assessment of increased risk in SCD, [212-214] however, at present, none of these have been accepted into routine clinical practice. Technology could help. As this thesis has demonstrated, much could be done at an individual level (optimise lead position, identify patients at risk of T wave oversensing and using vector transformation to reduce the likelihood of inappropriate therapy) to maximise the potential benefit (and reduce the unwanted consequences) of subcutaneous implantable defibrillators in particular.

Therefore, it seems logical that that ICD therapy ought to be tailored to the individual as much as possible. However, the hypothesis of whether a truly personalised approach to device therapy to reduce sudden cardiac death may be superior to 'off the shelf therapy' is valid but would need to be answered in future studies.

7.5 Final conclusion

Progress is being made towards the goal of an individual approach to the assessment and treatment in patients with subcutaneous implantable cardioverter defibrillators. Population studies are required to develop more sophisticated discrimination algorithms, vector transformation to reduce T wave oversensing and reducing morbidity associated with ICDs due to inappropriate therapy, individualisation of electrode placement and risk assessment for inappropriate shock occurs. A future of inappropriate shock free sudden cardiac death treatment which is appropriate for all patients with subcutaneous ICDs is a tangible reality.

Appendices

Appendix A

	Monitor Zone	Zone 1	Zone 2	Zone 3
Medtronic	133	167	250 (via VF)	200
St Jude	-	166	200	250
Boston	-	165	200	250
Sorin	135	165	200	240

Primary prevention ICD setting for University Hospital Southampton NHS Foundation Trust

Table 1 Standardised hospital programming for tachycardia zones for major ICD manufacturers in primary prevention patients with structural heart disease at University Hospital Southampton NHS Foundation Trust.

	Monitor Zone	Zone 1	Zone 2	Zone 3
Medtronic				
Detection	36 intervals	32 intervals	(via VF)	30/40 intervals
Redetection		12 intervals	(via VF)	12/16 intervals
St Jude				
Detection	-	25 intervals	25 intervals	25 intervals
Redetection	-	9 intervals	9 intervals	9 intervals
Boston				
Detection	-	9.0s	7.0s	6.0s
Redetection	-	3.0s	3.0s	1.0s (fixed)
Sorin				
Detection	50 intervals	30 intervals	20 intervals	20 intervals
Redetection	-	(fixed)	(fixed)	(fixed)

Table 2 Standardised hospital programming for discrimination settings for major ICD manufacturers in primary prevention patients with structural heart disease at University Hospital Southampton NHS Foundation Trust.

Primary Prevention Settings

The following protocols are a robust guide for PRIMARY PREVENTION patient settings. They do not take away the responsibility of clinicians and physiologists to consider individual patient requirements, patient heart rates, underlying rhythm, and the indication for device.

Contraindications: Secondary prevention, and inherited cardiac diseases and syndromes.

Medtronic

Zone	Threshold	Interval	SVT Disc	Therapy
VF	200bpm (300ms)	30 of 40	On	ATP during charging on • Deliver ATP if last 8 RR ≥ 200ms • Burst 8 at 88% • Charge saver ON, smart mode on All Shocks 35J • Reverse polarity of penultimate shock • Confirmation+ On
FVT via VF	240bpm (250ms)		On	Therapy 1: ATPx2 • Burst 8, 88%, 10ms, smart off Therapy 2: ATPx1 • Ramp 8, 84%, 10ms, smart off Therapy 3-6: Full output Shocks • Reversed polarity of penultimate shock
				Shared Settings • V-V Minimum ATP interval: 170ms
VT	Off			
Monitor	172 (370ms)	32	On	On for Ischaemic patients only, but use discretion.
SVT Discrimination				• As per out of the box setting (Unless contraindicated) • Collect morphology template (Test -> Wavelet) >70%?
Brady Setting:				If no pacing indication limit V-pacing 40bpm, AAI <->DDD (MVP)

Boston Scientific

Zone	Threshold	Duration	Detection Enhance	Therapy
VF	240bpm (250ms)	2.5s	N/A	Quick Convert ATP (300bpm) Full output shocks • Lead configuration
VT	200bpm (300ms)	12s	On	ATP • 2x Scan, 8 initial, 88%, min interval 200ms, Scan decrement 10ms • 1x Ramp, 8 initial, 84%, min interval 200ms ATP Time-out: OFF Full output shocks
Post Therapy			Post tachycardia pacing on	
SVT Discrimination			• Rhythm ID (Unless contraindicated) • Turn **Sustained rate duration OFF** in pre and post therapy	
Brady Settings:			If no pacing indication limit V-pacing 40bpm DDD with Rhythm IQ ATR mode switch is set to 0, 4, 4 DDIR.	

St Jude Medical

Zone	Threshold	Interval	SVT Disc	Therapy
VT-1	170bpm (370ms)	35	On	• Monitor Only
VT-2	200bpm (300ms)	35	On	Therapy 1: ATP Burstx2 • 8 stimuli, 88%, add stim off, 200ms min burst, re-adaptive on Therapy 2: ATP Rampx1 • 8 stimuli, 84%, 200ms min burst, re-adaptive on Therapy 3-4: Full output shocks
VT-3	240bpm (250ms)	12		Therapy 1: ATP whilst charging • Upper cut off 300bpm Therapy 2-4: Full output shocks • Max number of shocks (6)
SVT Discrimination				• As per out of the box setting (Unless contraindicated) • Collect morphology template
Brady Setting:				If no pacing indication limit V-pacing 40bpm, DDI (VIP)

Appendix B

ID	age at implant	Date of therapy	Details
302	60.6	01/04/2010	ATP for FVT CL 300ms
262	61.6	19/09/2013	ATP and shock for FVT CL250ms.
335	61.7	14/03/2014	VT 205 bpm ATP to SR
313	61.7	18/11/2014	Shock for VF 400bpm
393	62.3	21/03/2014	ATP for FVT 231 BPM
389	63.0	26/03/2014	ATP and shock for FVT CL260ms
391	64.6	14/11/2014	ATP then shock for FVT / VF
271	64.6	30/11/2014	ATP for FVT 240ms
372	64.7	02/03/2011	ATP for FVT via VF 290 msec
397	65.6	16/02/2013	ATP for VT 214bpm
380	65.7	17/07/2013	Shock for FVT CL 260 msec
366	66.7	13/03/2013	ATP for VF CL 230ms
248	68.0	11/10/2010	ATP CL 260 msec on 11/10/2010
289	68.1	12/05/2014	ATP for FVT CL 240ms
266	68.3	20/05/2010	ATP for FVT 213 bpm
246	68.9	13/01/2012	ATP for VT 210bpm
225	69.2	03/06/2014	ATP then shock FVT CL 240 msec
242	69.2	20/10/2011	Shock for FVT CL 230 msec
264	69.3	06/03/2012	ATP for VT CL 300 msec.
111	70.7	26/12/2009	ATP for VT CL 290ms
112	71.0	17/12/2014	ATP for CL <290ms then acceleration to shock zone
110	71.6	25/05/2010	ATP and shock during VT storm
108	71.7	17/04/2011	Shock for VF
124	72.2	20/05/2013	ATP for VT rate 200bpm which accelerated rhythm to VF ~300bpm > shocked
104	72.7	29/03/2013	ATP and shock FVT at 240BPM
102	73.5	13/05/2008	ATP in FVT zone
113	74.4	12/09/2009	ATP for FVT CL 260ms
114	74.8	28/02/2011	ATP for VT CL 290ms
103	75.6	25/05/2010	ATP for VT CL 280ms
115	76.2	24/06/2011	Shock for FVT rate 273bpm
106	77.0	23/04/2009	ATP for VT rate >230bpm
99	77.5	07/11/2014	ATP for VT rate 200bpm
105	77.7	02/11/2011	Shock for VF
91	78.0	21/04/2009	ATP for VT CL 280ms
107	78.7	21/11/2009	ATP and shock for FVT and syncope
135	78.8	23/05/2011	ATP for VT CL 280ms
100	78.9	18/08/2014	ATP for VT 222bpm
40	79.7	07/08/2012	ATP and shock for FVT
47	80.3	27/11/2011	ATP and shock for FVT/VF CL 270ms
42	80.4	22/02/2014	Shock for PMVT CL180ms
437	82.7	18/07/2012	Shock for FVT 280ms
36	82.8	24/01/2011	ATP and shock for FVT CL 270ms
41	83.9	06/05/2013	ATP for VT CL 300ms
451	89.9	13/10/2014	Shock for FVT 243ms

Table Details of therapy delivered for ventricular arrhythmias with rates ≥ 200bpm. ATP, anti-tachycardia pacing; VT, ventricular tachycardia; CL, cycle length; SR, sinus rhythm; VF, ventricular fibrillation; FVT, fast ventricular tachycardia; PMVT, polymorphic VT; VP, ventricular paced rhythm

ID	age at implant	Date of therapy	Details
364	60.2	13/03/2014	ATP VT 196 bpm
261	61.3	12/10/2011	ATP for VT CL 390ms
410	61.9	24/05/2011	ATP for VT CL 340ms
361	63.5	07/12/2012	ATP for VT 320ms
257	63.9	16/04/2012	ATP for VT CL380 ms
398	64.9	01/02/2011	ATP for slow VT
385	65.4	14/11/2014	ATP for VT rate 171bpm.
365	65.9	13/05/2010	ATP VT 179bpm > AsBiVp.
251	66.2	19/09/2011	ATP for VT CL 410 msec
254	67.6	06/07/2012	ATP for VT CL 340ms
341	67.7	09/03/2013	ATP for VT CL330ms 13 sec
406	68.6	24/09/2011	ATP for VT CL 310msec
243	69.7	30/09/2011	ATP for VT 320ms to SR
202	70.0	21/04/2010	ATP for VT CL 330ms.
173	70.5	25/08/2011	ATP for VT zone <200bpm. Subsequent ATP for VT rate 160bpm
175	70.5	14/09/2007	ATPs for VT 162-167bpm
132	70.6	12/12/2006	ATP for VT rate 145bpm
53	71.6	19/06/2010	ATP for VT for rates <200bpm
164	71.7	12/02/2013	ATP for VT CL 380ms
206	72.0	14/08/2009	ATP for VT 154bpm
153	72.2	08/09/2011	ATP for VT 166bpm
165	73.2	31/05/2009	ATP for VT CL 310ms
196	73.7	22/10/2009	ATP for slow VT rate 150-200bpm
120	73.8	14/11/2009	ATP for VT rate <200bpm
166	73.9	25/02/2011	ATP for VT-1 zone - No EGM available. Assumed VT <200bpm
127	74.1	09/08/2010	ATP for VT rate 162bpm
131	74.4	26/09/2012	ATP for VT CL 330ms
143	74.5	28/04/2011	ATP in VT-1 zone - no EGMs seen.
123	74.5	14/10/2009	ATP for VT CL 360ms
154	74.6	01/06/2012	ATP for VT 164bpm
56	75.5	04/08/2012	ATP for VT CL390ms
133	75.8	22/12/2008	ATP for VT rate between 120bpm and 130bpm > shock
160	75.9	04/10/2011	ATP for VT 167bpm
204	76.5	06/11/2012	VT CL 360ms > ATP
180	76.6	13/08/2013	ATP x 2 for VT rate 158-171bpm
49	77.8	01/02/2009	ATP for VT for rates <200bpm
167	78.9	07/07/2009	ATP for VT CL 390ms
95	79.2	29/03/2010	ATP for VT rate 153bpm
190	79.4	16/03/2014	ATP for VT CL 330ms
155	79.5	12/01/2010	ATP probably for rate <200bpm. No IEGMs to confirm
32	79.6	10/09/2010	ATP for VT rate 194bpm
423	80.7	15/07/2012	Details unavailable
441	80.7	07/10/2007	Details unavailable
428	80.9	04/02/2012	Details unavailable
38	80.9	01/02/2010	ATP for VT rate 135bpm
33	81.0	04/07/2013	Multiple episodes of ATP and VT CL 400ms
424	81.1	29/03/2012	ATP for slow VT
37	81.5	10/05/2012	ATP for VT 168bpm
427	82.5	04/06/2012	ATP for slow VT
35	82.7	15/04/2010	ATP VT 170bpm
39	85.7	06/12/2012	ATP for VT 171bpm

Table Details of therapy delivered for ventricular arrhythmias with rates < 200bpm. ATP, anti-tachycardia pacing; VT, ventricular tachycardia; CL, cycle length; SR, sinus rhythm; VF, ventricular fibrillation; FVT, fast ventricular tachycardia; PMVT, polymorphic VT; VP, ventricular paced rhythm

Bibliography

[1] Redekop WK, Mladsi D. The faces of personalized medicine: a framework for understanding its meaning and scope. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2013; **16**: S4-9.

[2] Schleidgen S, Klingler C, Bertram T, Rogowski WH, Marckmann G. What is personalized medicine: sharpening a vague term based on a systematic literature review. *BMC Med Ethics* 2013; **14**: 55.

[3] Agusti A, Anto JM, Auffray C, Barbe F, Barreiro E, Dorca J, et al. Personalized respiratory medicine: exploring the horizon, addressing the issues. Summary of a BRN-AJRCCM workshop held in Barcelona on June 12, 2014. *Am J Respir Crit Care Med* 2015; **191**: 391-401.

[4] Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. *The New England journal of medicine* 2012; **366**: 489-491.

[5] Auffray C, Chen Z, Hood L. Systems medicine: the future of medical genomics and healthcare. *Genome Med* 2009; **1**: 2.

[6] Gerich ME, McGovern DP. Towards personalized care in IBD. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 287-299.

[7] Sadee W. Genomics and personalized medicine. *Int J Pharm* 2011; **415**: 2-4.

[8] Pesce F, Pathan S, Schena FP. From -omics to personalized medicine in nephrology: integration is the key. *Nephrol Dial Transplant* 2013; **28**: 24-28.

[9] Jain KK. Nanobiotechnology and personalized medicine. *Prog Mol Biol Transl Sci* 2011; **104**: 325-354.

[10] Steinhubl SR, Topol EJ. Moving From Digitalization to Digitization in Cardiovascular Care: Why Is it Important, and What Could it Mean for Patients and Providers? *J Am Coll Cardiol* 2015; **66**: 1489-1496.

[11] Zhang W, Huang RS, Dolan ME. Integrating epigenomics into pharmacogenomic studies. *Pharmacogenomics and personalized medicine* 2008; **1**: 7-14.

[12] Prasad V, Fojo T, Brada M. Precision oncology: origins, optimism, and potential. *Lancet Oncol* 2016; **17**: e81-86.

[13] Sir Bruce Keogh. Personalised Medicine Strategy. *Board Paper - NHS England* 2015; **PB.24.09.15/05**: 1-6.

[14] Mehra R. Global public health problem of sudden cardiac death. *Journal of electrocardiology* 2007; **40**: S118-122.

[15] Alan D. Lopez CDM, Majid Ezzati, Dean T. Jamison, and Christopher J. L. Murray Global Burden of Disease and Risk Factors. *World Bank, Disease Control Priorities Project* 2006: Chapter 1 page 12.

[16] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS medicine* 2006; **3**: e442.

[17] Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. *Resuscitation* 2010; **81**: 1479-1487.

[18] Pell JP, Sirel JM, Marsden AK, Ford I, Walker NL, Cobbe SM. Presentation, management, and outcome of out of hospital cardiopulmonary arrest: comparison by underlying aetiology. *Heart* 2003; **89**: 839-842.

[19] Papadakis M, Sharma S, Cox S, Sheppard MN, Panoulas VF, Behr ER. The magnitude of sudden cardiac death in the young: a death certificate-based review in England and Wales. *Europace* 2009; **11**: 1353-1358.

[20] Perkins GD, Cooke MW. Variability in cardiac arrest survival: the NHS Ambulance Service Quality Indicators. *Emerg Med J* 2012; **29**: 3-5.

[21] Malhotra A, Rakhit R. Improving the UK's performance on survival after cardiac arrest. *BMJ* 2013; **347**.

[22] Causer JP, Connelly DT. Implantable defibrillators for life threatening ventricular arrhythmias. Are more effective than antiarrhythmic drugs in selected high risk patients. *BMJ* 1998; **317**: 762-763.

[23] Olde Nordkamp LRA, Dabiri Abkenari L, Boersma LVA, Maass AH, de Groot JR, van Oostrom AJHHM, et al. Clinical Research: The Entirely Subcutaneous Implantable Cardioverter-Defibrillator. Initial Clinical Experience in a Large Dutch Cohort. *Journal of the American College of Cardiology* 2012; **60**: 1933-1939.

[24] Jarman JWE, Todd DM. United Kingdom national experience of entirely subcutaneous implantable cardioverter-defibrillator technology: important lessons to learn. *Europace: European Pacing, Arrhythmias, And Cardiac Electrophysiology: Journal Of The Working Groups On Cardiac Pacing, Arrhythmias, And Cardiac Cellular Electrophysiology Of The European Society Of Cardiology* 2013; **15**: 1158-1165.

[25] Weiss R, Knight BP, Gold MR, Leon AR, Herre JM, Hood M, et al. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. *Circulation* 2013; **128**: 944-953.

[26] Killip T, 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *The American journal of cardiology* 1967; **20**: 457-464.

[27] Hinkle LE, Thaler HT. Clinical classification of cardiac deaths. *Circulation* 1982; **65**: 457-464.

[28] Albert CM, Chae CU, Grodstein F, Rose LM, Rexrode KM, Ruskin JN, et al. Prospective Study of Sudden Cardiac Death Among Women in the United States. *Circulation* 2003; **107**: 2096-2101.

[29] Stern S. Michel Mirowski. *Folia Cardio* 2006; **13**: 439-440.

[30] Kastor JA. Michel Mirowski and the automatic implantable defibrillator. *The American journal of cardiology* 1989; **63**: 977-982.

[31] Deyell MW T, S, Ignaszewski A. The Implantable Cardioverter Defibrillator: From Mirowski to it's current use. *British Columbia Medical Journal* 2010; **52**: 248-253.

[32] Mirowski M, Mower MM, Staewen WS, Tabatznik B, Mendeloff AI. Standby automatic defibrillator. An approach to prevention of sudden coronary death. *Archives of internal medicine* 1970; **126**: 158-161.

[33] Mirowski M, Mower MM, Gott VL, Brawley RK. Feasibility and effectiveness of low-energy catheter defibrillation in man. *Circulation* 1973; **47**: 79-85.

[34] Mirowski M, Mower MM, Langer A, Heilman MS, Schreibman J. A chronically implanted system for automatic defibrillation in active conscious dogs. Experimental model for treatment of sudden death from ventricular fibrillation. *Circulation* 1978; **58**: 90-94.

[35] Mirowski M, Mower MM, Reid PR. The automatic implantable defibrillator. *American heart journal* 1980; **100**: 1089-1092.

[36] Mirowski M, Reid PR, Mower MM, Watkins L, Jr., Platia EV, Griffith LS, et al. The automatic implantable cardioverter-defibrillator. *Pacing and clinical electrophysiology : PACE* 1984; **7**: 534-540.

[37] A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *The New England journal of medicine* 1997; **337**: 1576-1583.

[38] Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000; **102**: 748-754.

[39] Wever EF, Hauer RN, van Capelle FL, Tijssen JG, Crijns HJ, Algra A, et al. Randomized study of implantable defibrillator as first-choice therapy versus conventional strategy in postinfarct sudden death survivors. *Circulation* 1995; **91**: 2195-2203.

[40] Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000; **101**: 1297-1302.

[41] Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study. *European heart journal* 2000; **21**: 2071-2078.

[42] Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *The New England journal of medicine* 2005; **352**: 225-237.

[43] Bigger JT, Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. *The New England journal of medicine* 1997; **337**: 1569-1575.

[44] Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *The New England journal of medicine* 1999; **341**: 1882-1890.

[45] Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *The New England journal of medicine* 2004; **351**: 2481-2488.

[46] Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *The New England journal of medicine* 2004; **350**: 2151-2158.

[47] Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *The New England journal of medicine* 1996; **335**: 1933-1940.

[48] Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *The New England journal of medicine* 2002; **346**: 877-883.

[49] Santini M, Lavalle C, Ricci RP. Primary and secondary prevention of sudden cardiac death: who should get an ICD? *Heart* 2007; **93**: 1478-1483.

[50] Theuns DA, Smith T, Hunink MG, Bardy GH, Jordaens L. Effectiveness of prophylactic implantation of cardioverter-defibrillators without cardiac resynchronization therapy in patients with ischaemic or non-ischaemic heart disease: a systematic review and meta-analysis. *Europace* 2010; **12**: 1564-1570.

[51] Shun-Shin MJ, Zheng SL, Cole GD, Howard JP, Whinnett ZI, Francis DP. Implantable cardioverter defibrillators for primary prevention of death in left ventricular dysfunction with and without ischaemic heart disease: a meta-analysis of 8567 patients in the 11 trials. *European heart journal* 2017; **38**: 1738-1746.

[52] ICD Implantation in Patients with Nonischemic Heart Failure. *New England Journal of Medicine* 2017; **376**: 89-92.

[53] Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006; **8**: 746-837.

[54] Epstein AE, Dimarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: executive summary. *Heart Rhythm* 2008; **5**: 934-955.

[55] Foley PW, Addison CE, Whinney SB, Patel K, Cunningham D, Frenneaux MP, et al. Implantable cardioverter defibrillator therapy for primary prevention of sudden cardiac death after myocardial infarction: implications of international guidelines. *Pacing and clinical electrophysiology : PACE* 2009; **32 Suppl 1**: S131-134.

[56] Wilson D, Harding SA, Melton I, Lever NA, Stiles MK, Boddington D, et al. Geographic, ethnic and socioeconomic factors influencing access to implantable cardioverter defibrillators (ICDs) in New Zealand. *Heart, lung & circulation* 2012; **21**: 576-581.

[57] McComb JM, Plummer CJ, Cunningham MW, Cunningham D. Inequity of access to implantable cardioverter defibrillator therapy in England: possible causes of geographical variation in implantation rates. *Europace* 2009; **11**: 1308-1312.

[58] NICE. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure. *National Institute for Health and Clinical Excellence* June 2014; **Technology appraisal guidance [TA314]**

[59] Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac deathThe Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *European heart journal* 2015; **36**: 2793-2867.

[60] Betts TR, Sadarmin PP, Tomlinson DR, Rajappan K, Wong KCK, de Bono JP, et al. Absolute risk reduction in total mortality with implantable cardioverter defibrillators: analysis of primary and secondary prevention trial data to aid risk/benefit analysis. *Europace* 2013; **15**: 813-819.

[61] Goldenberg I, Gillespie J, Moss AJ, Hall WJ, Klein H, McNitt S, et al. Long-Term Benefit of Primary Prevention With an Implantable Cardioverter-Defibrillator: An Extended 8-Year Follow-Up Study of the Multicenter Automatic Defibrillator Implantation Trial II. *Circulation* 2010; **122**: 1265-1271.

[62] Tsai V, Goldstein MK, Hsia HH, Wang Y, Curtis J, Heidenreich PA, et al. Influence of age on perioperative complications among patients undergoing implantable cardioverter-defibrillators for primary prevention in the United States. *Circulation Cardiovascular quality and outcomes* 2011; **4**: 549-556.

[63] Chen CY, Stevenson Lw Fau - Stewart GC, Stewart Gc Fau - Seeger JD, Seeger Jd Fau - Williams L, Williams L Fau - Jalbert JJ, Jalbert Jj Fau - Setoguchi S, et al. Impact of baseline heart failure burden on post-implantable cardioverter-defibrillator mortality among medicare beneficiaries.

[64] Atwater BD, Daubert JP. Implantable cardioverter defibrillators: risks accompany the life-saving benefits. *Heart* 2012.

[65] Ezzat VA, Lee V, Ahsan S, Chow AW, Segal O, Rowland E, et al. A systematic review of ICD complications in randomised controlled trials versus registries: is our 'real-world' data an underestimation? *Open Heart* 2015; **2**: e000198.

[66] Al-Khatib SM, Lucas FL, Jollis JG, Malenka DJ, Wennberg DE. The relation between patients' outcomes and the volume of cardioverter-defibrillator implantation procedures performed by physicians treating Medicare beneficiaries. *J Am Coll Cardiol* 2005; **46**: 1536-1540.

[67] Tavernier R, Duytschaever M, Dossche K, Verleyen D, Van Den Brande F, De Greef Y, et al. Subacute implantable cardioverter defibrillator lead perforation: a potentially life-threatening event. *Europace* 2009; **11**: 966-967.

[68] Shahian DM, Venditti FJ, Jr. Hemothorax associated with anticoagulation after placement of implantable cardioverter defibrillator: possible similarity to postinfarction Dressler's syndrome. *Pacing and clinical electrophysiology : PACE* 1992; **15**: 1233-1235.

[69] Quigley RL, Hamer ME, Swiryn S. Migration of an automatic implantable cardioverter-defibrillator patch causing massive hemothorax. *Texas Heart Institute journal / from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital* 1996; **23**: 54-57.

[70] Merla R, Reddy NK, Kunapuli S, Schwarz E, Vitarelli A, Rosanio S. Late right ventricular perforation and hemothorax after transvenous defibrillator lead implantation. *The American journal of the medical sciences* 2007; **334**: 209-211.

[71] Kremers MS, Hastings JC, 3rd, Herndon WM, Howe H. Delayed ICD patch migration after thoracoscopic placement with resultant hemothorax. *Pacing and clinical electrophysiology : PACE* 1995; **18**: 1335-1337.

[72] Birnie D, Tung S, Simpson C, Crystal E, Exner D, Ayala Paredes F-A, et al. Complications associated with defibrillation threshold testing: The Canadian experience. *Heart Rhythm* 2008; **5**: 387-390.

[73] Rozmus G, Daubert J, Huang D, Rosero S, Hall B, Francis C. Venous Thrombosis and Stenosis After Implantation of Pacemakers and Defibrillators. *J Interv Card Electrophysiol* 2005; **13**: 9-19.

[74] Broka SM, De Roy LJ, Louagie YA, Collard EL, Ducart AR, Deheneffe YM, et al. Patent foramen ovale and implantable cardioverter defibrillator. *Acta chirurgica Belgica* 1999; **99**: 132-134.

[75] Radford D, Slaughter R. Coil embolization of iatrogenic arterio-venous fistula from pulmonary collateral artery to subclavian vein. *Cardiology in the young* 2001; **11**: 663-665.

[76] Ullah W, Chambers JB, Hunt BJ, Blauth C, Rinaldi CA. Massive thrombi on an implantable cardioverter-defibrillator lead in a patient with the antiphospholipid syndrome. *Europace* 2011; **13**: 1205-1206.

[77] Ezekowitz JA, Rowe BH, Dryden DM, Hooton N, Vandermeer B, Spooner C, et al. Systematic review: implantable cardioverter defibrillators for adults with left ventricular systolic dysfunction. *Annals of internal medicine* 2007; **147**: 251-262.

[78] Saxon LA, Hayes DL, Gilliam FR, Heidenreich PA, Day J, Seth M, et al. Long-term outcome after ICD and CRT implantation and influence of remote device follow-up: the ALTITUDE survival study. *Circulation* 2010; **122**: 2359-2367.

[79] Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, et al. 16-Year Trends in the Infection Burden for Pacemakers and Implantable Cardioverter-Defibrillators in the United States1993 to 2008. *Journal of the American College of Cardiology* 2011; **58**: 1001-1006.

[80] van Rees JB, Borleffs CJ, de Bie MK, Stijnen T, van Erven L, Bax JJ, et al. Inappropriate implantable cardioverter-defibrillator shocks: incidence, predictors, and impact on mortality. *J Am Coll Cardiol* 2011; **57**: 556-562.

[81] Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *The New England journal of medicine* 2008; **359**: 1009-1017.

[82] Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. *J Am Coll Cardiol* 2008; **51**: 1357-1365.

[83] Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, et al. Reduction in Inappropriate Therapy and Mortality through ICD Programming. *New England Journal of Medicine* 2012; **367**: 2275-2283.

[84] Kim JB, Spevack DM, Tunick PA, Bullinga JR, Kronzon I, Chinitz LA, et al. The Effect of Transvenous Pacemaker and Implantable Cardioverter Defibrillator Lead Placement on Tricuspid Valve Function: An Observational Study. *Journal of the American Society of Echocardiography* 2008; **21**: 284-287.

[85] Liu J, Brumberg G, Rattan R, Patel D, Adelstein E, Jain S, et al. Longitudinal follow-up of implantable cardioverter defibrillator leads. *The American journal of cardiology* 2014; **113**: 103-106.

[86] Goette A, Cantu F, van Erven L, Geelen P, Halimi F, Merino JL, et al. Performance and survival of transvenous defibrillation leads: need for a European data registry. *Europace* 2009; **11**: 31-34.

[87] Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, et al. Annual Rate of Transvenous Defibrillation Lead Defects in Implantable Cardioverter-Defibrillators Over a Period of >10 Years. *Circulation* 2007; **115**: 2474-2480.

[88] Maisel WH. Pacemaker and ICD generator reliability: meta-analysis of device registries. *JAMA : the journal of the American Medical Association* 2006; **295**: 1929-1934.

[89] Schron EB, Exner DV, Yao Q, Jenkins LS, Steinberg JS, Cook JR, et al. Quality of Life in the Antiarrhythmics Versus Implantable Defibrillators Trial: Impact of Therapy and Influence of Adverse Symptoms and Defibrillator Shocks. *Circulation* 2002; **105**: 589-594.

[90] Kamphuis HC, de Leeuw JR, Derksen R, Hauer RN, Winnubst JA. Implantable cardioverter defibrillator recipients: quality of life in recipients with and without ICD shock delivery: a prospective study. *Europace* 2003; **5**: 381-389.

[91] Poole JE, Gleva MJ, Mela T, Chung MK, Uslan DZ, Borge R, et al. Complication Rates Associated With Pacemaker or Implantable Cardioverter-Defibrillator Generator Replacements and Upgrade Procedures: Results From the REPLACE Registry. *Circulation* 2010; **122**: 1553-1561.

[92] Maisel WH, Hauser RG. Proceedings of the ICD Lead Performance Conference. *Heart Rhythm* 2008; **5**: 1331-1338.

[93] Rordorf R, Poggio L, Savastano S, Vicentini A, Petracci B, Chieffo E, et al. Failure of implantable cardioverter-defibrillator leads: a matter of lead size? *Heart Rhythm* 2013; **10**: 184-190.

[94] Eckstein J, Koller MT, Zabel M, Kalusche D, Schaer BA, Osswald S, et al. Necessity for Surgical Revision of Defibrillator Leads Implanted Long-Term: Causes and Management. *Circulation* 2008; **117**: 2727-2733.

[95] Hauser RG, Hayes DL. Increasing hazard of Sprint Fidelis implantable cardioverter-defibrillator lead failure. *Heart Rhythm* 2009; **6**: 605-610.

[96] Hauser RG, Kallinen LM, Almquist AK, Gornick CC, Katsiyiannis WT. Early failure of a small-diameter high-voltage implantable cardioverter-defibrillator lead. *Heart Rhythm* 2007; **4**: 892-896.

[97] Cheung JW, Al-Kazaz M, Thomas G, Liu CF, Ip JE, Bender SR, et al. Mechanisms, predictors, and trends of electrical failure of Riata leads. *Heart Rhythm* 2013; **10**: 1453-1459.

[98] Brunner MP, Cronin EM, Jacob J, Duarte VE, Tarakji KG, Martin DO, et al. Transvenous extraction of implantable cardioverter-defibrillator leads under advisory--a comparison of Riata, Sprint Fidelis, and non-recalled implantable cardioverter-defibrillator leads. *Heart Rhythm* 2013; **10**: 1444-1450.

[99] Hauser RG, Katsiyiannis WT, Gornick CC, Almquist AK, Kallinen LM. Deaths and cardiovascular injuries due to device-assisted implantable cardioverter-defibrillator and pacemaker lead extraction. *Europace* 2010; **12**: 395-401.

[100] Sears SF, Jr., Conti JB. Psychological aspects of cardiac devices and recalls in patients with implantable cardioverter defibrillators. *The American journal of cardiology* 2006; **98**: 565-567.

[101] Sears SF, Lewis TS, Kuhl EA, Conti JB. Predictors of quality of life in patients with implantable cardioverter defibrillators. *Psychosomatics* 2005; **46**: 451-457.

[102] Pedersen SS, van den Broek KC, Sears SF, Jr. Psychological intervention following implantation of an implantable defibrillator: a review and future recommendations. *Pacing and clinical electrophysiology : PACE* 2007; **30**: 1546-1554.

[103] Liew R. Inappropriate defibrillator shocks and mortality. *Heart* 2013; **99**: 1223-1224.

[104] Madhavan M, Friedman PA. Optimal programming of implantable cardiac-defibrillators. *Circulation* 2013; **128**: 659-672.

[105] Matlock DD, Peterson PN, Heidenreich PA, Lucas FL, Malenka DJ, Wang Y, et al. Regional variation in the use of implantable cardioverter-defibrillators for primary prevention: results from the National Cardiovascular Data Registry. *Circulation Cardiovascular quality and outcomes* 2011; **4**: 114-121.

[106] Matlock DD, Kutner JS, Emsermann CB, Al-Khatib SM, Sanders GD, Dickinson LM, et al. Regional variations in physicians' attitudes and recommendations surrounding implantable cardioverter-defibrillators. *Journal of cardiac failure* 2011; **17**: 318-324.

[107] Lubinski A, Bissinger A, Boersma L, Leenhardt A, Merkely B, Oto A, et al. Determinants of geographic variations in implantation of cardiac defibrillators in the European Society of Cardiology member countries--data from the European Heart Rhythm Association White Book. *Europace* 2011; **13**: 654-662.

[108] John Camm A, Nisam S. European utilization of the implantable defibrillator: has 10 years changed the 'enigma'? *Europace* 2010; **12**: 1063-1069.

[109] Chase D, Roderick PJ, Burnley H, Gallagher PJ, Roberts PR, Morgan JM. Is there unmet need for implantable cardioverter defibrillators? Findings from a post-mortem series of sudden cardiac death. *Europace* 2008; **10**: 741-746.

[110] Chae SH, Koelling TM. Patient and physician determinants of implantable cardioverter defibrillator use in the heart failure population. *Congestive heart failure (Greenwich, Conn)* 2010; **16**: 141-146.

[111] Gradaus R, Hammel D, Kotthoff S, Bocker D. Nonthoracotomy implantable cardioverter defibrillator placement in children: use of subcutaneous array leads and abdominally placed implantable cardioverter defibrillators in children. *Journal of cardiovascular electrophysiology* 2001; **12**: 356-360.

[112] Grace AA, Smith WM, Hood MA, Connelly DT, Murgatroyd FD, Crozier IG, et al. A prospective, randomized comparison in humans of defibrillation efficacy of a standard transvenous ICD system with a totally subcutaneous ICD system (The S-ICD® system). *Heart Rhythm* 2005; **2**: 1036.

[113] Burke MC, Coman JA, Cates AW, Lindstrom CC, Sandler DA, Kim SS, et al. Defibrillation energy requirements using a left anterior chest cutaneous to subcutaneous shocking vector: implications for a total subcutaneous implantable defibrillator. *Heart Rhythm* 2005; **2**: 1332-1338.

[114] Adgey AAJ, Spence MS, Walsh SJ. Theory and practice of defibrillation: (2) defibrillation for ventricular fibrillation. *Heart* 2005; **91**: 118-125.

[115] Zipes DP, Fischer J, King RM, Nicoll Ad, Jolly WW. Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium. *The American journal of cardiology* 1975; **36**: 37-44.

[116] Zhou X, Daubert JP, Wolf PD, Smith WM, Ideker RE. Epicardial mapping of ventricular defibrillation with monophasic and biphasic shocks in dogs. *Circulation research* 1993; **72**: 145-160.

[117] Jolley M, Stinstra J, Pieper S, Macleod R, Brooks DH, Cecchin F, et al. A computer modeling tool for comparing novel ICD electrode orientations in children and adults. *Heart Rhythm* 2008; **5**: 565-572.

[118] Killingsworth CR, Melnick SB, Litovsky SH, Ideker RE, Walcott GP. Evaluation of acute cardiac and chest wall damage after shocks with a subcutaneous implantable cardioverter defibrillator in Swine. *Pacing And Clinical Electrophysiology: PACE* 2013; **36**: 1265-1272.

[119] Crozier I, Hooks D, Daly M, Melton I. How the Subcutaneous Implantable Cardioverter Defibrillator Works: Indications/Limitations and Special Groups to Consider. *Cardiac Electrophysiology Clinics* 2014; **6**: 285-295.

[120] Hasdemir C, Shah N, Rao AP, Acosta H, Matsudaira K, Neas BR, et al. Analysis of troponin I levels after spontaneous implantable cardioverter defibrillator shocks. *Journal of cardiovascular electrophysiology* 2002; **13**: 144-150.

[121] Tokano T, Bach D, Chang J, Davis J, Souza JJ, Zivin A, et al. Effect of ventricular shock strength on cardiac hemodynamics. *Journal of cardiovascular electrophysiology* 1998; **9**: 791-797.

[122] Tung L, Tovar O, Neunlist M, Jain SK, O'Neill RJ. Effects of strong electrical shock on cardiac muscle tissue. *Annals of the New York Academy of Sciences* 1994; **720**: 160-175.

[123] Walcott GP, Killingsworth CR, Ideker RE. Do clinically relevant transthoracic defibrillation energies cause myocardial damage and dysfunction? *Resuscitation* 2003; **59**: 59-70.

[124] Zivin A, Souza J, Pelosi F, Flemming M, Knight BP, Goyal R, et al. Relationship between shock energy and postdefibrillation ventricular arrhythmias in patients with implantable defibrillators. *Journal of cardiovascular electrophysiology* 1999; **10**: 370-377.

[125] Lieberman R, Havel WJ, Rashba E, DeGroot PJ, Stromberg K, Shorofsky SR. Acute defibrillation performance of a novel, non-transvenous shock pathway in adult ICD indicated patients. *Heart Rhythm* 2008; **5**: 28-34.

[126] Jolley M, Stinstra J, Tate J, Pieper S, Macleod R, Chu L, et al. Finite element modeling of subcutaneous implantable defibrillator electrodes in an adult torso. *Heart Rhythm* 2010; **7**: 692-698.

[127] Cappato R, Castelvecchio S, Erlinger P, Sanghera R, Scheck D, Ostroff A, et al. Feasibility of defibrillation and automatic arrhythmia detection using an exclusively subcutaneous defibrillator system in canines. *Journal of cardiovascular electrophysiology* 2013; **24**: 77-82.

[128] Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, et al. An entirely subcutaneous implantable cardioverter-defibrillator. *The New England journal of medicine* 2010; **363**: 36-44.

[129] Olde Nordkamp LRA, Warnaars JLF, Kooiman KM, de Groot JR, Rosenmöller BRAM, Wilde AAM, et al. Which patients are not suitable for a subcutaneous ICD: incidence and predictors of failed QRS-T-wave morphology screening. *Journal of cardiovascular electrophysiology* 2014; **25**: 494-499.

[130] Bellardine Black CL, Stromberg K, van Balen GP, Ghanem RN, Breedveld RW, Tieleman RG. Is surface ECG a useful surrogate for subcutaneous ECG? *Pacing and clinical electrophysiology : PACE* 2010; **33**: 135-145.

[131] Gold MR, Theuns DA, Knight BP, Sturdivant JL, Sanghera R, Ellenbogen KA, et al. Head-to-head comparison of arrhythmia discrimination performance of subcutaneous and transvenous ICD arrhythmia detection algorithms: the START study. *Journal of cardiovascular electrophysiology* 2012; **23**: 359-366.

[132] Randles DA, Hawkins NM, Shaw M, Patwala AY, Pettit SJ, Wright DJ. How many patients fulfil the surface electrocardiogram criteria for subcutaneous implantable cardioverter-defibrillator implantation? *Europace: European Pacing, Arrhythmias, And Cardiac Electrophysiology: Journal Of The Working Groups On Cardiac Pacing, Arrhythmias, And Cardiac Cellular Electrophysiology Of The European Society Of Cardiology* 2014; **16**: 1015-1021.

[133] Lambiase PD, Barr C, Theuns DA, Knops R, Neuzil P, Johansen JB, et al. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. *European heart journal* 2014; **35**: 1657-1665.

[134] Allavatam V, Palreddy S, Sanghera R, Warren JA. Accurate cardiac event detection in an implantable cardiac stimulus device: Google Patents 2014.

[135] Brisben AJ, Burke MC, Knight BP, Hahn SJ, Herrmann KL, Allavatam V, et al. A new algorithm to reduce inappropriate therapy in the S-ICD system. *Journal of cardiovascular electrophysiology* 2015; **26**: 417-423.

[136] Wilson D, Yue A, Roberts PR, Morgan JM. Oversensing and Shock Delivery in the S-ICD: Five Shocks Two Mechanisms. *Pacing and clinical electrophysiology : PACE* 2015; **38**: 1009-1013.

[137] Kooiman KM, Knops RE, Olde Nordkamp L, Wilde AAM, de Groot JR. Inappropriate subcutaneous implantable cardioverter-defibrillator shocks due to T-wave oversensing can be prevented: implications for management. *Heart Rhythm: The Official Journal Of The Heart Rhythm Society* 2014; **11**: 426-434.

[138] Gold MR, Weiss R, Theuns DAMJ, Smith W, Leon A, Knight BP, et al. Use of a discrimination algorithm to reduce inappropriate shocks with a subcutaneous implantable cardioverter-defibrillator. *Heart Rhythm* 2014; **11**: 1352-1358.

[139] Burke M TW, Ludmer PL, Barr CS, Beshai JF, ONeill PG, et al. Poster Session 1: PO01-71 to PO1-119. *Heart Rhythm* 2009; **6**: S126.

[140] Olde Nordkamp LR, Knops Re Fau - Bardy GH, Bardy Gh Fau - Blaauw Y, Blaauw Y Fau - Boersma LVA, Boersma Lv Fau - Bos JS, Bos Js Fau - Delnoy PPHM, et al. Rationale and design of the PRAETORIAN trial: a Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy.

[141] Walsh EP. Sudden death in adult congenital heart disease: risk stratification in 2014. *Heart Rhythm* 2014; **11**: 1735-1742.

[142] Gallego P, Gonzalez AE, Sanchez-Recalde A, Peinado R, Polo L, Gomez-Rubin C, et al. Incidence and Predictors of Sudden Cardiac Arrest in Adults With Congenital Heart Defects Repaired Before Adult Life. *The American journal of cardiology* 2012; **110**: 109-117.

[143] Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, et al. Sudden cardiac death in adult congenital heart disease. *Circulation* 2012; **126**: 1944-1954.

[144] Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. *Journal of the American College of Cardiology* 1998; **32**: 245-251.

[145] Vehmeijer JT, Brouwer TF, Limpens J, Knops RE, Bouma BJ, Mulder BJM, et al. Implantable cardioverter-defibrillators in adults with congenital heart disease: a systematic review and meta-analysis. *European heart journal* 2016.

[146] Pettit SJ, McLean A Fau - Colquhoun I, Colquhoun I Fau - Connelly D, Connelly D Fau - McLeod K, McLeod K. Clinical experience of subcutaneous and transvenous implantable cardioverter defibrillators in children and teenagers.

[147] Jarman JW, Lascelles K Fau - Wong T, Wong T Fau - Markides V, Markides V Fau - Clague JR, Clague Jr Fau - Till J, Till J. Clinical experience of entirely subcutaneous implantable cardioverter-defibrillators in children and adults: cause for caution.

[148] Burke MC, Gold MR, Knight BP, Barr CS, Theuns DA, Boersma LV, et al. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-Year Results From a Pooled Analysis of the IDE Study and EFFORTLESS Registry.

[149] Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, et al. Reduction in inappropriate therapy and mortality through ICD programming. *New England Journal of Medicine* 2012; **367**: 2275-2283.

[150] Zumhagen S, Grace AA, O'Connor S, Loher A, Kobe J, Eckardt L, et al. Totally subcutaneous implantable cardioverter defibrillator with an alternative, right parasternal, electrode placement. *Pacing and clinical electrophysiology : PACE* 2012; **35**: e254-257.

[151] Kaczmarek KA, Winter J, Wranicz JK, Ptaszynski PA. Atypical position of subcutaneus implantable cardioverter-defibrillator as a solution in hypertrophic cardiomyopathy patient with initially negative electrocardiographic screening. *European heart journal* 2015.

[152] Ceresnak SR, Motonaga KS, Rogers IS, Viswanathan MN. Right-sided subcutaneous implantable cardioverter-defibrillator placement in a patient with dextrocardia, tetralogy of Fallot, and conduction disease. *HeartRhythm Case Reports*.

[153] Vincent GM, Abildskov JA, Burgess MJ, Millar K, Lux RL, Wyatt RF. Diagnosis of old inferior myocardial infarction by body surface isopotential mapping. *The American journal of cardiology* 1977; **39**: 510-515.

[154] Robinson MR, Curzen N. Electrocardiographic body surface mapping: potential tool for the detection of transient myocardial ischemia in the 21st century? *Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc* 2009; **14**: 201-210.

[155] McMechan SR, MacKenzie G, Allen J, Wright GT, Dempsey GJ, Crawley M, et al. Body surface ECG potential maps in acute myocardial infarction. *Journal of electrocardiology* 1995; **28 Suppl**: 184-190.

[156] Green LS, Lux RL, Haws CW, Williams RR, Hunt SC, Burgess MJ. Effects of age, sex, and body habitus on QRS and ST-T potential maps of 1100 normal subjects. *Circulation* 1985; **71**: 244-253.

[157] Aviva Petrie CS. *Medical Statistics at a Glance*: Wiley-Blackwell

July 2009: 180.

[158] MacLeod RS, Ni Q, Punske B, Ershler PR, Yilmaz B, Taccardi B. Effects of heart position on the body-surface electrocardiogram. *Journal of electrocardiology* 2000; **33, Supplement 1**: 229-237.

[159] Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, et al. Mortality in adult congenital heart disease. *European heart journal* 2010; **31**: 1220-1229.

[160] Mayerson HS, Davis Jr WD. The influence of posture on the electrocardiogram. *American heart journal* 1942; **24**: 593-601.

[161] Hirai Y, Nakano Y, Ogi H, Kihara Y. Postural change-dependent T-wave oversensing resulting in the administration of inappropriate shocks. *Journal of Arrhythmia* 2012; **28**: 280-283.

[162] Burke M TW, Ludmer PL et al. Comparisons during multiple posture of resting ECG's (COMPARE) study (abstract). *Heart Rhythm* 2009; **6(Suppl 5):S126**.

[163] Wilson D, Yue A, Roberts PR, Morgan JM. Oversensing and Shock Delivery in the S-ICD: Five Shocks Two Mechanisms. *Pacing and Clinical Electrophysiology* 2014: n/a-n/a.

[164] Burke MC, Gold MR, Knight BP, Barr CS, Theuns DA, Boersma LV, et al. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-Year Results From a Pooled Analysis of the IDE Study and EFFORTLESS Registry. *J Am Coll Cardiol* 2015; **65**: 1605-1615.

[165] Olde Nordkamp LR, Brouwer TF, Barr C, Theuns DA, Boersma LV, Johansen JB, et al. Inappropriate shocks in the subcutaneous ICD: Incidence, predictors and management. *International journal of cardiology* 2015; **195**: 126-133.

[166] Gold MR, Weiss R, Theuns DA, Smith W, Leon A, Knight BP, et al. Use of a discrimination algorithm to reduce inappropriate shocks with a subcutaneous implantable cardioverter-defibrillator. *Heart Rhythm* 2014; **11**: 1352-1358.

[167] Madias JE, Bazaz R, Agarwal H, Win M, Medepalli L. Anasarca-mediated attenuation of the amplitude of electrocardiogram complexes: a description of a heretofore unrecognized phenomenon. *J Am Coll Cardiol* 2001; **38**: 756-764.

[168] Fosbol EL, Seibaek M, Brendorp B, Torp-Pedersen C, Kober L. Prognostic importance of change in QRS duration over time associated with left ventricular dysfunction in patients with congestive heart failure: the DIAMOND study. *Journal of cardiac failure* 2008; **14**: 850-855.

[169] Al-Zaiti SS, Runco KN, Carey MG. Increased T wave complexity can indicate subclinical myocardial ischemia in asymptomatic adults. *Journal of electrocardiology* 2011; **44**: 684-688.

[170] Assanelli D, Di Castelnuovo A, Rago L, Badilini F, Vinetti G, Gianfagna F, et al. T-wave axis deviation and left ventricular hypertrophy interaction in diabetes and hypertension. *Journal of electrocardiology* 2013; **46**: 487-491.

[171] Hasan MA, Abbott D, Baumert M. Relation between beat-to-beat QT interval variability and T-wave amplitude in healthy subjects. *Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc* 2012; **17**: 195-203.

[172] Poulikakos D, Banerjee D, Malik M. T wave morphology changes during hemodialysis. *Journal of electrocardiology* 2013; **46**: 492-496.

[173] Walker BD, Krahn AD, Klein GJ, Skanes AC, Yee R. Drug induced QT prolongation: lessons from congenital and acquired long QT syndromes. *Current drug targets Cardiovascular & haematological disorders* 2003; **3**: 327-335.

[174] Dower GE, Yakush A, Nazzal SB, Jutzy RV, Ruiz CE. Deriving the 12-lead electrocardiogram from four (EASI) electrodes. *Journal of electrocardiology* 1988; **21 Suppl**: S182-187.

[175] Drew BJ, Pelter MM, Wung SF, Adams MG, Taylor C, Evans GT, Jr., et al. Accuracy of the EASI 12-lead electrocardiogram compared to the standard 12-lead electrocardiogram for diagnosing multiple cardiac abnormalities. *Journal of electrocardiology* 1999; **32 Suppl**: 38-47.

[176] Horacek BM, Warren JW, Feild DQ, Feldman CL. Statistical and deterministic approaches to designing transformations of electrocardiographic leads. *Journal of electrocardiology* 2002; **35 Suppl**: 41-52.

[177] Wehr G, Peters RJ, Khalife K, Banning AP, Kuehlkamp V, Rickards AF, et al. A vector-based, 5-electrode, 12-lead monitoring ECG (EASI) is equivalent to conventional 12-lead ECG for diagnosis of acute coronary syndromes. *Journal of electrocardiology* 2006; **39**: 22-28.

[178] Finlay DD, Nugent CD, Kellett JG, Donnelly MP, McCullagh PJ, Black ND. Synthesising the 12-lead electrocardiogram: Trends and challenges. *European journal of internal medicine* 2007; **18**: 566-570.

[179] Mendenhall GS. Implantable and surface electrocardiography: complementary technologies. *Journal of electrocardiology* 2010; **43**: 619-623.

[180] Kachenoura A, Poree F, Hernandez AI, Carrault G. Using intracardiac vectorcardiographic loop for surface ECG synthesis. *Eurasip Journal on Advances in Signal Processing* 2008.

[181] Mendenhall GS, Saba S. 12-lead surface electrocardiogram reconstruction from implanted device electrograms. *Europace* 2010; **12**: 991-998.

[182] Porée F, Kachenoura A, Carrault G, Dal Molin R, Mabo P, Hernandez AI. Surface electrocardiogram reconstruction from intracardiac electrograms using a dynamic time delay artificial neural network. *Ieee Transactions on Bio-Medical Engineering* 2013; **60**: 106-114.

[183] Frank E. General theory of heat-vector projection. *Circulation research* 1954; **2**: 258-270.

[184] Chantad D, Krittayaphong R, Komoltri C. Derived 12-lead electrocardiogram in the assessment of ST-segment deviation and cardiac rhythm. *Journal of electrocardiology* 2006; **39**: 7-12.

[185] Nelwan SP, Kors JA, Meij SH, van Bemmel JH, Simoons ML. Reconstruction of the 12-lead electrocardiogram from reduced lead sets. *Journal of electrocardiology* 2004; **37**: 11-18.

[186] Nelwan SP, Kors JA, Crater SW, Meij SH, van Dam TB, Simoons ML, et al. Simultaneous comparison of 3 derived 12-lead electrocardiograms with standard electrocardiogram at rest and during percutaneous coronary occlusion. *Journal of electrocardiology* 2008; **41**: 230-237.

[187] BH. M. *Correlation. In Statistical methods for healthcare research*: Lippincott Williams & Wilkins 2005: 239-258.

[188] Schreck DM, Fishberg RD. Derivation of the 12-lead electrocardiogram and 3-lead vectorcardiogram. *The American journal of emergency medicine* 2013; **31**: 1183-1190.

[189] Welinder AE, Wagner GS, Horacek BM, Martin TN, Maynard C, Pahlm O. EASI-Derived vs standard 12-lead electrocardiogram for Selvester QRS score estimations of chronic myocardial infarct size, using cardiac magnetic resonance imaging as gold standard. *Journal of electrocardiology* 2009; **42**: 145-151.

[190] Martinez JP, Laguna P, Olmos S, Pahlm O, Pettersson J, Sornmo L. Assessment of QT-measurement accuracy using the 12-lead electrocardiogram derived from EASI leads. *Journal of electrocardiology* 2007; **40**: 172-179.

[191] Feild DQ, Feldman CL, Horacek BM. Improved EASI coefficients: their derivation, values, and performance. *Journal of electrocardiology* 2002; **35 Suppl**: 23-33.

[192] Knops RE, Brouwer TF, Barr CS, Theuns DA, Boersma L, Weiss R, et al. The learning curve associated with the introduction of the subcutaneous implantable defibrillator. *Europace* 2015.

[193] Wilson D, Shi B, Harding S, Lever N, Larsen P. Implantable cardioverter-defibrillators: a long-term view. *Intern Med J* 2012; **42**: 554-561.

[194] Lambiase PD, Srinivasan NT. Early experience with the subcutaneous ICD. *Current cardiology reports* 2014; **16**: 516.

[195] Patel KHK, Lambiase PD. The subcutaneous ICD—current evidence and challenges. *Cardiovascular Diagnosis and Therapy* 2014; **4**: 449-459.

[196] Chan NY, Yuen HC, Mok NS. Right Parasternal Electrode Configuration Converts a Failed Electrocardiographic Screening to a Pass for Subcutaneous Implantable Cardioverter-Defibrillator Implantation. *Heart, lung & circulation* 2015.

[197] Waller JR, Salmon AP, Roberts PR. A right-sided subcutaneous implantable cardioverter defibrillator in a patient with congenital heart disease. *Europace* 2015; **17**: 77.

[198] Barmase S DS, Mukhopadhyay S. Wavelet Transform-Based Analysis of QRS complex in ECG signals. *CoRR* 2013; **abs/1311.6460**.

[199] Gritzali F, Frangakis G, Papakonstantinou G. Detection of the P and T waves in an ECG. *Computers and biomedical research, an international journal* 1989; **22**: 83-91.

[200] Coast DA, Stern RM, Cano GG, Briller SA. An approach to cardiac arrhythmia analysis using hidden Markov models. *IEEE Trans Biomed Eng* 1990; **37**: 826-836.

[201] Kyrkos A, Giakoumakis EA, Carayannis G. QRS detection through time recursive prediction techniques. *Signal Processing* 1988; **15**: 429-436.

[202] Pan J, Tompkins WJ. A real-time QRS detection algorithm. *IEEE Trans Biomed Eng* 1985; **32**: 230-236.

[203] Hu YH, Tompkins WJ, Urrusti JL, Afonso VX. Applications of artificial neural networks for ECG signal detection and classification. *Journal of electrocardiology* 1993; **26 Suppl**: 66-73.

[204] Kadambe S, Murray R, Boudreaux-Bartels GF. Wavelet transform-based QRS complex detector. *IEEE Trans Biomed Eng* 1999; **46**: 838-848.

[205] Kohler BU, Hennig C, Orglmeister R. The principles of software QRS detection. *IEEE engineering in medicine and biology magazine : the quarterly magazine of the Engineering in Medicine & Biology Society* 2002; **21**: 42-57.

[206] Min YJ, Kim HK, Kang YR, Kim GS, Park J, Kim SW. Design of wavelet-based ECG detector for implantable cardiac pacemakers. *IEEE transactions on biomedical circuits and systems* 2013; **7**: 426-436.

[207] Srinivasan NT, Patel KH, Qamar K, Taylor A, Baca M, Providencia R, et al. Disease Severity and Exercise Testing Reduce Subcutaneous Implantable Cardioverter-Defibrillator Left Sternal ECG Screening Success in Hypertrophic Cardiomyopathy. *Circulation Arrhythmia and electrophysiology* 2017; **10**.

[208] Kuschyk J, Stach K, Tulumen E, Rudic B, Liebe V, Schimpf R, et al. Subcutaneous implantable cardioverter-defibrillator: First single-center experience with other cardiac implantable electronic devices. *Heart Rhythm* 2015; **12**: 2230-2238.

[209] Gemein C, Haj M, Schmitt J. Combining an subcutaneous ICD and a pacemaker with abdominal device location and bipolar epicardial left ventricular lead: first-in-man approach. *Europace* 2016; **18**: 1279.

[210] Reynolds D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, et al. A Leadless Intracardiac Transcatheter Pacing System. *New England Journal of Medicine* 2016; **374**: 533-541.

[211] Tjong FVY, Brouwer TF, Smeding L, Kooiman KM, de Groot JR, Ligon D, et al. Combined leadless pacemaker and subcutaneous implantable defibrillator therapy: feasibility, safety, and performance. *EP Europace* 2016; **18**: 1740-1747.

[212] Briasoulis A, Mallikethi-Reddy S, Palla M, Alesh I, Afonso L. Myocardial fibrosis on cardiac magnetic resonance and cardiac outcomes in hypertrophic cardiomyopathy: a meta-analysis. *Heart* 2015; **101**: 1406-1411.

[213] Dagres N, Hindricks G. Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? *European heart journal* 2013; **34**: 1964-1971.

[214] Disertori M, Quintarelli S, Mazzola S, Favalli V, Narula N, Arbustini E. The need to modify patient selection to improve the benefits of implantable cardioverter-defibrillator for primary prevention of sudden death in non-ischaemic dilated cardiomyopathy. *Europace* 2013; **15**: 1693-1701.