UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

A study of novel electrographic body surface mapping for detection of transient regional myocardial ischaemia and development of sensing configuration of subcutaneous implantable cardioverter defibrillator

by

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Thesis for the degree of Doctor of Philosophy

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ABSTRACT

The diagnosis of ischemic heart disease (IHD) and the prevention of sudden cardiac death (SCD) remains a global challenge.

The diagnostic pathways for IHD are significantly dependant on the standard 12-lead electrocardiography (ECG), which itself has flaws due to a limited number of electrodes. The 80-electrode body surface mapping (BSM) allows more comprehensive assessment of electrocardiac activity. However, the interpretation of the BSM data is laborious and complex. Therefore, in order to simplify the analysis, we have introduced the concept of BSM Delta map, which is based on 80-electrode ECG. However, BSM Delta map needs to be evaluated in the clinical settings.

The role of the implantable cardioverter defibrillator (ICD) in the primary and secondary prevention of SCD is well established, however, due to the associated complications and its invasive nature, it is under utilised. The novel subcutaneous ICD (S-ICD) is considered minimally invasive and a suitable alternative, however, S-ICD is associated with high incidence of inappropriate shocks and sensing algorithm failures. The BSM has a potential to allow further exploration and improvement of S-ICD sensing algorithm.

The objectives of the studies in this thesis are: Firstly, to investigate the novel BSM Delta map, which is derived from 80-electrode body surface map (BSM) for the detection of reversible myocardial ischaemia and to assess its clinical efficacy in patients with stable and unstable IHD. Secondly, to use BSM as a tool with which to study and develop the sensing algorithm of S-ICD in patients with and without complex congenital heart diseases (C-CHD).

These studies are published and have led to significant changes in the current clinical practice and have provided a foundation for further improvement in the diagnostic algorithm of IHD and sensing algorithm of S-ICD. These studies have led to the development of a new automated device for the screening of patients for S-ICD.

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A STUDY OF NOVEL ELECTROGRAPHIC BODY SURFACE MAPPING FOR DETECTION OF TRANSIENT REGIONAL MYOCARDIAL ISCHAEMIA AND DEVELOPMENT OF SENSING CONFIGURATION OF SUBCUTANEOUS ICD

by

Mehmood Zeb

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DECLARATION OF AUTHORSHIP

I, Dr Mehmood Zeb declare that the thesis entitled: A study of novel electrographic body surface mapping for detection of transient regional myocardial ischaemia and development of sensing configuration of subcutaneous ICD, and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

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

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;

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

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.

I have acknowledged all main sources of help.

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;

Parts of this work have been published as listed in the next section overleaf.

Signed: ……..

Date: ……

PUBLICATIONS IN PEER REVIEWED JOURNALS

Original papers:

1. **Zeb M**, Garty F, Nagaraj N, Bannister W, Roderick P, Corbett S, Morgan J, Curzen N. Detection of transient regional myocardial ischemia using body surface Delta map in patients referred for myocardial perfusion imaging-A pilot study. ***Journal of Electrocardiol.*** 2013 Jul 15. doi:pii: S0022-0736(13)00314-2. 10.1016/j.jelectrocard.2013.06.005. [Epub ahead of print] PubMed PMID: 23866293.

2. **Zeb M**, Mahmoudi M, Garty F, Bannister C, Reddiar R, Nicholas Z, Crouch R, Heyworth J, Curzen N. Detection of regional myocardial ischaemia by a novel 80-electrode body surface Delta map in patients presenting to the emergency department with cardiac-sounding chest pain. ***Eur Journal of Emergency Med***. 2014 Apr;21(2):89-97.doi:10.1097/MEJ.0b013e3283642e27. PubMed PMID: 23883775. [Epub ahead of print] PubMed PMID: 23883775.

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1. **Zeb M**, Garty F. Nagaraj N, Bannister W, Curzen N. Detection of transient regional myocardial ischaemia with 80-electrode body surface delta map and its comparison with myocardial perfusion imaging and 12-lead ECG. ***Circulation Research*** 2011; 109 (Sup 1): AP308 to AP308.

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DEFINITIONS AND ABBREVIATIONS

ACS	Acute coronary syndrome
BSM	Body Surface Mapping
BMI	Body mass index
CAD	Coronary artery disease
CHD	Congenital heart disease
CVD	Cardiovascular disease
ED	Emergency Department
ECG	Electrocardiogram
ETT	Exercise tolerance test
GTN	Glyceryl trinitrate
HDL	High-density lipoprotein
IB	Ischaemic Burden
ICD	Implantable cardioverter defibrillator
IHD	Ischaemic heart disease
LAD	Lateral anterior descending coronary artery
LBBB	Left bundle branch block
LCX	Left circumflex artery
LDL	Low density lipoprotein
MI	Myocardial infarction

MPI	Myocardial Perfusion Imaging
MRI	Magnetic Resonance Imaging
NPV	Negative Predictive Value
NSTEMI	Non-ST segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PPV	Positive Predicative Value
PRIME®	Precise Rapid Ischemic Myocardial Evaluation
RCA	Right coronary artery
SEM	Standard Error of the Mean
S-ICD	Subcutaneous implantable cardioverter
SPSS	Statistical Program for Social Sciences
STEMI	ST segment elevation infarction
TRMI	Transient regional myocardial ischaemia
UA	Unstable angina

CHAPTER 1

INTRODUCTION

1 INTRODUCTION

1.1 GENERAL INTRODUCTION

The diagnosis of ischaemic heart disease (IHD) and prevention of sudden cardiac death (SCD) are leading global health challenges (1). Advances in the therapeutic interventions over the last few decades have reduced the mortality due to IHD and SCD. However, the UK deaths rates are still higher than many European countries (2). As such, research and development in modern medicine are primarily focused on preventative and therapeutic strategies to attenuate the scale of this mounting problem.

At the beginning of 20th century, the development of electrocardiography (ECG) was a breakthrough and marked the origin of cardiology. Even today, ECG has a fundamental role in the diagnosis of ischaemic heart disease (IHD) and arrhythmias. However, despite several known limitations, the currently used standard 12-lead ECG (derived from 10 electrodes) has evolved very little in the last century. Due to the anatomical location of the heart in the human thorax, and globular structure of the heart, several studies have suggested the use of a higher number of electrodes than currently used, to enable appropriate sampling of the electrocardiac activity.

The development of 80-electrodes body surface mapping (BSM) has offered a potential to improve the diagnostic algorithms of IHD. However, computation and understanding of the large amount of data derived from the 80-electrodes ECG have hampered its widespread adaptation in clinical practice, especially for the diagnosis of IHD. To simplify the IHD diagnostic algorithm of 80-electrodes ECG, our group has developed a technique, we call BSM Delta map, which is derived from 80-electrodes ECG and projects a printable result on a

computer screen on a pseudo-torso with colour coding to enable rapid understanding of the electro-cardiac data and diagnosis of IHD.

The diagnosis and management of cardiac rhythm is another important area where ECG is the only tool that can be reliably used. The diagnostic and therapeutic algorithms of life-saving devices like ICD utilises the electrical signals from the heart to function appropriately. The conventional ICD consists of a generator implanted under the skin, and a lead, which is extended through the larger veins and attached to the heart. The effectiveness of the ICD for the prevention of sudden cardiac death is well established. However, due to the requirement of a permanent lead in the venous system and cardiac chamber, it is associated with severe implant related complications and also exposes the recipient to life-long complications of a foreign body in the major vasculature and cardiac chambers. The novel subcutaneous implantable cardioverter (S-ICD) does not require insertion of the lead into the venous system and heart, both the lead and the generator is implanted under the skin and remains under the skin. Therefore, S-ICD has emerged as an attractive alternative, however; there are concerns regarding its sensing and diagnostic algorithms. The electrographic body surface mapping (BSM) provides an excellent platform to investigate and improve the sensing algorithm of S-ICD.

This thesis is based on the studies, (i) to explore the potential of BSM Delta map for the diagnosis of IHD and (ii) to use BSM for understanding, and development of the S-ICD sensing configuration.

Most of the work in this thesis has now been published in peer-reviewed international journals and has led to significant changes in the current clinical practice, and furthermore, has generated clinically relevant questions that may set the stage for future large-scale clinical investigation.

1.2 DIAGNOSIS OF ISCHAEMIC HEART DISEASE

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity worldwide. According to the World Health Organisation (WHO), an estimated 17.7 million people died of CVD in 2015, representing 31% of all cause mortality around the world. This trend of mortality has remained unchanged since 2008 (3). In the United Kingdom (UK), more than 2 million people have angina, and each year about 275,000 people suffer acute myocardial infarction (AMI), which results in around 88,000 deaths per year (2, 4). An early diagnosis and prompt treatment is required to reduce the mortality and morbidity associated with CVDs (5, 6).

Ischaemic heart disease (IHD) is the clinical manifestation of myocardial oxygen and nutrients demand and supply mismatch (7). The causes of myocardial ischaemia are given in [Table 1].

Table 1: Causes of myocardial ischaemia

I	**Mechanical obstruction**: • Atherosclerosis • Thrombus • Spasm • Embolus • Coronary arteritis (e.g., in SLE)
II	**Decreased oxygenated blood flow**: • Anaemia • Carboxyhaemoglobuninaemia • Hypotension, causing decreased coronary perfusion pressure
III	**Increased oxygen demand**: • Thyrotoxicosis • Myocardial hypertrophy

Adopted from: Kumar, Parveen J. (2012) Kumar & Clark's clinical medicine. 8th ed. Edinburgh: Saunders Elsevier.

Atherosclerosis is the most common cause of IHD. The pathogenesis of atherosclerotic plaque consists of a complex inflammatory process. Which is triggered by endothelial injury and dysfunction in the presence of predisposing risk factors such as diabetes, hyperlipidaemia, hypertension, smoking and

family history of IHD (8, 9). Yusuf et al. has described these factors in detail in a multicentre INTERHEART study (10) and identified nine modifiable risk factors that account for over 90% of the acute myocardial infarction.

Endothelial injury and dysfunction lead to an increased vascular permeability to oxidised lipoproteins. The macrophages engulf the oxidised lipoproteins and release cytokines, which potentiate a complex self-perpetuating chronic low-grade inflammatory process between the vascular endothelium and intima. The area is infiltrated by further inflammatory cells, and further cytokines are released (11, 12). Over a period of time, this leads to fibro-fatty plaque. The plaque continues to grow and leads to myocardial ischaemia and angina (11).

The term "Angina" (also known as angina pectoris) is derived from the Latin word "*angore,"* which means choking, suffocation, anxiety, terror or fear (7). William Heberden gave the first clear description of the symptoms of angina in 1768; however, angina was known even in the Middle Ages (7, 13).

Patients with typical angina symptoms, describe chest tightness in association with breathlessness, sweating and other features of sympathetic nervous system activation. They have recognisable precipitating factors, such as physical activity, mental stress, cold weather, heavy meals, and fever, as well as relieving factors such as rest or sublingual nitro-glycerine (7). These symptoms may last for 2–10 min (7). On average patients with stable IHD may suffer 1-2 episodes of angina per week (7). To avoid angina, many patients reduce their physical activity (7). However, substantive numbers of the patient have atypical symptoms, which make the assessment and diagnosis challenging.

1.2.1 Stable ischaemic heart disease

An approximately 70% reduction in the cross-section of one or more coronary arteries or >50% stenosis in the left main stem (LMS) results in significant haemodynamic compromise, and as a compensatory process the distal microvasculature (non-visible angiographically) become maximally dilated, resulting in minimal coronary flow reserve and at this stage any increase in myocardial oxygen demand due to increase workload would result in angina (7, 14), which is classified as stable if the symptoms are occurring with exertion and relieving by rest and glyceryl tri-nitrate (GTN). Episodes of angina may be associated with transient ECG changes.

1.2.2 Unstable ischaemic heart disease and acute coronary syndrome

Plaque rupture with super-imposed platelet aggregation leads to symptoms of angina at rest, which is classified as unstable ischaemic heart disease or acute coronary syndrome (ACS). The term ACS covers a spectrum of clinical presentation depending on the serum level of the biochemical markers, which represent myocardial injury and new or dynamic ECG changes. Symptoms at rest without an increased level of the biochemical markers and no persistent ECG changes is called unstable angina, symptoms with raised biochemical markers and minor ECG changes is called non-ST-elevation MI. However, symptoms of angina along with ST-segment elevation on the standard 12 leads ECG is called ST-elevation MI (7). Untreated unstable IHD is associated with significant mortality and morbidity, and therefore, urgent treatment is required. The mode of treatment depends on whether the patient has suffered

UA, NSTEMI or STEMI (7, 15). Therefore, 12-leads ECG plays an important role in determining the mode of treatment.

1.2.3 Assessment of patients with suspected stable angina

The presentation with chest pain is common, an estimated 20% to 40% of the general population suffer symptoms of chest pain at some point in their lives (16, 17). Jones at al conducted a systematic review of 6 observational studies and reported 2.8% to 6.6% per annum mortality in angina patients (18).

Initiation of pharmacological intervention has been shown to improve the prognosis by retarding plaque disease progression and by stabilising the surface endothelium (19). However, at present, there is no perfect tool for the screening and diagnosis of stable IHD.

1.2.3.1 National Institute for Health and Clinical Excellence (NICE) guidelines for the diagnosis of IHD (20)

The guidelines recommend the estimation of the likelihood of CAD on the basis of the clinical assessment as outlined in [Table 2], and the resting 12-lead ECG. Further diagnostic tests are recommended as below:

- Patients who have estimated likelihood of CAD >90% based on criteria defined in [Table 2], should be started on oral medical treatment (OMT) and invasive coronary angiogram should be considered.
- For estimated CAD likelihood of 61–90%, invasive coronary angiography is recommended.

- Functional tests are recommended for the estimated CAD likelihood of 30–60%.
- Computed tomographic calcium scoring (CTC) is recommended if the estimated likelihood is 10–29%.

Exercise ECG is no longer recommended as a first line test for the diagnosis of IHD in patients who have no previous diagnosis of CAD.

Table 2: An estimated risk of coronary artery disease based on symptoms, age, sex and risk factors.

	Non-anginal chest pain				Atypical angina				Typical angina			
	Men		Women		Men		Women		Men		Women	
Age	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi
35	3	35	1	19	8	59	2	39	30	88	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69	9	29	71	86	20	51	93	97	56	84

For men older than 70 with atypical or typical symptoms, assume an estimate > 90%. For women older than 70, assume an estimate of 61–90% except women at high risk Values are per cent of people at each mid-decade age with significant coronary artery disease (CAD) 1.

Hi = High risk = diabetes, smoking and hyperlipidaemia (total cholesterol > 6.47mmol/litre).
Lo = Low risk = none of these three.
The shaded area represents people with symptoms of non-anginal chest pain, who would not be investigated for stable angina routinely.
Note:
These results are likely to overestimate CAD in primary care populations.
If there are resting ECG ST-T changes or Q waves, the likelihood of CAD is higher in each cell of the table.
With typical symptoms where a risk of > 90% should be assumed.

Adopted from: NICE Guidelines 2010. Chest pain of recent onset Assessment and diagnosis.

1.2.3.2 Investigations for stable angina

The investigation for IHD can be divided into two categories, i.e. (i) functional tests, which provide information regarding myocardial perfusion, and (ii) anatomical tests, which demonstrate the coronary anatomy and the presence and extent of atherosclerosis.

1.2.3.2.1 Functional tests for stable angina

Functional tests include exercise tolerance test (ETT), myocardial perfusion imaging (MPI), stress echocardiogram and cardiac stress MRI. ETT has been the most commonly used investigation for the screening and diagnosis of ischaemic heart disease worldwide, however, due to its poor sensitivity and specificity, it is no longer recommended in the UK. The stress echocardiogram is difficult to interpret in the presence of left bundle branch block (LBBB) and atrial fibrillation (AF), the results are observer dependant and may not be possible in certain patients with poor echo windows. The use of MPI involves radiation, the results are observer dependent and the breast and abdominal adiposity can create artefacts and may make interpretation difficult. Similarly, cardiac MRI is not possible in claustrophobics and is absolutely contraindicated in a number of individuals with internal ferromagnetic foreign materials.

MPI, stress echocardiogram and cardiac MRI are expensive, requires specialised team and establishment, have a long waiting list, and each study takes a longer time to complete.

1.2.3.2.2 Anatomical tests for stable angina

Non-invasive anatomical test include CT calcium scoring (CTC) (21, 22), CT coronary angiography (CTCA), invasive coronary angiogram and Magnetic Resonance angiogram (MR angiogram). However, CTC and CTCA are expensive, require specialist training, team, and establishment, involve radiations and have significant limitations in the quantification of the extent of coronary stenosis. The invasive coronary angiogram is considered a “gold standard” for the diagnosis of coronary artery disease. However, it is associated with complications including death (0.1 to 0.2%), non-fatal MI (0.1%), and cerebrovascular events (0.1%) (23). Coronary angiogram requires extensive

training of doctors and requires expensive equipment along with trained nurses, physiologist, and radiographer.

MR angiogram has poor spatial resolution and lower signal to noise ratio, due to a cardiac and respiratory motion. Previous studies on MR angiogram have shown significant variation in the sensitivity and specificity (23, 24).

1.2.4 Assessment of patients with suspected unstable angina (UA) and acute coronary syndrome (ACS)

Suspected unstable angina or myocardial infarction accounts for 5% of the emergency department presentations, and around 40% of emergency hospital admissions (16, 25).

Early therapeutic interventions significantly improve outcomes in patients with acute myocardial infarction (AMI). Therefore, urgent assessment and identification of such patients is required, which includes clinical history, physical examination, acquisition of 12 lead standard ECG and measurement of cardiac biomarkers (26). This rapid assessment helps identification of higher risk patients, such as those with ST-elevation myocardial infarction (STEMI) or dynamic ECG changes with threatened AMI, who would require an emergency intervention such as primary percutaneous coronary intervention (PPCI).

There are several differential diagnosis of chest pain, which makes the diagnosis of AMI challenging, as described in the NICE guidelines “Chest pain of recent onset Assessment” (20).

1.2.4.1 Investigations for suspected unstable IHD

1.2.4.1.1 The use of resting 12-Lead ECG in the diagnosis of AMI

In the clinical practice an electrocardiogram (ECG) is taken both in the pre-hospital setting by paramedics, and on arrival to the hospital further serial ECGs are recorded for risk stratification in patients with suspected AMI. The poor sensitivity of the standard 12 lead ECG for the diagnosis of AMI is well established (20, 27).

In a systematic review of studies looking at the discriminatory features of ECG for the diagnosis of AMI, an ST-segment elevation (≥1mm in ≥2 contiguous limb leads or ≥2mm in ≥2 contiguous precordial leads) was the most discriminating single ECG change for a diagnosis of AMI in patients with acute chest with a positive likelihood ratio (PLR) of 13 (95%CI 8, 20, $P < 0.001$) (28).

The WHO criteria for the diagnosis of AMI consist of the two of the following three features: (i) symptoms suggestive of myocardial ischaemia, (ii) elevation of cardiac enzymes released with myocardial injury (iii) typical ECG changes (28).

Due to the limitations of 12 lead ECG; a completely normal ECG or equivocal ECG is not sufficient to exclude ACS. The current NICE guidelines emphasize further evaluation and testing (20), including a period of observation and serial ECG monitoring (28).

1.2.4.1.2 Coronary angiogram and primary percutaneous coronary intervention (PPCI)

If the initial assessment confirm the diagnosis of ST-elevation MI (STEMI) then the NICE guidelines, European society of cardiology (ESC), American Heart Association (AHA) and American College of Cardiology (ACC) guidelines recommend emergency reperfusion therapy, preferably by emergency coronary angiogram and primary percutaneous coronary intervention (PPCI) of the culprit lesion if possible (29). As a result, only very few centres in the UK offer pharmacological thrombolysis, and the reperfusion strategy of choice is PPCI. Coronary angiogram and PPCI is invasive, and the patient selection is based on the 12 leads ECG.

1.2.4.1.3 Cardiac biomarkers

Patients who present with suspected acute cardiac chest pain, and who do not have ST-elevation on 12 leads ECG are further assessed by interval measurement of a cardiac biomarker of myocardial injury in their blood, which are proteinaceous macromolecules (20, 30). Until the 1980s, only a few assays such as creatinine kinase (CK) and lactate dehydrogenase (LDH) were available which had lower sensitivity (31). However, recently, more sensitive and specific markers of myocardium necrosis like myoglobin, troponin I, and troponin T have become available.

The use of troponin T and I have become standard criteria for the diagnosis of AMI worldwide. The WHO definition of AMI and the Joint European Society of Cardiology (ESC) and the American College of Cardiology (ACC) committee published a consensus document in 2000 for the new definitions of AMI, which also include the measurement of troponin (26, 31, 32).

1.2.4.1.4 Troponin I and T

Troponin is a protein and makes a part of the cardiac, skeletal and smooth muscles and has an important function in the muscles contraction. There are three subtypes of troponin, (i) troponin I, which binds to actin, (ii) troponin T, which binds to tropomyosin, and (iii) troponin C, which binds to calcium ions. The cardiac troponin is structurally different from the troponin found in the skeletal muscles; therefore, a cardiac troponin specific antibodies assay has been developed, which has enabled quantitative analysis of cardiac troponin. Currently, assays for troponin I and troponin T are in clinical use. Traditionally, it is believed that the troponin I and T levels reaches to maximum level (peak level) in 6 to 12 hours after onset of symptoms of an AMI. Troponin I may remain elevated for 7 to 10 days, and troponin T may remain elevated up to 7

to 14 days (33). Recently, the widespread availability of high sensitivity troponin has further improved the ACS diagnostic pathways. Vatansever et al. compared the sensitivity and specificity of troponin, CK, and myoglobin (34) and reported the findings as given in Table 3. The disadvantages of the troponin include the time interval required for the repeat measurements, and its presence in blood in other conditions (35, 36).

Table 3: Summary of Vatansever et al. study results (34).

	Admission		2 hours after admission	
	Sensitivity	Specificity	Sensitivity	Specificity
Troponin T	76%	90%	97%	90%
CK-MB	64%	90%	79%	90%
Myoglobin	85%	90%	97%	90%

Data from: Vatansever S et al. The diagnostic value of troponin T and myoglobin levels in acute myocardial infarction: a study in Turkish patients. J Int Med Res. 2003;31(2):76-83.

1.2.4.1.5 The use of the multislice CT scanner in the emergency department

In recent years, multislice CT scanner to rule out ACS, pulmonary embolism (P.E) and aortic dissection (AD) also termed as Triple-Rule-Out (TRO) CT scan has gained significant popularity (37, 38). TRO CT scan is considered appropriate for the assessment of patients with suspected ACS, who have low to intermediate risk of ACS and in whom other life threatening pathologies like aortic dissection and pulmonary embolism required to be excluded (37). The TRO involves a very high dose of radiations, is expensive, and requires specialist team and establishment.

1.3 IHD, ELECTROCARDIOGRAPHY AND BODY SURFACE MAPPING

In 1791, the Italian scientist Aloysio Luigi Galvani described the neuronal activation by an artificial electrical stimulus. This was an important finding and provided the basis of electrophysiology (39, 40). For the next 100 years, various scientists contributed to the development of ECG. The first human ECG was recorded by Augustus D. Waller In 1887, which was named “electrogram.” However, due to the complicated process of ECG acquisition and due to the requirement of complex mathematical calculations A.D. Waller believed that it is unlikely that ECG could be of any clinical use (41-43). However, Einthoven made a significant contribution to the development of the ECG into a clinical tool, by reducing the size and complexity of interpretation through his innovative work. The Einthoven ECG consisted of three limb leads “Lead 1, Lead II, and Lead III”, which enabled the interpretation of the rhythm, changes in the axis and amplitude (44). Einthoven presented the first collection of normal ECGs in 1903 (45) and abnormal ECGs in 1906 (43). He also described the abnormality of ECG as a result of an experimental myocardial infarction in the dog heart (44). For recognition of his work, Einthoven was awarded a Nobel Prize in 1924 (46).

1.3.1 Beyond Lead I, II, III and development of 12 Lead ECG

The impact of Einthoven work was such that the three lead ECG remained a standard for three decades. In 1938, “The Cardiac Society of Great Britain and Ireland” together with “The American Heart Association” made recommendations for the use of four electrode ECG by placement of one chest lead at the point of apex beat on the precordium along with the three limb leads (47). In this report, the authors concluded that there was “insufficient

evidence to consider multiple chest leads." However, this statement was corrected in the same year and recommendations were made for the use of six chest leads V1-V6 in the same manner as we see today (48). In 1941, the 9 Lead ECG (from 10 electrodes) was augmented by the "aVr, aVl and aVf" leads by Goldberger to create the current standard 12 Lead ECG (49).

In 1963, Robert Bruce and colleagues described the incremental treadmill exercise test (Bruce Protocol) for the acquisition of exercise ECG (50, 51).

1.3.2 ECG and myocardial infarction

Acute MI results in "injury current" formation, which appears as an ST segment change (52). The total occlusion of a coronary artery results in myocardial infarction and appears as ST elevation in the electrodes directly facing the area of injury. However, this appears as ST depression in the electrodes facing that area from the opposite direction (52, 53). The interpretation of the ST segment changes has been made more complex by the fact that partial or subtotal occlusion of the coronary arteries gives rise to myocardial ischaemia, which appears as ST depression on the electrodes of ECG directly capturing electro cardiac activity from that area (53). The currently recommended clinical management strategies for the "ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI)" are significantly different (33). STEMI is considered a higher risk condition, and emergency revascularisation is recommended (previously administered through urgent thrombolytic therapy and currently carried out with PPCI (33). However, for NSTEMI immediate initiation of medical treatment and PCI within 24-48 hours on the same index hospital admission is recommended (54). Therefore, the presence of ECG ST changes is a key finding in the diagnosis of acute MI and its prognostic

classification. The 12 lead ECG collects data from only a narrow curved band of the front and lateral aspect of the chest (heart). Therefore, directly face only the territory supplied by one of the three coronary arteries, i.e., left anterior descending (LAD) coronary artery. It may therefore only see either ST elevation or depression in isolation or together depending on where the infarction occurs. From an electrocardiographic perspective, this makes no sense as depression may merely be a reciprocal change from an area of myocardial infarction with no electrodes facing it directly but may have electrodes facing it from the opposite direction (55). The difficulty for the clinician treating the patient is in deciding if ST depression is reciprocal (myocardial infarction) or due to ischaemia. Such difficulties are most apparent when trying to diagnose posterior infarctions (53, 56), where the ST elevation is not seen on the standard 12 lead, but the reciprocal ST depression is seen anteriorly (55, 57).

Kornreich challenged the fact that the placement of the 6 electrodes in its current locations are inappropriate and excessive, he demonstrated that the same amount of data can be obtained through fewer number of electrodes, from his work he recommended placement of electrodes at alternate areas on the thorax to obtained better coverage of the electro cardiac data (58). The understanding of the above limitations led to the development of body surface mapping (BSM).

1.3.3 Beyond the 12 Lead ECG and the origin of multielectrode Body Surface Mapping (BSM)

Whilst it may be surprising to us that the Einthoven three limb lead ECG remained standard technique for 30 years, by the same token it is perhaps more surprising that the current 12 Lead ECG with 6 precordial leads has

remained unchanged since 1938, particularly given the paucity of scientific justification for the number of electrodes and their position.

1.3.4 What is Body Surface Mapping (BSM)?

Body surface mapping is the electrical profile of the heart as it appears on the thoracic surface obtained through multiple electrodes (usually more than 10).

Waller published electrical potential data from all over the thorax (a torso map) in 1888 and 1889 (41). In 1934, Koch and Sceneyer demonstrated the flow of electrical potential across the precordium of the heart and the thoracic wall, and in particular plotted isopotential QRS maps across the thoracic surface for the first time, marking equal points of QRS magnitude reflecting the cardiac axis, which is the key feature of BSM (59-61).

The true work of BSM started when the direction of cardiac electrical impulse was studied. In 1951, Nahum plotted detailed isopotential maps of the cardiac electrical field (62). The early work showed that the cardiac field is multipolar in nature and therefore full investigation would demand to sample over a wide thoracic area (63).

In 1963, Taccardi et al. demonstrated electrographic potential over a large area of the thorax by application of electrodes over 400 different sites (64). Subsequently, the concept of electrographic vectors direction and BSM maxima and minima were described (65).

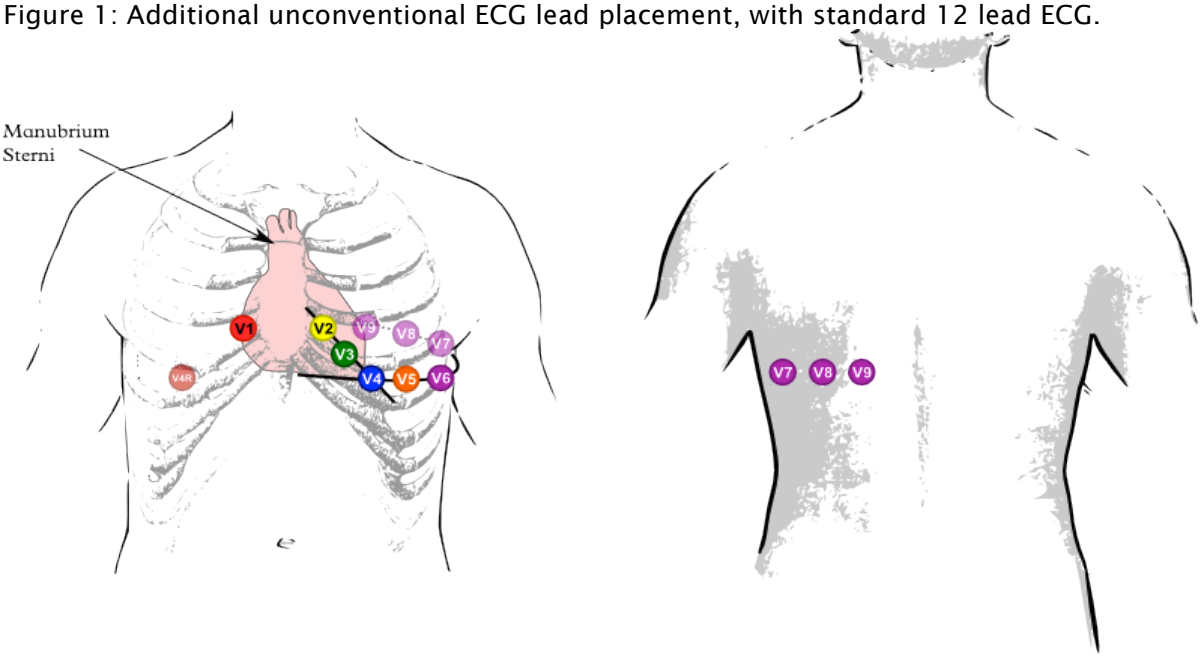
1.3.5 What is the benefit of BSM over additional ECG electrodes?

To overcome the limitations of the standard 12 lead ECG, at times the clinician choose to apply the electrodes at alternative locations in selected patients to

1.3.5 What is the benefit of BSM over additional ECG electrodes?

To overcome the limitations of the standard 12 lead ECG, at times the clinician choose to apply the electrodes at alternative locations in selected patients to increase the diagnostic ability of the ECG. However, this is not offered to all patients and not part of a standard practice. The most commonly used alternative locations are over "the right thorax to detect right ventricular changes or posteriorly to show posterior changes (V4R and V8-V9)" as illustrated in Figure 1.

Figure 1: Additional unconventional ECG lead placement, with standard 12 lead ECG.



Adopted from: http://en.ecgpedia.org/wiki/Basics

In 1993, Kornreich et al. reported that those locations on the torso where maximum electrographic changes can be observed during acute myocardial infarction are outside the currently used standard electrode placement for the 12 lead ECG (55). On the basis of this work, Wung and Drew used 18 electrode ECG involving sites suggested by Kornreich in 68 patients who were undergoing coronary angioplasty (66). Their study confirmed the findings of Kornreich (67).

1.3.6 Currently available BSM technologies

In a health technology assessment report on BSM Coeytaux et al. (68) identified seven ECG-based devices used for the diagnosis of CAD or to detect acute myocardial infarction [Table 4]. Of these devices, the PRIME® ECG, the Cardio3KG, and the 3DMP appear to be commercially available at this time, with only the PRIME® ECG and 3DMP having obtained FDA clearance for marketing. The FDA has cleared the Predictor, but it is no longer manufactured. Among the other four devices, which are not approved by FDA as yet, the production of the FDX-6521 and VCM-3000 by Fukuda Denshi and the production of the 1200 EPX by Arrhythmia Research Technology have been stopped, and these technologies are not available commercially. The Visual-ECG/Cardio3KGTM also known as Cardio3KG, manufactured by NewCardio is commercially available. In summary, out of seven devices, only three devices are available commercially. Among these three devices, PRIME® ECG and Cardio3KG are the only two body surface mapping devices. However, 3DMP utilises mathematical analysis.

1.3.6.1 Body Surface Mapping Devices

1.3.6.1.1 PRIME® ECG

The PRIME® ECG consists of an 80-electrode disposable vest and portable recording device. The 80-electrodes enable collection of electrocardiac activity from the front, back, and sides of the torso. The results are projected on pseudo-torso on a computer screen with colour coding.

1.3.6.1.2 Cardio3KG

The Cardio3KG extracts data from the standard 12-lead ECG to generate a

three- dimensional representation of cardiac electrical activity. This device does not require additional electrodes, and transforms 12-lead ECG information into X, Y, and Z components of the heart vector, normalises the lead vectors, and displays virtual lead voltages on a three-dimensional model of the heart.

1.3.6.2 Mathematical Analysis Devices

1.3.6.2.1.1 *3DMP*

The 3DMP device also known as MCG or mfEMT, derives the ECG data from only two (leads II and V5) out of the 12 standard leads. A recording is made for 82 seconds. Then the data is amplified, digitised, encrypted, and sent securely over the internet to Premier Heart Datacentre. The data is subjected to frequency and time domain analyses, and mathematical transformations are performed and compared to the pre-existing database. A diagnosis is established. The "Final Diagnosis" and "Severity Score"; is then reported back over the Internet within several minutes to the requesting provider.

1.3.1 BSM Delta map

Recent advances in the computer and technology have made the use of BSM possible in the acute clinical settings. PRIME® ECG appears to be the only true BSM technology available at present and has been validated in several studies. However, the interpretation of PRIME® ECG requires an understanding of the complex data, and therefore it has gain limited attention so far. Our group has developed a BSM Delta map, which is derived from 80-electrode ECG and is easy to interpret, as the complex data is interpreted through the automated algorithm, which displays only data of interest. Therefore, BSM Delta map

presents itself as a clinically valuable method for the detection, localisation, and quantification of regional myocardial ischaemia and infarction. However, this technique requires evaluation in the clinical settings

Table 4: ECG-based signal analysis devices (68).

Device name	Manufacturer	Commercially available*	FDA cleared†	Device type
FDX-6521	Fukuda Denshi	No	No	SA
VCM-3000	Fukuda Denshi	No	No	BSM
PRIME® ECG	Heartscape/Verathon	Yes	Yes	BSM
Visual ECG/Cardio3KGTM	New Cardio	Yes	No	BSM
3DMPTM/MCGTM/mfEMTTM	Premier Heart	Yes	Yes	MA
Model 1200	Arrhythmia Research Technology	No	No	SA
PredictorTM	Corazonix	No	Yes	SA

Abbreviations: BSM = body surface mapping; ECG = electrocardiogram; FDA = U.S. Food and Drug Administration; MA = mathematical analysis; SA = signal-averaging. *Commercially available from a device manufacturer. †Cleared for marketing the by FDA. *Adopted from: ECG-based signal analysis technologies. http://www.cms.gov/determinationprocess/downloads/id73TA.pdf.*

1.3.2 BSM Delta map and research questions

This report includes clinical studies as described in chapter 2, 3 and 4, to validate the use of BSM Delta map in clinical settings and to answer the following questions:

- To investigate the feasibility of using novel BSM Delta map in clinical settings.
- To determine sensitivity and specificity of the novel BSM Delta map for the diagnosis of ACS and stable angina using the current standard diagnostic tools as a reference standard.
- To investigate and validate the application of various thresholds for the ST shift as a marker of TRMI.
- To investigate and validate the application of new protocols for the Interpretation of BSM Delta map.
- To investigate and validate the novel concept of ischaemic burden (IB), (a numerical description of the extent of myocardial ischaemia).

1.4 SUDDEN CARDIAC DEATH, IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD) AND SUBCUTANEOUS ICD (S-ICD)

Death from cardiac causes occurring unexpectedly within 1 hour of onset of symptoms is defined as sudden cardiac death (SCD) (69). Worldwide IHD is the most common cause of sudden cardiac death (SCD) in adults (69-71). It is believed that around 80% of SCDs occur through a final common pathway of cardiac arrest due to ventricular arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF) (72). Several studies have explored the potential causes and mechanism of SCD (69, 72-76), VT (73, 77, 78), and VF (79, 80).

In the United Kingdom (UK) every year approximately 50,000–70,000 people suffer SCD (81). Increasing numbers of patients are surviving the first episode of a life threatening ventricular arrhythmia (failed SCD) these patients have a high risk of further fatal events (69, 81). Implantable cardioverter defibrillator (ICD) is a well-established treatment for the prevention of SCD in high-risk patients (82-89). The novel subcutaneous-ICD (S-ICD) is a significant improvement in this technology and has a potential to reduce the complications related to the conventional transvenous ICD (TV-ICD). However, the sensing algorithms of this device require further assessment.

1.4.1 Implantable cardioverter defibrillator (ICD)

In 1872, Mr Green reported the effective use of external battery powered electrical cardioversion for the treatment of cardiac arrest due to chloroform (90, 91). This method was further refined, and the use of external DC Cardioversion (Direct Current Cardioversion) with large battery powered devices became an established method in hospitals for the treatment of cardiac

arrest. However, the invention of the pacemaker in the early 1960's opened up a new era, and scientist around the world started working on a miniaturised implantable cardioverter defibrillator for the treatment and prevention of out of hospital cardiac arrest and SCD.

In 1962, the organisation of the coronary intensive care unit (CICU) conducted research in the aetiology and pathophysiology of SCD (92). In these initial studies on the aetiology of SCD, it became evident that 75% of the SCD victims had prior heart attacks (92). Furthermore, a heart attack damaging the left ventricular wall had a direct correlation with the SCD (92). This data was a breakthrough in the understanding of the mechanism of the risks of SCD.

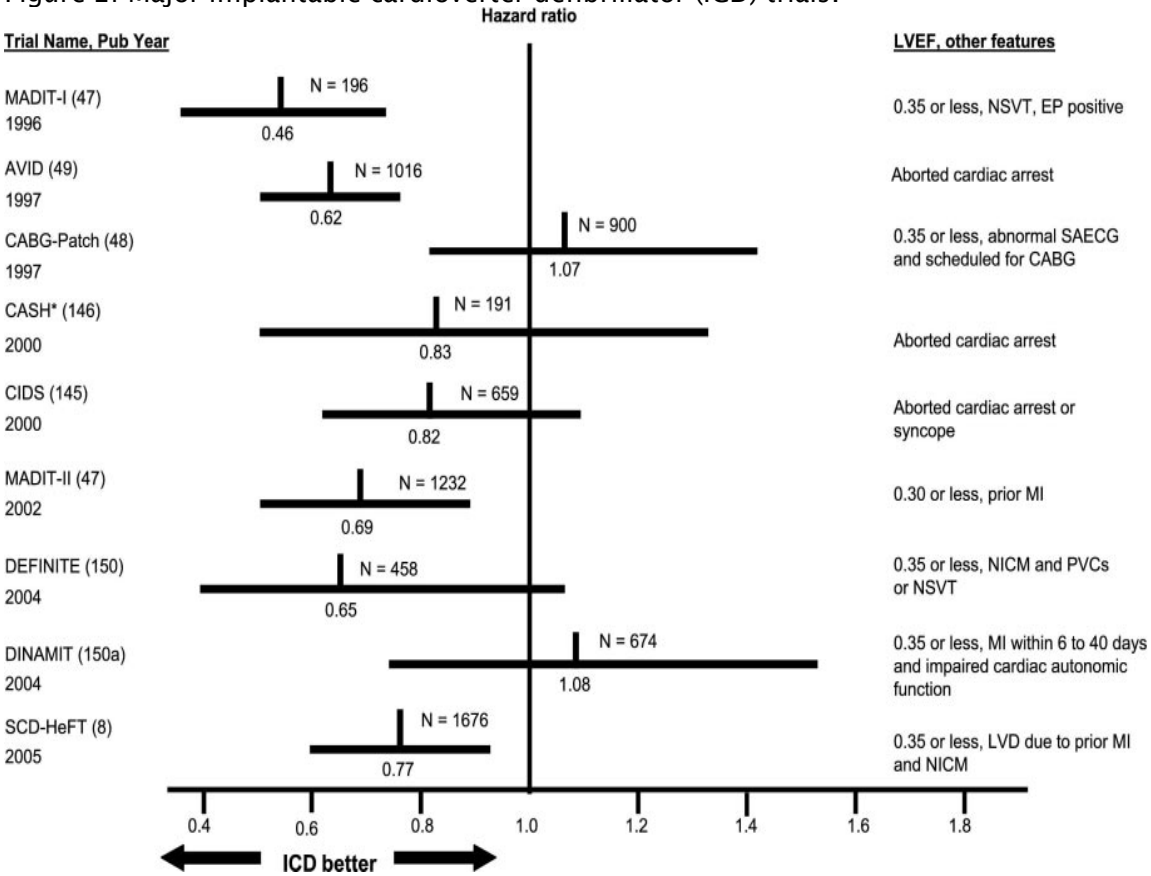
The development of the implantable defibrillator is predominantly attributed to the work of Mieczyslaw (Michael) Mirowski (92). After decades of experiments and difficulties, eventually, the first ICD was implanted in human on February 4, 1980 (93). This device was further refined in the next five years and was implanted in more than 800 patients deemed to be at higher risk of sudden cardiac death. The FDA approved the implantable defibrillator for general market release in October 1985, allowing its use in patients who have survived prior cardiac arrest or ventricular tachyarrhythmia and in whom VF can be induced (92).

Several large scale randomised control clinical trials have demonstrated significant mortality benefit of ICD for the primary prevention of SCD (patients who are at risk but had no prior aborted SCD) (82-84, 86, 87, 94-104) and the secondary prevention of SCD (patients who had previously aborted SCD) (85, 88, 105-114).

These multicentre randomised clinical trials demonstrated clear survival benefit and a mortality reduction of 23% to 55%, specifically in patients with LVEF <35%

due to previous MI and non-ischemic cardiomyopathy (82-89) [Figure 2]. This survival benefit was almost exclusively due to a reduction in SCD.

Figure 2: Major implantable cardioverter-defibrillator (ICD) trials.



Major implantable cardioverter-defibrillator (ICD) trials. Hazard ratios (vertical line) and 95% confidence intervals (horizontal lines) for death from any cause in the ICD group compared with the non-ICD group. For expansion of trial names, see ICD clinical studies section. CABG=coronary artery bypass graft surgery; EP=electrophysiological study; LVD=left ventricular dysfunction; LVEF=left ventricular ejection fraction; MI=myocardial infarction; N=number of patients; NICM=nonischemic cardiomyopathy; NSVT=nonsustained ventricular tachycardia; PVCs=premature ventricular complexes; SAECG=signal-averaged electrocardiogram. *Adopted from: Zipes et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias. Circulation. 2006;114(10):e385-484.*

1.4.2 Ischaemic cardiomyopathy and ICD

The myocardial scarring due to myocardial infarction may act as a focus for arrhythmogenesis and can give rise to VT in patients with even less severe LV systolic dysfunction. Aggressive pharmacological treatment and

revascularisation for ischaemia are recommended for patients with ischaemic cardiomyopathy (ICM) and VT (69).

The current guidelines recommend ICD therapy in two types of the patient population with CAD to reduce the risk of SCD:

(i) Patients with ICM and LVEF ≤40%, who have spontaneous non sustained VT (NSVT) and sustained monomorphic VT can be induced by EP testing (86).

(ii) Patients with ICM and LVEF <30%, who had MI ≥40 days (87).

All patients with ICD are maintained on maximally tolerated beta-blockers to reduce the chances of ICD shock. However, some patients need a combination of beta-blocker and amiodarone to reduce ICD therapies (69). Catheter based or surgical ablation may be required in patients in whom VT suppression is not possible despite medications or who are intolerant to drugs (69).

1.4.3 Congenital heart disease patients (CHD) and ICD

Congenital heart diseases (CHDs) represent a diverse group of anatomical and physiological cardiac anomalies. Individuals with congenital heart diseases (CHDs) are at higher risk of SCD at a young age due to abnormal heart structure, physiology and fibrosis as a result of scarring due to surgical repair, thus increasing the incidence of life threatening arrhythmias in this group at a young age (115, 116). Advancements in the surgical techniques have enabled the repair of almost all congenital heart defects at very young age and mostly in the neonatal period. However, over time, there is gradual deterioration in the cardiac structure and function, which increases the incidence of ventricular arrhythmias and SCD beyond the age of 20 years (117).

CHDs are classified into two broad groups: (i) simple CHDs and complex CHDs (C-CHDs). There are significant differences in the natural history of these conditions and mainly depends on the nature and extent of the cardiac defect. Observational studies have demonstrated a higher risk of SCD in adults with more C-CHD including tetralogy of Fallot (TOF), transposition of the great arteries (TGA) and single ventricle physiology (SVP) (117-120).

ICD is recommended for prevention of SCD in high-risk CHDs patients. However, ICD implantation is a challenge in this group, due to factors like closed venous circulation and lack of access to the physiological right ventricle, which is required for the insertion of the conventional TV-ICD-lead into the right ventricle (115, 116). Additionally, CHD patients have a high incidence of atrial (supraventricular) arrhythmias and therefore, often require dual chamber ICD to reduce the chances of inappropriate shocks for supraventricular arrhythmia (115, 116). The implantation of two leads (when possible) at a young age makes the TV-ICD implantation a less desirable mode of a preventive measure in CHDs, due lifelong exposure to the complications. The issue is made further complicated by the difficulties in the risk stratification and poorly understood markers of sudden death in this population (121, 122). Thus, many CHDs patients do not receive ICD, who nevertheless have the potential to benefit from it (115, 116). In this population, the data for the use of an alternative device that does not require endovascular lead insertion, e.g., the novel subcutaneous defibrillator (S-ICD) is limited. However, if suitable, then S-ICD would be an ideal option in this population.

Many of the ICD related complications are due to the transvenous lead and are cumulative over time (123). Many studies advocate the use of subcutaneous

devices; therefore the rationale for a less invasive treatment has grown (115, 116).

1.4.4 Beyond conventional transvenous ICD and development of S-ICD

Since the first human implant of ICD in 1980 these devices have evolved considerably in terms of implant technique (no thoracotomy required), implant site (sub-pectoral instead of intra-abdominal, previously requiring major surgery), lead technology (less bulky lead) and size and function (arrhythmia detection and treatment) (124, 125).

The conventional transvenous implantable cardioverter defibrillator (TV-ICD) requires an invasive procedure for implantation. At least one lead insertion into the right ventricle (RV) is required through the subclavian vein in case of single chamber TV-ICD. However, more frequently a second lead is inserted into the right atrium (RA) for better functionality and arrhythmias discrimination, these leads are then attached to a pulse generator that is implanted in a subcutaneous pocket, most commonly in the left subclavicular area (125). The TV-ICDs have the ability to directly sense the cardiac electrical activity and deliver therapies with the endocardial lead in the right ventricle myocardium. These devices also have the ability to pace when required (126).

Despite the well-known efficacy of TV-ICD in the high-risk population, its use is still conservative in Europe and especially in the UK (115, 125, 127, 128). Currently, the conventional TV-ICD is associated with a significant rate of both implant procedure related complications including pneumothorax, haemothorax, vein thrombosis, cardiac perforation (which can lead to life threatening tamponade) and long term complications such as lead fractures

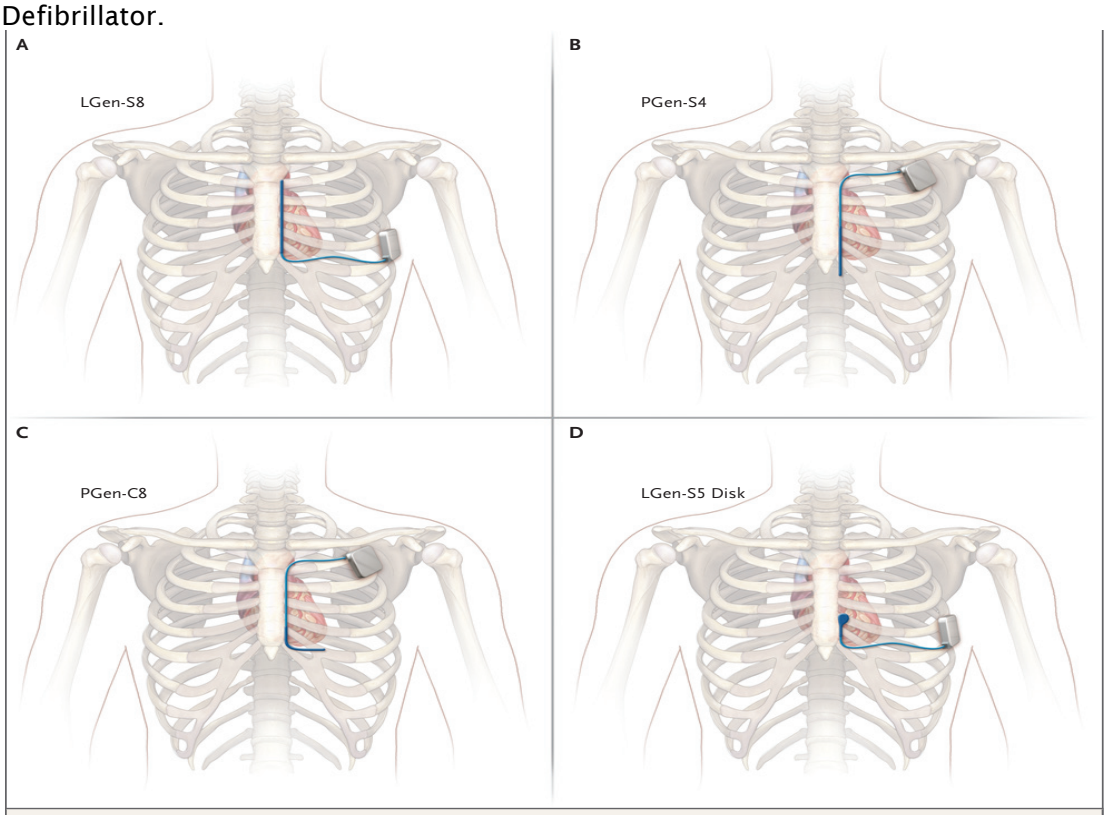
and sepsis (123). Additionally, the size of the TV-ICD lead with a coil is still considerably larger than normal pacing leads (129). The average lifespan of a TV-ICD lead is around 10 years and is around six years for the generator, after which a replacement is required (115, 125, 127, 128). The extraction techniques (such as radiofrequency and laser extraction) for the pre-existing non-functioning transvenous endocardial lead removal are associated with serious complications and risk of death (115, 125, 127, 128). The issue of replacement of both generator and lead is particularly pertinent to young patients, as they would have multiple exposures throughout their life (115). A prospective multicentre study of 7219 patients (European Jewel ICD investigators) reported that nearly 50% of the TV-ICD recipients experience some form of an adverse event within the first year of implantation (130). Most complications of TV-ICD are attributed to the need for transvenous insertion and implantation of leads. Therefore, increasing the need for the entirely subcutaneous ICD (S-ICD).

1.4.5 Subcutaneous defibrillators (S-ICD)

The currently available S-ICD consists of an active canister and “L” shaped lead implanted under the skin on the left side of the chest (131). Early trials for assessment of the efficacy of these devices have shown that the energy required for defibrillation is within a range that is feasible for S-ICD (132). Further comparative studies have demonstrated effective termination of VT and VF similar to TV-ICD (133, 134). In these studies, four distinct S-ICD device implantation sites were evaluated to determine the most effective configuration for defibrillation [Figure 3] (135). The combination of a canister (with sensing electrode) implantation in the left sub axillary region between the

the fifth and seventh intercostal space and a defibrillation lead with two sensing electrodes parallel to the left side of the sternum have been shown to be the most favourable configuration for the successful termination of "induced" ventricular tachycardia in all patients at a defibrillation threshold of 27±11 J (131, 135) [Figure 3].

Figure 3: Four Configurations of a Subcutaneous Implantable Cardioverter-Defibrillator.



Four configurations of a subcutaneous implantable cardioverter–defibrillator. The four systems that were tested to select the best of these candidates were a left lateral pulse generator with an 8-cm coil electrode positioned at the left parasternal margin, designated LGen-S8 (Panel A); a left pectoral pulse generator with a left parasternal 4-cm coil electrode at the inferior sternum, designated PGen-S4 (Panel B); a left pectoral pulse generator with an 8-cm coil electrode curving from the left inferior parasternal line across to the inferior margin of the left sixth rib, designated PGen-C8 (Panel C); and a left lateral pulse generator with a left parasternal 5-cm^2 oval disk, designated LGen-S5 (Panel D). *Adopted from Bardy et al. N Engl J Med. 2010;363(1):36-44.*

The S-ICD has a considerable future potential for prevention of SCD. However, the main limitation at present are concerns regarding the S-ICD sensing algorithms failures as observed in real world studies and the ability of only 30-second post-shock high amplitude transthoracic ventricular pacing and

inability to perform anti-tachy-pacing (ATP) or pace the heart if bradycardia occurs. It is anticipated that the S-ICD will inevitably undergo further advances to address these technical difficulties especially with emerging leadless pacing technologies (136).

1.4.6 Clinical studies on S-ICD

The world's first commercial implant of S-ICD was performed in July 2009. The initial studies on S-ICD were limited to the optimisation of configuration of shock vector and ability to terminate ventricular arrhythmia (137). However, the clinical efficacy for prevention of SCD is extrapolated from the TV-ICD.

The START study was designed to compare the sensing ability and arrhythmias discrimination ability of the S-ICD with the currently available 3 types of commercial TV-ICD (138). Overall, this study showed no statistically significant difference in the sensing abilities of the S-ICD and TV-ICD (>99 % appropriate detection). However, it was noted that S-ICD had superior supraventricular arrhythmias discrimination (98%) in comparison to the 2 out of 3 TV- tested (77% and 68% respectively). The authors recommended further research into the detailed analysis of S-ICD sensing.

The TV-ICD have been in use since 1980's, therefore, over the time, the sensing algorithm of these devices have been subject of research and several studies (139). However, S-ICD is relatively new, therefore, require further scrutiny of its sensing abilities, especially in the context that several studies have reported a higher rate of inappropriate shocks. Grönefeld et al. discussed the importance of improving sensing algorithms, which may influence the incidence of inappropriate shocks (140).

Table 5 summarises studies reporting the clinical studies of the S-ICD (131, 141-145).

Table 5: Published S-ICD case series.

	Jarman *et al.*(142)	**Jarman *et al.* (146)**	**Aydin *et al.*(143)**	**Köbe *et al.*(144)**	**Olde Nordkamp *et al.* (145)**	**Dabiri Abkenari *et al.* (141)**	**Bardy *et al.* (131)**
Number of patients	16	111	40	69	118	31	55
Patients age (range)/mean ± SD]	23 (10–48)	36 (10–87)	42 ± 15	46 ± 16	50 ± 14	53 ± 16	56 ± 13
Ischaemic or idiopathic dilated cardiomyopathy	0%	18%	45%	52%	57%	71%	85%
Mean/median follow-up duration (months)	9	12	8	7	18	9	10
Patients with re-interventions	19%	16%	13%	4%	14%	10%	11%
Patients with inappropriate shocks	25%	15%	5%	4%	13%	16%	9%

Adopted from: Jarman et al. Europace. 2013 Aug;15(8):1158-65.

Figure 4: Subcutaneous-Implantable Cardioverter Defibrillator.

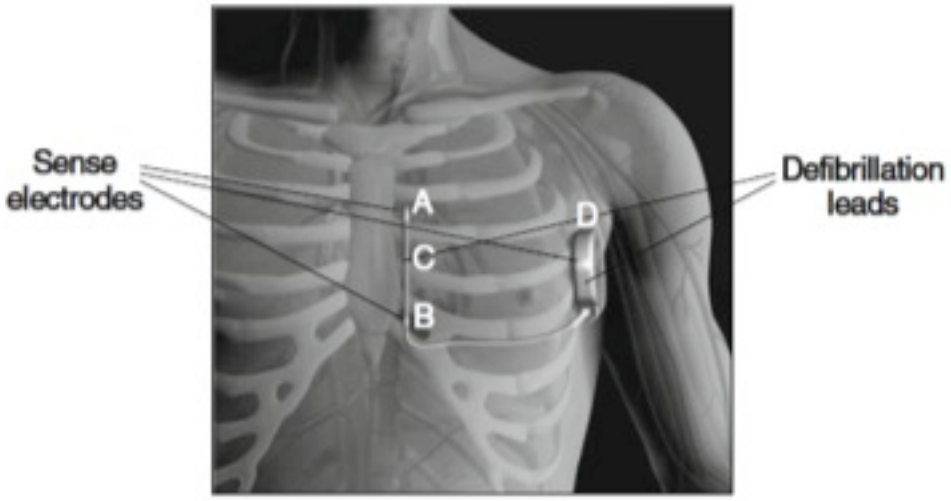


Illustration of the positioning of the S-ICD sensing and defibrillation electrodes.
Adopted from Cappato et al. J Interv Card Electrophysiol. 2012;34(3):325-32 (147).

1.4.7 Complications of S-ICD

1.4.7.1 Infection

In the literature, the risk of S-ICD infection is approximately 6%. However, most of these infections are superficial and managed with antibiotics, and only small proportion of patients may require S-ICD explantation (148).

1.4.7.2 Re-interventions

The literature review by the NICE technology appraisal reported 12% re-intervention rate due to infection, suboptimal lead or generator position, device failure, battery failure, discomfort, non-healing wound, generator migration, haematoma, incomplete insertion of the electrode into the generator and other issues like skin erosion (148).

1.4.7.1 Inappropriate shocks

In the above studies, an average of 12.4% inappropriate shocks due to sensing failure were observed over a follow-up period of 7 to 18 months.

Jarman et al. (142) reported 10 inappropriate shocks due to T-wave over-sensing in 25% patients (4/16) at a median follow-up of 9.5 months. As a result, new vectors were selected in 3 patients, however, despite that 2 out of 3 patients suffered further inappropriate shocks.

Olde Nordkamp et al. (145) reported 33 sensing failures in 13% patients (15/118). Majority of inappropriate shocks were due to T-wave oversensing (9-patients), followed by inappropriate sensing of myopotentials in three patients (2 due to lead migration), double counting due to RBBB in one patient, atrial flutter in one patient, and noise sensing due to transcutaneous electric nerve stimulation (TENS) therapy in one patient.

The reported rate of inappropriate shocks in the rest of studies is given in Table 5.

Inappropriate S-ICD shocks can be very distressing for patients, and although no incidence reported so far, inappropriate therapies can theoretically induce life-threatening arrhythmias; therefore, further studies are required for better understanding and improvement of S-ICD sensing.

1.4.8 Subcutaneous ICD summary and rationale for further studies

The role of ICD in the prevention of SCD is well established. S-ICD is an important new development, still requiring much research. The results of intra-operative testing have been overall impressive, with excellent ability to detect and terminate ventricular fibrillation (VF). However, the far-field sensing characteristics of the system critically depend on adequate discrimination between R-waves and T-waves, these parameters might be affected by factors such as body posture, cardiac pathologies, the location of electrode placement, gender, body habitus, age and device programming (142, 149). Therefore, more data on the sensing are needed, particularly among younger patients.

Recent studies have demonstrated a high risk of inappropriate shocks (7-13%) from S-ICD due to sensing algorithm failures, which could be extremely distressing for patients (150).

The sensing algorithm of the S-ICD is less well studied, the techniques and data for this device sensing configurations are mainly extrapolated from other subcutaneous and transcutaneous monitoring devices such as loop recorder and automated transcutaneous external defibrillation technology (137, 151). Due to a high rate of inappropriate therapies (shock) the current literature emphasises the importance of further studies for a better understanding of the S-ICD sensing parameters and characteristics of subcutaneous/body surface ECG in various circumstances like body postures and cardiac morphologies (141-143, 150, 152).

The currently available S-ICD devices have three subcutaneous sensing electrodes on the L-shape subcutaneous lead and generator. (I) One sensing

electrode is on the canister implanted in 5th-6th intercostal space in mid axillary line, on the left side. (II) Second electrode is in the left lower parasternal area 1cm left-lateral to xiphisternum. (III) The third one is 14 cm above the second electrode in the left upper parasternal border on a single "L" shape lead (152). The S-ICD uses these three subcutaneous arrays for the recording of ECGs to sense heart rhythms. The sensing algorithm of the S-ICD depends on the surface (subcutaneous) ECG morphology. Specifically the R-wave amplitude, T-wave amplitude R/T ratio, QRS duration and QT interval are integral components of sensing parameters. Therefore, a pre-implant screening tool has been developed by the manufacturers (Cameron Health/Boston Scientific) which take into account these parameters of ECG (153). The screening tool is used in all patients who are considered for S-ICD implantation, in order to select individuals with appropriate ECG morphology for S-ICD sensing algorithm (153).

However, to study the sensing algorithm of S-ICD, it is possible to substitute the subcutaneous ECG with surface ECGs. Bellardine et al. assessed the feasibility of substituting subcutaneous with surface ECGs and demonstrated a strong positive correlation (R=0.96) between them (154). Therefore, the manufacturers of the S-ICD (Cameron health/Boston scientific) also recommend a collection of three electrode bipolar surface ECG in standing and supine posture from potential candidates of S-ICD, which is then analysed through a pre-implant screening tool to determine the suitability of the potential candidate for S-ICD sensing algorithm and implant.

As a part of this thesis, studies were undertaken using body surface mapping to answer the following questions:

1. The CHD patients may be a target population for S-ICD placement, but it is unclear whether the S-ICD sensing algorithm is fit for this purpose in the context of altered cardiac anatomies not withstanding evidence for defibrillation efficacy of this technology in this regard (131).

2. The amplitude of “R”, “T” with “R/T ratio” and the duration of “QRS”, “QT” play a vital role in the sensing algorithm of S-ICD for rhythm discrimination and deployment of therapy (shock) when life threatening arrhythmias (VT/VF) are sensed (131, 138). Additionally, abnormalities of the surface ECG parameters of depolarisation and repolarization such as of QRS,(155) QTc,(156) Tpeak-end duration(157) are also known markers of ventricular arrhythmias. An integration of these parameters into sensing algorithm of these devices especially S-ICD would be highly valuable. This would enable a pre-alert, before the occurrence of life threatening arrhythmias, which may enable risk modification with medications before the onset of ventricular arrhythmias. However, the effect of change of posture on R-wave amplitude, T-wave amplitude, R/T ratio, QRS duration, QTc duration, and Tpeak-end duration in all possible postures (standing, sitting, supine, left lateral, right lateral and prone) is not known.

3. The pre-implant screening tool plays an integral role in the selection of patients for S-ICD. However, the diagnostic, discriminatory ability (sensitivity and specificity) is not known in the current literature.

4. Three subcutaneous sensing arrays generate three bipolar vectors for the sensing of the heart rhythm; Lead III termed as primary lead, Lead II also called a secondary lead and Lead I also known as alternative lead. However, the comparative performance of these leads with changing posture and different heart morphologies is not known.

To investigate these issues, I have performed a series of studies on the sensing algorithm of the commercially available S-ICD (153) using 80-electrode body surface mapping, the currently used S-ICD pre-implant criteria and semi automated and automated computer models; these studies are described in chapter 4, 5 and 6.

CHAPTER 2

THE USE OF BSM DELTA MAP FOR THE DIAGNOSIS OF UNSTABLE IHD IN THE EMERGENCY DEPARTMENT

2 THE USE OF BSM DELTA MAP FOR THE DIAGNOSIS OF UNSTABLE IHD IN THE EMERGENCY DEPARTMENT

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Detection of regional myocardial ischaemia by a novel 80-electrode body surface Delta map in patients presenting to the emergency department with cardiac-sounding chest pain

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Background **Presentation with acute chest pain is common, but the conventional 12-lead ECG has limitations in the detection of regional myocardial ischaemia. The previously described method of the body surface mapping system (BSM) Delta map, derived from an 80-electrode BSM, as well as a novel parameter total ischaemic burden (IB), may offer improved diagnostic sensitivity and specificity in patients with myocardial ischaemia.**

Methods **The feasibility of using the novel BSM Delta map technique, and IB, for transient regional myocardial ischaemia was assessed in comparison with 12-lead ECG in 49 patients presenting to the emergency department (ED) with cardiac-sounding chest pain.**

Results **The sensitivity and specificity of 12-lead ECG for the diagnosis of acute coronary syndrome (ACS) was 67 and 55%, respectively, positive likelihood ratio (+LR) 1.52 [95% confidence interval (CI) 0.86, 2.70] and negative likelihood ratio (−LR) 0.58 [95% CI 0.30, 1.12]. The sensitivity and specificity of the BSM Delta map for the diagnosis of ACS was 71 and 78%, +LR 3.19 [95% CI 1.31, 7.80], −LR 0.37 [95% CI 0.20, 0.68]. There was a significantly positive correlation between peak troponin-I concentration and IB ($r=0.437$; $P<0.002$).**

Conclusion **This pilot study confirms the feasibility of using the Delta map for the diagnosis of ACS in patients presenting to the ED with cardiac-sounding chest pain and suggests that it has promising diagnostic accuracy and has superior sensitivity and specificity to the 12-lead ECG. The novel parameter of IB shows a significant correlation with troponin-I and is a promising tool for describing the extent of ischaemia. The use of the BSM Delta map in the ED setting could improve the diagnosis of clinically important ischaemic heart disease and furthermore presents the result in an intuitive manner, requiring little specialist experience. Further larger scale study is now warranted.** ***European Journal of Emergency Medicine*** **21:89–97**

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Keywords: body surface mapping, electrocardiography, image interpretation, myocardial ischaemic burden, regional myocardial ischaemia

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2.1 INTRODUCTION

In the UK approximately 700,000 patients present to the Emergency Departments [ED] annually with undifferentiated chest pain(158), but only a one-third of these patients will ultimately be diagnosed with acute coronary syndrome (ACS) (158, 159). Presently the diagnosis of ACS in the ED is based on the combination of clinical assessment, 12 lead ECG and cardiac biomarkers (160, 161). Each component of this diagnostic assessment has important limitations. The history may not be typical of "cardiac pain" (162), and the troponin levels can only be reliably interpreted at 6-12 hours after the onset of symptoms and are occasionally also released as a result of non-ACS pathologies (163). Assessment of chest pain in the ED in many patients is significantly dependent on 12 lead ECG for both, (i) the detection of transient regional myocardial ischaemia (RMI), and (ii) for subsequent risk stratification and management (26, 36, 161, 164, 165). There are however important limitations of the 12 lead ECG in this diagnostic context. The 12 lead ECG provides myocardial electrographic activity from a relatively small area of the thorax, as it derives electrographic data from 10 electrodes, while only six unipolar electrodes are placed directly on thorax for detection of localised electrocardiac activity. Moreover, the six electrodes are placed on mainly at the front of the chest. Therefore, it can only detect data from the front of the heart. Now it is well established that myocardial ischaemia in territories arising from blood flow limitation in the two out of three coronary arteries including circumflex and right coronary artery (i.e., posterior and right ventricular) may not be clearly evident on the standard 12 lead ECG (55, 166, 167). Due to these limitations, the sensitivity of the 12 lead ECG in the identification of myocardial ischemia and infarction is quoted between 13-69% (163, 168).

Specifically, 15-18% of patients with acute myocardial infarction show no changes in their presenting 12 lead ECG, whilst a further 25% show non-diagnostic changes (166). It is possible that a large number of patients with no previous history of coronary artery disease (CAD) may be inappropriately reassured because the ECG is “normal” (169).

The currently adopted ACS diagnostic algorithms in the ED are designed to include or exclude myocardial damage due to CAD, but at present, there is no easily available tool or method for detection and quantification of transient RMI in the ED. The prognostic implication of acute presentation with myocardial ischaemia and the benefit of early pharmaco-invasive intervention have been demonstrated extensively (5, 6, 161).

It is well described that in the context of acute myocardial infarction (MI), the 80 electrode body surface mapping system can improve diagnostic accuracy, particularly, when posterior and right ventricular regions are involved (170-172). Much less has been reported about the potential for multi-electrode ECG system in the diagnosis of transient RMI. In this study, we have described a novel method for the detection and display of transient RMI called BSM Delta map. The concept for this is to display as a colour exchange only a shift in ST segment for each individual electrode between two BSM acquisitions. First acquisition is obtained when the patient is in pain and the second acquisition is obtained when the patient is pain-free. Automated software quantifies the change in ST segment for each electrode between 2 acquisitions. This is then displayed on a torso map as a colour (red represents ST elevation and blue ST depression), and intensity of the colour is dependent upon the amount of ST shift in individual electrodes. This provides an intuitive colour map displaying ST shift. Importantly, the amount of ST shift (i.e., the degree of displacement)

that leads to the colour being displayed can be altered, thus allowing for a threshold. This concept was previously studied in the context of single vessel coronary angioplasty (173). Furthermore, we employ a novel parameter, total ischaemic burden (IB) that produces a numerical description of the total ST shift across all 80 electrodes.

The aim of this pilot study was to assess the feasibility and diagnostic accuracy of the BSM Delta map and IB in patients presenting to the ED with cardiac-sounding chest pain. In order to do this, we compared them with conventional clinical tests and final diagnosis as references: namely (i) 12 lead ECG, (ii) troponin-I, and (iii) final clinical diagnosis of ACS.

2.2 METHODS

The study was undertaken in the Emergency and Cardiology departments of our university teaching hospital. The recruitment was carried out during normal office hours by the dedicated research team.

2.2.1 Ethical Consideration

The study protocol was given full approval by the Hampshire & Isle of Wight Ethical Committee (Committee-A under REC-06/Q1702/49) and the Research and Development Department of Southampton University Hospitals NHS Trust (SUHT).

2.2.2 Consent

All subjects provided written informed consent prior to the study inclusion. The local Research Ethics Committee prospectively approved the consent form (attached in the appendix).

2.2.3 Inclusion and exclusion criteria

Only patients over 18 years of age and those who were able to provide fully informed consent were recruited. Patients with acute haemodynamic or electrical instability, permanent pacemaker (continuously paced rhythm), and subjects of other studies were excluded from the study.

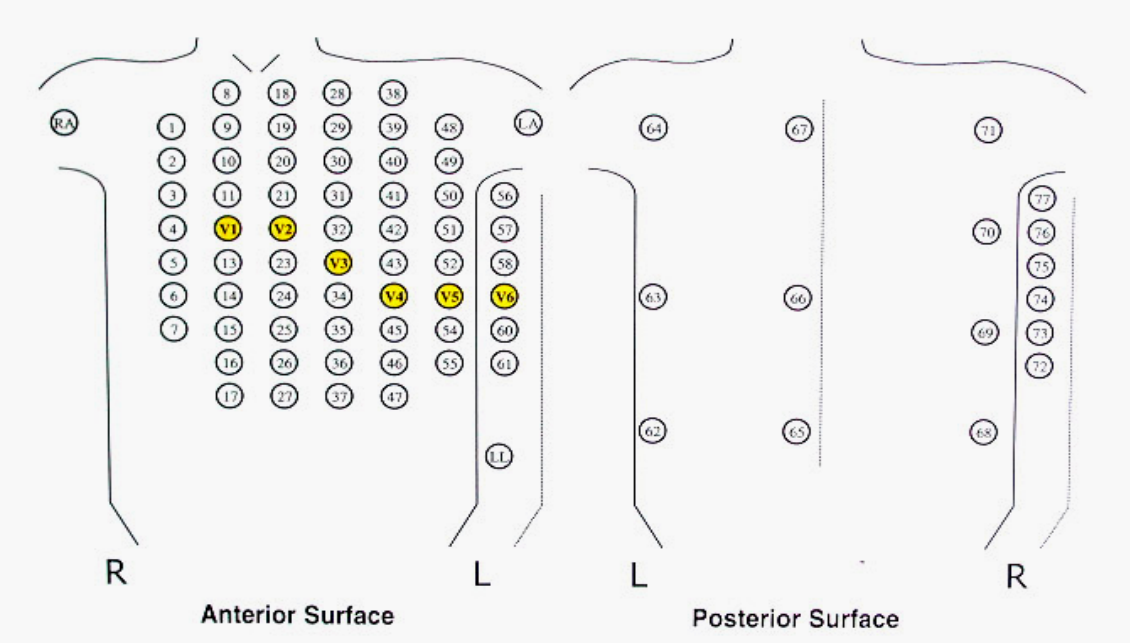
2.2.4 Study population

In this study, fifty adult patients presenting to emergency department with suspected unstable IHD symptoms were recruited.

2.2.5 The collection of 80-electrode PRIME® ECG Body Surface Map

PRIME® (Precise Rapid Ischemic Myocardial Evaluation) ECG (manufactured by Meridian Medical Technologies, Belfast, Northern Ireland and currently owned by Verathon international corporation limited) is a body surface mapping (BSM) system which records electrocardiac activity using a total of 80 electrodes placed all around the thorax [Figure 5].

Figure 5: PRIME® ECG system electrodes location.



Location of the 80 electrodes on the thorax with the PRIME® ECG system. The conventional ECG chest leads are highlighted. *Adopted from Heartscape Technologies Ltd, now acquired by Verathon Inc.*

2.2.5.1 The PRIME® ECG components

The PRIME® ECG consists of the following parts:

- PRIME® ECG recording unit.
- PRIME® ECG vest.

2.2.5.1.1 PRIME® ECG recording unit

PRIME® ECG recording unit is a portable machine and consists of the following components [Figure 6]:

- A colour display screen, which projects the 80 electrode data in various required formats as described in the PRIME® data acquisition section.
- Onboard computer to control the simultaneous collection of 80 ECG channels. The computer is attached to a keyboard for the recording of patient's details and a trackball to move the cursor on the screen.
- A large-capacity hard disk, used to store patient data and maps in a structured database.
- A mass storage device, used to copy and export patient data and maps from the hard disk. □
- A color printer, used to print patient data and maps if required.
- Cables to attach the PRIME® ECG vest [Figure 9] (174).
- A power supply unit that is configurable for 220/240 VAc and 110/120 VAc mains power. It includes a battery backed Uninterruptible Power Supply (UPS) for short-term use away from a mains outlet. Generally, the manufacturers recommend to keep the device connected to the mains

outlet and to use the UPS support for the transportation of the equipment from one place to another.

Figure 6: PRIME® ECG in use.

Various components of PRIME® ECG and patient positioning. Adopted from Heartscape Technologies Ltd, now acquired by Verathon Inc (174).

2.2.5.1.2 PRIME® ECG vest

The PRIME® ECG vest consists of two parts [Figure 7 & 8], i.e., flexible plastic anterior and posterior electrodes vests containing 80-electrodes for data collection (172, 174). Electrocardiac data is recorded through 55 electrodes placed over the anterior, 6 electrodes placed over the left lateral part of the chest, 6 electrodes over the right lateral part of the chest, 10 electrodes placed over the posterior chest and three electrodes placed over the limbs, thus enabling the recording of 77 simultaneous unipolar and 3 bipolar ECG signals (174). The vest is arranged in vertical strips referenced to their anatomical landmarks, as described below:

2.2.5.1.2.1 Anterior vest:

Consist of seven vertical strips and each strip is marked for an appropriate anatomical position. The anterior vest is attached in the following order [Figure 8] (174):

[i] Right mid-clavicular line.

[ii] Right parasternal (VI) line.

[iii] Left parasternal (V2) line.

[iv] Left medial-clavicular (V3) line.

[v] Left mid-clavicular (V4) line.

[vi] Left anterior-axillary (V5) line.

[vii] Left mid-axillary (V6) line.

2.2.5.1.2.2 Posterior vest

Consist of four vertical strips and each strip is marked for an appropriate anatomical position. The posterior vest is attached in the following order [Figure 7] (174).

[i] Left posterior axillary line.

[ii] Left para-spinal line.

[iii] Right posterior axillary line.

[iv] Right mid-axillary line.

Vest application typically takes 3-4 minutes (172).

2.2.5.2 Preparation for the PRIME® Data Acquisition

The PRIME® ECG machine was turned on by pressing the power button. The following steps describe the PRIME® ECG data acquisition:

2.2.5.2.1 Patient preparation

- The patient was asked to take off the shirt to expose the front and back of the torso and to lie down on a bed; the backrest of the bed was set at 45 to 60 degree to the horizontal. The patient legs were kept straight out in front of them. □
- Skin preparation was required in some individuals including shaving off any excess body hair on the torso. Alcohol wipes were required for the patients with greasy skin.

2.2.5.3 Application of PRIME® vest

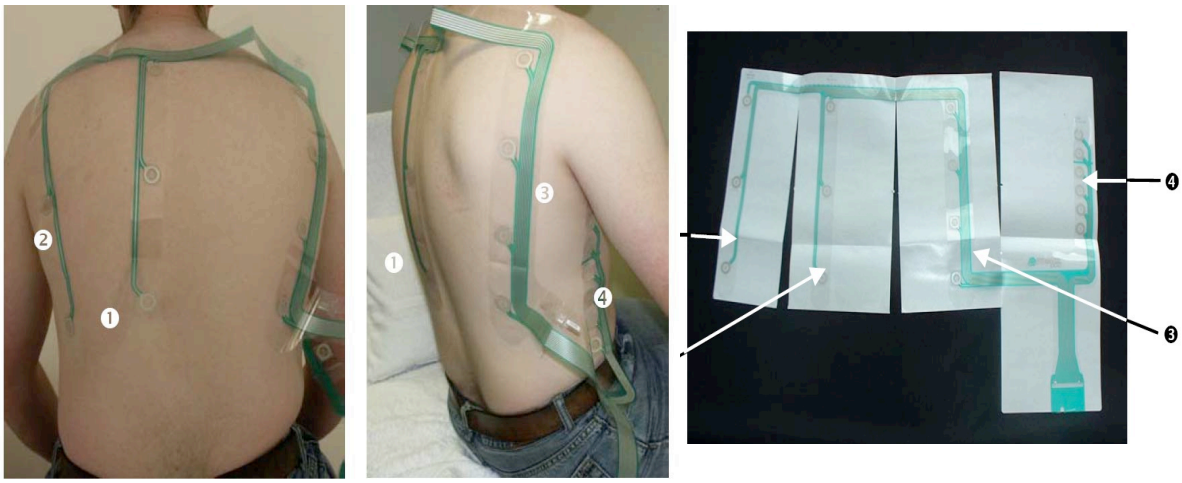
- The PRIME® vest packaging was opened on a flat surface by peeling off one side of the packaging.
- The anterior and posterior vests were taken out and placed on a flat surface as shown in the Figures 8.

2.2.5.3.1 Application of posterior vest

- The posterior vest was applied first by asking the patient to sit forward. Before application of the vest, each strip was separated out by tearing through the links in the backing paper sheet as shown in Figure 7 below.

- First, the strip with the printed marking “Left spine” (electrodes 65 to 67), was applied vertically to the left of the spine after peeling the backing paper, which is the second strip from the left in the picture below.
- Then the strip with printed marking “Left posterior axilla” (electrodes 62 to 64) was applied in the same manner, which is the first strip from the left in the picture below.
- Followed by the “Right post axilla” (electrodes 68 to 71) strip, which is the third strip from the left in the above picture.
- The “Right mid axilla” (electrodes 72 to 77) strip, which is the fourth strip from the left in the above picture was applied last on the back.
- Each strip was applied from top to bottom and then settled on the skin by running the thumb over each strip to ensure appropriate adhesion.

Figure 7: PRIME® ECG posterior vest.



Adopted from Heartscape Technologies Ltd, now acquired by Verathon Inc.

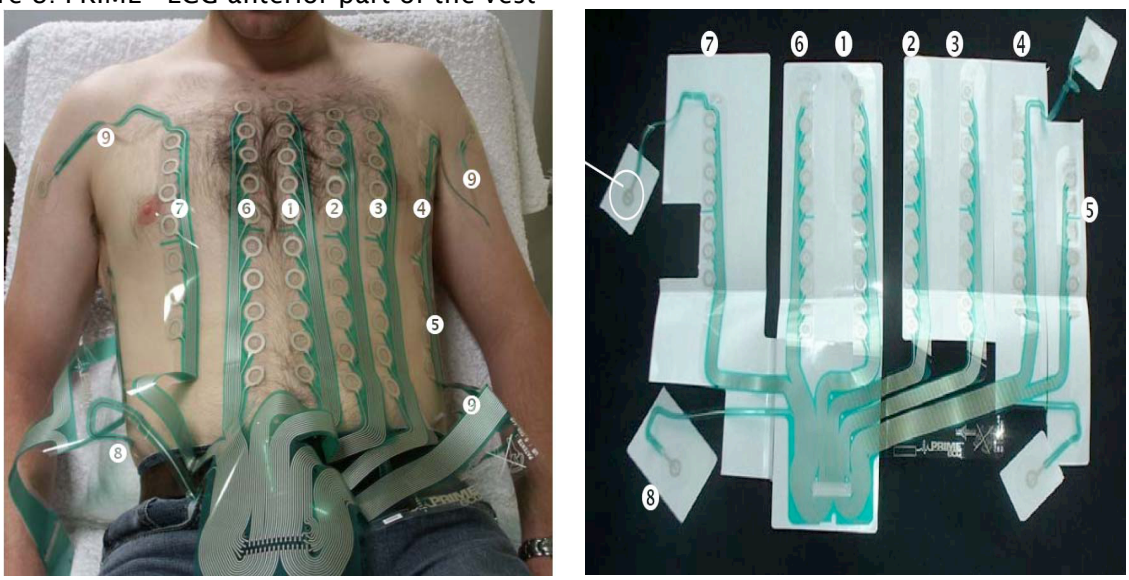
2.2.5.3.2 Application of anterior vest

- For the application of the anterior vest, the patient was asked to rest the back against the backrest of the bed; the patient was advised to avoid friction with the bed to reduce the disturbance of the posterior electrodes.
- The anterior vest was placed on a flat surface; the backing papers of each strip were separated in the same manner as before.
- The backing paper was peeled off from each strip just before the application. The strips were applied from top to bottom, according to the anatomical markings from the sternum outwards in the following order:
- First, the strip marked as “Left sternal notch” (electrodes 18 to 27) was applied, which is the third strip from the left in Figure 8 below.
- Second, the strip marked as “V3 line” (electrodes 28 to 37) was applied, which is the fourth strip from the left in Figure 8 below.
- Third, the strip marked as “Left mid clavicular” (electrodes 38 to 47) was applied, which is the fifth strip from the left in Figure 8 below.
- Fourth, the strip marked as “Left anterior axilla” (electrodes 48 to 55) was applied, which is the sixth strip from the left in Figure 8 below.
- Fifth, the strip marked as “Left mid axilla” (electrodes 56 to 61) was applied, which is the seventh strip from the left in Figure 8 below.
- Sixth, the strip marked as “Right sternal notch” (electrodes 8 to 17) was applied, which is the second strip from the left in Figure 8 below.
- Seventh, the strip marked as “Right mid clavicular (electrodes 1 to 7) was applied, which is the first strip from the left in Figure 8 below.

- Finally, the limb leads/electrodes were applied according to their anatomical marking.

Similarly, each line of electrodes was applied from top to bottom, and thumb was run over each line to ensure adherence to the skin.

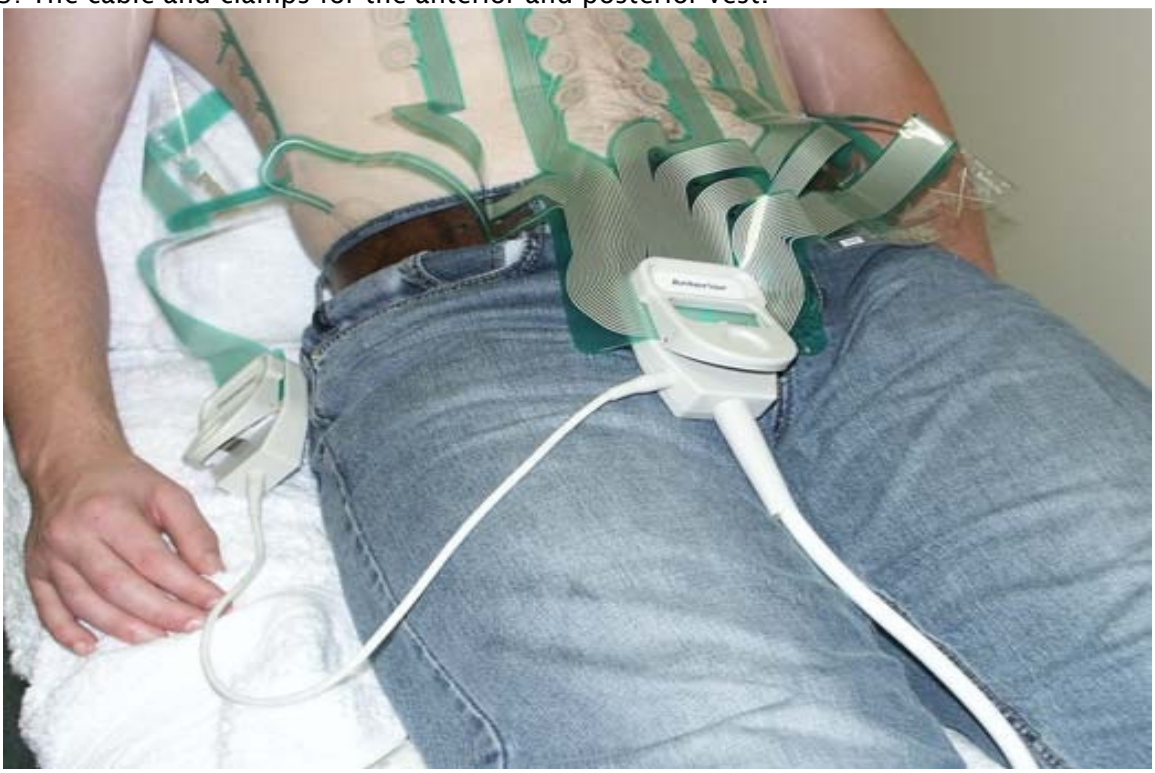
Figure 8: PRIME® ECG anterior part of the vest



Adopted from Heartscape Technologies Ltd, now acquired by Verathon Inc.

- After application of the vest, it was attached to the PRIME® unit through the clamps on the cable labelled separately for attachment to the anterior and posterior vest as shown in Figure 9 below.

Figure 9: The cable and clamps for the anterior and posterior vest.



2.2.5.4 Viewing the real time ECG

Continuous 80-electrode ECG can be seen on the colour display screen as soon as the cables are attached to the vest, as shown in Figure 10. During real-time display, the electrode view shows traces from all electrodes on the vest set. Adjacent traces are shown in different colours to differentiate them clearly.

Traces displayed in red indicate that readings being obtained from that channel are of low quality.

2.2.5.5 Signals quality check

Prior to recording, signal quality was checked in banks of 8-leads, and any poor signal was identified and corrected [Figure 11 and 12]. All the electrodes

were viewed by scrolling through them in banks of 8-leads by pressing on the yellow arrow, which can be seen in Figure 11 and 12.

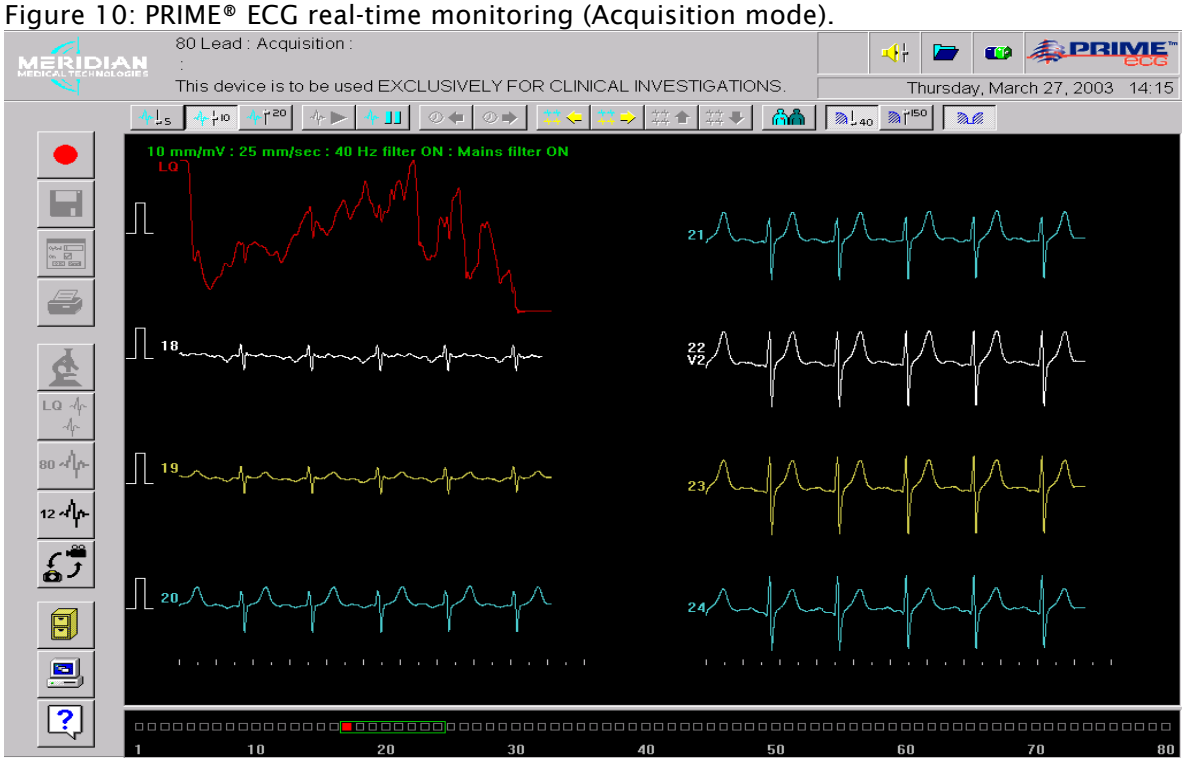
The most common causes of low-quality readings are the following:

- The vest displacement due to the patient's movement.
- An electrode that has become unstuck from a patient.
- Connection fault due to inappropriate clamp connection to the vest or the unit.

The following steps were taken to rectify the low-quality signals/traces.

- Check that the electrode was still applied to the body and making good contact. If it was due to peeling off, the skin was cleaned, or skin adhesion tap was applied.
- The cable and clamps were checked to ensure it was not pulling on the vest. Putting the cable along the line of the legs prevents it slipping off the side of the bed. □
- The cable clams were compressed shut to ensure proper contact with the vest. □

Figure 10: PRIME® ECG real-time monitoring (Acquisition mode).



Real-time monitoring (Acquisition mode). Linear View Screen with automatic low quality (LQ) electrode designation at channel 17. LQ appears red; the white colour is given to electrodes with good quality, the yellow and blue colour electrodes are good quality but can be improved. Adopted from Heartscape Technologies Ltd, now acquired by Verathon Inc.

2.2.5.6 PRIME® ECG controls

The PRIME® ECG controls can be seen in the above figure 10 on the left-hand side placed vertically and horizontally on the top of the screen.

Controls	Function
	This button is used for acquisition.

This button is used for saving the data to the PRIME® hard disc.

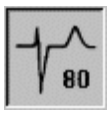
This button is used for beat marking.

This button is used to view different format of ECG recording.

Used for switching between real-time and recorded tracings.

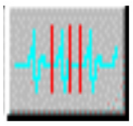
Used for scrolling between the electrodes.

To display conventional 12 lead ECG.



To display 80-electrodes ECG.

Used for low-quality signals assessment.



For the selection of single lead display and viewing/correction of beat markers.

To retrieve previously saved data.

Printing manager, to manage printing queue and change the output dialogue.

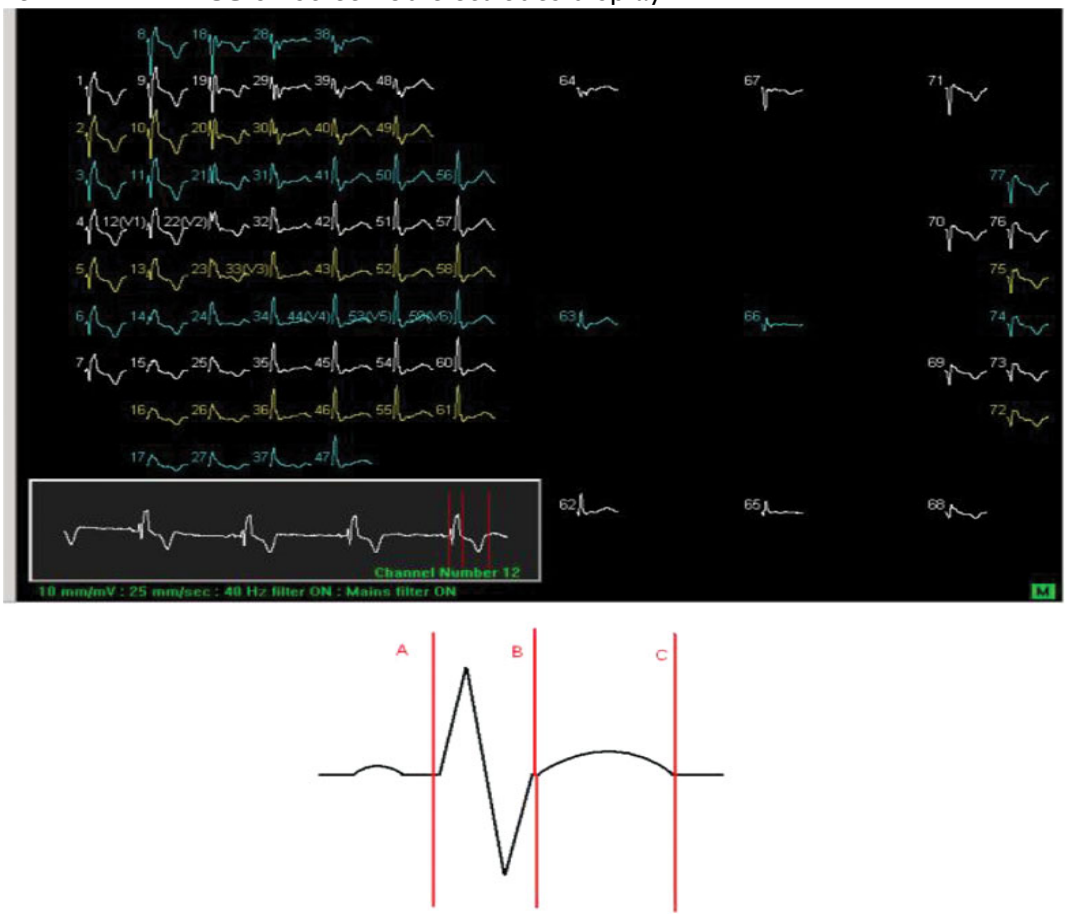
For switching between 2D colour map and 3D torso colour map.

2.2.5.7 Data acquisition and beat marking

Before the acquisition of the data, poor quality signals were identified and rectified as described above. Then the data was acquired by pressing the "Record" button; the PRIME® ECG allows recording of ten-seconds electrograms at a sampling rate of 1000Hz. Following data acquisition and correction of poor signals a single lead display was selected, and a single beat which was artefact free (best beat) in each of the 80 leads was chosen on which the QRS onset, QRS offset (J point) and T wave offset beat markers were placed [Figure 11-12]. The BSM system automatically approximates beat marker positions, which were then optimised by manual adjustment. Conventionally the earliest QRS onset and the latest T wave (or, if present, T-U complex) offset were chosen, since the spatial dispersion of QRS onset and T wave offset of the

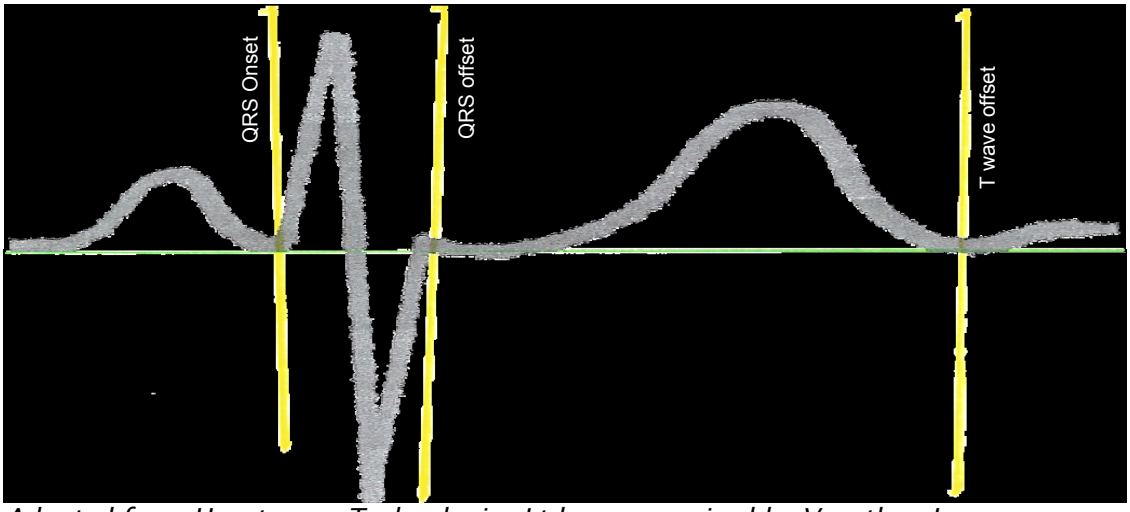
selected beat may occur across the 80-leads. Beats from an ectopic focus or with significant baseline wander were considered unsuitable as these result in erroneous variable calculations (174).

Figure 11: PRIME® ECG on screen 80 electrodes display.



A multi-electrode map, displaying electrical activity in 61 anterior chest leads and 16 posterior chest leads. Limb leads not displayed. (B) Placement of beat markers for body surface mapping analysis where (A) is the QRS onset, (B) is the QRS offset, positioned at the J point, and (C) is the T-wave offset, positioned at the end of the T wave or U wave if present Shows the beat marking. Adopted from Heartscape Technologies Ltd, now acquired by Verathon Inc.

Figure 12: PRIME® ECG Best beat marking.



Adopted from Heartscape Technologies Ltd, now acquired by Verathon Inc.

2.2.5.8 Body Surface Map

Patient maps are pictorial representations of the electrical activity recorded. Placement of beat markers enables custom software to calculate the following variables, which allows the formation of the map (174):

(i) QRS and ST-T isointegrals: Integration (i.e., area) of the ECG signal under the QRS and ST-T curves respectively at each electrode site, measured in mVms.

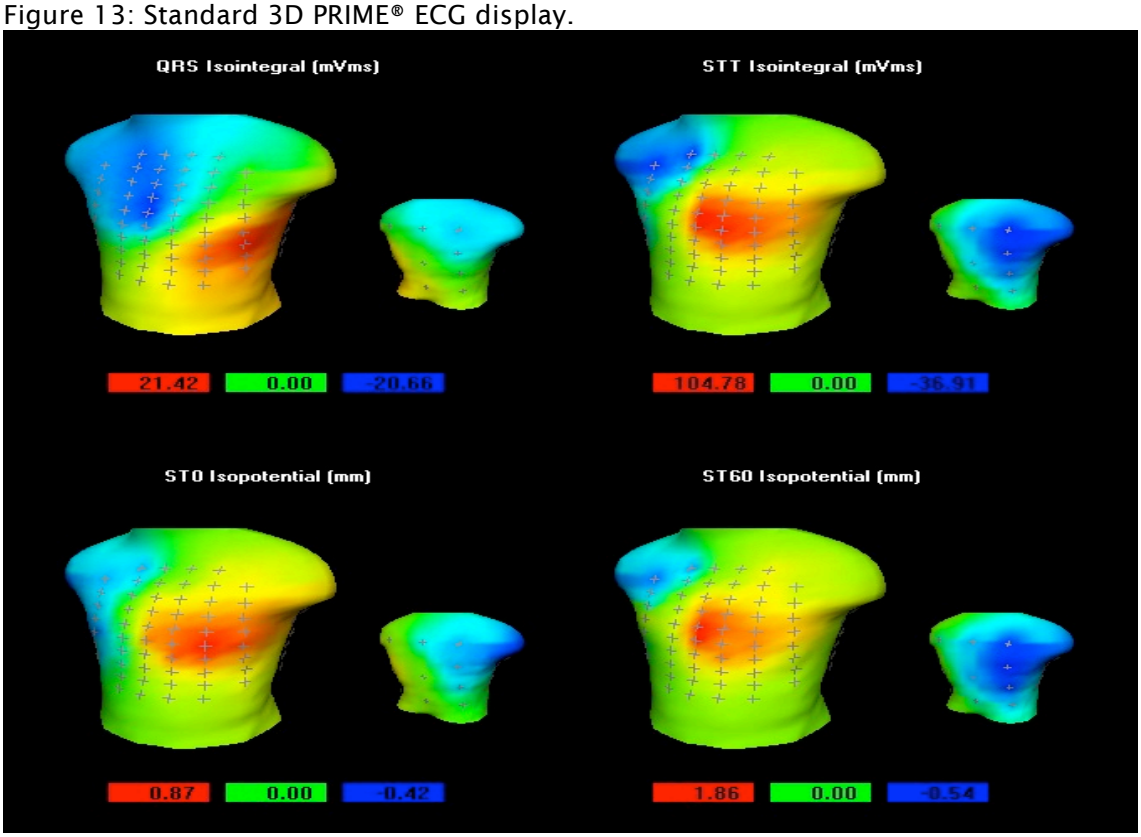
(ii) STO and ST60 isopotentials: The potential at each electrode site at the J point (STO), or 60 msec after the J point (ST60), displayed in mm (1mm = 0.1 mV) (55, 174-176).

2.2.5.9 Display of results

Once a given BSM variables are calculated, the value at each of the 80 electrodes is plotted or 'mapped' using a colour contour display [Figure 13 and 14]. Each colour contour line joins points of equal value and is scaled from red (maximum), through green (zeroed), to blue (minimum). Where the leads

density is less, for instance, on the posterior surface, automatic interpolation is performed by the PRIME® software, which makes continuous smooth display possible (174). The area surrounding the maximum is termed the 'maxima', and the area surrounding the minimum, the 'minima.' The cardiac vector is drawn from minimum to maximum (174).

Figure 13: Standard 3D PRIME® ECG display.



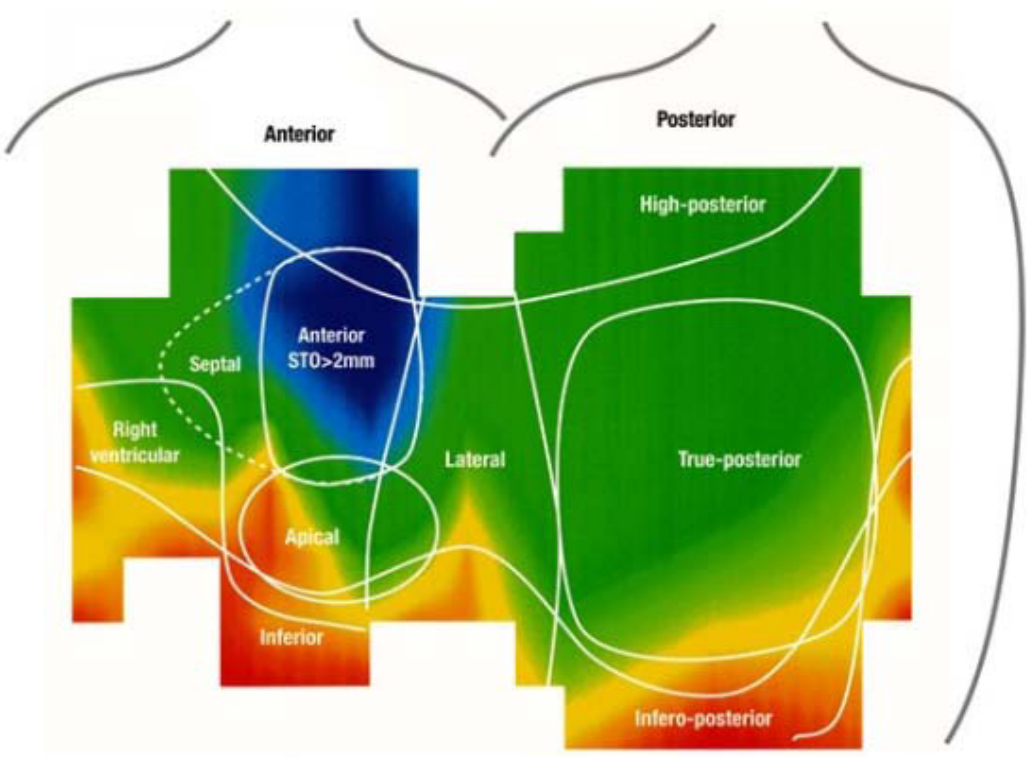
Top Left. The QRS Isointegral-map is a map of DEPOLARISATION that defines the AREA of the QRS Complex at each electrode site; obtained from data between the QRS onset and offset beat markers.

Top Right. The STT Isointegral Map is a map of REPOLARISATION that defines the AREA of the ST segment and the T wave in 80 leads, obtained from data between the QRS offset and T wave offset beat markers.

Bottom Left. The ST0 Map is a map of REPOLARIZATION. It displays the potential in each of 80 leads at the J point, assesses ST segment shift from the isoelectric line.

Bottom Right. The ST 60 map is a map of REPOLARIZATION that displays the POTENTIAL in each of 80 leads at 60msec past the J point, used to confirm the information of the ST0 map; helpful in the assessment of ST depression. Adopted from Heartscape Technologies Ltd, now acquired by Verathon Inc.

Figure 14: A key for the 2D map interpretation and identification of an area of ischaemia.



Adopted from Heartscape Technologies Ltd, now acquired by Verathon Inc.

2.2.5.9.1 Conventional ECG format

The data is displayed as a series of ECG complexes in the distribution that they would be seen on the chest wall, as shown in Figure 10 & 11 above (174).

2.2.5.9.2 Isointegral contour Plot

Values are determined by calculating the area between 2 points on the single/same beat of the ECG (e.g., between the start and finish of the QRS complex) [Figure 15]. The area between the two plots is integrated, and it is this value that is plotted, which determines maxima and minima display on the 3D pseudo-torso [Figure 16] (174).

Figure 15: Calculation of QRS and STT isointegral.

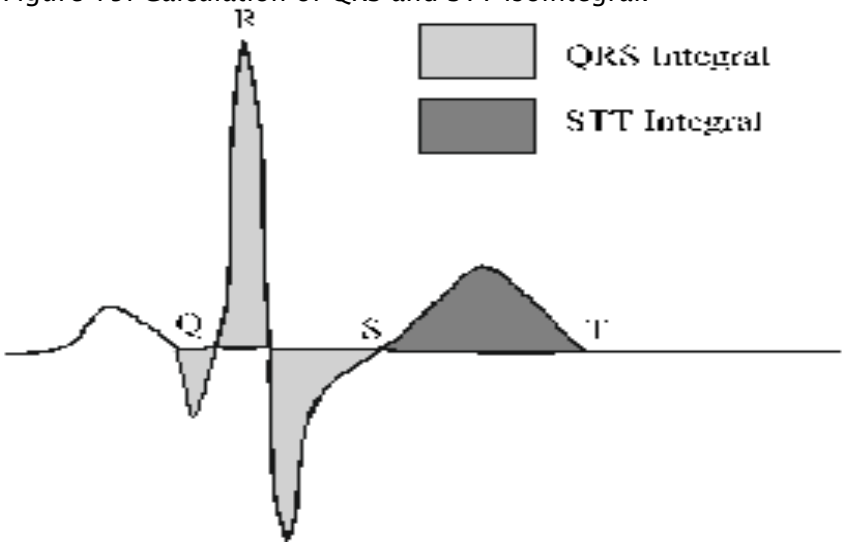
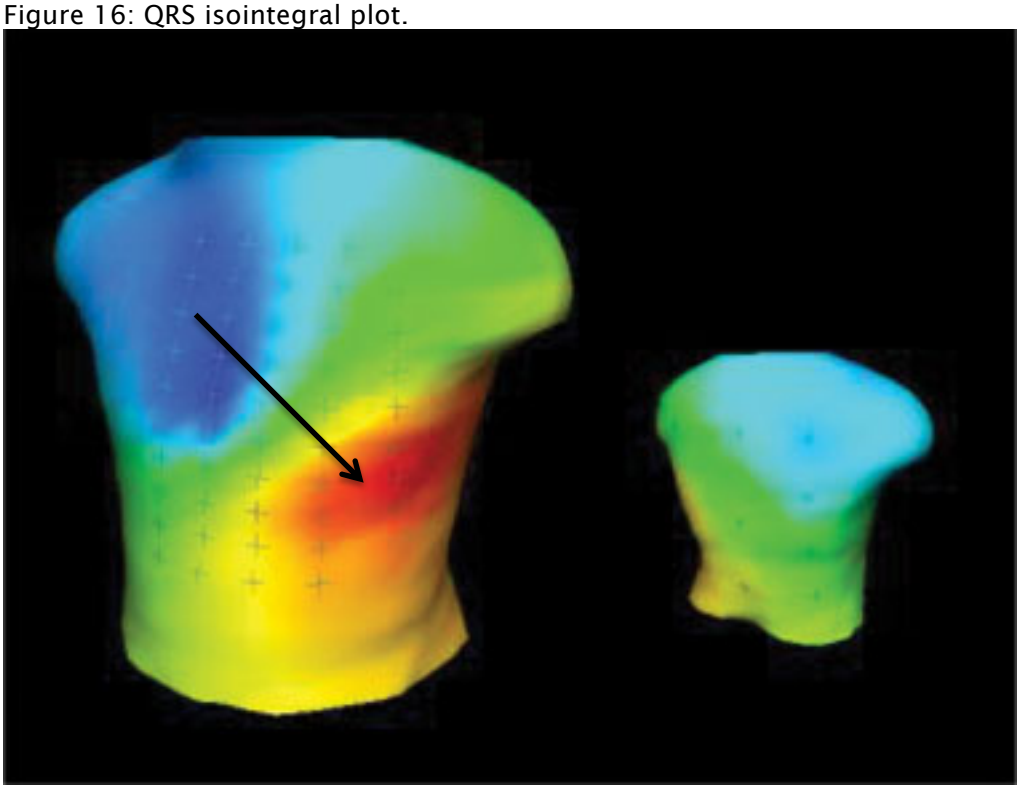


Figure 16: QRS isointegral plot.



This QRS isointegral plot from a normal patient shows the area under the QRS complex plotted on a 2-dimensional representation of the thorax (anterior on the left, posterior on the right). Positive areas are shown in red, negative in blue and neutral in green. As expected the mean QRS axis appears to go from the right shoulder (blue) to the apex of the heart (red). The minima-maxima are shown by the direction of the arrow. Equal values at different points on the thorax are represented by the same colour. Adopted from Heartscape Technologies Ltd, now acquired by Verathon Inc.

2.2.5.9.3 Isopotential contour Plot

Areas of equal potential at a single point of the ECG (e.g., STO) are joined by a line (as a contour on a hill side joins points of equal height). This produces a map showing a series of electrically identical lines (174).

2.2.5.9.4 Perspective contour plot

The data from a contour plot is expressed as a 3D plot, with high areas of electrical potential appearing as hills on a landscape (174).

2.2.5.9.5 Cine map display

Isopotential maps from a sequential number of time points can be viewed as a cine-film to show how the electrical potentials flow across the thoracic surface (174).

2.2.5.9.6 Difference map

The recorded map is subtracted from a standard map to demonstrate the points that show a difference [Figure 17]. The standard map may be from the individual subject, or from an averaged normal map (174, 177).

2.2.5.9.7 Departure map

This is similar to the Difference map, but only plots those values that are more than 2 standard deviations outside the normal range (174).

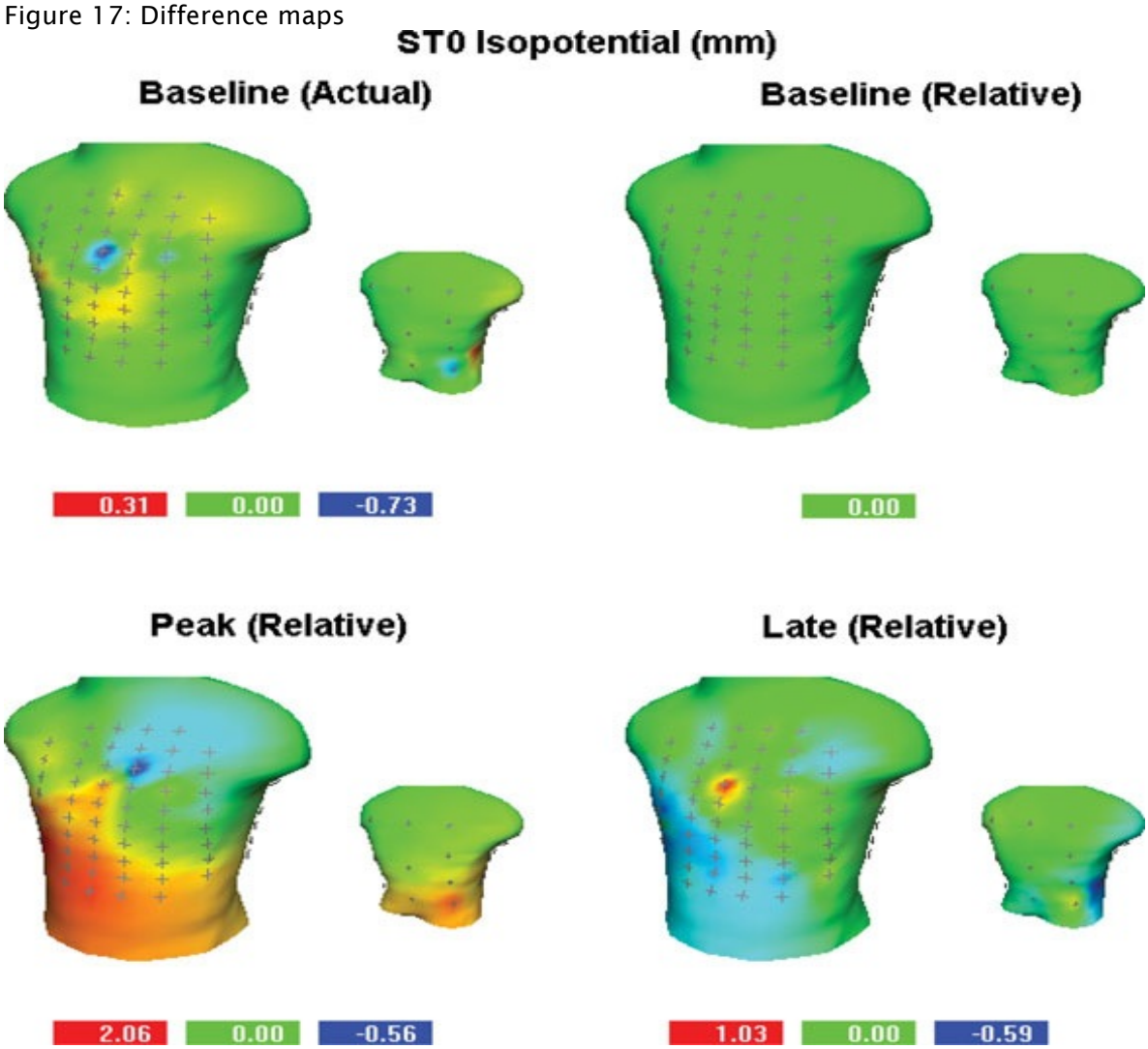
2.2.5.9.8 Discriminant map

Kornreich has described a map by dividing the difference map by the standard deviation of the normal map (55, 174).

2.2.5.10 PRIME® ECG handling of poor signals and missing data

The PRIME® ECG unit has an automatic algorithm with a mathematical solution to smooth the baseline and utilises data from the adjacent electrodes above and below to replace missing data due to poor signal in order to produce a reliable and uniform result. However, there is a limit on the number of missing data points, conventionally there should be no more than six missing points (poor electrodes recording) in total, and specifically, there should be no more than one missing electrode on the posterior aspect of the torso (174).

Figure 17: Difference maps



This figure shows more intuitive presentation of abnormal values by the initial acquisition of base line BSM map (top left), all the values at each point are accepted as normal creating a neutral map (top right). These values are considered baseline normal for that individual; this makes subtraction of any further maps possible. In the above example, regional myocardial ischemia was induced by coronary artery occlusion during angioplasty to the right coronary artery (RCA). A baseline neutral map is created, which is then subtracted from the BSM map acquired after 1minute balloon inflation (peak) (bottom left), and again after 3 minutes recovery (late) (bottom right) showing development and resolution of regional myocardial ischaemia. *Adopted from Heartscape Technologies Ltd, now acquired by Verathon Inc.*

2.2.5.11 Interpretation of conventional PRIME® BSM (178)

Step by step method for the interpretation of the PRIME® ECG body surface map is given below (178):

1. Satisfactory signal quality is ensured.

2. The 12-lead ECG obtained from the BSM is reported in a conventional manner.

3. Then the colour contour maps are reviewed stepwise.

The map interpretation is based on three factors:

I. Location of the maxima and minima. Maxima (represented by red colour), which is the area of the map with higher values above the set threshold or the baseline, and minima (represented by blue colour), which is an area of the map with lower values below the set threshold or the baseline.

II. The intensity of the colour, which represents higher value.

III. The numerical value, associated with the red and blue colour. This numerical value represents the lead with the highest value above baseline (maxima-red colour) and below baseline (minima-blue colour).

The assessment of colour contour maps is conventionally started with the depolarisation (QRS isointegral) map, any abnormalities in the location or values of the maxima and minima are analysed. Some inter-subjects variability is expected. However, the typical QRS minima is located on the right shoulder, which is blue colour coded and the maxima is located over the left anterior chest (red colour) (178). Similarly, inter-subjects variability in the normal values of QRS minimum and maximum is also expected. Nevertheless, a QRS minimum of up to -50 mVms and QRS maximum of up to 50 mVms are usually considered within normal limits (178). Following this initial assessment, the QRS duration is analysed. This can be best analysed on the 12 lead display. On the 12-lead display a QRS duration of >120 msec is required for the diagnosis

of right or left bundle branch block, however, in PRIME® ECG the upper limit is 120-150 msec (178).

The next step is usually to analyse the repolarization maps (STT isointegral; STO and ST60 isopotentials), any abnormality in the locations or values of the minimum and maximum are assessed (178).

STT isointegral: Inter-subject variations are expected. Therefore, an STT maximum of up to 90 mVms and an STT minimum of up to -40 mVms are usually considered within normal limits (178).

STO isopotential (i.e., J point map): In this map normally no minima and maxima are expected. However, red colour represents ST elevation at J point, and blue colour represents depression at J point beyond the set threshold. Abnormality of the values depends on its location on the pseudo torso/territory.

A maximum value of ≥1 mm (0.1 mV) in the anterior region is considered normal, whilst the maximum value of up to 2 mm (0.2 mV) is considered normal in the anteroseptal region. The upper limit of normal maximum value in the posterior region is 0.5 mm (0.05mV) due to the relative distance from the generator. Generally, for ST0 maximum value of >1mm (0.1mV) at any location, it is recommended to investigate the morphology of the underlying ST segment to exclude changes suggestive of acute myocardial infarction.

Similarly, minimum values of -1mm (-0.1mV) on the anterior surface and -0.5mm (-0.05mV) on the posterior surface are considered normal (178).

ST60 isopotential: This map displays changes in the ST segment at 60msec from J point. Therefore, the findings on this map are confirmatory of the ST segment changes in the ST0 map. Additionally, the ST segments at this location are usually free from confounding factors like rate related ST

depression or high take off. The interpretation of the ST60 is similar to the ST0 map. (178).

The exact values and locations of maximum and minimum in both the ST0 and ST60 maps play an important role in the diagnosis of myocardial ischaemia and infarction.

4. Finally, a general review of all the 80 electrodes is undertaken, and specifically, focusing on the electrodes which are contributing to any abnormality on the map to exclude Q or S waves, which could produce abnormal isointegral minima in the absence of any true ST depression or T wave inversion (178). Similarly, it is important to exclude early repolarisation (high take off) or pericarditis related changes, which may mimic ST elevation MI on ST0 map (178). The presence of a significant reciprocal minimum may be helpful although it lacks specificity for ruling out acute myocardial infarction (178). If the ST morphology is equivocal, comparison with the previous baseline maps if available or serial maps taken at 15-30 minute time intervals may be required to distinguish evolving acute infarction from other differential diagnoses (178).

2.2.6 BSM Delta map

As described above, the understanding and interpretation of the PRIME® ECG is complex and requires time and specialist training, which is one of the important reasons for the PRIME® ECG and BSM not becoming a part of a routine clinical practice until now. The BSM Delta map is specially written software to create subtraction map of individual electrode-specific ST60 data at one data acquisition time-point with the other. For example for the diagnosis of stable ischaemic heart disease, the BSM Delta map can be used with the

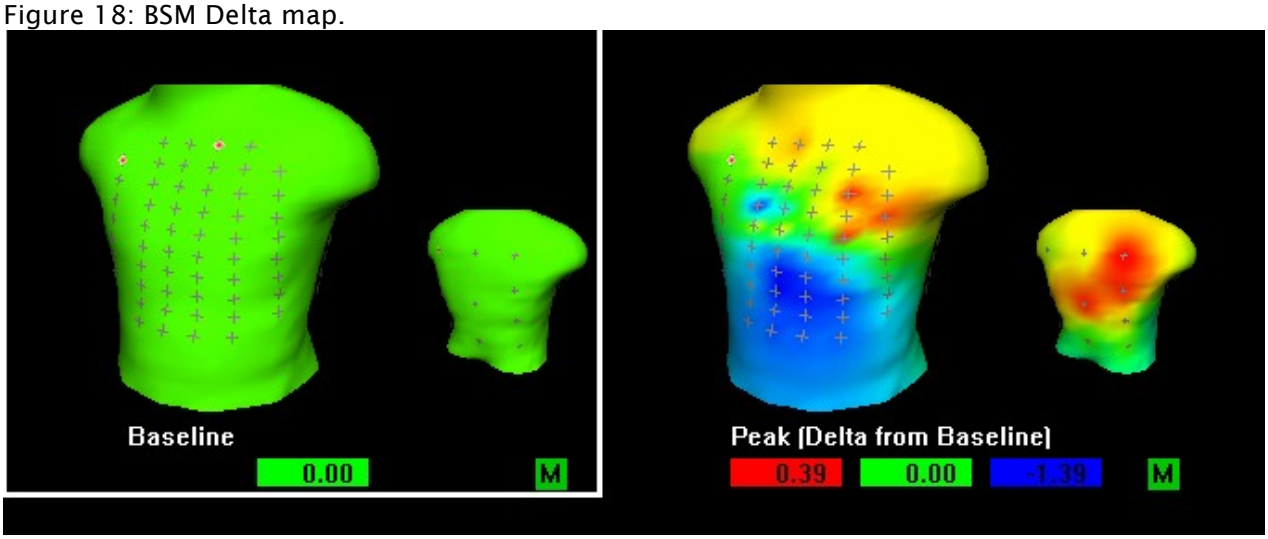
cardiac stress protocol and the baseline PRIME® ECG map can be obtained at rest and a second PRIME® ECG map can be obtained at peak stress and then using the automated algorithm to display the resultant difference in the ST60 data. The cardiac stress can be achieved by measured physical exertion or by the use of pharmacological agents such as Dobutamine. Similarly, in the acute setting, such as in patients with unstable IHD or ACS, PRIME® ECG can be acquired while the patient is symptomatic with chest pain and then in pain-free state after the patient receives initial treatment. The automated algorithm allows the interpretation of the difference between the two maps, thus making it simple to interpret the data of interest rapidly (172, 173). The digitally subtracted ST shift is labelled by colour scale exchanging, and the result projected on to a virtual three-dimensional torso image [Figure 18].

This novel algorithm also allows the variation of the colour scale threshold so that a certain level of ST shift is required below which only green (neutral) colour will be displayed. This method does not require the understanding and learning of complex interpretation of PRIME® BSM and simplifies the interpretation of the resultant map. This hypothesis was tested by our group for the diagnosis of transient regional myocardial ischaemia (TRMI) in patients undergoing coronary arteries angioplasty for single vessel disease using 80 electrodes PRIME® ECG (173). In this study 25 patients (11 with RCA lesions, 9 with LAD lesions and 5 with circumflex lesions) were studied and PRIME® ECG was acquired at baseline and then at 30 seconds and 60 seconds post angioplasty balloon inflation in the target vessel obstructing blood flow downstream (173). This study confirmed that 80-electrode PRIME® ECG (BSM) could detect and display TRMI. With the help of this study, automatic algorithms were developed into the PRIME® ECG software allowing for selection of the relevant acquisitions and subtraction, which we call BSM Delta map. The

BSM Delta map also provides a platform to calculate the ST shift at ST60 as an absolute sum and present this as an ischaemic burden (described in detail in the methods section)

This method produces intuitive results in the form of colour display, and shows ST segment shift using patients own baseline PRIME® ECG as a reference point for each electrode and thus require very little training for interpretation.

Figure 18: BSM Delta map.



Subtraction of 80-electrode BSM ST segments at base line (or CP free state) from second acquisition at peak stress (or CP state).

2.2.6.1 BSM Delta map data Acquisition

The PRIME® BSM was acquired as described above. For each patient to be included in the analysis they had to complete two PRIME® BSM data acquisitions: one whilst in pain and a second one when pain-free. Where possible BSM vests were left in place in most of the patients for the acquisition of the second BSM. Following each episode of data acquisition, the best beat markers were manually placed at the start of and end of the QRS and ST-T

segments. Isopotential maps at 60ms after the J-point [ST60] were created from the best beat in each recording as has been previously described (172). To generate BSM Delta map, both the acquisitions were saved to the hard disc. Then the two maps were highlighted within the saved data, followed by the BSM Delta map mode activation, by pressing the dedicated button, which displayed the resultant BSM Delta map instantaneously by automated subtraction of the BSM acquired during pain-free state from BSM acquired during pain.

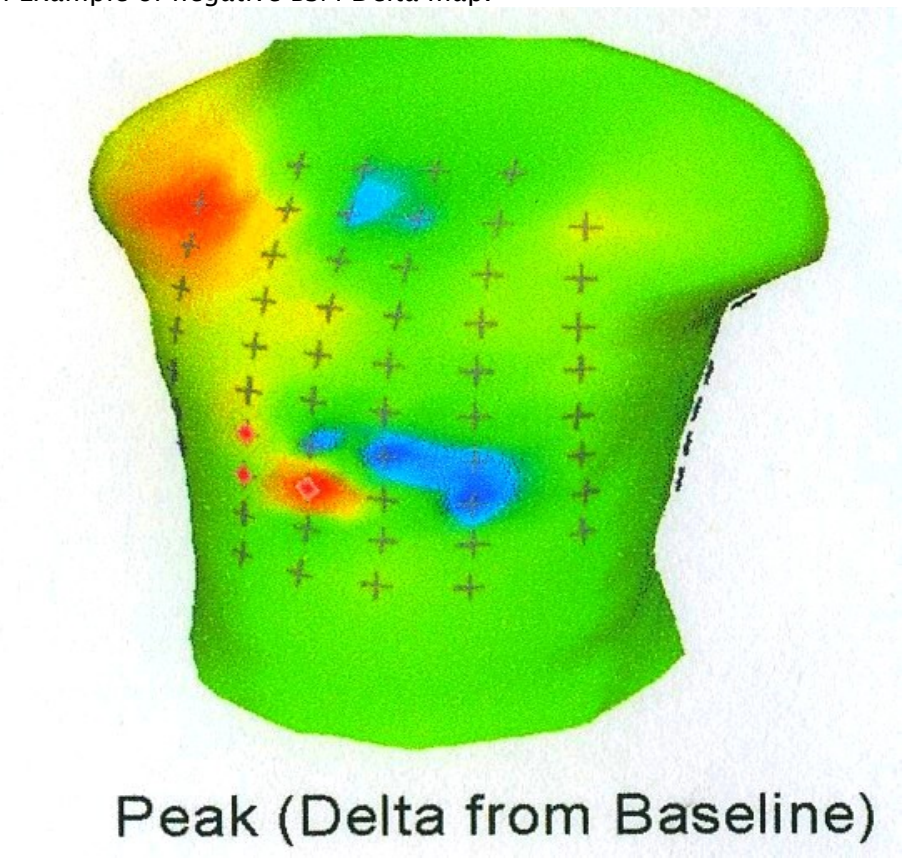
The BSM Delta map show only the ST segment shift (changes) between the two states (acquisitions) and displays the result as a colour map on the torso demonstrating the locality, extent, and direction of ST segment shift (depression= blue, elevation= red).

2.2.6.2 BSM Delta map interpretation

All anonymised colour BSM Delta maps were interpreted by two cardiologists experienced with this method, who were blinded to all other patient data. At present, there is no published data to guide that how many electrodes with abnormal findings would constitute an abnormal PRIME® BSM. The manufacturer (Heartscape Technologies Ltd/Verathon Inc) recommends that a PRIME® BSM should be considered abnormal if it has more than two electrodes with abnormal findings. Their recommendation is based on the fact that a standard 12 lead ECG is considered abnormal if it has abnormal findings in two are more leads, which itself is based on common sense and general observations. However, in comparison to 10 electrodes derived 12 lead ECG, the PRIME® ECG/BSM has 80 electrodes; therefore a varied number of electrodes combinations are possible. This aspect of PRIME® BSM interpretation

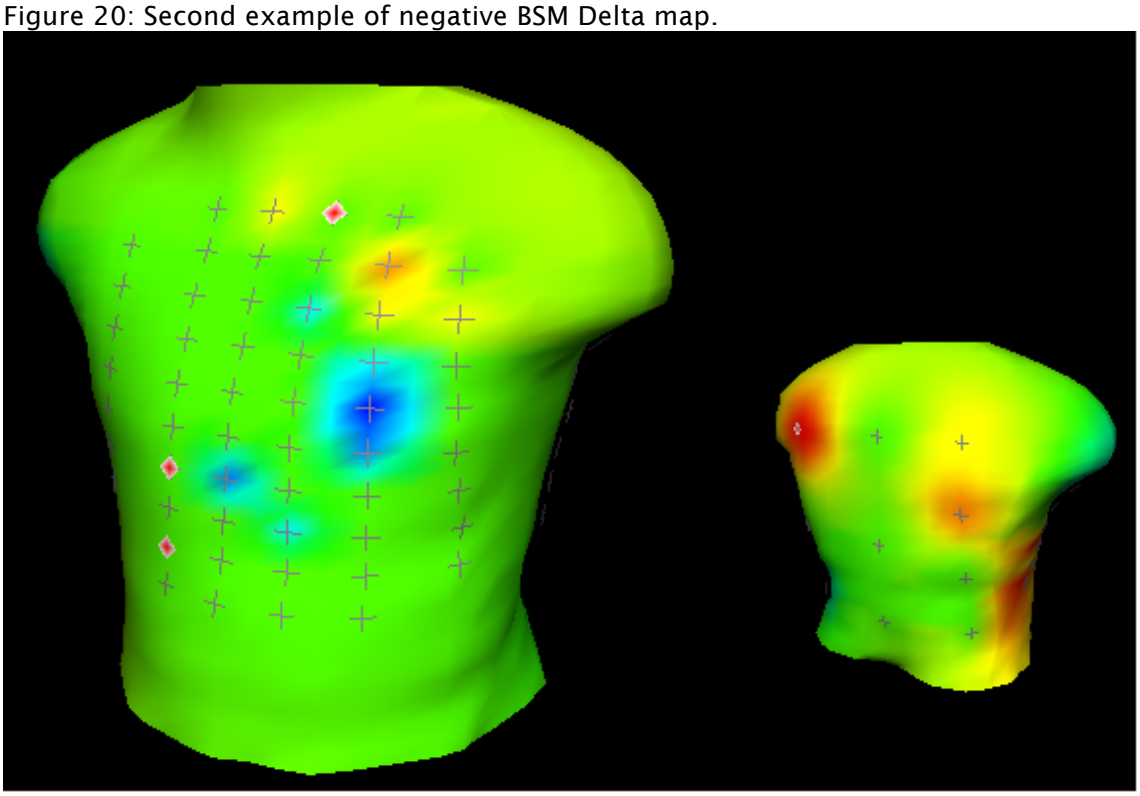
needs further evaluation, which is out of the scope of this thesis. In order to provide a formalized framework for the interpretation and to eliminate false positive results for the BSM Delta map, due to noise in ST-segments in single electrodes resulting in localized patchy colour [Figure 19, 20], two parameters for interpretation of the colour maps were used in this study to ensure that only regions of ischaemia/infarction are detected: (a) in the anterior and lateral territory a colour change involving at least 4 contiguous leads in more than one vertical column was considered diagnostic [Figure 21 & 22], and (b) in the posterior territory a colour change confluent between two adjacent electrodes was considered diagnostic. This method was based upon observations from the previous extensive analysis of multiple BSM maps in studies by our group (Professor Curzen and colleagues) for the diagnosis of transient regional myocardial ischaemia (TRMI) (173). This method enabled us to eliminate localized spurious colour changes due to “noise” affecting one or two electrodes.

Figure 19: Example of negative BSM Delta map.



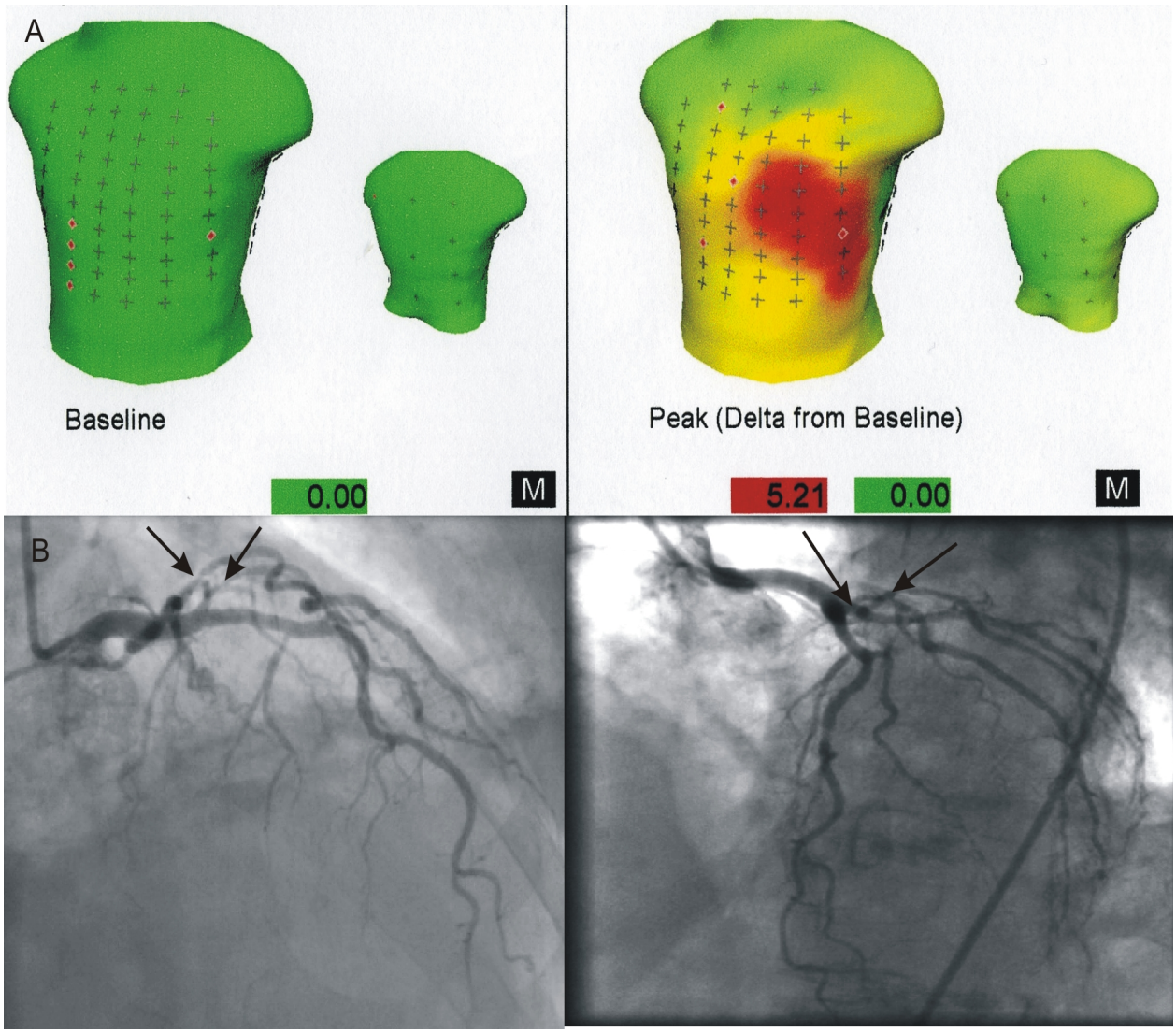
This image shows patchy colour changes; this was interpreted as negative by virtue of the parameters described in methods section. The coronary angiogram in this patient demonstrated normal coronary arteries.

Figure 20: Second example of negative BSM Delta map.



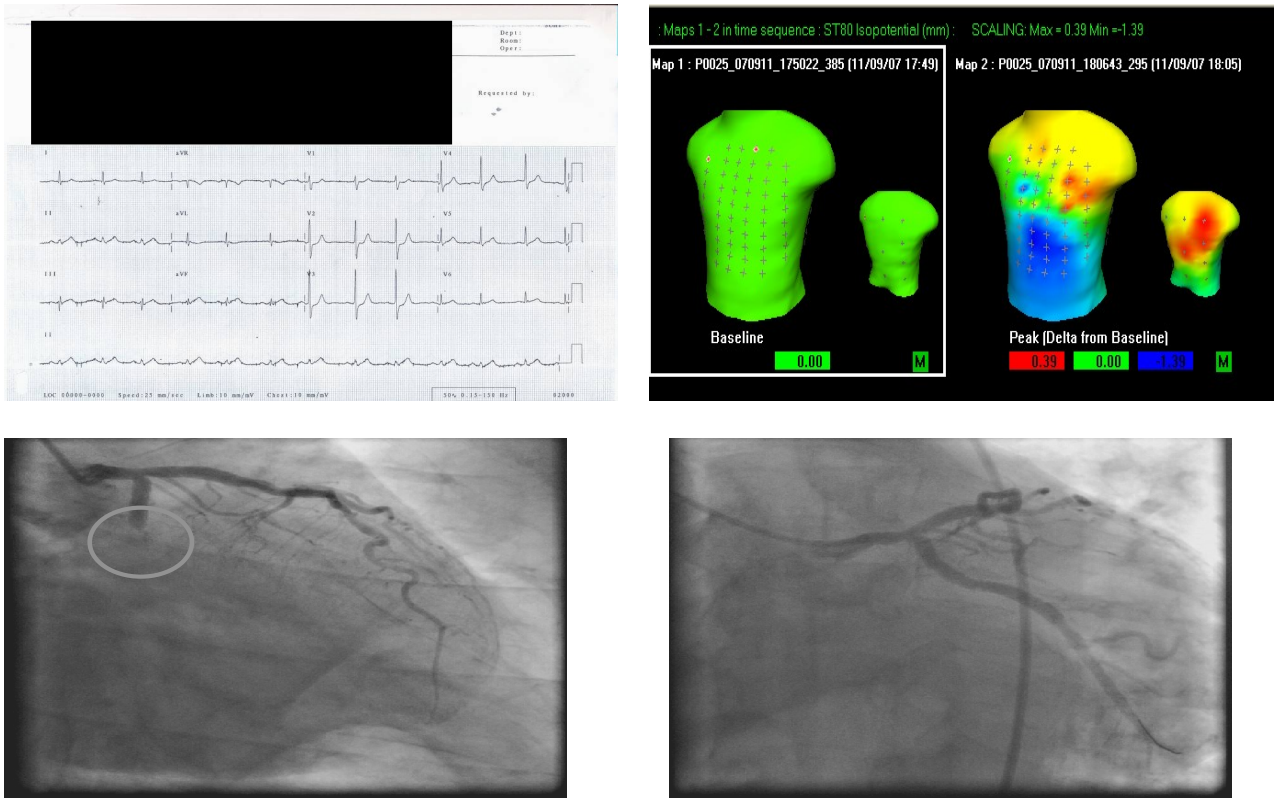
This image shows patchy colour changes; this was interpreted as negative by virtue of the parameters described in methods section. The MPI in this patient was normal.

Figure 21: Example of positive BSM Delta map



(a) BSM Delta map that is positive, demonstrating regional myocardial ischemia (Red) in the anterolateral territory. (b) Coronary angiogram in the same patient showing critical stenosis in the first diagonal and intermediate coronary arteries (Arrows) in (LEFT panel) right anterior oblique and (RIGHT panel) left anterior oblique projections.

Figure 22: A clinical example of BSM Delta map.



Standard 12 Lead ECG, BSM Delta map and pre-angioplasty and post-angioplasty angiogram in a 65 years old gentleman, who presented to our emergency department with cardiac sounding chest pain, but normal standard ECG, BSM Delta map showed posterior ST segment elevation MI (red colour) and subsequent angiogram confirmed circumflex coronary artery total occlusion, which was treated with percutaneous intervention (PCI) (175).

2.2.6.3 Application of thresholds for detection of ischaemia

In the current clinical diagnostic algorithm ST-segment shift on standard 12 lead ECG plays an important role in the diagnosis of IHD, and generally, ST-segment shift of more than 1mm is considered important and diagnostic (29). However, in the 80-electrode PRIME® ECG, the ST-segment shift cannot be directly measured, and a complex method of interpretation is used as described above.

PRIME® ECG derived BSM Delta map allows adjustment of the threshold for the ST segment shift. Therefore the data can be interpreted on the basis of ST-segment shift. In this method, a given threshold can be set up, and the BSM Delta map will show colour changes over and above that given threshold and below which any change in ST segment is not displayed therefore ignores unnecessary detailed data and displays only the data of interest and prognostically important changes in ST segments. In these studies, we applied sequential multiple thresholds for the ST-segment shift with in the BSM Delta map diagnostic algorithm, in order to define an optimum threshold.

This new development has made the BSM Delta map more intuitive and allows more accurate and rapid analysis of potential ischaemic changes. To validate this method, we studied the ST changes with 12 thresholds for dynamic ST segment shift, i.e., 0.5mm (0.05mV) to 1.5mm (0.15mV) and 2mm (0.2mV). These thresholds were uniformly applied for both ST elevation and depression, and represent the level of ST shift below which no colour would be displayed on the map. Specifically, a red colour is displayed for ST segment elevation above the assigned threshold and blue colour for ST depression below the threshold for the ST shift below the baseline. This analysis was performed using dedicated software offline and takes approximately 2-3 minutes. An analysis was then performed using coloured BSM Delta maps generated at all these thresholds and the sensitivity and specificity from each applied to ROC analysis. We tested a range of thresholds in order to determine the optimum threshold that correlated best with reference gold standard.

2.2.7 Total Ischaemic Burden

The novel concept of the total ischaemic burden (IB) from BSM is to summate the entire ST segment shift that is detected in the process of the BSM Delta map generation in all 80 electrodes. IB thus represents a single numerical value that incorporates both (a) the extent of colour and (b) its intensity variation. In order to measure the total ST segment shift, graphical parameter plots were taken at 60ms after the J-point [ST60] in all 80-electrodes for the two time-points ("pain" and "pain-free") and were analysed at 12 different thresholds for ST-depression and ST-elevation. The total positive and negative ST shift in millimetres were calculated only from those electrodes where the subtracted ST shift was above the given threshold, and the sum of these absolute values resulted in the total IB for that particular threshold. BSM Delta map IB was compared with peak troponin-I level in ED study.

2.2.8 Clinical assessment

All patients underwent routine clinical evaluation and management according to the Trust clinical protocol.

2.2.9 12 lead ECG

Serial 12 lead ECGs were recorded in all patients. Simultaneous 12 lead ECGs were also recorded with BSM acquisition at 2 time-points: (a) during pain and (b) when pain-free. Two cardiologists blinded to all clinical details interpreted ECGs. The presence of new or presumed new ST elevation (≥0.1 mV in all leads and ≥0.2mV in V_2–V_3 in men ≥ 40 years; ≥0.25 mV in men <40 years or ≥0.15mV in women) was considered diagnostic for ST elevation myocardial

infarction. Similarly, the presence of new or presumed new left bundle branch block was also considered diagnostic for acute myocardial infarction. However, the presence of new horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or T inversion ≥0.1 mV in two contiguous leads with prominent R wave or R/S ratio ≥1 was considered diagnostic for acute coronary syndrome.

The calculations of 12 lead ECG sensitivity and specificity was based on the dynamic changes (evolving or new diagnostic changes during the indexed admission or new changes in comparison to old ECG where available) or when the diagnostic criteria were met as described above.

2.2.10 Troponin-I

Troponin-I was measured at 12 hours after onset of symptoms according to routine clinical practice guidelines (161). Where troponin was measured more than once the peak level was used for this analysis. Troponin I was measured by a chemiluminescence method at 37°C (ACS 180; Bayer Diagnostics plc., Newbury, UK). The lower limit of detection according to the manufacturer was 0.15 μg/litre. Troponin I level above 0.15 μg/litre was considered positive at our centre at the time of the study.

2.2.11 Coronary Angiography

The decision to undertake coronary angiography was made in all cases at the discretion of the clinical cardiologist in charge of the patient's care. The coronary angiograms were interpreted by two cardiologists, according to the CASS (Coronary Artery Surgery Study) coding system (26). A stenosis of ≥50 in

the left main or ≥70% of the left anterior descending left circumflex, right coronary arteries or their major branches were considered significant in this study.

2.2.12 Final diagnosis of myocardial ischaemia

The final clinical diagnosis of myocardial ischaemia was made by the physician/cardiologist responsible for the care of the patient, who was blinded to the BSM Delta map results. This diagnosis was based on the clinical history, results of standard ECGs, combined with cardiac biomarkers release, coronary angiogram or myocardial stress test in the form of exercise tolerance test (ETT), cardiac MRI or myocardial perfusion imaging (14). This final diagnosis was recorded on the discharge correspondence and was therefore used by the full-time coders for their ICD classification.

2.2.13 Statistical methods

This is a pilot, feasibility study; therefore the sample size was not calculated. However, a prospective approval for 50 patients was obtained from the local area ethics committee and research and development department of the hospital for the emergency department arm of the study.

Data were analysed by using SPSS software [version 18.0; SPSS, Chicago, USA]. Continuous variables are expressed as mean ± SD; however, non-parametric continuous variables are expressed as a median and interquartile range (IQR). Binary or dichotomous variables are expressed as percentages. Statistical significance was taken at the 95% confidence level, $p < 0.05$. Subgroup analysis was performed using an independent t test method. However, Mann-Whitney U

test was used for non-parametric variables. Spearman's Correlation Coefficient was used to assess the correlation between IB and peak Troponin-I. Cross tabulations were used to calculate the sensitivities, specificities, positive predictive values (PPV), negative predictive value (NPV) and likelihood ratios with 95% confidence interval (95% CI).

Receiver operating characteristic (ROC) curve was used to identify optimum thresholds for the diagnosis of transient regional myocardial ischaemia (TRMI) and to calculate the area under the curve (AUC) for BSM Delta map. ROC curves were also used to calculate AUC and identify an optimum threshold for IB calculation as well as determining a cut-off value of IB.

2.3 RESULTS

2.3.1 Baseline characteristics

A total of 50 patients were both recruited and achieved complete data acquisition. One patient was excluded from the study due to an intermittently paced rhythm. Thus the total number of patients included in the study analysis was 49. The baseline characteristics of the 49 patients are summarised in [Table 6].

Table 6: Baseline characteristics of patients.

Characteristics	Patient Frequency	% Population	Characteristics	Mean ± SD
Male: Female	34:15	69:31	Age (years)	62.55 ± 12.9
Hypertension	28	57.0	Height (m)	1.7 ± 0.1
Diabetes Mellitus	11	22.4	Weight (kg)	86.8 ± 20.2
Hypercholesterolaemia	28	57.0	BMI (kg/m²)	29.8 ± 7.2
Current Smoker	18	36.7	Waist (cm)	109.0 ± 16.7
Previous Smoker	39	79.6	Hip (cm)	109.9 ± 17.2
Family History CAD	25	51.0	WHR	1.0 ± 0.05
Known IHD	22	45.0	Ethanol (u/wk.)	6.9 ± 11.4
Ethnicity-Caucasian	49	100		

Table 7: Reasons for screening failure.

Reason for screening failure	Number of patients (Total 356)
Pain-free at the time of study	284
Pleuritic chest pain	29
Pericarditis	10
Pleurisy	7
Musculoskeletal	5
Abdominal (Gallbladder, pancreatitis, renal)	4
Atypical (very low clinical suspicion)	3
Pulmonary embolism	3
Patients declined	3
Patient too unwell	3
Equipment failure	1
Addiction	1
Back pain	1
Gastro-oesophageal reflux (GERD)	1
Arrhythmias	1

A final diagnosis of ACS was made in 31 (63%) patients including 16 ST-elevation myocardial infarction (STEMI) and 15 non-ST-elevation myocardial infarction (NSTEMI). Troponin I was positive in 29 patients. However, two patients with diagnosis of ACS had negative Troponin, they had symptoms of unstable angina and in one patient coronary angiogram showed 70% LMS stenosis requiring inpatient coronary artery bypass graft surgery (CABG), and second patient who had dynamic ECG changes, coronary angiogram showed >70% Stenosis in RCA requiring percutaneous intervention (PCI). Eighteen (37%) patients had a final non-cardiac diagnosis including musculoskeletal pain (6 patients), gastritis (2 patients), “pleurisy” (1 patient), myocarditis (1 patient), non-cardiac (unknown aetiology) (8 patients). Standard 12 lead ECG and Troponin I was performed in all patients, while further confirmatory tests were performed in 43 (88%) of the patients at the discretion of the cardiologist in charge of their care. Specifically, 40 (82%) patients had coronary angiography, 2 patients had exercise tolerance test, and 1 patient had a cardiac stress MRI.

2.3.2 12 lead ECG

The 12 lead ECG was abnormal in 29 (59%) patients. Dynamic ECG changes were recorded in 21 (43%) patients. ST segment elevation was observed in 17 (35%) patients. When the final diagnosis of ACS was used as a reference test the sensitivity and specificity of 12 lead ECG was 67% (21/31) and 55% (10/18) with PPV and NPV of 72% (21/29) and 50% (10/20), positive likelihood ratio (+LR) 1.52 [95% CI 0.86,2.70] and negative likelihood ratio (-LR) 0.58 [95% CI 0.30,1.12]. The sensitivity and specificity of 12 lead ECG was 65% (21/32) and 53% (9/17) with PPV and NPV of 72% (21/29) and 45% (9/20), +LR 1.39 [95% CI

0.79,2.45], -LR 0.65 [95% CI 0.34,1.25], when a positive troponin-I was used as a reference test.

2.3.3 Troponin-I

Troponin-I was positive in 32 (65.3%) patients. The mean peak troponin-I rise in the whole cohort was 25 ± 29ng/mL (median 12, IQR 4,41). The mean troponin rise was significantly higher in the STEMI cohort than the NSTEMI cohort (38 ± 33, median 32, IQR 8,59 versus 11± 14 ng/mL, median 8.6, IQR 0.3,15, p 0.01). The sensitivity and specificity of troponin-I for the final diagnosis of ACS was 94% (29/31) and 83% (15/18) respectively with PPV 91% (29/32) and NPV of 88% (15/17) respectively, +LR 5.61 [95% CI 1.99,16], -LR 0.08 [95% CI 0.02,0.30].

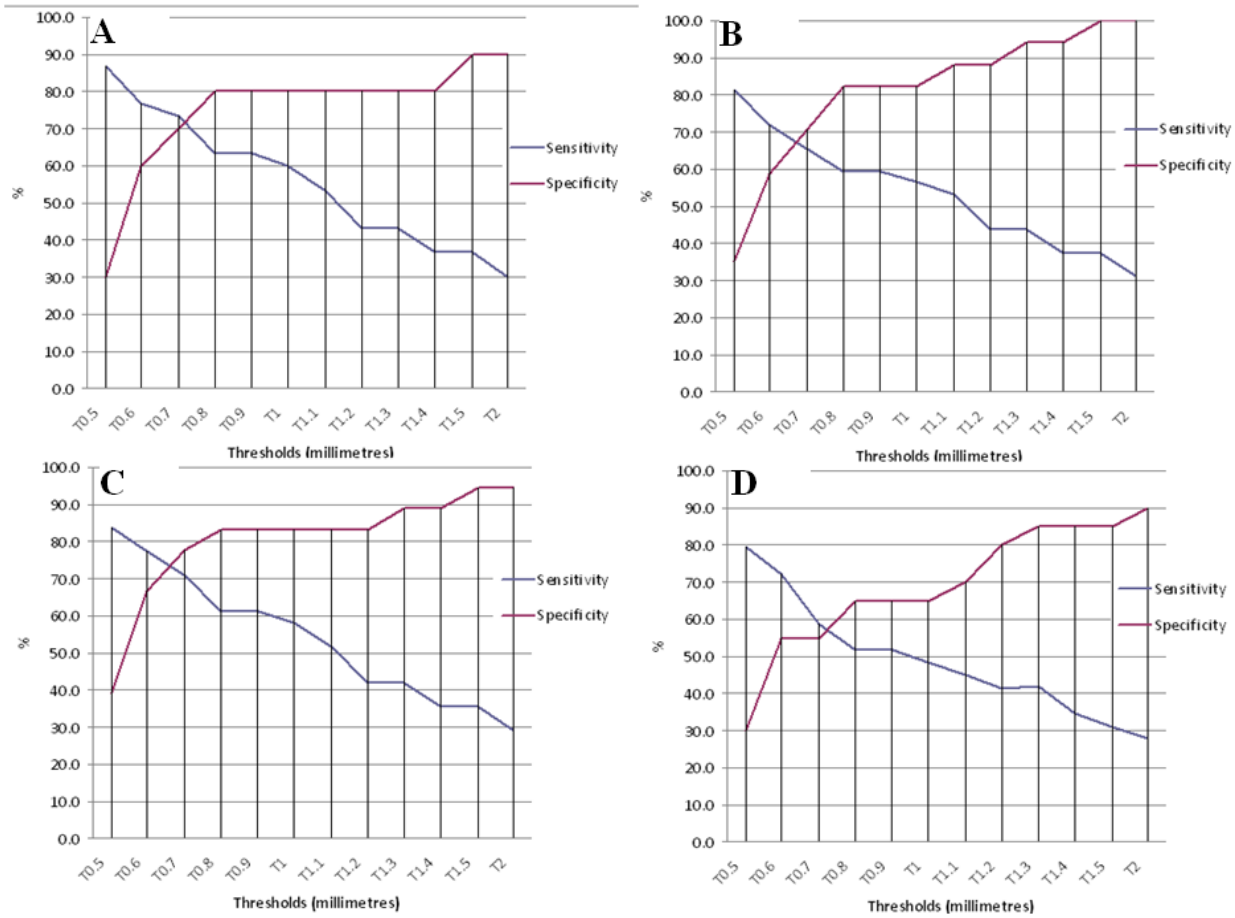
2.3.4 The BSM Delta map

BSM Delta maps were created at 12 different thresholds, and the sensitivity, specificity, PPV, and NPV of BSM Delta map was determined at each threshold considering troponin-I and final diagnosis of ACS as the reference parameters. The BSM Delta map sensitivity, specificity, PPV, and NPV were optimum at 0.7mm (0.07mV) threshold against all modalities as reference test [Table 9 & 10, and Figure 23 & 24].

When the final diagnosis of ACS was used as a reference test the sensitivity and specificity of BSM Delta map was 71% (22/31) and 78% (14/18) with PPV and NPV of 85% (22/26) and 61% (14/23), +LR 3.19 [95% CI 1.31,7.80], -LR 0.37 [95% CI 0.20,0.68]. The sensitivity and specificity of the BSM Delta map was 66% (21/32) and 71% (12/17) with PPV and NPV of 81% (21/26) and 52%

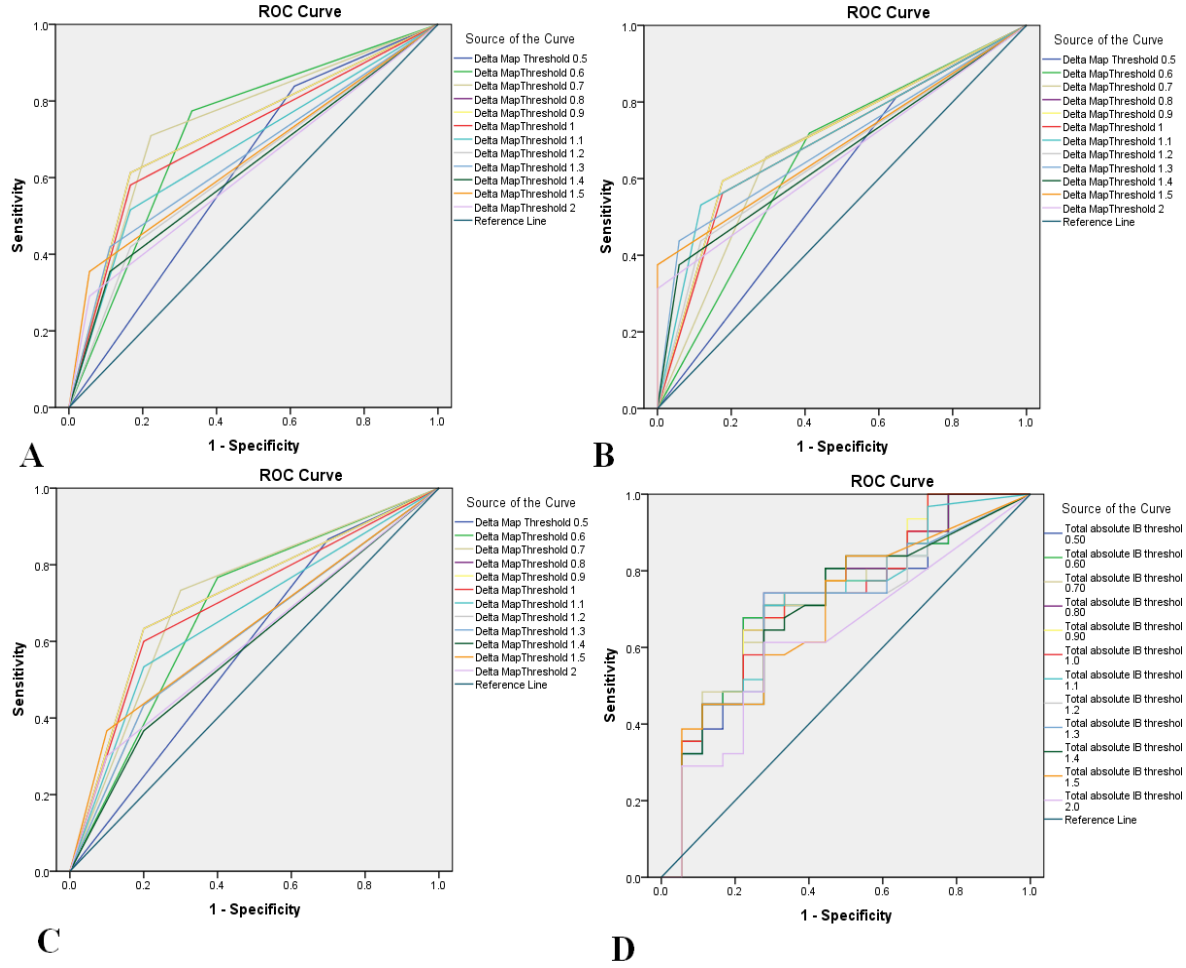
(12/23), +LR 2.23 [95% CI 1.02,4.86], -LR 0.49 [95% CI 0.28,0.86] when a positive troponin-I was used as a reference test.

Figure 23: Demonstrating sensitivity and specificity of BSM Delta map.



Sensitivity and specificity of BSM Delta map at 12 different thresholds for the diagnosis of: A. coronary angiographic >70% stenosis; B. Troponin positive chest pain; C. Final diagnosis of myocardial ischaemia; and D. dynamic 12 lead ECG change.

Figure 24: Receiver operating characteristic (ROC) curve, demonstrating optimum threshold.



A. Receiver operating characteristic (ROC) curve, demonstrating optimum threshold of 0.7mm (0.07mV) of ST shift for diagnosing ACS through BSM Delta map; B. Receiver operating characteristic (ROC) curve, demonstrating optimum threshold of 0.7mm (0.07mV) of ST shift for diagnosing troponin I positive chest pain through BSM Delta map; C. Receiver operating characteristic (ROC) curve, demonstrating optimum threshold of 0.7mm (0.07mV) of ST shift for diagnosing ≥70% coronary artery disease through BSM Delta map; D. Receiver operating characteristic (ROC) curve, demonstrating optimum threshold of 0.7mm (0.07mV) for IB for diagnosing ACS

Table 8: Sensitivity and specificity of BSM Delta-map at 12 different thresholds.

Threshold for ST-segment shift in mV	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	X^2 P value	AUC	95% CI
A. For final diagnosis of ACS							
T0.5	83.9	38.9	70.3	58.3	0.074	0.614	0.444 - 0.783
T0.6	77.4	66.7	80	63.2	0.002	0.720	0.566 - 0.875
T0.7	71	77.8	84.6	60.9	0.001	0.744	0.598 - 0.890
T0.8	61.3	83.3	86.4	55.6	0.002	0.723	0.576 - 0.870
T0.9	61.3	83.3	86.4	55.6	0.002	0.723	0.576 - 0.870
T1	58.1	83.3	85.7	53.6	0.005	0.707	0.558 - 0.856
T1.1	51.6	83.3	84.2	50	0.016	0.675	0.521 - 0.828
T1.2	41.9	83.3	81.3	45.5	0.069	0.626	0.467 - 0.785
T1.3	41.9	88.9	86.7	47.1	0.024	0.654	0.500 - 0.808
T1.4	35.5	88.9	84.6	44.4	0.062	0.622	0.464 - 0.780
T1.5	35.5	94.4	91.7	45.9	0.019	0.650	0.496 - 0.803
Threshold for ST-segment shift in mV	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**X^2 P value**	**AUC**	**95% CI**
T2	29	94.4	90	43.6	0.049	0.617	0.460 - 0.775
B. For the diagnosis of troponin-I positive chest pain							
T0.5	81.3	35.3	70.3	50	0.2	0.583	0.410 - 0.756
T0.6	71.9	58.8	76.7	52.6	0.036	0.653	0.488 - 0.819
T0.7	65.6	70.6	80.8	52.2	0.0165	0.681	0.522 - 0.840
T0.8	59.4	82.4	86.4	51.9	0.005	0.709	0.558 - 0.859
T0.9	59.4	82.4	86.4	51.9	0.005	0.709	0.558 - 0.859
T1	56.3	82.4	85.7	50	0.009	0.693	0.541 - 0.846
T1.1	53.1	88.2	89.5	50	0.005	0.707	0.559 - 0.855
T1.2	43.8	88.2	43.8	45.5	0.23	0.660	0.505 - 0.815
T1.3	43.8	94.1	93.3	47.1	0.006	0.689	0.542 - 0.837
T1.4	37.5	94.1	92.3	44.4	0.017	0.658	0.505 - 0.811
T1.5	37.5	100	100	45.9	0.004	0.688	0.542 - 0.833
Threshold for ST-segment shift in mV	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**X^2 P value**	**AUC**	**95% CI**

T2	31.3	100	100	43.6	0.01	0.656	0.505 - 0.807
C. For the diagnosis of ≥70% coronary artery disease							
T 0.5	86.7	30	78.8	42.9	0.23	0.644	0.479 - 0.809
T 0.6	76.7	60	85.2	46.2	0.032	0.699	0.543 - 0.855
T 0.7	73.3	70	88	46.7	0.014	0.761	0.620 - 0.903
T 0.8	63.3	80	90.5	42.1	0.017	0.738	0.595 - 0.881
T 0.9	63.3	80	90.5	42.1	0.017	0.738	0.595 - 0.881
T 1	60	80	90	40	0.028	0.721	0.575 - 0.867
T 1.1	53.3	80	88.9	36.4	0.067	0.688	0.537 - 0.838
T 1.2	43.3	80	86.7	32	0.187	0.638	0.481 - 0.794
T 1.3	43.3	80	86.7	32	0.187	0.664	0.512 - 0.816
T 1.4	36.7	80	84.6	29.6	0.33	0.631	0.474 - 0.787
T 1.5	36.7	90	91.7	32.1	0.111	0.657	0.505 - 0.809
Threshold for ST-segment shift in mV	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**X^2 P value**	**AUC**	**95% CI**
T 2	30	90	90	30	0.206	0.624	0.468 - 0.780

Sensitivity and specificity of BSM Delta-map at 12 different thresholds for the diagnosis of: A. Final diagnosis of myocardial ischaemia; B. Troponin positive chest pain; C. coronary angiographic >70% stenosis. [PPV=positive predictive value, NPV=negative predictive value, X2 P value=chi-square p value, AUC=area under the curve, CI=confidence interval].

2.3.5 Ischaemic Burden

There was a significantly positive correlation between peak troponin and ischaemic burden (r= 0.437; p=0.002, n= 49) at 0.9mm (0.09mV) threshold [Figure 25]. The average number of electrodes showing ≥ 0.5mm (0.05mV) ST elevation or ST depression was significantly higher in patients presenting with STEMI rather than NSTEMI [60 ± 3 versus 29 ± 3; p=0.001]. Furthermore, the average total IB was significantly higher in the STEMI cohort than the NSTEMI cohort [75 ± 62 versus 23 ± 24; p=<0.001].

Figure 25: The correlation between the troponin-I and total ischemic burden (IB). (n=49) (r= 0.437; p=<0.002, n= 49).

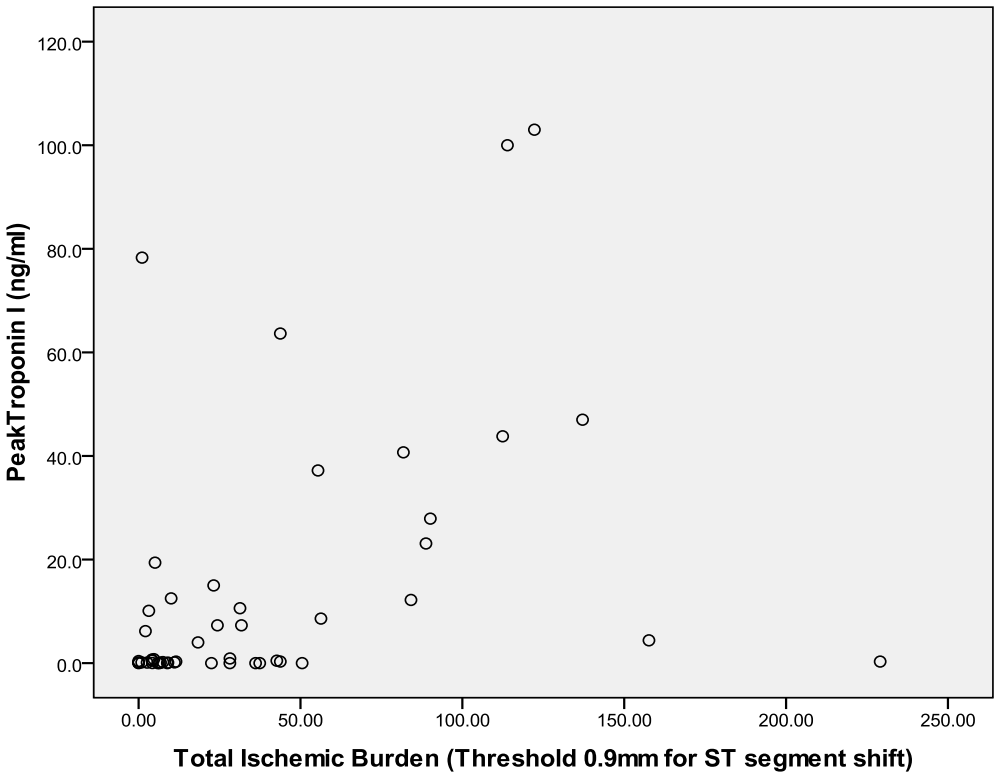


Table 9: Comparison of BSM Delta map sensitivity and specificity with 12 lead ECG and troponin I.

Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	X^2 p value	95% CI	+LR [95% CI]	-LR [95% CI]
A. For final diagnosis of ACS								
12-lead ECG	67.7	55.5	72.4	50.0	0.110	0.05, 0.51	1.52[0.86,2.70]	0.58[0.30,1.12]
Delta-map threshold 0.7mV	71	77.8	84.6	60.9	0.001	0.60, 0.89	3.19[1.31,7.80]	0.37[0.20,0.68]
Peak Troponin I	93.5	83.3	90.6	88.2	0.0001	0.77, 0.98	5.61 [1.99,16]	0.08[0.02,0.30]
B. For the diagnosis of troponin-I positive chest pain								
12-lead ECG	65.6	52.9	72.4	45.0	0.20	0.11, 0.47	1.39[0.79,2.45]	0.65 [0.34,1.25]
Delta-map threshold 0.7mV	65.6	70.6	80.8	52.2	0.01	0.52, 0.84	2.23[1.02,4.86]	0.49[0.28,0.86]

Sensitivity and specificity of 12-lead ECG, Delta-map, peak troponin I. [PPV= positive predictive value, NPV= negative predictive value, X^2 p value= pearson Chi-Square p value, CI= confidence interval, +LR= positive likelihood ratio, -LR= negative likelihood ratio.

2.4 DISCUSSION

This pilot study has successfully demonstrated the feasibility of using BSM Delta map in patients presenting to the ED with acute cardiac-sounding chest pain. Specifically, it shows that the BSM Delta map has superior sensitivity and specificity than 12 lead ECG. Furthermore, the novel total ischaemic burden (IB) appears to represent a promising single figure parameter to describe the degree of ischaemic insult that has been experienced, and this correlated with peak troponin level in this cohort.

2.4.1 Why did we use PRIME® ECG?

The PRIME® ECG appears to be the only relevant device in the published literature that has been evaluated in patients with acute chest pain (68). PRIME® ECG was used in six studies involving the assessment of stable angina (outpatients with chest pain), and in seven studies in the assessment of high-risk inpatients with chest pain (possible unstable IHD).

These studies enrolled subjects at higher risk. The current evidence favours the use of PRIME® ECG compared to the standard ECG for the assessment of patients with chest pain who are deemed high risk based on clinical features, e.g., patients with positive biomarkers for myocardial injury (68). However, data for the patient population at low to an intermediate risk of CAD is limited (68).

Limited published evidence suggests that the 3DMP may have adequate retest reliability, but studies are needed that fully evaluate the inter-rater reliability and appropriate electrode placement. This technology also has limitations as it

uses only 2 electrodes of the conventional 12 lead ECG for the data acquisition and the data analysis is performed at data centre requiring secure internet, which is considered less time efficient (68).

As PRIME® ECG examines the whole thorax, it provides more detailed electrographic data from the whole heart. Early work in the 1970's involving animal models of myocardial infarction demonstrated an excellent correlation between maps derived from the epicardium and body surface (179, 180). At the same time experimentation in humans was limited because of the technical difficulties of obtaining maps involving cumbersome mathematical calculations requiring significant time. With technological developments, it has become possible to perform BSM on patients during the acute phases of their illness. A number of studies have examined the characteristic changes on BSM during AMI [Table 11].

Table 10: Clinical studies on PRIME® ECG.

Study	Subjects	Setting	Threshold	Reference	Outcomes
Menown et al., 1998(181)	Chest pain (n = 760; 125 controls, 635 patients)	Emergency department, medical wards or mobile CCU; controls from WHO screening program	Not specified; developed from 28 variables via logistic regression	AMI – criteria not specified	Sensitivity = 80% (132/165) Specificity = 86% (134/156)
Menown et al., 2001(182)	Ischemic type chest pain < 24 hours and 1 mm ST segment depression (n = 54)	Cardiology – via emergency department or mobile CCU	Algorithm: visual display using QRS & ST-T isointegrals and ST60 isopotential + multivariate model	MI by chest pain > 20 minutes + abnormal biomarkers	Sensitivity = 69% (11/16) Specificity = 71% (10/14)
McClleland et al., 2003(183)	Ischemic type chest pain (n = 103)	Cardiology – via emergency department or mobile CCU	Algorithm: QRS width and axis, QRS and ST-T isointegrals, ST0 and ST60 isopotentials	MI by chest pain > 20 minutes + abnormal biomarkers	Sensitivity = 64% (34/53) Specificity = 94% (47/50) Physician ECG Sensitivity = 45% (24/53) Specificity = 94% (47/50)

Navarro et al., 2003 (184)	Had ECG, BSM, biomarkers (n = 379)	Cardiology – via emergency department or mobile CCU	Algorithm: epicardial - ST0 isopotential from subset of study sample	MI by abnormal biomarkers	Body surface potential Sensitivity = 62% (106/171) Specificity = 80% (166/208) Epicardial potential Sensitivity = 78% (133/171) Specificity = 80% (166/208) Physician ECG Sensitivity = 54% (93/171) Specificity = 97% (202/208)
Owens et al., 2004(185)	Ischemic type chest pain (n = 294)	Mobile CCU	Cardiologist interpreted using ST0 maxima, ST 60 minima, and vector magnitude	MI by abnormal biomarkers	Sensitivity = 80% (146/182) Specificity = 92% (103/112) ECG Sensitivity = 57% (104/182) Specificity = 94% (105/112)
Owens et al., 2008(186)	Ischemic type chest pain (n = 755)	Cardiology – via emergency department or mobile CCU	Region specific ST segment elevation on isopotential map	MI by abnormal biomarkers	Sensitivity = 76% (402/529) Specificity = 92% (208/226) ECG Sensitivity = 49% (238/291) Specificity = 92% (208/226)

Studies evaluating performance characteristics of the PRIME® ECG*. [*PRIME® ECG (FDA cleared; commercially available; initially Meridian Medical Technologies, Belfast – then owned by Heartscape Technologies, Columbia MD, now owned by Verathon Inc.). Abbreviations: BSM = body surface mapping; CCU = coronary care unit; ECG = electrocardiogram; MI = myocardial infarction; WHO = World Health Organization]. Adopted from: ECG-based signal analysis technologies. http://www.cms.gov/determinationprocess/downloads/id73TA.pdf.

Recently a multicentre observational study evaluating the effects of the PRIME® ECG on clinical outcomes (OCCULT MI) was published (167). This study was designed to determine the percentage of STEMI missed by standard ECG, which can be detected by BSM and compared the angiographic appearance and prognosis of BSM STEMI to 12 lead ECG STEMI (167). Adults (n = 1830) presenting to 12 tertiary care emergency departments with suspected myocardial infarction who had features of moderate to high risk for adverse cardiovascular outcomes were recruited. Subjects underwent testing with a standard 12 lead ECG and the PRIME® ECG, but logistical difficulties prevented a substantial number of subjects with STEMI on standard ECG from completing the PRIME® ECG. Thus direct comparisons were not possible. Clinical outcomes of 12 lead ECG STEMI were compared to STEMI detected only by PRIME® ECG including 30-day mortality, myocardial infarction, and rehospitalisation. In effect, these analyses evaluated the value of PRIME® ECG use as an “add-on” test to the standard ECG in emergency department patients with symptoms of the acute coronary syndrome.

Out of 1830 subjects enrolled, 91 (4.97 percent) had STEMI by standard ECG. Of the remaining 1736 patients, 25 had STEMI by PRIME® ECG. Therefore, a diagnostic strategy that used the PRIME® ECG as an add-on test detected a total of 116 subjects with STEMI (6.34 percent) versus 91 by standard ECG alone (4.97 percent). Therefore, with the use of PRIME® ECG 1.43 percent more patients with STEMI were detected. A subset of those with PRIME® ECG STEMI (n = 14) underwent coronary angiography that showed similar anatomy to those with STEMI by standard ECG. Additionally, the clinical outcomes at 30 days were not significantly different between 12 lead ECG STEMI and PRIME® ECG only STEMI. However, sample sizes were small, and the study was not powered to detect a clinically significant difference. These results provide preliminary

data that the PRIME® ECG can detect a small subset of patients with STEMI, who would otherwise be missed by the standard ECG and who have similar angiographic and clinical outcomes to individuals with 12 lead ECG STEMI (167).

2.4.2 BSM studies on prognosis

The role of BSM in determining prognosis following myocardial infarction has also been investigated by studies shown in [Table 12]. These studies demonstrated worst prognosis in patients with an abnormality on the map. This is unsurprising as a more abnormal map probably represents a higher ischaemic burden.

2.4.3 BSM studies to determine infarct size

The ability to sample the whole thoracic surface led researchers to evaluate the ability of BSM to quantify infarct size. This is another area where the 12 lead ECG is known to have limitations [Table 13].

Table 11: Studies using BSM to assess prognosis in patients with ischaemic heart disease.

Authors	Patient Group	Study Type	Key results	Key findings	Study Weaknesses
Walker SJ et al. 1987(187)	100 patients with inferior MI	Prognostic study using 50 lead BSM	Relationship between maximal ST change and prognosis	There was a linear relationship between maximum ST change and prognosis. These maxima were not always within 12 lead ECG territory	Small study. All patients known to have MI. BSM taken a mean of 8.25 hrs after pain.
Bell et al. 1989 (188)	100 patients with inferior wall MI	Prognostic study using departure maps	Significance of anterior ST depression on BSM	Higher mortality in patients with more abnormal BSM when depression was greater than elevation	Small study.

Table 12: BSM and quantification of infarct size.

Authors	Patient Group Study	Study Type	Key results	Key findings	Weaknesses
Murray et al. 1979(189)	41 patients with anterior MI. 35 lead anterior mapping system	Observational. Comparison of map vs. techniciam scanning	Prediction of infarct size	Sum of ST elevations relate to infarct size as seen on tech scan	Small numbers. Not true BSM as small electrode array.

The above studies have demonstrated that PRIME® ECG has ability to identify the location of myocardial infarction more accurately and specifically, more patients with ST elevation infarcts were identified with BSM, who had equivocal 12 lead ECGs but had a similar prognosis to patients who were diagnosed with STEMI by conventional ECG.

2.4.4 Limitations of the previous PRIME® BSM studies

Low and intermediate risk patients were not included in most of the studies. An enriched prevalence may affect how a test is interpreted (most likely by lowering the implicit threshold defining a positive test result). Both of these effects (higher prevalence and a tendency to lower the threshold for an abnormality) can result in an overestimate of test performance. Furthermore, potential differences in patient characteristics such as body habitus, comorbid conditions, or prevalence of conduction abnormalities, might affect test performance.

These studies reported exclusively on test performance. They did not provide direct evidence pertaining to the impact of ECG based signal analysis technologies on decision-making.

Additional information that is lacking in the published literature but that would help in the evaluation of ECG based signal analysis technologies includes practical considerations. Such as how long it takes to administer the tests and obtain interpretable data, the training required to operate the equipment and interpret the findings, the extent of ancillary support or additional space requirements, and whether it is feasible to administer the test to certain subgroups of patients, such as obese or very thin patients or patients with certain comorbid conditions.

Another limitation of the current studies is that they do not allow for comparative analysis of the performance of the new devices (e.g., 3DMP versus PRIME® ECG) due to the use of different reference standards and substantial diversity in study populations.

2.4.5 Applications of PRIME® ECG outside of the acute setting

Much work has been done using BSM techniques in other areas of cardiology. In particular, it has been used by electrocardiologists for the detection of accessory pathways (190), origin of premature ventricular contractions (191), localisation of pacing sites (191, 192), prognosis of VT (193), prognosis of acute MI (187, 194) and localisation of late potentials (188, 195). Uijen et al. also demonstrated that BSM has better performance than 12 lead ECGs for the diagnosis of old MI (196).

2.4.6 Advantages of BSM over 12 lead ECG

The use of multielectrode electrocardiographic mapping system in diagnosis of heart attack, in particular, has been investigated and described by other groups in the past (167). Thus, it has been reported that the diagnosis of AMI is improved using conventional BSM ECG (167, 182, 197-199).

Kornreich et al. (55) demonstrated that the optimal leads for detecting myocardial ischaemia actually lie outside of the conventional sites used for the 12 lead ECG, a finding confirmed by Menown et al. (168). In particular, posterior, posterio-lateral, and basal segments of the left ventricle and the right ventricle are poorly assessed, leading to difficulties in identification of RMI and infarction in these regions. Hoekema et al. demonstrated that at least

64-electrodes are required for comprehensive electrocardiographic assessment (200). Therefore due to limitation of 12 lead ECG it is possible that significant numbers of patients presenting to the ED with transient RMI associated with chest pain and negative troponin may remain undiagnosed, and this factor may be contributing to the false positive results of the BSM Delta map leading to decrease in specificity when final diagnosis is used as a reference.

Carley et al. (201) demonstrated the PRIME® ECG sensitivity of 57% and specificity of 83% of BSM for the diagnosis of AMI in a prospective observational study of 178 high-risk ED patients. Similarly, McClelland et al (183) showed sensitivity of 64%, specificity of 94% of BSM for the diagnosis of non-ST elevation myocardial infarction in patients presenting to the ED with chest pain. However, it is important to note, that novel BSM Delta map was not used in these studies.

2.4.7 Why BSM has not replaced 12 lead ECG?

Further development of the BSM and its wide spread use in the clinical setting has been hampered by four important factors:

- Acceptance of 12 Lead ECG by convention.
- Lack of agreement on a set number of electrodes.
- Data processing.
- Data acquisition.

2.4.7.1 Acceptance of 12 lead ECG by convention

The 12 Lead ECG has remained unchanged for nearly a century. Physicians have been trained and have used 12 lead ECG in clinical settings for more than a hundred years. Most of the current modern algorithms for important risk stratification and decision-making of IHD are based on the 12 lead ECG so due to this bias; it has made it harder for multi-electrodes BSM to find its way in the clinical use. On the other hand, a substitute test to 12 lead ECG has to be more sensitive, specific, noninvasive, intuitive, easily administrable and has to be low cost. BSM could not qualify most of these criteria due to the need for cumbersome calculations and understanding of complex algorithms.

2.4.7.2 Lack of agreement on a set number of electrodes

There is no common consensus on the number of electrodes in BSM. This made the comparisons of studies and evaluation of technologies impossible. Most investigators of BSM agree on the beneficial impact of using multiple electrodes around the torso for appropriate assessment of electrocardiographic activity from the heart to improve identification of the pathological pattern, however, as yet there is no uniform consensus among them on optimal number and location of electrode placement. Various studies have used a range of locations and numbers, involving 24 to 400 electrodes at different locations (202). Additionally, the display and interpretation methods also vary (202). These factors have made it impossible to conduct or compare multicentre studies. To address this issue the “European Commission” sponsored the “non-invasive evaluation of the myocardium (NEMY) project” with the aim to standardise BSM (202). The NEMY project recommended a

minimum of 64 electrodes for BSM to enable appropriate myocardial electrographic assessment (200).

Despite, in depth studies to determine optimal electrode position there are still variations in the site of electrode placement. Studies by Hoekema and colleagues showed some degree of variability even in the normal subjects despite using uniform electrode placement location suggesting the impact of thorax shape and cardiac position within the thorax as a potential source of these minor differences (203). However, the impact of this on the accuracy of BSM has not been demonstrated, also the standard 12 lead ECG has been noted to have similar inter-individual variability as well (204).

2.4.7.3 Data processing

The extensive data from multiple electrodes was difficult to process in the absence of advanced computers, and the early investigators had to do many manual calculations for the creation of electrographic body surface mapping. However, in recent years, the computer technology has made significant advancement, therefore, now it has become possible to do more complex calculations and data processing with the modern computers.

2.4.7.4 Data acquisition

Multiple methods were used for application of multiple electrodes, including scaffold-mounted rods, the use of multiple suction bulbs, inflatable vests, and the use of rubber strip with multiple electrodes. However, the use of these electrodes remained challenging in clinical practice. The development of lighter self-adhesive gel coated screen-printed plastic strips with electrodes and

landmarks have made it possible to reliably apply 80-electrodes within few minutes.

2.4.1 Beyond conventional BSM (PRIME® ECG) and development of BSM Delta map

2.4.1.1 Limitations of conventional BSM technologies

Despite developments and improvements in the conventional BSM, its interpretation for the diagnosis of IHD is still quite complicated and laborious, requiring the understanding of a large amount of data acquired and then interpreting it in context of clinical settings, which needs specialist training as described in methods and material section.

Additionally, different BSM technologies have different ways of data interpretation.

Also the parameters for interpretation of normal and abnormal are less well defined and have limited scientific basis, for example, the manufacturers of PRIME® ECG recommends that diagnosis of ischaemia should not be made on the basis of abnormal readings in one or two electrodes, however it is not clear that abnormal findings in how many electrodes would constitute the diagnosis of myocardial ischaemia.

It is most probably these aspects of BSM that has restricted its use in the clinical settings.

2.4.1.2 Development of BSM Delta map

In order to address above limitations, the concept of BSM Delta map was developed, which involves the acquisition of two 80 electrodes BSM, e.g., in-pain and pain-free or at rest and peak cardiac stress. The subtraction of one BSM from another gives a net result of ST segment deviation at ST60 (60 milliseconds from the J point), which is projected on a pseudo body torso by colour exchange, the red colour demonstrating ST segment elevation, blue colour ST depression and green colour representing no change. This hypothesis was tested by our group for the diagnosis of transient regional myocardial ischaemia (TRMI) in patients undergoing coronary arteries angioplasty for single vessel disease using 80 electrodes PRIME® ECG (173). In this study 25 patients (11 with RCA lesions, 9 with LAD lesions and 5 with circumflex lesions) were studied and PRIME® ECG was acquired at baseline and then at 30 seconds and 60 seconds post angioplasty balloon inflation in the target vessel obstructing blood flow downstream (173). This study confirmed that 80 electrode PRIME® ECG (BSM) could detect and display TRMI. With the help of this study, automatic algorithms were developed into the PRIME® ECG software allowing for selection of the relevant acquisitions and subtraction.

This method shows ST segment shift using patients own baseline PRIME® ECG as a reference point for each electrode and thus require very little training for interpretation.

Further cases have been presented to illustrate the ability of the BSM Delta map to display transient RMI in the same locality as simultaneous stress perfusion scan abnormality (176), and in a patient with chest pain and NSTEMI due to a critical circumflex coronary artery lesion in whom the 12 lead ECG was non-diagnostic (175).

Furthermore, in contrast to the 12 lead ECG the interpretation of the colour BSM Delta map generated by this method is (a) intuitive and (b) facilitates locality.

The BSM Delta map also provided a platform to calculate the ST shift at ST60 as an absolute sum and present this as an ischaemic burden.

The prognostic importance of the quantity of ischaemia is well established (205, 206).

Previous studies have shown a close relationship between the amount of myocardial ischaemic damage and quantitative measurement of troponin (207).

The overall concept of IB has been previously validated with 12 lead ECG during single vessel angioplasty induced ischaemia during balloon inflation (208). It has been suggested that not only the severity of ischaemia, (measured by the amount of ST elevation or depression), but also its extent, (according to the number of electrodes involved), should be taken into account when estimating IB, a parameter that itself has been shown to correlate with prognosis. However, this is the first time that the BSM Delta map has been used to calculate a total IB. The single figure description of the total extent of ischaemia complements the intuitive colour map as a quantitative addition. The potential value of a numerical description of the total IB is that the extent of ischaemia may correlate with prognosis. The comparison of total IB calculated through BSM Delta map to the troponin in this cohort of patients showed significantly positive correlation. This result suggests that BSM Delta map IB may indeed be a useful tool for the description of extent of regional myocardial ischaemia. However, this warrants further investigation.

2.5 LIMITATIONS

There are several limitations of this study. Firstly, as a pilot study aiming at validation of the BSM Delta map, we included only patients with cardiac-sounding pain. It is not appropriate therefore to extrapolate the findings to a wider cohort of patients presenting to the ED with undifferentiated chest pain without a larger clinical trial, however subject to larger studies, BSM Delta map may have a role in ED in selected patients, especially those who have normal 12 lead ECG with chest pain. Secondly, we have tested only one commercially available multielectrode vest and have demonstrated encouraging but preliminary results. It is not possible from these data to suggest that 80 electrodes are the ideal number for such activity. Third, only the patients considered to need angiography by the consultant incharge of their care received this test. It would appropriately be considered unethical to perform coronary angiography on all of the other patients in the study, but necessarily assumption about the accuracy of BSM Delta map need to be explored in more detail since there is no gold standard arbiter test. Fourth, the BSM Delta map requires one acquisition during active chest pain and second at pain-free state.

2.6 CONCLUSIONS

In conclusion, the BSM Delta map is a rapid and intuitive bedside method for identifying RMI with satisfactory sensitivity, specificity, positive and negative predictive values as determined by the final diagnosis of ACS. The data indicate that there is diagnostic superiority for BSM Delta map when compared to conventional ECG in this context, as determined by sensitivity and specificity. Furthermore, the intuitive nature of this system compared to ECG interpretation would allow the access of less experienced staff to this

diagnostic tool in the clinical practice, as the acquisition and interpretation of BSM Delta map requires very little training. Although troponin estimation is a sensitive test for myocardial infarction, however, it can be negative in TRMI even in the presence of severe CAD, while in comparison Delta map gives the diagnosis of both TRMI as well as acute MI. In addition, IB shows encouraging results and offers the prospect of numerical quantification of the extent of ischaemia to complement the qualitative and intuitive colour map. This could facilitate communication of both the presence and extent of ischaemia in this clinical context. Further larger studies are now required to investigate the potential for this system as a clinically valuable method for the detection, localisation and quantification of RMI.

CHAPTER 3

THE USE OF BSM DELTA MAP FOR THE DIAGNOSIS OF SUSPECTED STABLE IHD

3 THE USE OF BSM DELTA MAP FOR THE DIAGNOSIS OF SUSPECTED STABLE IHD

ELSEVIER

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Detection of transient regional myocardial ischemia using body surface Delta map in patients referred for myocardial perfusion imaging—A pilot study☆

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Abstract

Background: The diagnosis of transient regional myocardial ischemia (TRMI) in patients presenting with stable chest pain is a challenge. Exercise Tolerance Test (ETT) is no longer recommended in most cases due to its flaws. Alternative tests are more expensive and less readily available. The BSM Delta map is an intuitive color display of digitally subtracted ST-segment shift derived from two 80-electrode BSM recordings at baseline and at peak stress, and has shown promise as a tool for detection of TRMI.

Objectives: The purpose of this pilot study was to assess the feasibility of BSM Delta map as a tool to detect TRMI using dobutamine stress ECG gated single-photon emission computed tomography myocardial perfusion imaging (MPI) as a reference.

Method: Forty consecutive patients were recruited who were referred for MPI with a history of angina-like symptoms. The BSM Delta map was derived from two 80-electrode body surface mapping system recordings carried out simultaneously with MPI at (a) baseline and (b) peak dobutamine stress. Standard 12-lead ECGs were also recorded at the same time points.

Results: The mean patient age was 68 ± 7.1 years, and 52% (21/40) were female. Using MPI as the reference the sensitivity of BSM Delta map was 82% (9/11) and specificity was 86% (25/29) (95% CI 0.688–0.992), positive likelihood ratio 5.93 (95% CI 2.29–15), negative likelihood ratio 0.21 (95% CI 0.06–0.75). The sensitive of the 12-lead ECG was 36% (4/11) and specificity was 76% (22/29) (95% CI 0.356–0.767), positive likelihood ratio 1.51 (95% CI 0.55–4.15), negative likelihood ratio 0.84 (95% CI 0.51–1.37). BSM Delta map is more sensitive and specific (McNemar's chi-square test $p = 0.03$ (95% CI, 0.448–0.924). The PPV and NPV for BSM Delta map were 69% (9/13) and 93% (25/27) respectively, compared with 36% (4/11) and 76% (22/29) for 12-lead ECG.

Conclusion: This pilot study confirms the feasibility of using Delta map in this context and suggests that it has promising diagnostic accuracy and is superior to the 12-lead ECG. It could potentially represent a clinically suitable screening tool for TRMI in patients presenting with stable chest pain, since it is near patient and requires little specialist training for acquisition and interpretation. A larger clinical study is now required.

3.1 INTRODUCTION

Ischaemic heart disease (IHD) is a leading cause of mortality and morbidity worldwide. The incidence of angina is increasing with an estimated age-standardized annual incidence of 2-3 per 100 in individuals aged 45 to 89 years (209). Accurate diagnosis and treatment of angina is a priority in order to improve symptoms and reduce subsequent clinical events including mortality (5, 6, 169). However, the conventional tools for the diagnosis of myocardial ischaemia are flawed, particularly in the context that the majority of patients referred for investigation of chest pain do not prove to have of angina or IHD (161). This is particularly pertinent now that NICE guidelines in the UK no longer recommend ETT as a primary tool for investigation of many patients presenting with stable chest pain due to the poor predictive value of ETT for risk assessment (33). However, the American Heart Association (AHA) still recommends ETT as an initial test for patients with symptoms suggestive of a low and intermediate risk of IHD (161). Rapid Access Chest Pain Clinics (RACPC) have traditionally used ETT exclusively for detection of TRMI (33). According to NICE guidelines, more referrals should be made for coronary angiography (33). The weaknesses of this strategy are that angiography: (a) is invasive and therefore carries risk; (b) is expensive (210); (C) exposes the patient to radiation; (d) provides anatomical information that has poor correlation with ischaemia (7, 161). Other diagnostic options include myocardial perfusion imaging (MPI), stress cardiac magnetic resonance (CMR), computed tomographic coronary angiogram (CTCA) and stress echocardiography. However, such tests are (a) not universally available; (b) subject to significant waiting times; (c) expensive and (d) require specialist interpretation(161).

An inexpensive, near patient test with no requirement for specialist training for its interpretation would, therefore, have widespread clinical applicability. ETT results are mainly based on the 12 lead ECG. However, the limitations of the standard 12 lead ECG are well described (55, 211). Firstly, electrocardiac activity is only sampled from a limited portion of the frontal and horizontal plane of the chest wall (212). It is well established that this cannot reliably detect electrocardiac changes from some regions of the myocardium, particularly right ventricular and posterior wall of the heart (212). The 80-electrode ECG vest samples more extensively around the chest wall (172). Body surface mapping (BSM) Delta map is a technique first described by this group that can detect TRMI and displays it as an area of colour superimposed on a torso map (173). Previous data from this group has demonstrated the ability of the BSM Delta map to display TRMI in the setting of (i) single vessel coronary angioplasty (173), (ii) acute cardiac chest pain (175) and (iii) in a patient with stable angina and positive MPI (176).

The aim of this pilot study was to assess the feasibility of using BSM Delta map to assess for TRMI in patients with stable chest pain being investigated by MPI. Our objectives were to determine sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for BSM Delta map using SPECT MPI as the reference and compare it with 12 lead ECG acquired at the same time.

3.2 METHODS

3.2.1 Patient population

A separate cohort of forty patients was recruited in this arm. This study was undertaken in the nuclear medicine department of University Hospital Southampton. All patients were assessed and referred by a consultant cardiologist for MPI to investigate for suspected IHD on the basis of on-going stable symptoms. The decision of referral for MPI was made before patient screening and was not influenced by their potential participation. All patients were aged 18 years or over and had the ability to give informed consent.

Exclusion criteria were: (a) Patients with a permanent pacemaker. (b) Involvement in other studies. (c) Contraindications to Dobutamine stress testing. (d) Contraindication to atropine. (e) Dysrhythmias, making the interpretation unreliable, for example, frequent premature ventricular complexes and atrial fibrillation (AF).

3.2.2 Single Photon Emission Computed Tomography Myocardial Perfusion Imaging (MPI) using Dobutamine stress

MPI is performed through a gamma camera, after intravenous injection of a radiotracer agent. The radiotracer is washed out from most tissues except viable myocardium. The gamma camera enables acquisition of tomographic images of myocardium by recording the radioactivity in the myocardium. MPI is based on the principals that (i) a viable and well-perfused myocardium has a uniform distribution of radiotracer, (ii) less well-perfused regions of myocardium and non-viable areas of myocardium have no or reduced density

of radiotracer. Using these principles, a full MPI study is performed in two stages: at rest and under stress, usually 24 hours apart. A uniform distribution of radiotracer both at rest and stress is normal and excludes significant IHD. A uniform distribution of radiotracer at rest and reduced or absent radiotracer at stress in a single or multiple areas represents reduced myocardial perfusion during stress and significant disease in the coronary artery supplying that territory. Reduced or absent radiotracer both at rest and stress in a particular area represent myocardial infarction and non-viable myocardium. ECG gating during acquisition allows to create images during different stages of the cardiac cycle and helps in assessment of the left ventricular function (33, 213).

Graded exercise with an incremental increase or pharmacological agents, such as Adenosine, Dipyridamole, and Dobutamine are used to increase myocardium workload and induce stress. A large body of evidence supports the use of MPI and validates the sensitivity, specificity and prognostic value of MPI (6, 214-216). Two types of gamma emitting radiotracer agents are used for MPI: thallium (Tl-201) and technetium (Tc-99m). Technetium based radiotracer agents are preferred over the thallium. Two types of technetium-99m radiotracer agents have licensed in the UK, Tc-99m sestamibi (MIBI) and Tc-99m tetrofosmin (Myoview) (214).

3.2.2.1 Study protocol for MPI

In this study, MPI was performed in two parts according to the local clinical protocol. The baseline study was performed first, and the stress study was performed at least 24 hours after the baseline study (217).

All subjects were advised to withhold β-Blockers, nitrates, xanthine analogues and rate-limiting calcium antagonists for 5 half lives (generally 48 hours) prior to the stress test. Subjects were advised not to take caffeine-containing drinks or medication for 24 hours prior to the study (217).

For the stress part of the study, Dobutamine was infused through the antecubital vein starting at a dose of 10μg/kg/min, increasing by 10μg/kg/min every 3 min to a maximum of 40–50μg/kg/min. In some patients, where the target heart rate (85% of the maximal heart rate predicted for age) could not be achieved at the maximal Dobutamine dose, an atropine was administered according to local clinical protocol, at incremental doses and up to 2 mg, to increase the heart rate though vagolytic action, while the Dobutamine infusion was continued (217, 218). Heart rhythm was monitored throughout the stress test and recovery. Blood pressure measurements and electrocardiograph recordings were performed every 3 minutes. Criteria for termination of the test included the following. (i) Achieving target heart rate. (ii) Severe chest pain. (iii) ST-segment depression > 2 mm, ST-segment elevation > 1 mm on the standard ECG. (iv) Significant ventricular or supraventricular arrhythmia. (v) Hypertension (blood pressure ≥ 240/120 mm Hg), systolic blood pressure drop of >40 mm Hg. (vi) Any intolerable side effect regarded as being the result of Dobutamine (219).

Tc-99m 1, 2-bis [bis (2-ethoxyethyl) phosphino] ethane (tetrofosmin) was used as radioactive isotope (214). The dose of tetrofosmin (TF) was adjusted for the body weight, (body wt <80Kg 500 MBq; 80Kg – 110Kg 600 MBq; >110Kg 800 MBq) (217). For the stress study, the isotope was injected at peak target heart rate of 85%, and the Dobutamine infusion was continued for one minute after

the injection of radio tracer (214). Stress images were acquired 1 hour after the injection of radio tracer (214).

Single Photon Emission Computed Tomography (SPECT) imaging was performed using a dual head gamma camera (Infinia Hawkeye GE Healthcare USA) equipped with low energy high-resolution parallel hole collimators and connected to a dedicated computer system. SPECT images (64 projections) were obtained with a non-circular orbit over a 180˚ starting at 45˚ right anterior oblique (RAO), and finishing at 45˚ left posterior oblique (LPO). All images were acquired with a 64 × 64 matrix for 35 sec/projection for both baseline and stress imaging. Images were gated at 16 frames per cycle using an R-wave trigger with an accepted range of 20%, and only gated data were processed using QGS/QPS (Cedars-Senai Medical Centre) software. Tomographic reconstructions were obtained with filtered back projection and no attenuation correction. Images were processed using Ramp and Butterworth filters on a Xeleris Nuclear Workstation (GE Healthcare USA). Reconstructed tomographic slices were reoriented in the short, horizontal long and vertical long axis of the left ventricle for visual image interpretation.

3.2.2.2 MPI interpretation

Baseline and stress tomographic slices were analysed from the apical-mid-basal short axis and apical vertical slices using 17 segments. A semi-automated 5-point scoring system was used to describe radiotracer uptake in myocardium (0 = normal uptake, 1 = mildly reduced, 2 = moderately reduced, 3 = severely reduced and 4 = absent uptake). In a single segment 0-1 scores were considered normal, and 2-4 scores were considered abnormal (215). Each segment was scored individually. An abnormal segment was defined as

reversible if there was an augmentation in segment activity at baseline imaging. Regions were then interpreted as normal perfusion, stress-induced perfusion defect, or fixed perfusion defect [Table 14 & 15]. MPI data were interpreted by two consultants nuclear medicine independently who were blinded to ECG and Delta map findings.

Table 13: MPI interpretation.

Score	Category	Count density
0	Normal Perfusion	70-100%
1	Mild reduction in counts	50-70%
2	Moderate reduction in counts	30-50%
3	Severe reduction in counts	10-30%
4	Absent counts	0-10%

Left ventricular segments semi-quantitative assessment by tomographic slices through MPI, according to the level of perfusion. Adopted from, Sabharwal N, Yee-Loong C, Kelion A. Nuclear cardiology. Oxford; New York: Oxford University Press, 2008. Chapter 9: Image interpretation. Table 9.2: Semi-quantitative scoring. P130.

3.2.2.3 Summed difference score (SDS) (215)

Quantitative assessment of regional myocardial ischaemia was made according to standard methodology. Specifically, the left ventricular myocardium was divided into 17-segments on the basis of anatomical coronary artery supply. Each segment was assigned with a score on a five-point scale, as above. The scores for the segments at baseline produce a summed rest score (SRS), and at stress produce a summed stress score, (SSS). A quantitative measurement of

TRMI was obtained by subtracting the SRS from the SSS, generating a summed difference score (SDS) (215).

Table 14: MPI quantification of myocardial ischaemia.

Extent	% of myocardium	Segments of 17
Small	5-10%	1-2
Medium	15-20%	2-3
Large	>20%	≥4

This table shows the defect extent according to a number of left ventricular segments showing TRMI in the semi-quantitative assessment of tomographic slices in stress MPS. Adopted from: Sabharwal N, Yee-Loong C, Kelion A. Nuclear cardiology. Oxford; New York: Oxford University Press, 2008. Chapter 9: Image interpretation. Table 9.3: Semi-quantitation of defect extent. P130.

3.2.3 12 lead ECG

Serial 12 lead ECGs were recorded every three minutes during Dobutamine stress and recovery. 12 lead ECGs were also recorded simultaneously with BSM acquisitions at 2 time-points: (a) at Baseline and (b) at peak stress. 12 lead ECGs were analysed by two cardiologists blinded to the MPI and BSM data. Dynamic 12 lead ECG ST changes of ≥1mm in two or more leads at peak heart rate were considered positive.

3.2.4 80-electrodes BSM Data Acquisition

The 80-electrode PRIME® ECG system was used for data collection as described in detail in the "Methods" section in chapter 2. For each patient to be included in the analysis they had to complete 2 data acquisitions: one at the baseline

before starting Dobutamine infusion and the second at peak heart rate at the time of the injection of radiotracer. Following each episode of data acquisition, the best beat markers were manually placed at the start and end of the QRS complexes and ST-T segments as described in detail in the “Methods” section in chapter 2. Isopotential maps at 60ms after the J-point [ST60] were created from the best beat in each recording as has been previously described in detail in the “Methods” section in chapter 2 (55).

3.2.5 Digital subtraction BSM Delta map

Using especially written software, BSM Delta map data was created by subtraction of individual electrode-specific ST60 data at one data acquisition time-point with the other (i.e., “Stress” minus “Baseline” time-points) as previously described in detail in the “Methods” section in chapter 2 (173) [Figure 26].

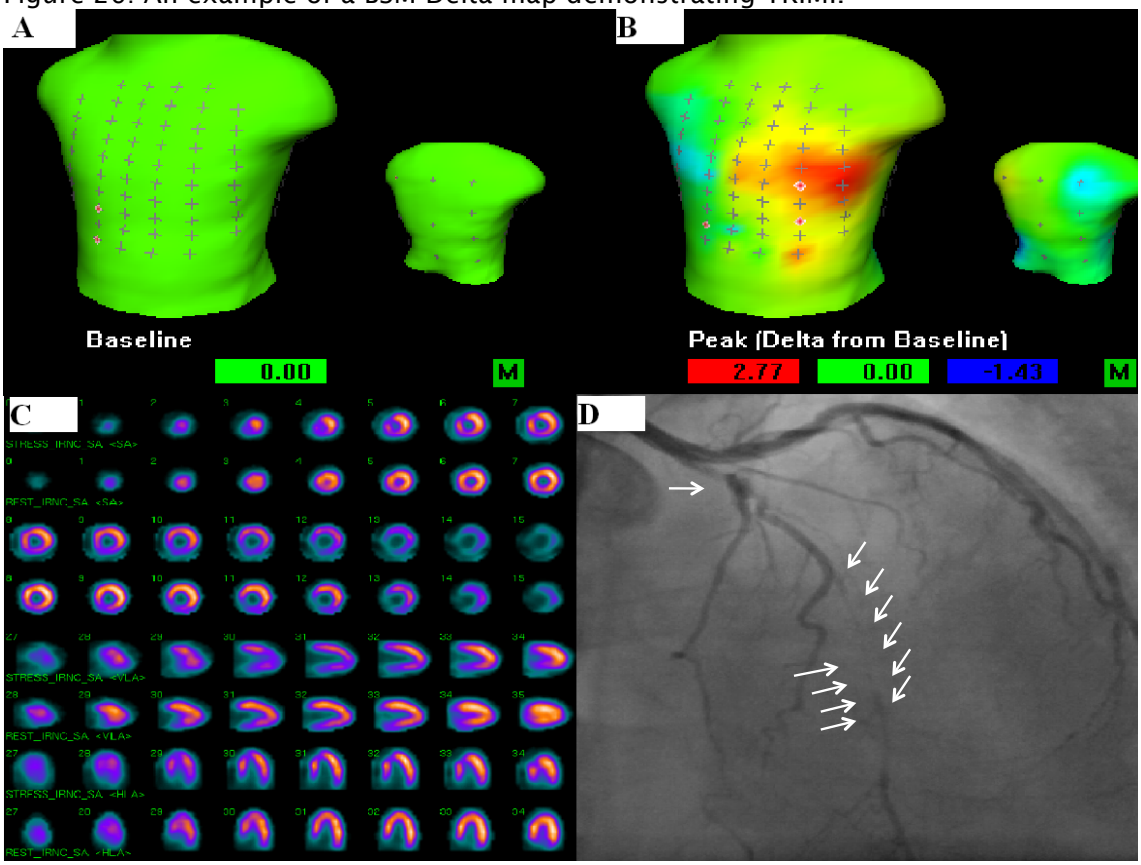
3.2.5.1 Application of thresholds for detection of ischaemia

In this study 12 thresholds for the ST segment change (0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5 and 2.0 millimetres) were applied as described in detail in the “Methods” section in chapter 2.

3.2.5.2 BSM Delta map interpretation

The BSM Delta maps were analysed as described in detail in the “Methods” section in chapter 2.

Figure 26: An example of a BSM Delta map demonstrating TRIMI.



(A). & (B). BSM Delta map derived by subtraction of the baseline map from stress, demonstrating regional myocardial ischemia (Red) in the anterior territory; (C). MPI in the same patient, Short axis, vertical long axis and horizontal long axis slices at peak stress (top rows) and baseline (bottom rows) are displayed. The scan demonstrates inducible ischaemia in the anterio-septal territory; (D). Coronary angiogram in the same patient showing sub-totally occluded left anterior descending coronary artery. [TRIMI= Transient regional myocardial ischaemia, BSM= Body surface mapping, MPI= Myocardial perfusion imaging].

3.2.6 Total Ischaemic Burden

To measure the total ST-segment shift graphical parameter plots were taken at 60ms after the J-point [ST60] in all 80-electrodes for the two time-points ("Stress" and "Baseline") and were analysed at 12 different thresholds for ST-depression and ST-elevation. The total positive and negative ST shift in millimetres was calculated only from those electrodes where the subtracted ST shift was above the given threshold, and the sum of this resulted in the IB-value for that particular threshold. BSM Delta map IB was compared with MPI-derived SDS.

3.2.7 Statistical analysis

This is a pilot, feasibility study; therefore the sample size was not calculated. However, a prospective approval for 40 patients was obtained from the local area ethics committee and research and development department of our institution for this arm of the study.

Data were analysed by using Statistical Programme for Social Sciences (SPSS) [version 19.0; IBM SPSS, New York, USA], and the analysis was undertaken in consultation with a clinical epidemiologist (PR) with expertise in medical statistics. Continuous variables are expressed as the mean ± standard deviation (SD). However, a median value with interquartile range (IQR) 25%-75% is used for non-parametric continuous variables, and binary or dichotomous variables are expressed as percentages. Statistical significance was taken at the 95% confidence level, $p < 0.05$. Spearman's Correlation Coefficient was used to assess the correlation between IB and SDS. Cross tabulation with Pearson Chi-square was used to calculate the sensitivities, specificities, positive predictive values, (PPV), negative predictive value, positive likelihood ratio (+LR) and negative likelihood ratio (-LR) with their corresponding 95% confidence interval. McNemar Chi-square exact test and confidence interval (CI) was used to determine the statistically significant difference in performance of BSM Delta map and 12 lead ECG. Receiver operating characteristic (ROC) curves were used to identify an optimum thresholds for the diagnosis of TRMI and to calculate the area under the curve (AUC) for BSM Delta map. ROC curves were also used to calculate AUC and identify an optimum threshold for IB calculation as well as determining a cut-off value of IB.

3.3 RESULTS

3.3.1 Baseline characteristics

A total of 61 consecutive patients were screened during the nine months study period. Seven patients declined the offer to take part in the study, 7 patients could not be recruited due to staff shortage at the nuclear medicine department, 2 patients had permanent pacemakers, 2 patients could not be recruited due to non availability of research staff and one patient did not stop Beta blocker so had MPI with Adenosine [Figure 27]. Prospective informed consent was obtained from all subjects. Two participants were excluded from the final analysis, one because Adenosine was used as the stress agent (instead of Dobutamine which represents a protocol violation) and the other due to the presence of multiple frequent ventricular ectopics on the ECG making the selection of best beat and interpretation impossible.

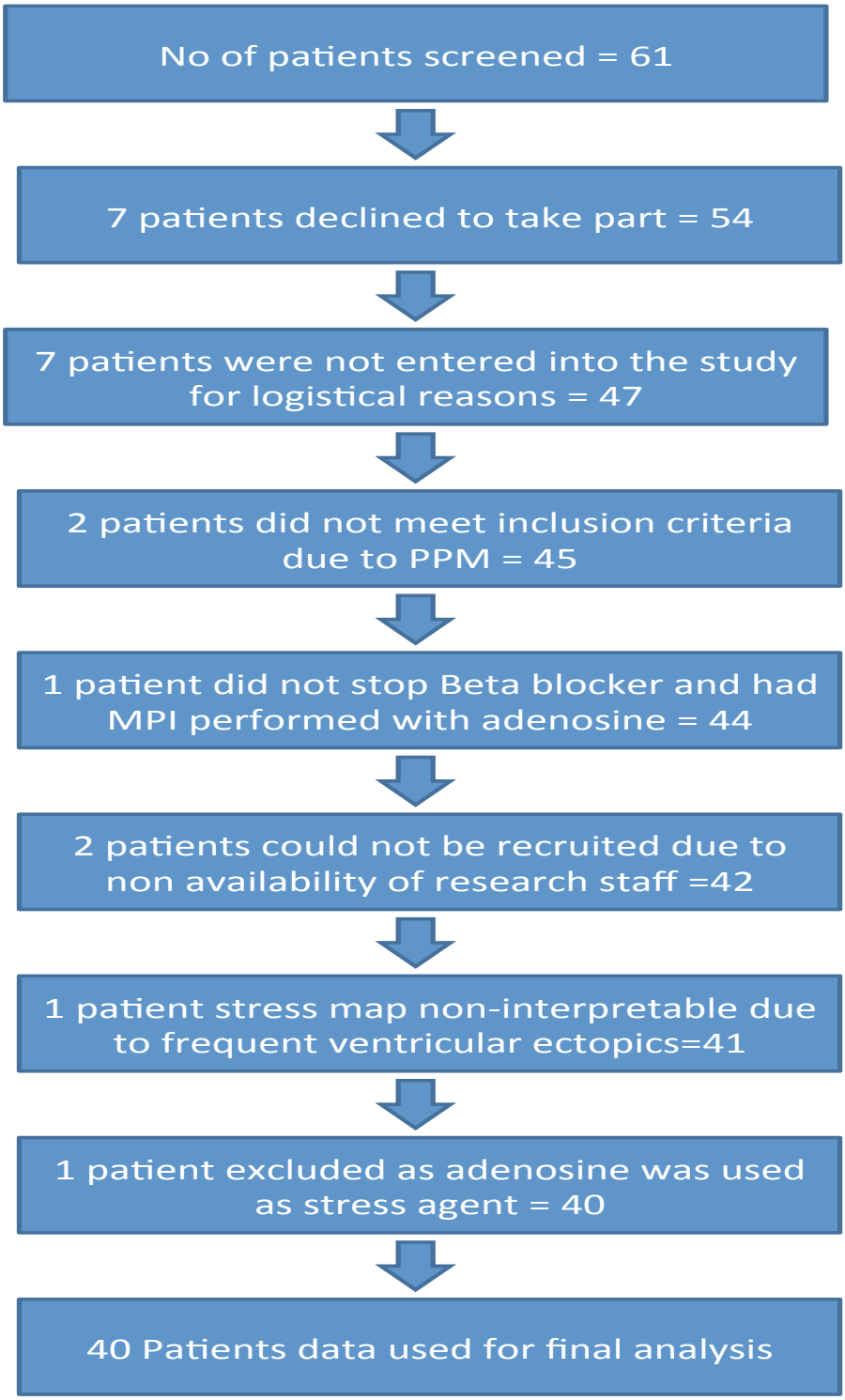
The mean age of the study population was 67 ± 1.48 years, and 21 (52%) were female. The mean body mass index (BMI) was 31± 1.30 kg/m2. Twenty-one (53%) patients had history of typical cardiac sounding symptom of chest pain (recorded prospectively in patient's notes by the referring consultant cardiologist), while 16 (40%) patients had atypical symptoms, two patients (5%) were investigated due to strong family history and one patient due to high calcium scoring.

Details of the baseline characteristics and reasons for referral are shown in [Table 16]. Target heart rate of 85% (220 - age x 0.85) was achieved in 27 (67.5%) of participants, but the mean peak heart rate of 84.3+12 % was achieved in all patients.

Table 15: Demographic details of all patients and reason for referral for MPI.

Demographic Characteristics	**Participant frequency (%)**
Male	19 (47.5%)
Female	21 (52.5%)
Chest pain prior to referral	29 (72.5%)
Hypertension	24 (60.0%)
Hyperlipidaemia	29 (72.5%)
Diabetes	10 (25.0%)
Smoking history	22 (55.0%)
Cardiac disease history	21(52.5%)
Family history of cardiac disease	25 (62.5%)
Negative stress MPS result	29 (72.5%)
Target heart rate met	26 (65.0%)
Reasons for referral for SPECT-MPI	**Number (percentage)**
History of chest pain	29 (72.5%)
Recent onset Shortness of breath on exertion (no respiratory disease)	3 (7.5%)
Pre-operative pts with history of stable angina	1 (2.5%)
Further analysis after high Calcium scoring on CT Coronary angiogram	1 (2.5%)
Adequacy of revascularisation post MI	2 (5%)
Significance of coronary LAD lesion	2 (5%)
Risk factors and strong family history of IHD	2 (5%)

Figure 27: Flow chart demonstrating subjects' recruitment.



3.3.2 Primary outcome

The end point was positive MPI determined by SDS > 2 in a single segment.

3.3.2.1 Single Photon Emission Computed Tomography Myocardial Perfusion Imaging (MPI)

The MPI was positive in 11 (27.5%) patients. The mean SSS was 3.68±4.2 (median 2, IQR 1-5.75). The mean SRS was 1.23±2.8 (median 0.00, IQR 0.00-1). The mean SDS was 2.38±2.8 (median 2, IQR 0.00-4). SDS was 0 in 15 patients, 1 in four patients, 2 in seven patients, 3 in three patients and 4 or more in 11 patients.

3.3.2.2 12 lead ECG comparison with MPI

New dynamic 12 lead ECG ST changes of ≥1mm in two or more leads at peak heart rate were recorded in 11 (28%) patients, including ST depression in 9 (23%) patients and ST elevation in 2 patients. The sensitivity and specificity of 12 lead ECG dynamic changes by comparison with MPI were 36% (4/11) and 76% (22/29) respectively with a positive predictive value (PPV) of 36% (4/11) and negative predictive value (NPV) of 76% (22/29), +LR 1.51[95% CI 0.55,4.15], -LR 0.84[95% CI 0.51,1.37].

3.3.2.3 The BSM Delta map comparison with MPI

The BSM Delta maps were analysed using 12 different thresholds against MPI [Figure 28, Table 17 and Table 18]. At each threshold, the sensitivity and

specificity were calculated. The receiver operating characteristic (ROC) curve demonstrated the optimum thresholds of 1.0 and 1.1mm, [Table 19] with area under the curve (AUC) 0.840, p=0.001 (95% CI, 0.688-0.992) [Table 19] and sensitivity of 82% (9/11), specificity of 86% (25/29), PPV of 69% (9/13) and NPV of 93% (25/27) [Figure 28], +LR 5.93[95% CI 2.29,15], -LR 0.21[95% CI 0.06,0.75].

The sensitivity and specificity of BSM Delta map were significantly superior to 12 lead ECG changes at peak stress for the diagnosis of TRMI; McNemar's Chi square test p=0.03.

At the optimum threshold of 1mm BSM Delta map was positive in 13 (33%) patients, among these nine (75%) patients, were both MPI and BSM Delta map positive. In these 9 patients, the region of ischaemia detected by BSM Delta map was matching with the region of ischaemia detected by MPI in 7 (78%) patients.

Table 16: BSM Delta map sensitivity, specificity using MPI as a reference test.

Threshold for ST-segment shift in mm	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	X^2 p value	95% CI	+LR [95% CI]	-LR [95% CI]
Delta Map against SPECT MPI								
T0.5	91.0	20.7	30.3	85.7	0.389	0.364 - 0.753	1.15[0.88,1.49]	0.44[0.06,3.25 1
T0.6	91.0	38.0	35.7	91.7	0.076	0.465 - 0.834	1.46[1.04,2.06]	0.24[0.03,1.64 1
T0.7	81.8	51.7	39.1	88.2	0.055	0.486 - 0.840	1.69[1.06,2.71]	0.35[0.10,1.29 1
T0.8	81.8	65.5	47.4	90.5	0.007	0.566 - 0.907	2.37[1.34,4.21]	0.28[0.08,1.00 1
T0.9	81.8	72.4	52.9	91.3	0.002	0.606 - 0.926	2.97[1.54,5.69]	0.25[0.07,0.90 1
T1	81.8	86.2	69.2	92.6	0.0001	0.688 - 0.903	5.93[2.29,15]	0.21[0.06,0.75 1
T1.1	81.8	86.2	69.2	92.6	0.0001	0.688 - 0.903	5.93[2.29,15]	0.21[0.06,0.75 1
T1.2	63.6	89.7	70.0	86.7	0.001	0.581 - 0.853	6.15[1.93,20]	0.41[0.18,0.90 1
T1.3	54.5	89.7	66.7	83.9	0.003	0.524 - 0.818	5.27[1.59,17]	0.51[0.26,0.98 1
T1.4	54.5	93.1	75.0	84.4	0.001	0.542 - 0.834	7.91[1.87,33]	0.49[0.25,0.94 1
T1.5	45.5	93.1	71.4	81.8	0.004	0.489 - 0.807	6.59[1.49,29]	0.59[0.34,1.01 1
T2	36.4	96.6	80.0	80.0	0.005	0.455 - 0.871	11[1.32,84]	0.66[0.42,1.04 1

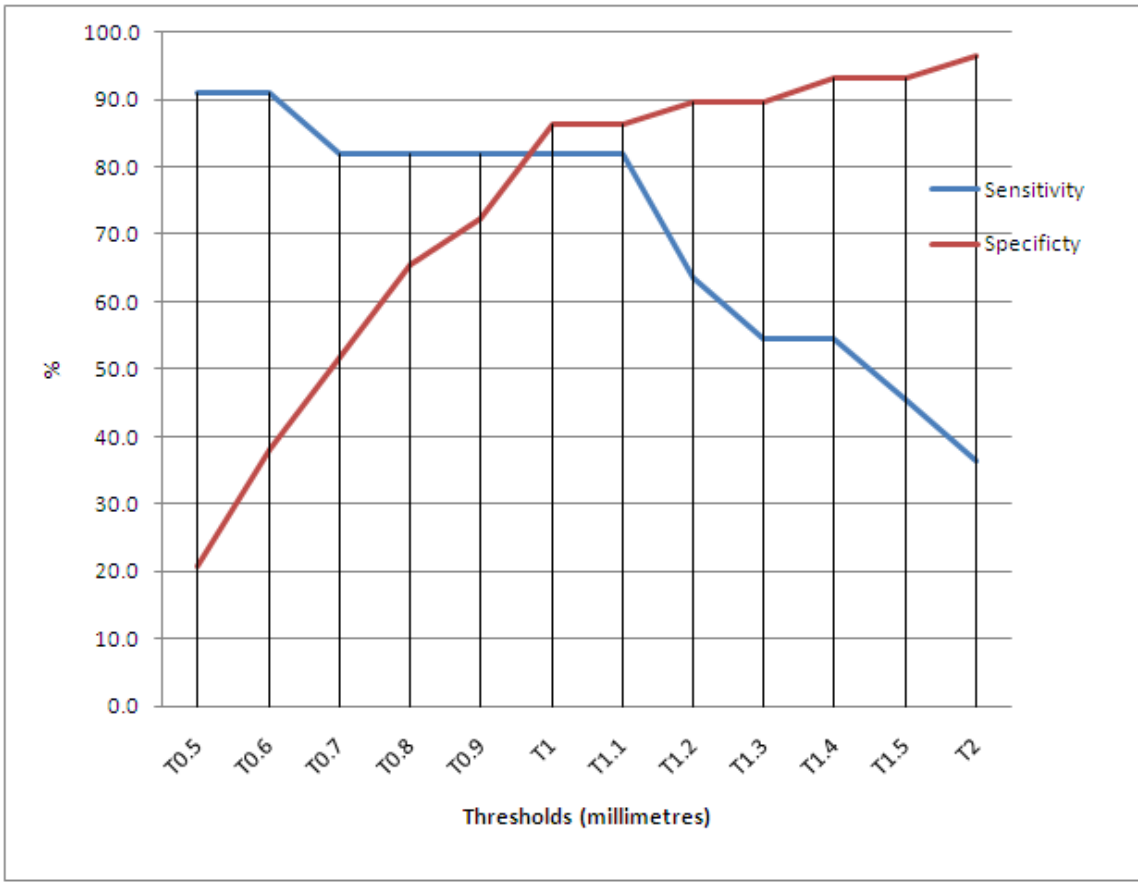
BSM Delta map sensitivity, specificity, pearson chi-square p-value, 95% CI, positive likelihood ratios, negative likelihood ratios and their corresponding 95% CI at various thresholds against MPI are given, demonstrating sensitivity of 82% and specificity of 86% at threshold 1.0mm and 1.1mm. [BSM= Body surface mapping, MPI= Myocardial perfusion imaging, PPV= positive predictive value, NPV= negative predictive, value, X^2 p value= Pearson Chi-Square p value, CI= confidence interval, +LR= positive likelihood ratio, -LR= negative.

Table 17: Comparative sensitivity, specificity of BSM Delta map and 12 lead ECG using MPI as a reference test.

Modality	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**X^2 p value**	**95% CI**	**+LR [95% CI]**	**-LR [95% CI]**
Comparison of 12-lead ECG and Delta-map against SPECT-MPI*.								
12-lead ECG*	36.4	75.9	36.4	75.9	0.5	0.35, 0.77	1.51[0.55,4.15]	0.84[0.51,1.37]
Delta-map threshold 1mm*	81.8	86.2	69.2	92.6	0.0001	0.69, 0.99	5.93[2.29,15]	0.21[0.06,0.75]
* McNemar Chi-square test p=0.03 for comparison of BSM Delta map and 12 lead ECG sensitivity and specificity against MPI as a reference test.								

Comparative sensitivity, specificity, positive predictive valve and negative predictive valve for 12 lead ECG and BSM Delta map derived from the results of MPI. [BSM= Body surface mapping, MPI= Myocardial perfusion imaging, PPV= positive predictive value, NPV= negative predictive value, X^2 p value= Pearson Chi-Square p value, CI= confidence interval, +LR= positive likelihood ratio, -LR= negative likelihood ratio].

Figure 28: Graphical representation of BSM Delta map sensitivity and specificity at various thresholds against MPI.



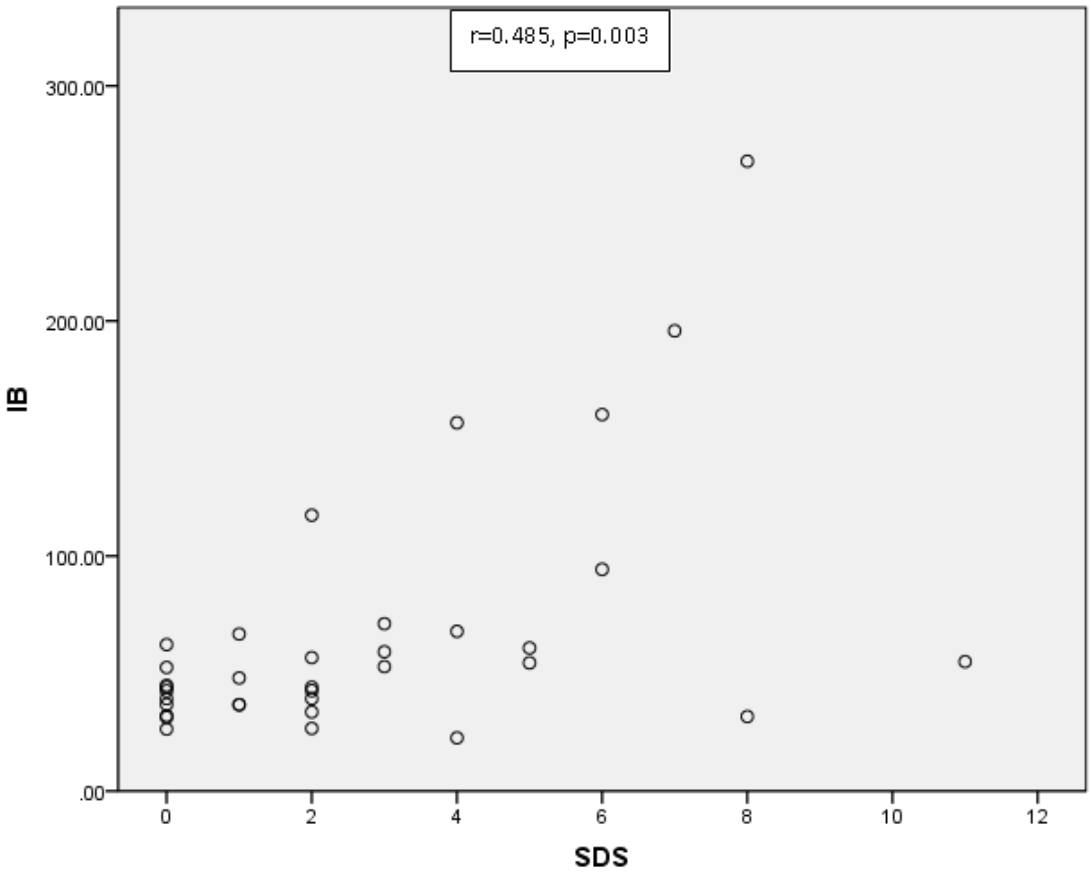
This figure is demonstrating BSM Delta map sensitivity of 82% and specificity of 86% at threshold 1.0mm and 1.1mm when MPI was used as a reference test for detection of TRMI. [MPI= myocardial perfusion imaging, TRMI= transient regional myocardial ischaemia].

3.3.3 Secondary outcomes

3.3.3.1 Ischaemic Burden

MPI derived SDS was compared with the BSM Delta map ischaemic burden calculated at 12 different thresholds, as described above. There was a significant correlation at 1mm threshold (r=0.485, p=0.003) [Figure 29]. The ROC curve analysis of IB and the MPI result showed the optimum threshold of 1mm with AUC 0.815, p=0.002, (95% CI 0.626-1.0) [Table 19], with a sensitivity of 82% and specificity of 86.2% at a cut off IB value of 30.3 for the diagnosis of MPI demonstrable TRMI.

Figure 29: Correlation between MPI derived SDS score and BSM Delta map ischaemic burden.



Correlation between MPI derived SDS score and BSM Delta map ischaemic burden at 1mm threshold (r=0.485, p=0.003). [MPI= myocardial perfusion imaging, SDS= sum difference score].

Table 18: ROC curve derived AUC for IB with reference to MPI at various thresholds with p value and 95% CI.

Thresholds for Total IB	**Area**	**Std. Error**	**P value**	**95% CI**
T0.5	0.793	0.104	0.005	0.59, 0.99
T0.6	0.803	0.103	0.003	0.60, 1.00
T0.7	0.796	0.105	0.004	0.59. 1.00
T0.8	0.809	0.100	0.003	0.61, 1.00
T0.9	0.806	0.102	0.003	0.60, 1.00
T1	0.815	0.096	0.002	0.62, 1.00
T1.1	0.809	0.098	0.003	0.62, 1.00
T1.2	0.809	0.096	0.003	0.62, 0.99
T1.3	0.809	0.096	0.003	0.62, 0.99
T1.4	0.807	0.097	0.003	0.62, 0.99
T1.5	0.777	0.099	0.007	0.58, 0.97
T2	0.721	0.106	0.033	0.513 - 0.929

3.4 DISCUSSION

This pilot study has demonstrated that BSM Delta map is a feasible option for the detection of TRMI in patients with stable IHD and has promising sensitivity and specificity, using MPI as a reference. Specifically, BSM Delta map is more sensitive and specific than 12 lead ECG in this clinical setting. This study has also demonstrated that a novel parameter, BSM Delta map IB, correlates with the extent of transient ischaemia as assessed by SDS on MPI.

In the current clinical practice, functional tests including ETT, MPI, stress echocardiogram and cardiac stress MRI are most widely utilised for the diagnosis of IHD.

Exercise tolerance test (ETT) is the most commonly used, low cost, non-invasive, first line investigation for suspected IHD worldwide (220). Exercise with treadmill or cycle ergometer devices is used to induce stress. During the incremental increase in the workload an ECG, heart rate, blood pressure and the development of symptoms are monitored and recorded. Exercise is continued until symptoms or ECG changes develop or in the absence of these until ≥85% of the maximum age predicted heart rate (220-age X 100) is achieved and maintained (7, 221). There are several flaws in ETT. Firstly, it is dependent on 12 leads ECG, which itself has significant limitations and provides only limited information about localisation of ischaemia; therefore ETT has lower diagnostic sensitivity and specificity (7). Secondly, a substantial proportion of patients are not suitable for ETT due to lack of fitness or other comorbidities affecting their ability to exercise (7). Thirdly, ETT may be difficult to interpret in patients with pre-existing ECG changes, e.g., ST, T wave changes or in patients with left or right bundle branch block (7).

Gianrossi et al. (222) conducted a systematic review of 147 studies involving 24074 patients on the diagnostic performance of ETT that used coronary angiography as a reference standard to detect CAD, and reported a broad range of sensitivity 68±16 % (23% -100%) and specificity 77±17 %, (17%-100%), with 66% prevalence of CAD (222). In a large multicentre study of a cohort of 8176 patients undergoing ETT, Sekhri et al. demonstrated that 47% of all events during a median follow-up of 2.46 years occurred in patients with a negative exercise ECG (223). It is a testament to the limited diagnostic value of ETT that the NICE in the UK no longer recommends the use of ETT for the diagnosis of recent onset chest pain in the majority of patients (20).

Until the development of the recent new technologies, MPI has served as a gold standard test for non-invasive investigation of the IHD. Heijenbrok-Kal et al. (216) performed a meta-analysis of the diagnostic ability of MPI for CAD and examined sensitivity and specificity of MPI with various modalities of stress, where coronary angiogram was used as a reference standard, results are shown in Table 20 (216):

Table 19: Results summary, Heijenbrok-Kal et al. meta-analysis of the diagnostic ability of MPI (216)

Stress Modality	Sensitivity (95% CI)	Specificity (95% CI)
Exercise	88% (86, 90)	67% (63, 75)
Adenosine	91% (89, 92)	81% (74, 89)
Dipyridamole	90% (87, 94)	75% (66, 85)
Dobutamine	84% (78, 89)	75% (71, 79)
Combined pool	88% (87, 90)	73% (69, 77)

Data from: Heijenbrok-Kal et al. Heart J. 2007;154(3):415-23.

A large body of evidence validates the sensitivity, specificity and prognostic value of MPI (6, 214-216). MPI is less claustrophobic and relatively low cost. However, MPI involves a significant radiation dose of around 6 to 8mSv; it is not readily available, is expensive and require specialist training for the acquisition and interpretation. Additionally, the results are observer dependent, and the breast and abdominal adiposity can create artefacts.

In stress echocardiography, the baseline study is performed at rest and then with exercise or pharmacological stress. The left ventricle images are examined for regional wall motion abnormality and wall thickening. On the basis of meta-analysis of the studies on stress echocardiography for the diagnosis of IHD Heijenbrok-Kal et al (216) reported the following findings; sensitivity 83% and specificity 84% with exercise stress; sensitivity 79% and specificity 92% with Adenosine stress; sensitivity 72% and specificity 95% with Dipyridamole stress; and sensitivity 81%, and specificity 84% with Dobutamine stress. The stress echocardiography combined pooled sensitivity was 79% and specificity 87% (216). Stress echocardiography is non-invasive and also provides information regarding cardiac structure and function but requires a substantive specialist training. In certain conditions, like left bundle branch block (LBBB) and atrial fibrillation (AF) stress echocardiography may be difficult to interpret. Moreover, the results are also observer dependant.

Magnetic resonance imaging (MRI) also called nuclear magnetic resonance imaging (NMRI) consists of a tube and a computer system. An image is created by computer software based on the difference in relaxation and energy emission by different tissues. MRI has a high degree of spatial and temporal resolution and allows accurate visualisation of cardiac structures. Cardiac

stress MRI requires pharmacological stress agents' such as Adenosine, Dipyridamole, or Dobutamine and a contrast agent called gadolinium.

MRI provides information about the presence of ischaemia, myocardial fibrosis, cardiac chambers and valve structure and function. Nandalur et al. performed meta-analysis of the 37 studies, which evaluated the diagnostic performance of cardiac stress MRI. In these studies, coronary angiographic diameter stenosis of ≥50% was used a reference standard. Nandalur et al. reported the following findings (224): (i) Myocardial MR perfusion method, sensitivity of 91% (95%CI 88, 94) and specificity 81% (95%CI 77, 85) with a CAD prevalence 57.4% (224), (ii) Stress induced wall motion abnormalities imaging, sensitivity 83% (95%CI 79% to 88%) and specificity 86% (95%CI 81% to 91%) with CAD prevalence 70.5% (224). MRI images are highly reproducible and are less operator-dependent. However, MRI is expensive, requires specialised team and establishment, takes a longer time to perform, not possible in claustrophobics and is absolutely contraindicated in a number of individuals with internal ferromagnetic foreign materials.

The investigation of stable patients with suspected TRMI is more challenging in the context of widely accepted flaws in the ETT and the lack of a universally available, inexpensive, intuitive and near patient alternative. Specifically, in the UK, NICE guidelines no longer support ETT in most patients with new onset chest pain, but recommend either other non-invasive tests such as coronary calcium scoring, stress echo, CMR, MPI, or invasive angiography instead (33). However, evidence suggests that an increase in the rate of referral for coronary angiography without a prior test to demonstrate TRMI may lead to inappropriate revascularisation (225). Furthermore, clinical guidelines that recommend only limited applicability of the ETT will lead to a substantial

increase in demand for more specialised and expensive non-invasive tests such as MPI and CMR. ETT was a routine investigation in 59% of the chest pain clinics in the United Kingdom and was part of the initial assessment in 76% of patients with angina in the recent Euro heart survey (220). Indeed the current American College of Cardiology/ American Heart Association guidelines still recommends that conventional ETT should be performed as the initial test in low to intermediate-risk patients who present with ischaemic symptoms and can exercise (161). These recommendations are mainly based on feasibility, ease of use and cost assessment (161).

There would, therefore, be considerable clinical value in a new, inexpensive, near patient, intuitive test for TRMI and BSM Delta map may represent a candidate test.

In this study, Dobutamine was used as a stress agent. The other options for the myocardial stress are measured physical exercise, Adenosine, and Dipyridamole. Exercise with treadmill or cycle ergometer devices is a natural way to induce myocardial stress. During the incremental increase in the workload an ECG, heart rate, blood pressure and the development of symptoms are monitored and recorded. Exercise is continued until ≥85% of the maximum age predicted heart rate (220-age X 100) is achieved and maintained (7, 221). However, in this study due to the PRIME® ECG vest and its associated clamps exercise was considered inappropriate, because sweating and movement result in the displacement of the electrodes. In the future with further improvement in the vest, it may become possible to use BSM Delta map with physical exercise. Adenosine is the most commonly used agent in the UK for MPI and cardiac stress MRI, which is a direct vasodilator and naturally occurring substance throughout the body and is produced intra-cellularly as

Adenosine triphosphate pathways, which regulates blood flow through its action at the terminal vessels to many organs, including the heart. Adenosine has two types of receptors at the cell surface, A1, and A2. The interaction of Adenosine with A2 receptor produces adenylate cyclase, which converts into cyclic Adenosine monophosphate (cAMP). cAMP inhibits calcium uptake by the sarcolemma, resulting in smooth muscle relaxation and vasodilation. The activation of the A1 receptor leads to the production of guanylate cyclase, which converts into guanosine monophosphate, which is also a vasodilator (213).

Dipyridamole inhibits Adenosine reuptake, and deamination, therefore, acts as an indirect vasodilator (213).

The vasodilation of Adenosine and Dipyridamole is effective only in the terminal arteries perfused by the normal segments of coronary arteries. However, the terminal coronary arteries distal to significant stenosis are already maximally dilated and have no reserves, therefore, remain unaffected, which produces relative flow heterogeneity in the coronary arteries (213, 215).

Adenosine has a short half-life. Its effects wear off in 10-15 seconds. However, its use is associated with transient side effects in 50% to 80% of patients, which include shortness of breath, chest tightness, flushing, transient bradyarrhythmias and an acute bronchospasm may occur in patients with pre-existing obstructive airways disease, which may require treatment (213). I did not use Adenosine and Dipyridamole as the effect of these agents is short lived, and for the acquisition of PRIME® ECG, I was aiming for sustained ischaemia for at least 10 seconds. However, in future, the BSM Delta map can be validated with Adenosine infusion.

Similar to physical exertion, Dobutamine also increases the myocardial workload and stimulates increased blood flow through the coronary arteries (213, 226). Therefore, Dobutamine is used as a cardiac stress agent, to unmask coronary insufficiency (7, 213, 226). Generally, Dobutamine stress is well tolerated; the side effects are usually minor and include nausea, anxiety, arrhythmias, and chest pain (7, 213, 226). Dobutamine is a commonly used synthetic cardiac inotrope, which has a complex mechanism of action. Dobutamine is a strong beta-1 receptors agonist, therefore, increases myocardial contraction, additionally; it is weak beta-2 (peripheral vasodilators) and alpha-1 (peripheral vasoconstrictors) receptors agonist thus the stimulation of these two receptors balances out the effect on the peripheral vasculature. However, the increased cardiac output by the Dobutamine relaxes the sympathetic tone. Therefore, the net effect of Dobutamine is increased myocardial contraction with reduced total peripheral vasculature resistance (213, 226). On the basis of these properties, I elected to use Dobutamine as a stress agent.

The concept of BSM Delta map to detect and localise transient myocardial ischaemia was previously first described in a study of balloon angioplasty in patients with single vessel disease (173). We have also described the clinical utility of this approach in patients presenting to the ED (227). In addition, we have previously presented cases to illustrate the ability of the BSM Delta map to display TRMI in the same locality as simultaneous stress perfusion scan abnormality (176), and in a patient with recurrent chest pain with acute myocardial ischaemia due to a critical circumflex coronary artery lesion in whom the 12 lead ECG was non-diagnostic (175). The Optimal Cardiovascular Diagnostic Evaluation Enabling Faster Treatment of Myocardial Infarction (OCCULT-MI) (167) trial demonstrated that 80-lead ECG provides an

incremental 27.5% increase in STEMI detection versus the 12 lead ECG (167), although this study was performed in the context of acute myocardial infarction and did not involve the use of BSM Delta map.

The comparison of total IB calculated through BSM Delta map to the SDS in this cohort of patients showed significantly positive correlation ($p=0.001$, $r=0.485$). This result suggests that BSM Delta map IB may indeed be a useful tool for the description of the extent of TRMI, a parameter that itself has been shown to correlate with prognosis. However, the SDS has the limitation that it is derived only from segmentation of left ventricle (215, 217), whereas the BSM Delta map captures electrical activity from a much wider region, including right ventricle (228).

In these studies, sequential multiple thresholds were applied for the ST-segment shift with in the Delta map diagnostic algorithm, in order to define an optimum threshold for the diagnosis of IHD. In this study the optimum threshold was 1mm (0.1mV) for the appropriate sensitivity and specificity of BSM Delta map and IB, using MPI as a gold standard. However, the optimum threshold in the emergency department population was 0.7 mm (0.07 mV). The reason for this difference is not clear. However, one of the explanations is the difference in the two cohorts of patients and the acute nature of IHD in emergency department population, leading to a richer prevalence of the disease.

3.5 LIMITATIONS

There are several limitations of this study. Firstly this is a pilot, feasibility study aiming at validation of using BSM Delta map and IB to assess TRMI in patients with suspected stable angina, and as such has a small sample size. It is not

appropriate therefore to extrapolate the findings to a wider cohort of patients with undifferentiated chest pain without a larger clinical trial. Secondly, by the nature of this type of investigation, there is no perfect comparator: MPI itself has a false positive and negative rate and have a sensitivity of 90% and specificity of between 81% and 100% (229), but we cannot take this into account. For the purpose of a reference, the assumption has to be made in this study that MPI results are always correct. Thirdly coronary angiographic data was not obtained in this study to support the origin and locality of TRIMI. In this population, we could not have justified requiring a coronary angiogram as part of our study where this test was not indicated on clinical grounds. Lastly, according to our local guidelines, only pharmacological stress was used in this study; moreover, a single stress agent was used in order to maintain uniformity in all subjects. Therefore, subjects undergoing Adenosine stress were excluded. Adenosine is a cardiac vasodilator and dilates coronary vessels, which causes increased blood velocity and flow rate in normal vessels and has less of a response in stenotic vessels. However, Dobutamine is a cardiac inotrope and chronotrope. The heart responds to Dobutamine similarly to the way it responds to exercise, therefore in this study we preferred to use Dobutamine.

3.6 CONCLUSIONS

In conclusion, this pilot study demonstrates the feasibility of BSM Delta map in detecting TRMI in stable chest pain and suggests it is superior for this compared to 12 lead ECG.

Further large scale clinical studies are now required. BSM Delta map appears to be a candidate as an inexpensive, near patient test for detection of TRMI in the clinic/outpatient setting.

CHAPTER 4
DETECTION OF MULTIREGIONAL TRANSIENT MYOCARDIAL ISCHAEMIA USING A NOVEL 80-ELECTRODE BODY SURFACE DELTA MAP.

4 DETECTION OF MULTIREGIONAL TRANSIENT MYOCARDIAL ISCHAEMIA USING A NOVEL 80-ELECTRODE BODY SURFACE DELTA MAP.

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Detection of multiregional transient myocardial ischaemia using a novel 80-electrode body surface Delta map☆

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4.1 ABSTRACT

This case study has been published in a peer reviewed journal, which illustrates the diagnostic utility of the BSM Delta map in a patient who was known to have multivessel coronary artery disease and presented to our unit with chest pain and suspected myocardial ischaemia. The BSM Delta map accurately displayed the transient multiregional myocardial ischaemia, which was also detected by a simultaneous Dobutamine stress SPECT MPI. These data were confirmed invasively using the coronary angiography and pressure wire study.

4.2 INTRODUCTION

Accurate diagnosis of a patient presenting with possible angina is a frequent and challenging clinical dilemma. An ideal non-invasive test would not only provide a high degree of certainty about the presence or absence of objective evidence of myocardial ischaemia and locality but would also be inexpensive, readily available, accessible and point-of- care. Based on feasibility and cost, the American College of Cardiology/American Heart Association guidelines recommend that exercise tolerance test (ETT) with electrocardiogram (ECG) as the initial test in patients who present with symptoms suggestive of low to intermediate-risk of ischaemic heart disease (IHD) and who can exercise (161, 223). However, recent studies have challenged the prognostic value and effectiveness of ETT for risk assessment. In a study of 8176 patients being assessed for the diagnosis of new angina, 47% of all events during a median follow up of 2.46 years occurred in patients with a negative exercise ECG (223). It is a reflection of the limited diagnostic value of ETT that the National Institute for Health and Clinical Excellence (NICE) no longer recommend the use of ETT for the diagnosis of IHD in many patients (20). Despite this ETT with ECG remains the most commonly used front line test for ischaemia in most patients with stable angina like symptoms, so this introduces an important diagnostic dilemma. Other superior, non-invasive tests such as cardiac magnetic resonance imaging (CMR), single-photon emission computed tomography myocardial perfusion imaging (MPI) or stress echocardiography are less readily available, more expensive and require specialist interpretation. These challenges have highlighted the potential value of a low cost, accurate and near patient test with minimal requirement for specialist training, such a test would have widespread clinical applicability. First described by this group,

the BSM Delta map is derived from an 80-electrode body surface mapping (BSM) and is an intuitive digital colour display of transient reversible myocardial ischaemia that requires little specialist training and could represent a potential new tool for the diagnosis of IHD [4–6].

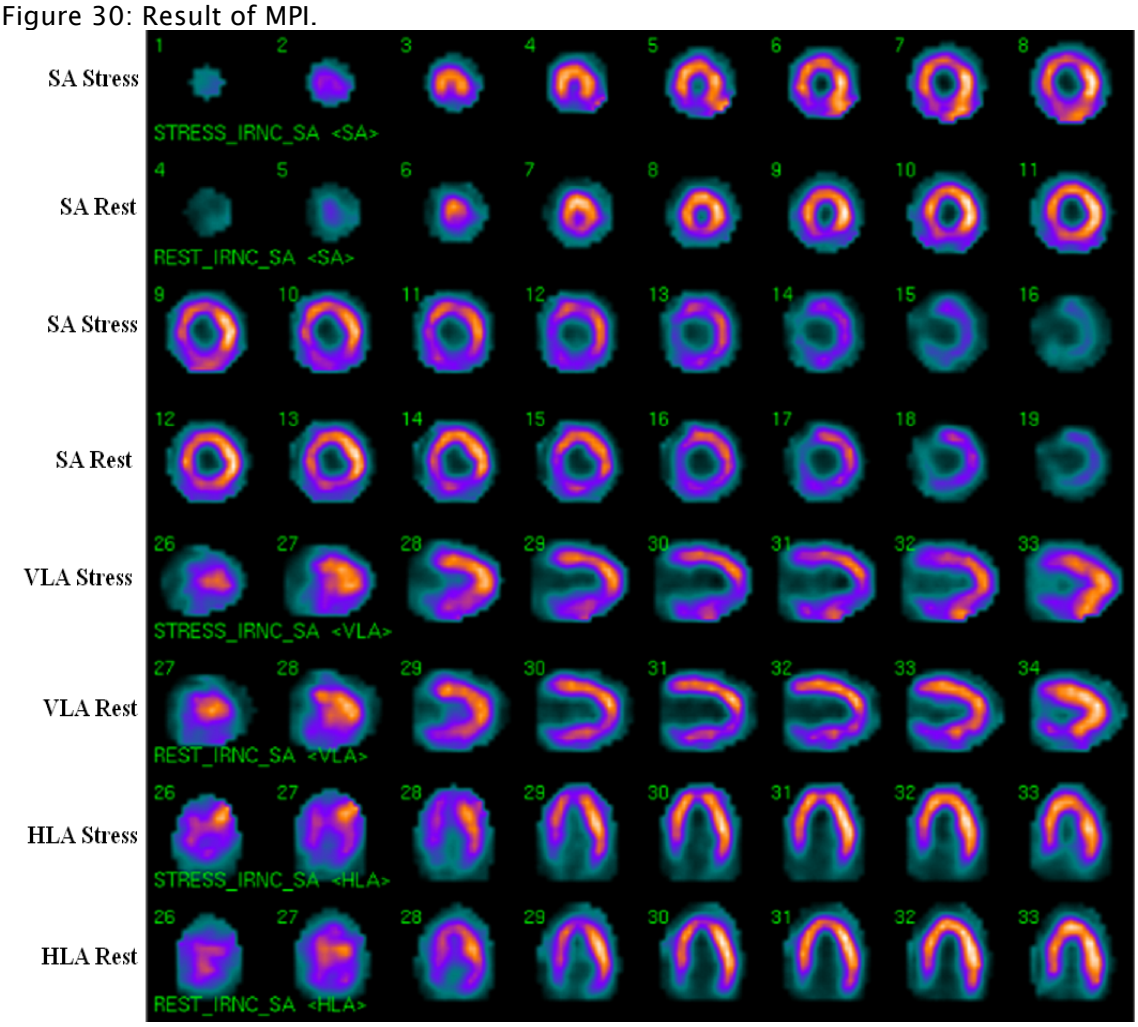
4.3 CLINICAL CASE

A 53-year old hypertensive, hyperlipidaemic man was referred for MPI because of recurrent exertional chest pain. Eight years ago his second obtuse marginal (OM2) coronary artery was treated with a drug-eluting stent. Having been symptom free for seven years a further drug-eluting stent was inserted into a culprit lesion in his proximal left anterior descending (LAD) coronary artery as a primary percutaneous intervention for anterior ST-elevation myocardial infarction (STEMI) one year ago. At that stage, a long segment of moderate disease in the right coronary artery (RCA) was noted, and the OM2 stent had the appearance of a chronic occlusion. After six months without symptoms, he presented again with troponin negative chest pain without ECG changes. He was referred for MPI to assess for objective evidence of reversible regional myocardial ischaemia. The MPI was carried out with Dobutamine stress as per standard protocol (217), and simultaneous PRIME® ECG was also carried out at baseline and peak stress in order to generate BSM Delta map, as described in detail elsewhere in chapter 2 “Methods” section. Both tests were reported by two individuals independently of each other and blinded from the other test result.

MPI demonstrated reduced radiotracer uptake in the inferio-apical territory at peak stress, which normalised with rest [Figure 30], suggesting reversible ischaemia in the distal LAD and posterior descending artery (PDA) territory.

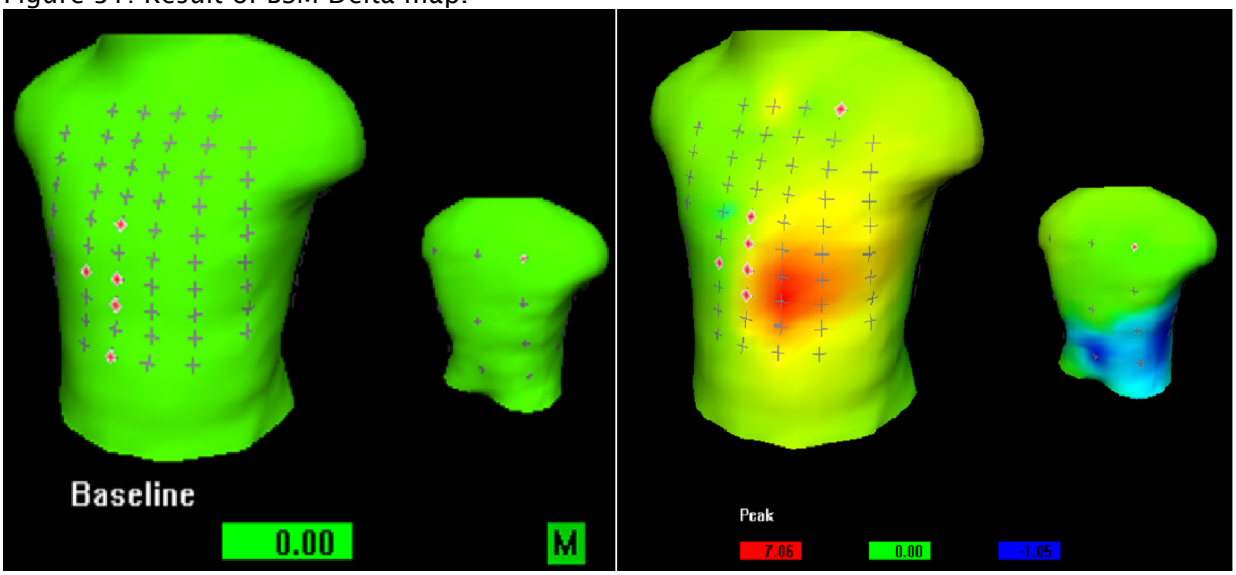
The PRIME® Delta map demonstrated significant ischaemia in the apical region as red colour (ST elevation) and inferio-posterior ischaemia as blue (ST depression) [Figure 31].

Figure 30: Result of MPI.



Single-photon emission computed tomography myocardial perfusion imaging showing Dobutamine stress induced transient reversible ischaemia in left ventricle apical and inferior region. Left ventricular ejection fraction was 42%. [SA = short axis; VLA = vertical long axis; HLA = horizontal long axis].

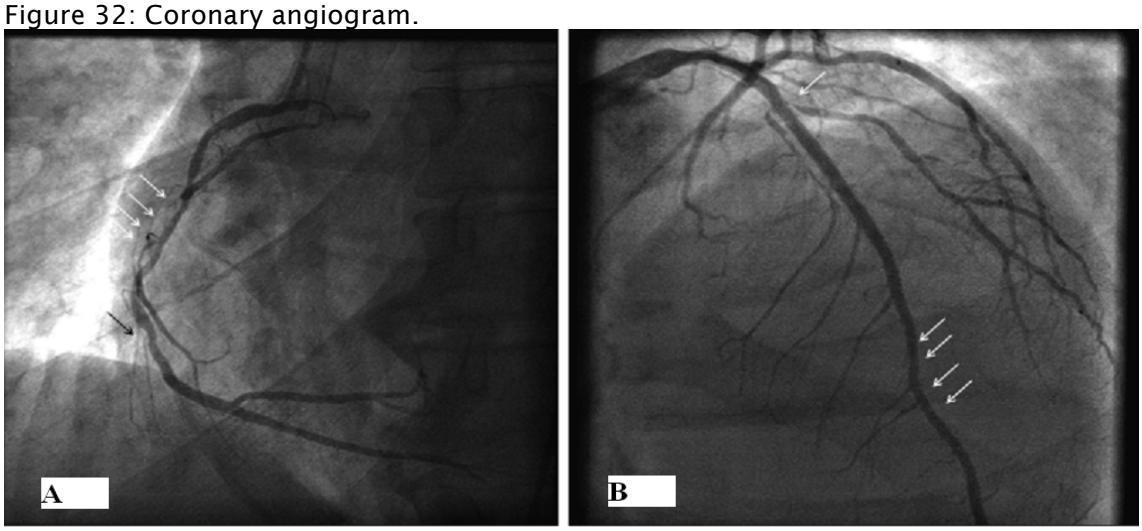
Figure 31: Result of BSM Delta map.



Baseline and peak stress PRIME® Delta map. The peak stress PRIME® Delta map demonstrating significant ischaemia in the apical region as red colour (ST elevation) and inferio-posterior ischaemia as blue (ST depression).

Repeat coronary angiogram showed moderate lesion in distal LAD and 70% long segmental lesion in proximal RCA, however the pressure wire study of LAD showed a fractional flow reserve (FFR) of 0.79 in the distal LAD. FFR in the distal RCA was also significant at 0.76 [Figure 32]. Due to significant multivessel disease, the patient was referred for coronary artery bypass grafting (CABG).

Figure 32: Coronary angiogram.



A. Right coronary angiogram in LAO-45 projection, demonstrating long segment of mid RCA disease and significant stenosis in distal RCA(arrow) FFR 0.76. B. Left coronary angiogram in RAO cranial projection showing a moderate stenosis in the distal mid LAD artery, FFR 0.79; and significant stenosis at the ostium of D1 (arrow). [LAO= Left Anterior Oblique, RCA=Right Coronary Artery, FFR= Fractional Flow Reserve]

4.4 DISCUSSION

This case illustrates the diagnostic ability and intuitive nature of the BSM Delta map in displaying transient multi-regional myocardial ischaemia (TRMI), which was consistent with the findings of simultaneous MPI and confirmed with coronary angiogram and invasive pressure wire analysis.

The diagnostic value of the conventional ETT is now considered un-acceptably low for the general population. Therefore, the limited availability and high cost of superior tests for objective evidence of ischaemia is leaving a gap in our diagnostic armoury.

The novel BSM Delta map is a digital colour display of the dynamic ST-segment shift between two time-points (baseline and peak stress) derived from 80-electrode BSM. Data are collected from 64- electrodes placed anteriorly and 16 electrodes posteriorly. This case has demonstrated that the PRIME® Delta map may be a candidate of a cost effective, near the patient, non-invasive, intuitive

tool, with wide- spread applicability. This requires minimum training for interpretation. Clinical studies are now required to further explore the potential value of the BSM Delta map in the diagnosis of TRMI.

CHAPTER 5

POTENTIAL ELIGIBILITY OF CONGENITAL HEART DISEASE PATIENTS FOR SUBCUTANEOUS IMPLANTABLE CARDIOVERTER DEFIBRILLATOR BASED ON SURFACE ECG MAPPING

5 POTENTIAL ELIGIBILITY OF CONGENITAL HEART DISEASE PATIENTS FOR SUBCUTANEOUS IMPLANTABLE CARDIOVERTER DEFIBRILLATOR BASED ON SURFACE ECG MAPPING

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CLINICAL RESEARCH

Potential eligibility of congenital heart disease patients for subcutaneous implantable cardioverter-defibrillator based on surface electrocardiogram mapping

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Aims The eligibility of complex congenital heart disease (C-CHD) patients for subcutaneous implantable cardioverter-defibrillator (S-ICD) has yet to be determined. The aim of this study was to determine in C-CHD patients: (i) the S-ICD eligibility, (ii) the most effective sensing vector, (iii) the impact of posture change on screening eligibility, and (iv) the impact of using two vs. six postures for screening. Adults with structurally normal hearts were used as controls.

Methods and results The Boston Scientific ECG screening tool was used to determine eligibility for S-ICD in two and six different postures in 30 patients with C-CHD and 10 controls. Statistical significance was determined using Fisher's exact test. In total, 1440 bipolar vectors were collected. The mean age was 36.3 years, 57% subjects were men. Over all 86.7% of C-CHD patients and 100% controls ($P > 0.05$) met S-ICD eligibility. In controls, the primary vector (PV) was the most effective, and the alternate vector (AV) was least effective. In C-CHD patients, the AV was comparable to the PV. Posture change did not significantly affect S-ICD eligibility in C-CHD patients and controls ($P > 0.05$). Screening with six postures vs. two did not significantly affect S-ICD eligibility of C-CHD patients (83% vs. 87%, $P > 0.05$) or controls (90% vs. 100% $P = >0.05$).

Conclusion No significant differences were observed between S-ICD eligibility in C-CHD patients and controls. The AV and PV are most suitable in C-CHD patients. No significant impact of postural change was observed for S-ICD eligibility between the two groups. No significant difference was observed in S-ICD eligibility when screening using two or six postures in both groups.

Keywords Sudden cardiac death • Congenital heart disease • Subcutaneous implantable cardioverter-defibrillator • Sensing algorithm

5.1 INTRODUCTION

The role of implantable cardioverter defibrillator (ICD) in the primary and secondary prevention of sudden cardiac death is well established (82, 85, 87, 89). However, the conventional TV-ICD requires placement of endovascular leads in the right side of the heart. Such leads offer stable electrogram sensing ability but the implant procedure to insert the endovenous lead carries the risk of complications such as infection, pneumothorax, myocardial perforation, tamponade, and vessel trauma (129). The leads themselves are at risk of acute dislodgement as well as longer term complications, such as disruption of lead insulation and lead fracture (129). These issues are of greater importance in young patients who are likely to require multiple generator exchanges and lead replacements with the increased risk of complications associated with these procedures. Younger patients have a higher incidence of lead-related complications such as lead fracture as they are more active and traditionally have had smaller diameter leads implanted (230, 231). Failed leads may result in inappropriate shocks and management includes lead extraction with its attendant risks (230). These factors may militate against optimal TV-ICD uptake and have acted as a stimulus for the development of the subcutaneous ICD (S-ICD) (131). Unlike conventional TV-ICD, the S-ICD detects cardiac rhythm change by far-field sensing of cardiac electrical activity using three subcutaneous (body surface) sensing electrodes. The S-ICD sensing algorithm discriminates normal rhythm from arrhythmia through the analysis of this sensed subcutaneous electrocardiographic (ECG) morphology (138). However, it is inevitable that the surface ECG morphology may vary due to anatomical differences between patients and within patients due to posture-related change in cardiac orientation relative to the fixed subcutaneous sensing electrodes

(155). This is likely to be particularly pertinent in the anatomically heterogeneous CHD population.

Some subgroups with CHD are at elevated risk of arrhythmia and sudden death as a consequence of cardiac structural abnormalities, pressure and volume overload, myocardial fibrosis, and myocardial scar related to palliative surgery (232, 233). However, the rate of the TV-ICD implant in this group is relatively low (234). This is partly due to poor risk stratification (121), but also because of young age (higher risk of endovenous lead complications) and implantation challenges due to naturally occurring or surgically created barriers to safe endovenous lead placement (230). Furthermore, in CHD subgroups with intra-cardiac shunts and single ventricle anatomy, there is a higher risk of thromboembolism in the presence of a transvenous lead (235). Conceptually the CHD patients may be a target population for S-ICD placement, but it is unclear whether the S-ICD sensing algorithm is suitable in the context of CHD anatomies, not withstanding evidence for defibrillation efficacy of this technology in this context (131).

The aim of this study was to determine in high-risk complex CHD patients: (1) suitability for S-ICD, (2) the most suitable sensing vector, (3) the impact of posture change on screening and (4) differences due to screening between use of two postures compared to six postures and using morphologically normal adults as a reference group.

5.2 METHODS

5.2.1 Ethical consideration

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

5.2.2 Study population

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

Forty patients were recruited into the following subgroups.

1. Adults with morphologically normal heart [N=10].

2. Adult CHD patients with Fontan circulation and single ventricle physiology (SVP) [N=10].

3. Adult CHD patients with repaired tetralogy of Fallot (TOF) [N=10].

4. Adult CHD patients with transposition of great arteries (TGA) [N=10].

These three groups of CHD represent relatively common, highly complex patients with high risk of sudden death (117).

Patients in arrhythmias or a paced rhythm were excluded from these studies.

5.2.3 Consent

All subjects provided written informed consent prior to study inclusion. The consent form (attached in the appendix) was approved by the Research Ethics Committee to include participants.

5.2.4 Inclusion and exclusion criteria

Only patients over 18 years of age and those who were able to provide fully informed consent were recruited. Patients with acute haemodynamic or electrical instability, permanent pacemaker (continuously paced rhythm), and subjects of other studies were excluded from these studies.

5.2.5 Bipolar three channel ECGs collection

Previous studies have validated body surface ECG as an adequate surrogate for subcutaneous ECGs (154). Therefore the manufacturer (Boston Scientific) of the only commercially available S-ICD recommends pre-implant screening, using a three-lead surface ECG in two postures (standing and supine). Using this pre-implant screening method, bipolar vectors were collected with a three-channel bipolar ECG at a sweep speed of 25 mm/s, using a sampling rate of 1kHz, and an ECG gain between 5-20 mm/mV, for 10 seconds, in 6 postures (standing, sitting, supine, left lateral, right lateral and prone). Prior skin preparation was carried out (alcohol wipe and shaving hair where necessary) to allow adequate adhesion of individual ECG skin electrodes and high-quality signal collection. Three bipolar electrodes (commonly known as LL, LA, RA) of the standard ECG machine (GE MAC 5500, USA) were used for data collection. The electrode LL was placed in the 5th intercostal space along the left mid-axillary line; electrode

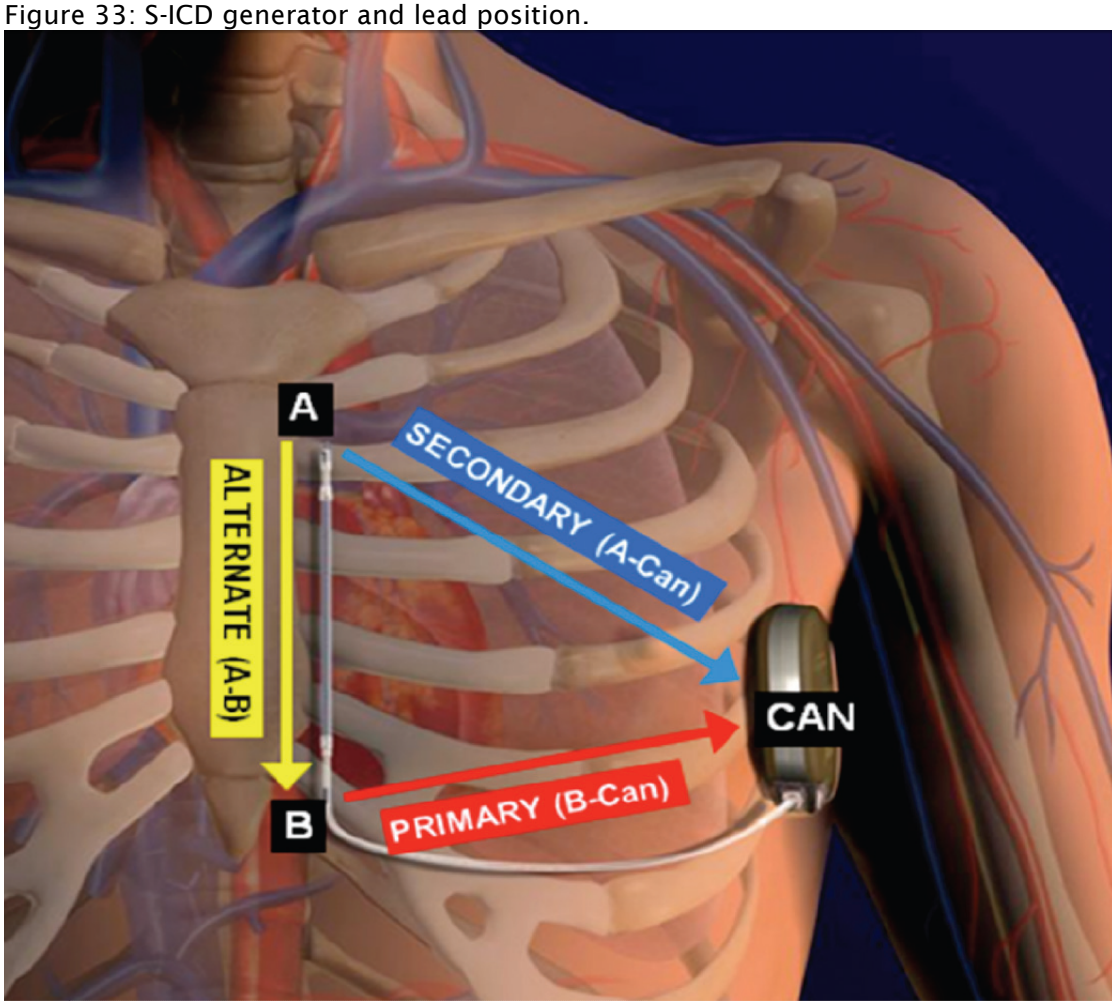
LA was placed 1 cm left lateral of the xiphoid and electrode RA was placed 14 cm superior to the LA electrode and 1 cm left lateral to the sternal margin [Figure 33]. The bipolar vector lead I was derived from RA and LA, lead II from RA and LL and lead III from LA and LL, representing surface ECG equivalent of Boston Scientific sense vectors (Primary = lead III, Secondary = lead II, Alternate = lead I). A single investigator collected the data and two trained investigators, who were blinded to the patients' details, analysed all ECGs separately.

5.2.6 ECG analysis

The manufacturer of the currently available S-ICD (Boston Scientific) has developed an ECG morphology-based pre-implant screening tool to identify patients with acceptable sensing characteristics prior to the implant of S-ICD (153). This is a template (printed chart) containing six coloured profiles of varying sizes, simulating the automatic gain adjustment function of S-ICD. This template has a horizontal line passing through all the colour profiles for adjustment of the isoelectric baseline. Each colour profile has an identical window above and below the baseline to account for the positive and negative amplitude of R-wave and T-wave contours. Each window is subdivided by a dotted line, and the peak of R-wave has to lie within this sub-window for one of the six profiles to be appropriate for sensing. Additionally, the trailing T-wave has to be contained within the same colour profile as the R-wave for the vector to be appropriate for sensing [Figure 34] (153). This screening tool was used to evaluate each sensing vector. QRS complexes with minimum noise were analysed for each vector. For biphasic signals, the larger peak was used to determine the appropriate colour map. The left edge of the selected coloured map was aligned with the onset of the QRS complex. If, when printed at the

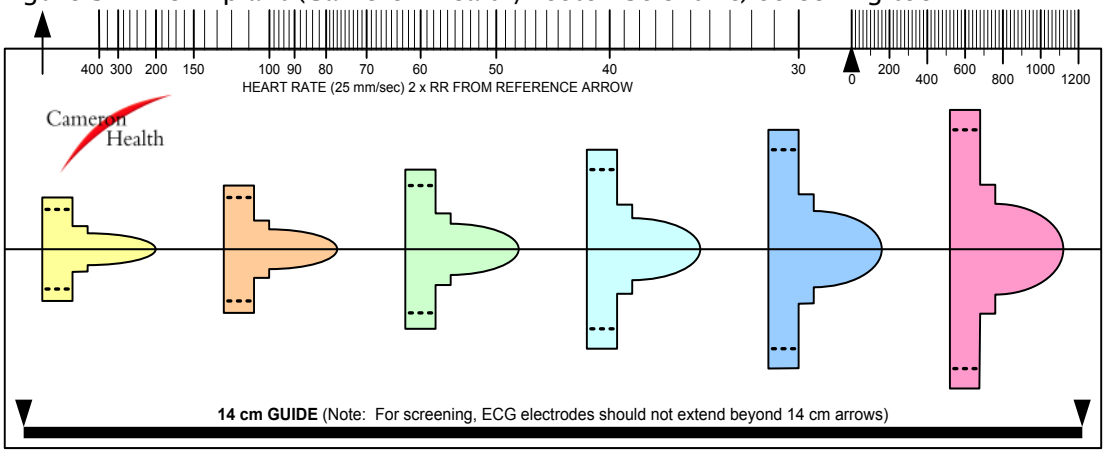
maximum 20-mm/mV gain, the QRS peak did not reach the minimum boundary (dotted line) of the smallest coloured profile, the vector was considered unacceptable. If the entire QRS complex and trailing T-wave were contained within the coloured profile, the vector/posture combination was considered suitable. If any portion of the QRS complex or trailing T-wave extended outside of the coloured profile, the sense vector was considered unacceptable. All vectors were examined individually. A patient was considered a candidate for S-ICD implant if at least one sense vector was acceptable for all tested postures (153). The data were analysed with the screening template on the basis of six postures as well as the currently used conventional pre-implant analysis of two postures.

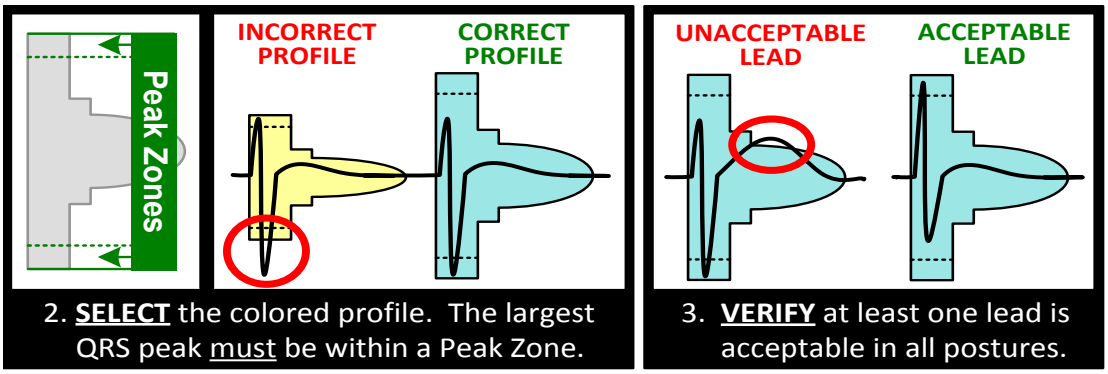
Figure 33: S-ICD generator and lead position.



This figure shows the position of subcutaneous sensing arrays and location of bipolar three electrodes placement to generate lead I, lead II and lead III for S-ICD pre-implant screening. [ECG= Electrocardiology, S-ICD= subcutaneous implantable cardioverter defibrillator]. *Adopted from Cameron Health/Boston Scientific.*

Figure 34: Pre-implant (Cameron Health/Boston Scientific) screening tool.





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

5.2.7 Criteria for subject and vector suitability

A patient was considered a candidate for S-ICD implant if at least one and the same sense vector was acceptable for all tested postures (153). Similarly, any given vector was considered suitable if it satisfied the screening tool in all tested postures (153) (e.g. a patient/subject who had primary vector suitable, then that subject had to have the primary vector suitable in all the tested postures, if the patient had the primary vector unsuitable in any of the tested posture but had secondary vector suitable in the given posture despite of that the subject/patient was declared unsuitable for the reason that the current generation of S-ICD is limited in its ability to automatically switch between sensing vectors.

5.2.8 Statistical analysis

Statistical analyses were performed using the SPSS 20.0 software package (IBM SPSS limited). Continuous variables are expressed as mean ±1 SD. The proportion of patients fulfilling ECG criteria is presented as percentages with

95% confidence interval (95% CI) using Wilson procedure without a correction for continuity as described by Robert Newcombe (236). Fisher Exact test was used to determine significant differences. The suitability of CHD groups was compared against normal control, and the suitability of leads was compared against lead III (primary vector). The suitability of postures was compared against supine posture. A $p<0.05$ was considered significant.

5.3 RESULTS

The subjects mean age was 36.3±14.4 years, and 57% were male. A total of 1440 vectors were obtained from 40 subjects in six postures, through three electrodes, in at least two gain settings. Using the pre-implant screening mapping system 750/1440, 52% (95% CI: 49-54) vectors were suitable for S-ICD sensing. For the purpose of analysis, a vector suitable at one or more gain setting was counted as +1 and a vector not suitable for sensing at any gain setting counted as -1. Thus the final number of vectors for analysis was 720, and 494/720, 69% (95% CI: 65-72) vectors were suitable either at one or more gain settings.

5.3.1 Eligibility of CHD patients for S-ICD in comparison to normal controls

The proportion of CHD patients meeting the S-ICD screening criteria was compared to normal controls.

Based on conventional two-posture screening (standing and supine) 100% (95% CI: 72-100) subjects with structurally normal heart and 87% (95% CI: 70-95) CHD patients [TOF 80% (95% CI: 49-98), TGA 100% (95 CI: 72-100), and SVP 80% (95% CI: 49-98)] met the S-ICD pre-implant screening criteria. (all p=>0.05 by comparison against control) [Table 21].

Based on six postures 90% (95% CI: 60-98) subjects with structurally normal heart, and 83% (95% CI: 66-93) of CHD patients [SVP 80% (95% CI: 49-98), TGA 90% (95% CI: 60-98) and TOF 80% (95% CI: 49-98) (all p=>0.05 by comparison against control)] met pre-implant S-ICD ECG screening criteria [Table 21].

5.3.2 Effect of postures on vectors suitability

Figure 35, 36, 37 and Table 22 shows the impact of posture on vectors suitability. The variation of vectors suitability in different postures was statistically insignificant ($p>0.05$) both in the individual with normal cardiac morphology and CHD.

5.3.3 Screening with two and six postures

The differences in eligibility due to screening with two postures and six postures in normal subjects (100% vs. 90%) and patients with CHD (87% vs. 83%) were statistically insignificant.

5.3.4 Differences in leads

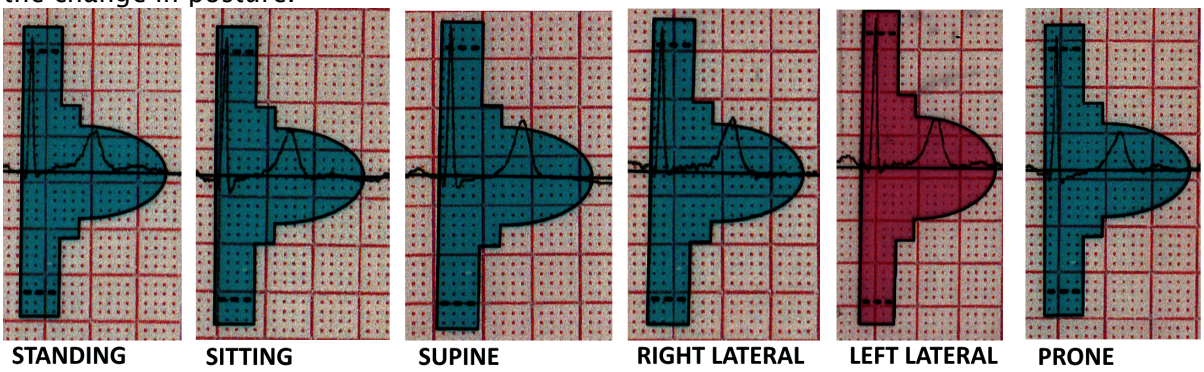
Table 21 and Table 22 shows the suitability of leads in the four groups, in two and six postures. In normal subjects lead III (primary vector) was the most suitable vector (90%), followed by lead II (secondary vector) (80%), while lead I (alternate vector) was least suitable (30%). However, in CHD patients lead I (alternate vector) suitability (67%) was comparable to lead III (73%) and better than lead II (46%). Over all the suitability of lead III was statistically superior to lead I and lead II ($p=<0.05$). Table 23 shows the reason for vectors failure.

5.3.5 Suitable number of vectors

Table 21, shows the number of suitable vectors in normal subjects and subjects with CHD in two and six postures screening. The suitability of one,

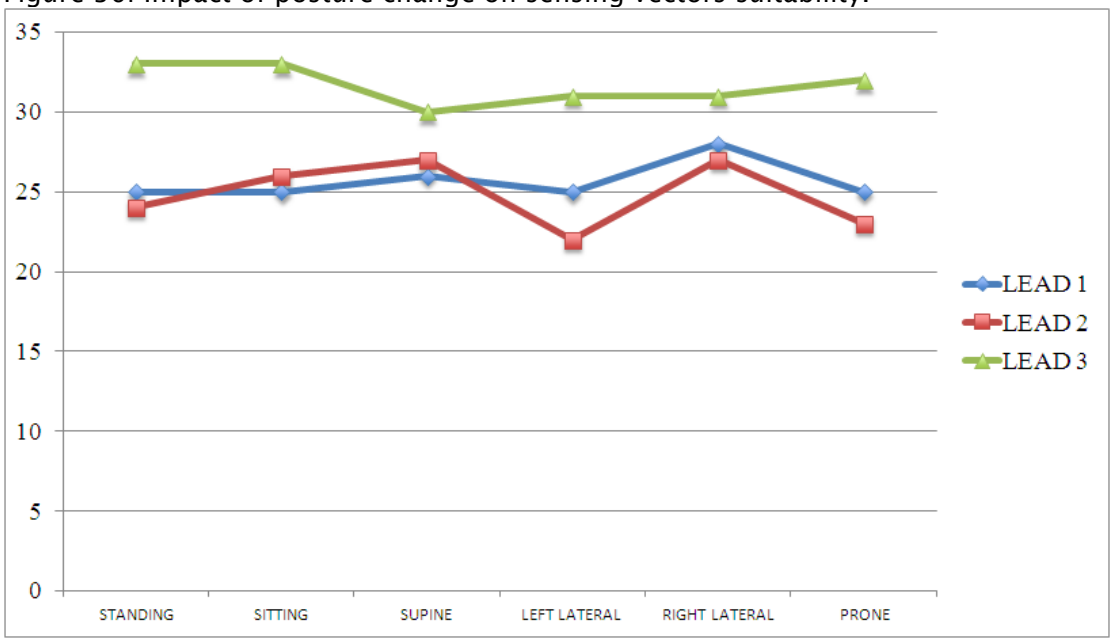
two and three vectors were fairly uniform across all the groups, without any statistically significant difference.

Figure 35: Transient changes in Primary vector (lead III) R and T-wave amplitude with the change in posture.



Transient changes in Primary vector (lead III) R and T-wave amplitude due to change in posture with the screening tool templates demonstrating the impact on suitability of the same vector for S-ICD [obtained at a sweep speed of 25 mm/s, using a sampling rate of 1kHz, and at ECG gain setting of 10 mm/mV]. The vector in this example is suitable in standing, sitting and prone postures; however, the amplitude of T-wave is clearly unsuitable in supine and right lateral postures. The amplitude of R and T-wave are larger in left lateral posture requiring larger template at the same gain setting.

Figure 36: Impact of posture change on sensing vectors suitability.



Variation of Lead I, Lead II and Lead III suitability for S-ICD sensing with posture in all patients including individuals with structurally normal hearts, and complex CHD (TOF, TGA, SVP). [S-ICD= subcutaneous implantable cardioverter defibrillator, CHD=congenital heart diseases, TOF= tetralogy of Fallot, TGA= transposition of great arteries, SVP= single ventricle physiology].

Table 20: Summary of the percentage of acceptable profiles.

			1 suitable vector		2 suitable		3 suitable		Primary vector		Secondary vector		Alternate vector	
Number of postures in	Group	N	% of acceptable profiles	95% C.I.	% of acceptable profiles	95% C.I.	% of acceptable profiles	95% C.I.	% of acceptable profiles	95% C.I.	% of acceptable profiles	95% C.I.	% of acceptable profiles	95% C.I.
Six	All	4	85	70-93	60	45-	17	09-	67	52-	47	33-	47	33-
Two			90	76-96	67	52-	35	22-	57	42-	55	40-	57	42-
Six	Normal	1	90	60-98	70	40-	20	05-	80	49-	80	49-	20	05-
Two			100	72-	70	40-	30	11-	90	60-	80	49-	30	11-
Six	All CHD	3	83	66-93	56	39-	50	24-	63	45-	37	22-	56	39-
Two			87	70-95	70	52-	37	22-	73	55-	47	30-	67	49-
Six	TOF	1	80	49-98	40	17-	20	06-	40	17-	50	24-	50	24-
Two			80	49-98	60	31-	40	17-	70	40-	50	24-	60	31-
Six	TGA	1	90	60-98	80	49-	30	11-	80	49-	40	17-	80	49-
Two			100	72-	80	49-	50	24-	80	49-	60	31-	90	60-
Six	SVP	1	80	49-98	50	24-	0		70	40-	20	06-	40	17-
Two			80	49-98	50	24-	20	06-	70	40-	30	11-	50	24-

Summary of the percentage of acceptable profiles when using the S-ICD screening tool in the standard two versus six postures across different groups and vectors. A patient was considered a candidate for S-ICD implant if at least one and the same sense vector was acceptable for all tested postures. Similarly, any given vector was considered suitable if it satisfied the screening tool in all tested postures. [S-ICD= subcutaneous implantable cardioverter defibrillator, CHD=congenital heart diseases, TOF= tetralogy of Fallot, TGA= transposition of great arteries, SVP= single ventricle physiology].

Table 21: Primary, secondary and alternate vectors suitability in 6 postures and four groups.

		SUPINE		STANDING		SITTING		LEFT LATERAL		RIGHT LATERAL		PRONE	
Group	Vector	% of acceptable profiles	95% C.I.	% of acceptable profiles	95% C.I.	% of acceptable profiles	95% C.I.	% of acceptable profiles	95% C.I.	% of acceptable profiles	95% C.I.	% of acceptable profiles	95% C.I.
All patients N=40													
	Primary	75.0	60-86	82.5	68-91	82.5	68-91	77.5	62-88	77.5	62-88	80.0	65-89
	Secondary	67.5	52-80	60.0	45-74	65.0	50-78	55.0	40-69	67.5	52-80	57.5	42-71
	Alternate	65.0	50-78	62.5	47-76	62.5	47-76	62.5	47-76	70.0	54-82	62.5	47-76
Normal N=10													
	Primary	90.0	60-98	100.0	72-	100.0	72-	90.0	60-98	90.0	60-98	100.0	72-
	Secondary	80.0	49-94	80.0	49-94	80.0	49-94	80.0	49-94	80.0	49-94	80.0	49-94
	Alternate	40.0	17-69	40.0	17-69	30.0	11-60	50.0	24-76	60.0	31-83	60.0	31-83
Tetralogy of Fallot N=10													
	Primary	50.0	24-76	80.0	49-94	70.0	40-89	60.0	31-83	60.0	31-83	60.0	31-83
	Secondary	50.0	24-76	70.0	40-89	70.0	40-89	60.0	31-83	60.0	31-83	50.0	24-76
	Alternate	60.0	31-83	70.0	40-89	80.0	49-94	50.0	24-76	60.0	31-83	50.0	24-76
Transposition of great arteries N=10													
	Primary	90.0	60-98	80.0	49-94	90.0	60-98	90.0	60-98	90.0	60-98	90.0	60-98
	Secondary	70.0	40-89	60.0	31-83	70.0	40-89	50.0	24-76	60.0	31-83	70.0	40-89

Alternate	90.0	60-98	90.0	60-98	80.0	49-94	90.0	60-98	90.0	60-98	90.0	60-98
Single ventricle physiology												
Primary	70.0	40-89	70.0	40-89	70.0	40-89	70.0	40-89	70.0	40-89	70.0	40-89
Secondary	70.0	40-89	30.0	11-60	40.0	17-69	30.0	11-60	70.0	40-89	30.0	11-60
Alternate	70.0	40-89	50.0	24-76	60.0	31-83	60.0	31-83	70.0	40-89	50.0	24-76

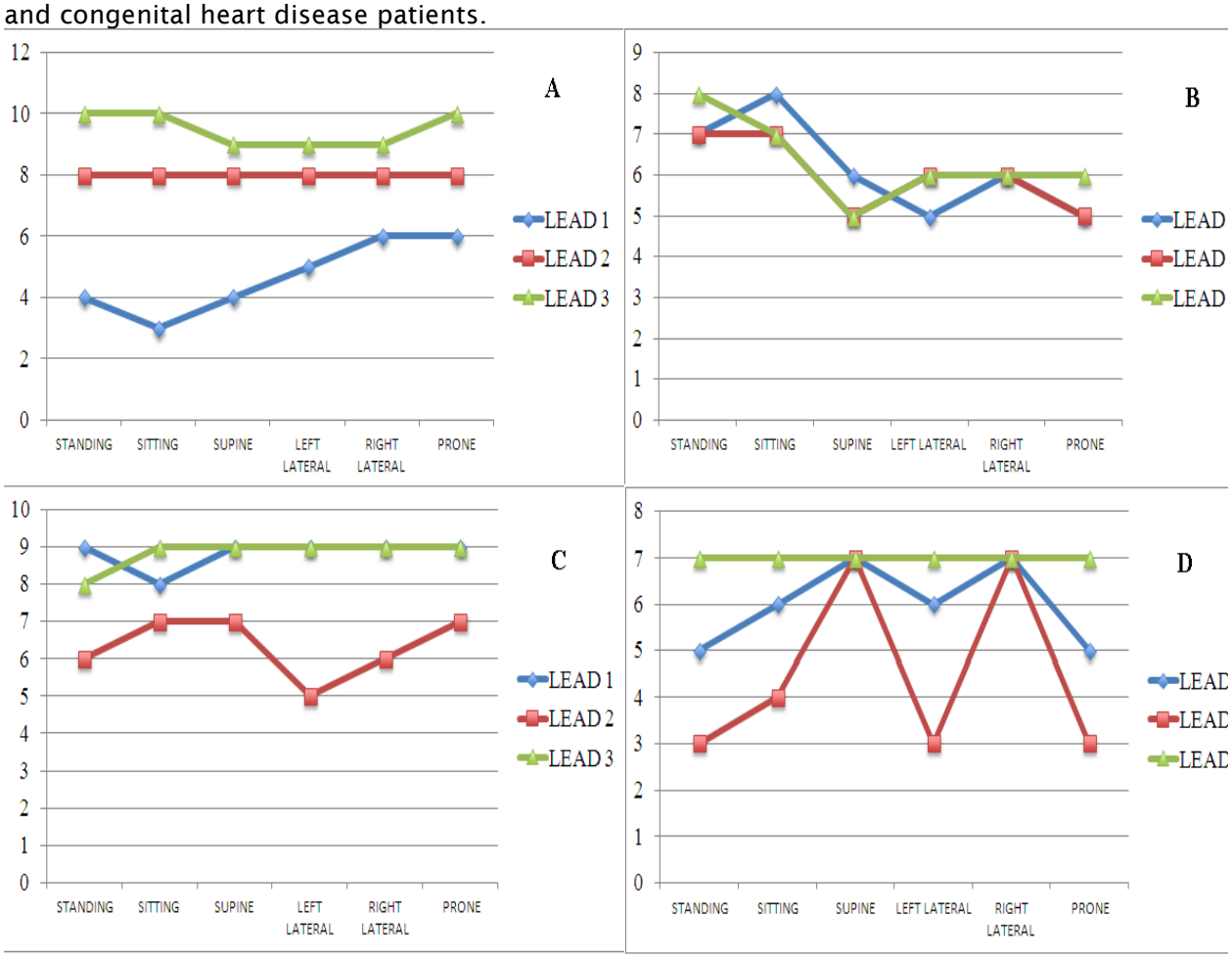
Percentage of acceptable profiles when using the S-ICD patient screening tool in the primary, secondary and alternate vectors in all groups in all postures. (TOF, TGA, SVP) at six postures. A patient was considered a candidate for S-ICD implant if at least one and the same sense vector was acceptable for all tested postures. Similarly, any given vector was considered suitable if it satisfied the screening tool in all tested postures. [S-ICD= subcutaneous implantable cardioverter defibrillator, CHD=congenital heart diseases, TOF= tetralogy of Fallot, TGA= transposition of great arteries, SVP= single ventricle physiology].

Table 22: Reasons for vectors failure.

	ECG parameter	Lead I (Alternate vector)	Lead II (Secondary vector)	Lead III (Primary vector)
Normal	Large R-Wave			
	Large T-Wave	40%	10%	20%
	Large T-Wave, small R-Wave	30%		
	Large R-Wave and T-Wave		10%	
TOF	Large R-Wave			
	Large T-Wave	30%	20%	10%
	Large T-Wave, small R-Wave	10%		
	Large R-Wave and T-Wave	10%	30%	50%
TGA	Large R-Wave		10%	
	Large T-Wave	10%	30%	
	Large T-Wave, small R-Wave		10%	
	Large R-Wave and T-Wave			10%
SVP	Large R-Wave	20%	20%	
	Large T-Wave	30%	50%	30%
	Large T-Wave, small R-Wave			
	Large R-Wave and T-Wave	10%		

Reasons for failure of Lead I (Alternate vector), Lead II (Secondary vector), Lead III (Primary vector) in normal subjects and congenital heart disease patients. [TOF= tetralogy of Fallot, TGA= transposition of great arteries, SVP= single ventricle physiology].

Figure 37: Impact of posture change on sensing vectors suitability in normal subjects and congenital heart disease patients.



Pane A: Variation of Lead I, Lead II and Lead III suitability for S-ICD sensing with posture in individuals with structurally normal hearts. Pane B: Variation of Lead I, Lead II and Lead III suitability for S-ICD sensing with posture in individuals with TOF. Pane C: Variation of Lead I, Lead II and Lead III suitability for S-ICD sensing with posture in individuals with TGA. Pane D: Variation of Lead I, Lead II and Lead III suitability for S-ICD sensing with posture in individuals with SVP. [S-ICD= subcutaneous implantable cardioverter defibrillator, TOF= tetralogy of Fallot, TGA= transposition of great arteries, SVP= single ventricle physiology].

5.4 DISCUSSION

This study has demonstrated no significant differences in eligibility of complex CHD patients (TOF, TGA, SVP) and subjects with structurally normal hearts for commercially available S-ICD using the pre-implant ECG screening criteria. However, we have demonstrated that whilst CHD patients and normal controls met the S-ICD implant criteria using the primary vector more frequently, the alternate vector is more suitable in CHD patients. This study has also demonstrated the impact of body posture on sensing vector choice [Figure 37 and Table 22], and consequently, potential lead location in the thoracic subcutaneous tissues. The primary vector lead III was suitable in most postures in most cases, including controls as well as all groups of CHD; this may be due to the horizontal orientation of this lead in comparison to the vertical and diagonal orientation of lead I and lead II. Lead I suitability varied with posture in normal subjects. However lead I showed less variation with posture change in individuals with CHD [Figure 37], and specifically in patients with TOF, we speculate that right ventricular hypertrophy that occurs in patients with CHD and specifically TOF may have this effect on sensing vector effectiveness. Lead II showed variation with postural change in all CHD groups and specifically in individuals with SVP and was least suitable in this group [Figure 37]. The screening with six (standing, sitting, supine, left lateral, right lateral and supine) and two postures (standing and supine) showed a trend towards higher suitability at two postures. However, the difference was not statistically significant. Adding an additional four postures excluded 2/40 patients (5%) due to T-wave enlargement (oversensing) in the left lateral posture in the effected subjects. These two subjects would have otherwise satisfied the S-ICD implant criteria. This has potentially important implications for T-wave

oversensing susceptibility that could be reduced by ECG screening with 6 postures.

The current body of published literature in relation to the experience of S-ICD in CHD is limited (142, 146). The recently published early results from the EFFORTLESS S-ICD registry had only 7% (33/472) patients with CHD. However the detailed description of the underlying CHD anatomy, the pre-implant screening results, fall out rate, the reason for S-ICD implant and the performance of S-ICD have not been described separately (237).

Table 23 shows the reasons for vectors failure. The screening tool is used as a proxy to identify QRS-T complexes that are likely to satisfy the S-ICD sensing algorithm and avoid inappropriate sensing performance. An R/T ratio <3 in the lead with the largest t wave on the standard surface 12 lead ECG has been identified to be a strong predictor (OR 14.6) of failed QRS-T morphology screening for the S-ICD (238). We have found that an R/T ratio alone is less predictable of vectors suitability as despite suitable R/T ratio the overall vector may not be suitable for sensing due to very large or small amplitude of both or individual R-wave and T-wave. The vector suitability also depends on the QRS duration and QT interval, as prolongation of these intervals makes the T-wave unsuitable.

Suitability of more than one vector would make more stable sensing possible; however, the current generation of S-ICD are limited in its ability of automatic mode switching between sensing vectors, and this has to be done manually with the device programmer, thus in current settings, the suitability of multiple vectors have limited role.

Our study has several limitations. Firstly, the sample sizes are small; it is possible that larger numbers may have revealed the smaller differences in

eligibility of the groups studied to be significant. However, this study was designed to demonstrate any major differences between normal subjects and patients with complex congenital heart diseases. Also, the number of complex congenital heart diseases patients attached to any single centre are small and difficult to recruit; therefore, 10 near age and sex matched subjects were recruited from normal control, TOF, TGA, and SVP to reduce compounding factors. Moreover prior to the result of this study power calculation would not have been possible. Additional, all data was collected by a single investigator to reduce variation, and furthermore, the sample size for the current study was selected to mimic preclinical drug safety studies (239). Secondly, since ECGs were collected from individuals in sinus rhythm at rest, there is a possibility of variation in the morphologies of ECGs during exercise and arrhythmia. However, in this study the Boston Scientific S-ICD pre-implant screening method was followed which recommends collection and analysis of resting surface ECGs and more recently screening is also performed on ECGs acquired during exercise (153). Thirdly, the pre-implant screening process also assumes that vectors suitable at pre-implant screening fulfil criteria for the sensing algorithm of the S-ICD when implanted and forms the basis of implant decision-making. The defibrillation ability of S-ICD is beyond the scope of this study.

5.5 CONCLUSIONS

Using current pre-implant screening criteria, no statistically significant differences were observed between the proportion of CHD patients meeting S-ICD screening criteria and normal controls. No statistically significant impact of the postural change was observed on the eligibility of normal subjects and patients with CHD. Lead III (primary vector) met the screening criteria more

frequently in CHD patients and normal controls. Lead I (alternate vector) was least suitable in subjects with structurally normal heart; however, this was more often suitable in CHD patients. Screening at two and six postures had no statistically significant effect on the suitability of either normal subjects or patients with CHD using the current “conventional” screening approach, but we speculate that screening with six postures could reduce the problem of T wave oversensing. This hypothesis requires further evaluation but is an important observation given the impact of T wave oversensing on inappropriate shock therapies in S-ICD recipients.

CHAPTER 6

IMPACT OF POSTURE, SENSING ELECTRODE POSITION AND CARDIAC MORPHOLOGIES ON SURFACE ELECTROCARDIOGRAM SIGNALS

6 IMPACT OF POSTURE, SENSING ELECTRODE POSITION AND CARDIAC MORPHOLOGIES ON SURFACE ELECTROCARDIOGRAM SIGNALS OF S-ICD SENSING

6.1 ABSTRACT

6.1.1 Background

Ambulatory cardiac monitoring devices and the novel subcutaneous ICD (SICD) sensing algorithms are based on surface electrocardiograms (ECGs) parameters for detection and discrimination of arrhythmias. However, the impact of posture, cardiac morphology, site of electrode placement and gender on these parameters are not known.

6.1.2 Aim

To determine the impact of posture (standing, sitting, supine, left lateral, right lateral and prone) and bipolar electrode location (Lead I, Lead II, Lead III), cardiac morphology (normal, tetralogy of Fallot (TOF), transposition of the great arteries (TGA), single ventricle physiology (SVP)) and gender on R-wave amplitude, T-wave amplitude, R/T ratio, QRS duration, QTc interval, Tpeak-end duration determined by surface ECG.

6.1.3 METHODS

720 bipolar vectors were collected in a set of three lead (Lead I, Lead II, Lead III) transcutaneous ECGs at 10 mm/mv gain, 25mm/second speed from three locations similar to the S-ICD sensing arrays in 6 postures from 40 subjects (10

normal controls, 10 patients with TOF, 10 with SVP, 10 with TGA). The ECGs were digitally measured and analysed using repeated-measures ANOVA and Post hoc Helmert contrast pairwise analysis with Bonferroni adjustment.

6.1.4 Results

A total of 8,640 ECG components (1440 R-wave amplitudes, 1440 T-wave amplitudes, 1440 R/T ratios, 1440 QRS duration, 1440 QTc interval and 1440 Tpeak-end duration) were measured and analysed. The mean R-wave amplitude was significantly smaller in right lateral posture in comparison to left lateral posture ($p=0.02$) and in Lead I than Lead III ($p=0.025$). The T-wave amplitude in subjects with TOF was significantly greater than subjects with normal cardiac morphology ($p=0.013$) and SVP ($p=0.005$). The mean QRS duration in subjects with normal cardiac morphology was significantly lower than subjects with TOF ($p=0.0001$) and SVP ($p=0.006$). The mean QRS duration in females was significantly smaller than males in the whole group ($p=0.03$). There were no statistically significant differences in the mean R/T ratio, QTc interval, Tpeak-end duration between subgroups, six postures and three lead ($p>0.05$).

6.1.5 Conclusions

Posture, electrode location, and cardiac morphology have a significant impact on the surface ECG parameters. These differences may have to be considered while designing sensing algorithm for monitoring devices and specifically SICD.

Key words: Body surface electrocardiograms; rhythm monitoring; sensing algorithm; subcutaneous ICD; congenital heart disease; postural variation.

6.2 INTRODUCTION

The current generation of cardiac monitoring devices aims to detect and record heart rhythm automatically. Therefore, it is necessary for these devices to discriminate between different components of the surface electrocardiogram (ECG) (151). The novel subcutaneous implantable cardioverter defibrillator (S-ICD) sensing algorithm also depends on similar parameters of the surface ECG to detect and treat life-threatening arrhythmias. Specifically, the amplitude of "R," "T" with "R/T ratio," the duration of "QRS," and "QT" play an important role in the sensing algorithm of such devices (131, 138). Abnormalities in the surface ECG parameters of depolarisation and repolarisation such as QRS,(155) QTc,(156) Tpeak-end duration (157) are also known markers of ventricular arrhythmias. Potentially, integration of such parameters in the sensing algorithm of devices like S-ICD could be highly valuable in raising a pre-alert to ventricular tachyarrhythmia. However, the effects of posture on R-wave amplitude, T-wave amplitude, R/T ratio, QRS duration, QTc interval, and Tpeak-end duration could affect the clinical utility of these systems. Furthermore, the highly variable cardiac morphology seen in congenital heart diseases (CHD) is likely to have an important impact on these parameters (142). This is particularly pertinent to SICD as many CHD patients have elevated risk of sudden death (142). In view of this risk and of the difficulties intrinsic in implanting transvenous systems in CHD patients, these people potentially would be suitable candidates for the S-ICD. However,

extrapolation of the sensing algorithm of S-ICD based on studies on normal adults may be inappropriate for CHD patients (142).

The aim of this study was to determine the impact of posture (standing, sitting, supine, left lateral, right lateral and prone), electrode location (used for deriving bipolar Lead I, Lead II, and Lead III), cardiac morphology (normal, tetralogy of fallot (TOF), transposition of great arteries (TGA), single ventricle physiology (SVP)), and gender on R-wave amplitude, T-wave amplitude, R/T ratio, QRS duration, QTc interval, Tpeak-end duration.

6.3 METHODS

6.3.1 Patient population

This study was undertaken in the cardiology department of a university teaching hospital that is the regional tertiary care unit for adult cardiology, paediatric cardiology, and adult congenital heart diseases. The study received approval from an independent review board of the Hampshire & Isle of Wight Ethical Committee (REC Reference No: 08/HQ504/55). All subjects were aged 18 years or over (mean age 36.3years and 57% male) and had the ability to give informed consent. All subjects provided written informed consent for participation in the study.

Forty subjects were recruited into the following subgroups.

1. Adults with morphologically normal hearts (N=10).

2. Patients with Fontan circulation and single ventricle physiology (N=10).

3. Patients with repaired tetralogy of fallot (N=10).

4. Patients with transposition of great arteries (N=10).

Patients with arrhythmias and those with a permanent pacemaker and paced rhythm were excluded from the study.

6.3.2 Electrocardiographic measurements

Previous studies have shown good correlation between subcutaneous and corresponding body surface ECGs (154). In each patient, a three-channel bipolar surface ECG at a speed of 25 mm/s, and sampling rate of 1kHz, at a

gain of 10 mm/mV was recorded for 10 seconds in each of 6 postures (standing, sitting, supine, left lateral, right lateral and prone posture), using a GE (MAC 5500, USA) ECG machine. Adequate adhesion of individual ECG skin electrodes and consequently high-quality signal collection was ensured through prior skin preparation; shaving hair where necessary and using an alcohol wipe. According to the S-ICD manufacturer's (Boston Scientific, Marlborough, MA) recommendations, three standard ECG electrodes (LL, LA, RA) were used for data collection. The electrodes were placed at locations similar to the S-ICD sensing arrays as specified by the manufacturer [Figure 33]; LL was placed at the fifth intercostal space along the mid-axillary line, LA was placed 1 cm left lateral to the xiphoid and RA was placed 14 cm superior to the LA electrode, 1 cm left lateral of the sternal margin. The bipolar Lead I was derived from RA and LA, Lead II from RA and LL and Lead III from LA and LL, representing surface ECG equivalent of Boston Scientific sense vectors (Primary = Lead III, Secondary = Lead II, Alternate = Lead I). The data were collected by a single investigator. All ECGs were digitally scanned, and measurements were made by two experienced investigators, blinded to clinical data, using a digital ECG calliper at approximately 400% magnification (240).

6.3.3 Measurement of surface ECG parameters

The parameters measured from each lead and in six postures were; (i) amplitude of R wave, (ii) amplitude of T wave, (iii) R/T ratio, (iv) duration of QRS complex, (v) QTc interval and (vi) Tpeak-end interval. The measurement of each parameter was obtained by averaging two consecutive best beats with minimum noise. The ECG baseline was determined by the TP segment (241). The amplitude of R wave was measured from the baseline to the peak of R

wave (mV), and similarly, the amplitude of T wave measured from baseline to the peak of T wave (mV) (240). Where both R wave and S wave were present, the deflection from baseline with the larger amplitude was measured, and a similar method was applied to negative or biphasic T wave. The duration of the QRS-complex (msec) was measured from the initial deflection at the beginning of the QRS complex to the return of the QRS complex to the isoelectric baseline of the ST segment (240). The QT interval (msec) was defined as the time interval between the initial deflection of the QRS complex and the point at which a tangent can be drawn to the steepest portion of the terminal part of T wave, where it crosses the isoelectric line (242). The QTc-intervals were corrected for the heart rate using Bazett's formula (243). The Tpeak-end duration (msec) was obtained from the difference between the QT interval and QT peak interval, measured from the beginning of the QRS until the peak of the T wave . In the case of negative or biphasic T waves, the QT peak was measured to the nadir of the T wave (244).

6.3.4 Statistical analysis

Statistical analyses were performed using the SPSS 19.0 software package (NY: IBM Corp). Continuous variables are expressed as mean ±1 SD and were compared using Student's *t* test. Comparison of dichotomous categorical variables was made by x^2 test. The relationship between the ECG parameters in different postures, leads, gender and the four groups was evaluated using General Linear Model (GLM) factorial repeated-measures analysis of variance (repeated-measures ANOVA) and mixed design factorial repeated-measures ANOVA. Multivariate analysis with Pillai's Trace was conducted to determine any significant difference within the groups. *Post hoc* Helmert contrast pairwise

analysis, with Bonferroni adjustment was carried out to determine significant differences between individual postures, leads, gender and cardiac morphologies. A r value of less than 0.05 was considered significant.

6.4 RESULTS

A total of 8,640 ECG components (1440 R-wave amplitudes, 1440 T-wave amplitudes, 1440 R/T ratios, 1440 QRS duration, 1440 QTc interval and 1440 Tpeak-end duration) were measured and analysed.

Tables 24-29 and Figure 38 summarize the results of analyses to assess the effects on the ECG parameters of electrode position, body posture, and cardiac morphology.

6.4.1 Effect of posture on the surface ECG parameters

There was a significant difference in the R-wave amplitude, between the postures (□=0.013). Specifically, the pairwise comparison showed significantly smaller R-wave amplitude in the right lateral posture compared with the left lateral posture (□ =0.02). However, there were no significant differences between the other postures.

There were no statistically significant differences in the T-wave amplitude, the R/T ratio, the QRS duration, the QTc interval, and the Tpeak-end duration between the six postures considered (supine, standing, sitting, left lateral, right lateral and prone).

6.4.2 Cardiac morphology and surface ECG signals

There was no statistically significant difference in the R-wave amplitude between control subjects, with normal hearts, and patients with CHD (□ =0.850). However, there were statistically significant differences in the T-wave amplitude within the different patient groups (□ =0.003). Specifically, on the

post hoc pairwise comparison, the T-wave amplitude in subjects with TOF was significantly greater than both subjects with normal cardiac morphology (r=0.013) and SVP (r=0.005). There were no significant differences between the other subgroups. There was no statistically significant difference in the R/T ratio between the four groups (normal, TOF, TGA, SVP) (r=0.056).

There were significant differences in the QRS duration within the four groups (p=0.0001). The QRS duration in subjects with normal cardiac morphology was significantly shorter than that seen in subjects with TOF (r=0.0001) and SVP (r=0.006).

There was no significant difference in either the QTc interval or the Tpeak-end duration between the four groups (normal, TOF, TGA, SVP).

6.4.3 Effect of electrode position on the surface ECG signals

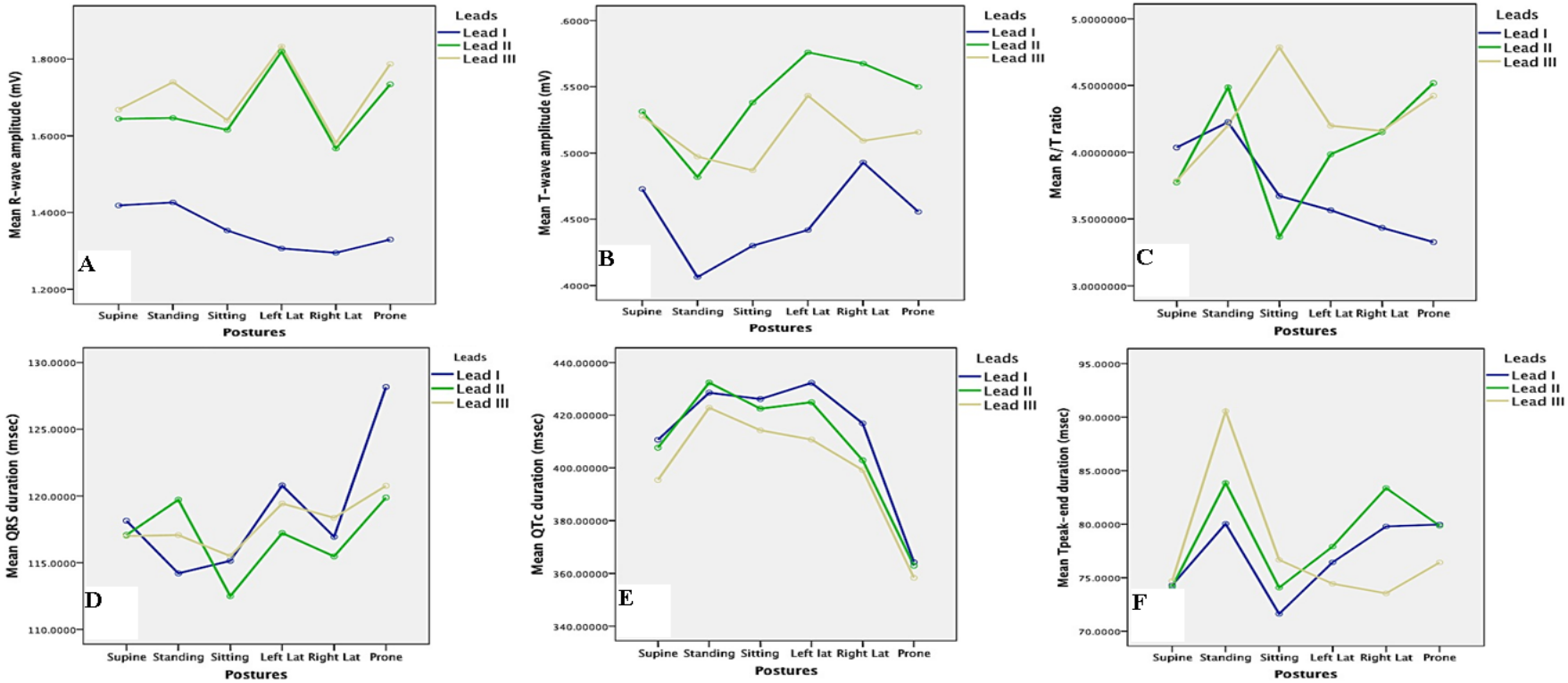
There was a statistically significant difference in the R-wave amplitude between the three leads (r=0.02). On *post hoc* pairwise comparison, the R-wave amplitude in Lead I was significantly smaller than Lead III (r=0.025), but there was no difference compared with lead II (r=0.139). No difference in the R-wave amplitude between lead II and lead III was seen (r=0.1).

There were no statistically significant differences in the T-wave amplitude, the R/T ratio, the QRS duration, the QTc interval and the Tpeak-end duration between the three leads (Lead I, Lead II, and Lead III).

6.4.4 Effect of gender on surface ECG signals

There were no statistically significant differences in the R-wave amplitude (□=0.964), the T-wave amplitude and in the R/T ratio between male and female subjects. The QRS duration in female subjects was significantly smaller than that seen in male subjects (□=0.03). There was no significant difference in either the QTc interval or the Tpeak-end duration between male and female subjects.

Figure 38: Variations in various ECG parameters with change in posture.



A. Variations in the mean R-wave amplitude (mV) with change in posture in the three bipolar vectors (Lead 1, Lead 2, Lead 3) in 40 subjects; B. Variations in the mean T-wave amplitude (mV) with change in posture in the three bipolar vectors (Lead 1, Lead 2, Lead 3) in 40 subjects; C. Variations in the mean R/T ratio with change in posture in the three bipolar vectors (Lead 1, Lead 2, Lead 3) in 40 subjects; D. Variations in the mean QRS duration (msec) with change in posture in the three bipolar vectors (Lead 1, Lead 2, Lead 3) in 40 subjects; E. Variations in the mean QTc duration (msec) with change in posture in the three bipolar vectors (Lead 1, Lead 2, Lead 3) in 40 subjects; F. Variations in mean Tpeak-end duration (msec) with change in posture in the three bipolar vectors (Lead 1, Lead 2, Lead 3) in 40 subjects.

Table 23: Mean R-wave amplitude pairwise Comparisons

(I)	(J)	Mean Difference (I-J)	Std. Error	Sig.[a]	95% CI for Difference[a]	
					Lower	Upper
A. Mean R-wave amplitude pairwise comparisons of Leads						
Lead I	Lead II	-.316	.153	.139	-.702	.069
Lead II	Lead III	-.037	.157	1.000	-.434	.359
Lead III	Lead I	.354*	.125	.025	.037	.671
B. Mean R-wave amplitude pairwise comparisons of postures						
Supine	Standing	-.027	.060	1.000	-.218	.164
	Sitting	.041	.043	1.000	-.097	.179
	Left Lateral	-.076	.034	.488	-.184	.032
	Right	.096	.039	.292	-.028	.220
	Prone	-.040	.053	1.000	-.208	.128
Standing	Sitting	.068	.063	1.000	-.131	.267
	Left Lateral	-.049	.066	1.000	-.257	.160
	Right	.123	.055	.477	-.051	.297
	Prone	-.013	.073	1.000	-.244	.218
Sitting	Left Lateral	-.117	.047	.281	-.266	.033
	Right	.055	.052	1.000	-.111	.222
	Prone	-.081	.051	1.000	-.242	.081
Left Lateral	Right	.172*	.049	.019	.018	.326
	Prone	.036	.056	1.000	-.142	.214
Right Lateral	Prone	-.136	.057	.349	-.317	.045
C. Mean R-wave amplitude pairwise comparisons of normal and CHD						
Normal	TOF	-.312	.250	1.000	-1.016	.392
	TGA	-.071	.258	1.000	-.798	.656
	SVP	.052	.258	1.000	-.675	.779
TOF	TGA	.242	.250	1.000	-.462	.946
	SVP	.364	.250	.931	-.339	1.068
TGA	SVP	.123	.258	1.000	-.604	.850
D. Mean R-wave amplitude pairwise comparisons of male and female						
Male	Female	-.008	.180	.964	-.375	.358
Based on estimated marginal means						
a. Adjustment for multiple comparisons: Bonferroni.						

A. Mean R-wave amplitude pairwise comparisons of Leads; B. Mean R-wave amplitude pairwise comparisons of postures; C. Mean R-wave amplitude pairwise comparisons of normal and CHD; D. Mean R-wave amplitude pairwise comparisons of male and female.

Table 24: Mean T-wave amplitude pairwise comparison

(I)	(J)	Mean Difference (I-J)	Std. Error	Sig.[a]	95% CI for Difference[a]	
					Lower Bound	Upper Bound
A. Mean T-wave amplitude pairwise comparisons of Leads						
Lead I	Lead II	-.091	.048	.204	-.212	.031
	Lead III	-.063	.035	.241	-.152	.025
Lead II	Lead III	.027	.047	1.000	-.092	.147
B. Mean T-wave amplitude pairwise comparisons of postures						
Supine	Standing	.049	.016	.074	-.002	.100
	Sitting	.026	.015	1.000	-.022	.073
	Left Lateral	-.010	.016	1.000	-.060	.041
	Right Lateral	-.013	.025	1.000	-.092	.067
	Prone	.004	.020	1.000	-.059	.066
Standing	Sitting	-.023	.016	1.000	-.074	.028
	Left Lateral	-.059	.020	.083	-.121	.004
	Right Lateral	-.061	.028	.575	-.152	.029
	Prone	-.045	.019	.344	-.105	.015
Sitting	Left Lateral	-.035	.019	1.000	-.095	.024
	Right Lateral	-.038	.026	1.000	-.120	.043
	Prone	-.022	.020	1.000	-.085	.041
Left Lateral	Right Lateral	-.003	.029	1.000	-.094	.089
	Prone	.013	.019	1.000	-.046	.072
Right Lateral	Prone	.016	.024	1.000	-.059	.091
C. Mean T-wave amplitude pairwise comparisons of normal and CHD						
Normal	TOF	-.283	.085	.013	-.522	-.045
	TGA	-.283*	.087	1.000	-.218	.274
	SVP	.028	.087	1.000	-.300	.192
TOF	TGA	.283*	.085	.005	.073	.550
	SVP	.311*	.085	.065	-.009	.467
TGA	SVP	-.311*	.087	1.000	-.328	.164
D. Mean T-wave amplitude pairwise comparisons of Gender						
1	2	.082	.061	.708	-.101	.147
Based on estimated marginal means						
a. Adjustment for multiple comparisons: Bonferroni.						

A. Mean T-wave amplitude pairwise comparisons of Leads; B. Mean T-wave amplitude pairwise comparisons of postures; C. Mean T-wave amplitude pairwise comparisons of normal and CHD; D. Mean T-wave amplitude pairwise comparisons of Gender.

Table 25: R/T ratio pairwise comparisons

(I)	(J)	Mean Difference (I-J)	Std. Error	Sig.[a]	95% CI for Difference[a]	
					Lower Bound	Upper Bound
A. R/T ratio pairwise comparisons of Leads						
Lead I	Lead II	-.337	.680	1.000	-2.056	1.382
	Lead III	-.549	.474	.767	-1.748	.649
Lead II	Lead III	-.212	.596	1.000	-1.719	1.295
B. R/T ratio pairwise comparisons of postures						
Supine	Standing	-.439	.241	1.000	-1.205	.326
	Sitting	-.076	.229	1.000	-.802	.649
	Left Lateral	-.051	.176	1.000	-.609	.507
	Right Lateral	-.050	.255	1.000	-.860	.760
	Prone	-.224	.240	1.000	-.986	.539
Standing	Sitting	.363	.330	1.000	-.684	1.411
	Left Lateral	.388	.216	1.000	-.295	1.072
	Right Lateral	.390	.354	1.000	-.734	1.513
	Prone	.216	.271	1.000	-.644	1.075
Sitting	Left Lateral	.025	.290	1.000	-.894	.944
	Right Lateral	.027	.374	1.000	-1.160	1.213
	Prone	-.148	.315	1.000	-1.148	.853
Left Lateral	Right Lateral	.001	.292	1.000	-.924	.927
	Prone	-.173	.287	1.000	-1.082	.736
Right Lateral	Prone	-.174	.362	1.000	-1.323	.975
C. R/T ratio pairwise comparisons of normal and CHD						
Normal	TOF	1.131	.761	.882	-1.009	3.272
	TGA	-.999	.786	1.000	-3.210	1.212
	SVP	.703	.786	1.000	-1.508	2.915
TOF	TGA	-2.131	.761	.052	-4.271	.010
	SVP	-.428	.761	1.000	-2.569	1.713
TGA	SVP	1.703	.786	.227	-.509	3.914
D. R/T ratio pairwise comparisons of gender						
Male	Female	.592	.547	.288	-.523	1.706
Based on estimated marginal means						
a. Adjustment for multiple comparisons: Bonferroni.						

A. R/T ratio pairwise comparisons of Leads; B. R/T ratio pairwise comparisons of postures; C. R/T ratio pairwise comparisons of normal and CHD; D. R/T ratio pairwise comparisons of gender.

Table 26: Mean QRS duration pairwise comparisons

(I)	(J)	Mean Difference (I-J)	Std. Error	Sig.[a]	95% CI for Difference[a]	
					Lower Bound	Upper Bound
A. Mean QRS duration pairwise comparisons of Leads						
Lead I	Lead II	1.920	3.347	1.000	-6.536	10.377
	Lead III	.876	3.279	1.000	-7.408	9.160
Lead II	Lead III	-1.044	2.576	1.000	-7.554	5.465
B. Mean QRS duration pairwise comparisons of postures						
Supine	Standing	.409	1.845	1.000	-5.442	6.261
	Sitting	3.029	1.611	1.000	-2.079	8.138
	Left	-1.740	1.694	1.000	-7.111	3.632
	Right	.480	1.469	1.000	-4.179	5.140
	Prone	-5.533	2.711	.744	-14.133	3.067
Standing	Sitting	2.620	1.442	1.000	-1.953	7.193
	Left	-2.149	2.323	1.000	-9.516	5.218
	Right	.071	1.973	1.000	-6.187	6.328
	Prone	-5.942	2.893	.723	-15.118	3.234
Sitting	Left	-4.769	2.311	.709	-12.100	2.562
	Right	-2.549	2.004	1.000	-8.907	3.809
	Prone	-8.562	2.759	.060	-17.312	.188
Left Lateral	Right	2.220	1.453	1.000	-2.390	6.830
	Prone	-3.793	3.157	1.000	-13.807	6.221
Right	Prone	-6.013	2.552	.371	-14.106	2.080
C. Mean QRS duration pairwise comparisons of normal and CHD						
Normal	TOF	-43.379*	9.024	.000	-68.758	-17.999
	TGA	-22.136	9.320	.142	-48.347	4.076
	SVP	-33.819*	9.320	.006	-60.031	-7.608
TOF	TGA	21.243	9.024	.149	-4.136	46.623
	SVP	9.559	9.024	1.000	-15.820	34.939
TGA	SVP	-11.684	9.320	1.000	-37.896	14.528
D. Mean QRS duration pairwise comparisons of gender						
Male	Female	14.490*	6.487	.033	1.277	27.703
Based on estimated marginal means						
*. The mean difference is significant at the						
b. Adjustment for multiple comparisons: Bonferroni.						

A. Mean QRS duration pairwise comparisons of Leads; B. Mean QRS duration pairwise comparisons of postures; C. Mean QRS duration pairwise comparisons of normal and CHD; D. Mean QRS duration pairwise comparisons of gender.

Table 27: Mean QTc duration pairwise comparisons

(I)	(J)	Mean Difference (I-J)	Std. Error	Sig.[a]	95% CI for Difference[a]	
					Lower	Upper
A. Mean QTc duration pairwise comparisons of Leads						
Lead I	Lead II	4.246	3.451	.683	-4.473	12.966
	Lead III	12.986	5.720	.090	-1.464	27.437
Lead II	Lead III	8.740	6.106	.486	-6.687	24.167
B. Mean QTc duration pairwise comparisons of postures						
Supine	Standing	-23.310	13.983	1.000	-67.662	21.042
	Sitting	-16.362	16.693	1.000	-69.309	36.585
	Left Lateral	-18.039	12.943	1.000	-59.091	23.012
	Right	-1.732	19.890	1.000	-64.821	61.356
	Prone	42.760	23.679	1.000	-32.345	117.865
Standing	Sitting	6.948	12.922	1.000	-34.037	47.933
	Left Lateral	5.271	8.408	1.000	-21.398	31.940
	Right	21.578	17.229	1.000	-33.070	76.225
	Prone	66.070	22.125	.081	-4.106	136.247
Sitting	Left Lateral	-1.677	12.607	1.000	-41.664	38.309
	Right	14.630	20.649	1.000	-50.864	80.123
	Prone	59.122	23.726	.271	-16.132	134.377
Left Lateral	Right	16.307	15.773	1.000	-33.721	66.335
	Prone	60.800	20.020	.071	-2.699	124.298
Right	Prone	44.493	20.321	.540	-19.962	108.947
C. Mean QTc duration pairwise comparisons of normal and CHD						
Normal	TOF	-10.957	25.081	1.000	-81.492	59.579
	TGA	-8.737	25.903	1.000	-81.586	64.112
	SVP	-10.341	25.903	1.000	-83.190	62.508
TOF	TGA	2.220	25.081	1.000	-68.316	72.755
	SVP	.615	25.081	1.000	-69.920	71.151
TGA	SVP	-1.604	25.903	1.000	-74.453	71.245
D. Mean QTc duration pairwise comparisons of gender						
Male	Female	-.213	18.028	.991	-36.935	36.509
Based on estimated marginal means						
a. Adjustment for multiple comparisons: Bonferroni.						

A. Mean QTc interval pairwise comparisons of Leads; B. Mean QTc interval pairwise comparisons of postures; C. Mean QTc interval pairwise comparisons of normal and CHD; D. Mean QTc interval pairwise comparisons of gender.

Table 28: Mean Tpeak-end duration pairwise comparisons

(I)	(J)	Mean Difference (I-J)	Std. Error	Sig.[a]	95% CI for Difference[a]	
					Lower Bound	Upper Bound
A. Mean Tpeak-end duration pairwise comparisons of Leads						
Lead I	Lead II	-1.841	2.608	1.000	-8.430	4.749
	Lead III	-.695	2.436	1.000	-6.850	5.461
Lead II	Lead III	1.146	2.261	1.000	-4.567	6.859
B. Mean Tpeak-end duration pairwise comparisons of postures						
Supine	Standing	-10.430	3.539	.089	-21.655	.795
	Sitting	.264	1.889	1.000	-5.729	6.257
	Left Lateral	-1.880	2.023	1.000	-8.298	4.538
	Right Lateral	-4.516	1.839	.295	-10.348	1.315
	Prone	-4.366	2.379	1.000	-11.913	3.181
Standing	Sitting	10.694	3.470	.063	-.313	21.701
	Left Lateral	8.550	3.489	.299	-2.516	19.617
	Right Lateral	5.914	3.668	1.000	-5.721	17.550
	Prone	6.064	3.662	1.000	-5.552	17.681
Sitting	Left Lateral	-2.144	2.381	1.000	-9.697	5.410
	Right Lateral	-4.780	2.679	1.000	-13.278	3.718
	Prone	-4.630	2.622	1.000	-12.948	3.688
Left Lateral	Right Lateral	-2.636	1.985	1.000	-8.934	3.661
	Prone	-2.486	1.657	1.000	-7.743	2.771
Right	Prone	.150	1.740	1.000	-5.369	5.669
C. Mean Tpeak-end duration pairwise comparisons of normal and CHD						
Normal	TOF	-10.244	5.476	.423	-25.644	5.156
	TGA	-8.547	5.655	.843	-24.452	7.358
	SVP	-7.672	5.655	1.000	-23.577	8.233
TOF	TGA	1.696	5.476	1.000	-13.704	17.096
	SVP	2.572	5.476	1.000	-12.828	17.971
TGA	SVP	.875	5.655	1.000	-15.030	16.780
D. Mean Tpeak-end duration pairwise comparisons of gender						
Male	Female	1.669	3.936	.674	-6.349	9.686
Based on estimated marginal means						
a. Adjustment for multiple comparisons: Bonferroni.						

A. Mean Tpeak-end duration pairwise comparisons of Leads; B. Mean Tpeak-end duration pairwise comparisons of postures; C. Mean Tpeak-end duration pairwise comparisons of normal and CHD; D. Mean Tpeak-end duration pairwise comparisons of gender.

6.5 DISCUSSION

The sensing algorithm of the S-ICD depends on the surface (subcutaneous) ECG morphology, specifically the QRS duration, QT interval, R-wave amplitude, T-wave amplitude and R/T ratio for rhythm discrimination (153). However, considering the potential inter-individual variability in these components, the manufacturers of the S-ICD (Cameron Health/Boston Scientific, Marlborough, MA) have developed a pre-implant screening tool (153), that is applied to three bipolar ECG vectors derived from pre-specified locations mimicking the S-ICD sensing electrode sites, in standing and supine posture and takes into account these parameters of ECG (153). Despite this, a high incidence (7-13%) of inappropriate shocks by S-ICD within one year of the implant has been reported (131, 138, 147, 237). The extent of the variability of sensing parameters in different postures, electrode location, cardiac morphology and gender for optimisation of screening methodology and sensing algorithm remained unknown.

This study demonstrated variation in the R-wave amplitude in postures as shown in Figure 38, although the postural variation was significant only between left lateral and right lateral postures. However, it is possible that variations that do not reach statistical significance may have an impact on the sensing algorithm because even slight variations in the borderline cases would affect the sensing ability of S-ICD. In order to avoid inappropriate sensing, we suggest that every patient should be screened in all postures.

The assessment of CHD patients compared with individuals with normal cardiac morphology showed no significant difference in the R-wave amplitude and the variation with posture was also similar. However, the T-wave amplitude in individuals with TOF was significantly greater than individuals with normal

cardiac morphology (r=0.013) and SVP (r=0.005). This finding is keeping with the reported high incidence of T wave oversensing in patients with CHD (131, 138, 147). However, our study suggests that the issue of T wave oversensing may be limited to certain groups of cardiac morphologies. For example, in this study, patients with TOF, and these patients may need further evaluation and scrutiny for optimization of the sensing algorithm.

In this study Lead III, which represents S-ICD primary sensing vector, demonstrated less variation with changes in posture. Lead III is derived from two electrodes, one placed at the left lower sternal edge, 1cm left lateral to *manubrium sterni* and the second one at the S-ICD generator at the mid-axillary line in the fifth and sixth intercostal space. Therefore, anatomically, this lead is derived from two electrodes, which are placed horizontally on the body. In terms of S-ICD sensing vectors, this means that sensing vectors horizontal on the thorax are less likely to suffer changes from postural variation. This finding can be further exploited by placement of electrodes at various angles to derive multiple vectors at several angles to determine the optimal placement of the sensing electrode that would suffer less variation with changes in the posture.

Animal models of macaques (245) and dogs (246) showed changes in the amplitude of R wave with the change in posture, but no significant changes in QRS and QTc interval were reported.

The only previous human study in this area was performed by Madias et al (247), using unipolar precordial electrodes of a 12-lead ECG in 26 subjects, with no known congenital anomaly, with the aim of evaluating changes in ECG parameters of ischaemia (P-wave, QRS complex and ST-segment) while standing, sitting or supine . This study did not show any changes in R-wave

amplitude, QRS duration and QTc interval in the three postures tested. Our study, by contrast, included analysis of R wave, T wave, R/T ratio, QRS duration, QTc interval and Tpeak-end in normal subjects as well as subjects with complex CHD, in all the possible postures, with three bipolar electrodes mimicking surface/subcutaneous ECG recording and analysis by monitoring devices and S-ICD.

This study has several limitations. Firstly, considering the population who are likely to receive an ICD, the CHD cohort sampled was limited to three groups – tetralogy of fallot, transposition of the great arteries and single ventricle physiology. However, these conditions represent the most complex congenital structural abnormalities (117). Secondly, the sample size was limited due to constraints on time and resources, and difficulty recruiting appropriate patients to the study. These rare defects represent patients who have a high burden of arrhythmias and risk of sudden death (117). Although the sample size is small, with high-quality signal data the estimate of variation should also be small. All data were collected by a single investigator to reduce variation, and the sample size for the current study was selected to mimic preclinical drug safety studies (239). Thirdly, ECGs were collected from individuals in sinus rhythm; therefore there is a chance of variation in the morphologies of ECGs during arrhythmia. However, in this study, the Boston Scientific S-ICD pre-implant screening method, recommending collection and analysis of resting surface ECGs (153) was strictly followed.

6.6 CONCLUSIONS

This study confirms that the amplitude of the R wave varies with posture and sensing electrode position, the amplitude of the T wave varies with cardiac morphology, and the QRS duration varies with gender and cardiac morphology. These variations may have important implications in relation to the sensing ability of monitoring devices, therefore care is required when selecting patients for S-ICD as R waves and T waves are dynamic and changes may affect the sensing quality by the S-ICD.

Posture, cardiac morphology, sensing electrode position and gender had no significant impact on the surface ECG's R/T ratio, QTc interval, Tpeak-end duration, therefore it would be feasible to develop an algorithm for S-ICD in order to raise a pre-alert to ventricular tachyarrhythmia based on surface ECG markers of malignant arrhythmias (QTc and Tpeak-end duration).

CHAPTER 7

SENSITIVITY AND SPECIFICITY OF THE SUBCUTANEOUS IMPLANTABLE CARDIOVERTER DEFIBRILLATOR PRE-IMPLANT SCREENING TOOL

7 THE STUDY OF SENSITIVITY AND SPECIFICITY OF THE SUBCUTANEOUS IMPLANTABLE CARDIOVERTER DEFIBRILLATOR PRE-IMPLANT SCREENING TOOL

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Sensitivity and specificity of the subcutaneous implantable cardioverter defibrillator pre-implant screening tool

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ABSTRACT

Background: The sensitivity and specificity of the subcutaneous implantable cardioverter defibrillator (S-ICD) pre-implant screening tool required clinical evaluation.
Methods: Bipolar vectors were derived from electrodes positioned at locations similar to those employed for S-ICD sensing and pre-implant screening electrodes, and recordings collected through 80-electrode PRIME®-ECGs, in six different postures, from 40 subjects (10 healthy controls, and 30 patients with complex congenital heart disease (CCHD); 10 with Tetralogy of Fallot (TOF), 10 with single ventricle physiology (SVP), and 10 with transposition of great arteries (TGA)). The resulting vectors were analysed using the S-ICD pre-implant screening tool (Boston Scientific) and processed through the sensing algorithm of S-ICD (Boston Scientific). The data were then evaluated using 2×2 contingency tables. Fisher exact and McNemar tests were used for a comparison of the different categories of CCHD, and $p < 0.05$ vs. controls considered to be statistically significant.
Results: 57% of patients were male, mean age of 36.3 years. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the S-ICD screening tool were 95%, 79%, 59% and 98%, respectively, for controls, and 84%, 79%, 76% and 86%, respectively, in patients with CCHD ($p = 0.0001$).
Conclusion: The S-ICD screening tool was comparatively more sensitive in normal controls but less specific in both CCHD patients and controls; a possible explanation for the reported high incidence of inappropriate S-ICD shocks. Thus, we propose a pre-implant screening device using the S-ICD sensing algorithm to minimise false exclusion and selection, and hence minimise potentially inappropriate shocks.

7.1 INTRODUCTION

Implantable cardioverter defibrillators (ICD) are considered the most effective treatment for primary and secondary prevention of sudden cardiac death (SCD) (89, 107, 108, 234, 248). The main function of ICD is to sense and terminate potentially fatal ventricular arrhythmias. However, the conventional TV-ICDs carry risks of a variety of complications (129, 130, 249). These complications include procedural (bleeding, pneumothorax, vascular damage and myocardial perforation), short-term (infection, thrombosis) and long-term (lead failure, inappropriate shocks) factors (130).

The use of TV-ICD is conservative in patients with congenital heart diseases (CHD) because of the anatomical challenges and a higher risk of life long complications; despite the fact that these people experience a high rate of SCD at a young age and would benefit most from ICD (115, 116). The totally subcutaneous implantable cardioverter defibrillator (S-ICD) has been developed and used in a selected number of patients because of the limitations of TV-ICD. S-ICDs are entirely subcutaneous and aim to reduce complications through avoidance of the use of intracardiac leads (131, 144, 250). However, despite these advantages, the S-ICD is limited by the inability to provide anti-tachy pacing (ATP) and can provide post shock brady pacing for 30 seconds only (131). Additionally, selection for S-ICD implant is based on pre-implant electrographic body surface mapping (153).

The S-ICD consists of a pulse generator (SQ-RX® pulse generator Boston Scientific) (153), implanted subcutaneously in the left mid-axillary line at the level of the fifth and sixth intercostal spaces (153). The L-shaped lead is inserted parallel to the left sternum and is connected to the pulse generator (Q-TRAK® lead, Boston Scientific) (153). This configuration offers three sensing

vectors [Figure 33] (131, 138). Pre-implant screening identifies the most appropriate sensing vector, which is then confirmed by post implant device interrogation. However, the current generation of S-ICD do not automatically select the sensing vector. The S-ICD uses subcutaneous electrocardiogram (ECG) signals to monitor cardiac output and discriminate between shockable and non-shockable rhythms (138).

Early trials of S-ICD defibrillation ability have demonstrated effective termination of VT and VF similar to TV-ICDs (131, 138). However, recent clinical studies have reported inappropriate shocks in at least 7-13% cases within one year of implant suggesting that the sensing algorithm requires further evaluation (131, 138, 141-145, 147, 251).

Bellardine et al. have demonstrated a good correlation between subcutaneous and the corresponding transcutaneous body surface ECGs (154), suggesting that it is feasible to study the sensing algorithm of S-ICD through surface ECG measurements. Additionally, patient selection for S-ICD implant is based on pre-implant screening; carried out using a three-lead surface ECG, acquired in both supine and standing postures. The ECG tracings are then mapped out using the Boston Scientific screening tool; intended to identify patients with acceptable sensing characteristics (138, 153). However, the diagnostic and discriminatory ability (sensitivity and specificity) of the pre-implant screening tool against the sensing algorithm of S-ICD is not known.

In this study, we have tested the sensitivity and specificity of the pre-implant screening tool against the sensing algorithm of the S-ICD in six postures (standing, sitting, supine, left lateral, right lateral, prone) for three vectors. Four subgroups were considered; including normal adults and adults with

complex congenital heart diseases (Tetralogy of Fallot (TOF), transposition of great arteries (TGA) and single ventricle physiology (SVP).

7.2 METHODS

7.2.1 Ethical consideration

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

7.2.2 Study population

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

Forty patients were recruited into the following subgroups.

1. Adults with a morphologically normal heart on echocardiogram or cardiac magnetic resonance [N=10].

2. Adult CHD patients with Fontan circulation and single ventricle physiology (SVP) [N=10].

3. Adult CHD patients with repaired tetralogy of Fallot (TOF) [N=10].

4. Adult CHD patients with transposition of great arteries (TGA) [N=10].

These three groups of CHD represent relatively common, highly complex patients with high risk of sudden death (117).

Patients in an arrhythmias or a paced rhythm were excluded from these studies.

7.2.3 Consent

All subjects provided written informed consent prior to study inclusion. The consent form (attached in the appendix) was approved by the Research Ethics Committee to include participants.

7.2.4 Inclusion and exclusion criteria

Only patients over 18 years of age and those who were able to provide fully informed consent were recruited. Patients with acute haemodynamic or electrical instability, permanent pacemaker (continuously paced rhythm), and subjects of other studies were excluded from these studies.

7.2.5 Electrocardiographic data collection

Electrocardiographic body surface mapping was performed through 80-electrode ECG (PRIME®-ECG Verathon Inc.); a detailed description of PRIME® BSM is given in chapter 2.

In each subject, 80-electrode ECGs were recorded in six postures (standing, sitting, supine, left lateral, right lateral, prone), for 10 seconds, at a sweep speed of 25 mm/s, and a sampling rate of 1kHz. Adequate adhesion of individual ECG skin electrodes and good quality signal collection were ensured through prior skin preparation, shaving hair where necessary and using alcohol wipes. Three bipolar vectors were created from electrodes at locations mimicking the placement of the S-ICD sensing electrodes as recommended by the manufacturers (Boston Scientific) for pre-implant screening [Figure 34] (153). The bipolar vectors Lead I, Lead II and Lead III were derived, representing surface ECG equivalent of Boston Scientific sense vectors (Primary

= Lead III, Secondary = Lead II, Alternate = Lead I). Each vector was created at gain 5, 10, 15 and 20 mm/mV.

7.2.6 Screening tool and bipolar vectors analysis

The use of screening tool is described in detail above. All vectors were examined individually at four gains (5, 10, 15 and 20 mm/mV). A vector suitable at any of these gains was considered suitable.

7.2.7 Analysis of the bipolar vectors by S-ICD sensing algorithm

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

7.2.8 Statistical analysis

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

on the basis of cardiac morphology, lead position, and postures. A □< 0.05 was considered significant.

7.3 RESULTS

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

In all subjects the screening tool sensitivity was 86% (95% CI. 81, 90), specificity was 79% (95% CI. 74, 82), positive predictive value (PPV) was 73% (95% CI. 68, 77), negative predictive value (NPV) was 89% (95% CI. 86, 92), positive likelihood ratio (+LR) was 4 (95% CI. 3, 5) and negative likelihood ratio (-LR) was 0.2 (95% CI. 0.1, 0.2).

In subjects with normal heart morphology the screening tool sensitivity was 95% (95% CI. 83, 99), specificity was 79% (95% CI. 70, 85), PPV was 59% (95% CI. 47, 70), NPV was 98% (95% CI. 93, 99), +LR was 4 (95% CI. 4, 6) and -LR was 0.06 (95% CI. 0.01, 0.2).

In subjects with C-CHD the screening tool sensitivity was 84% (95% CI. 79, 89), specificity was 79% (95% CI. 74, 83), PPV was 76% (95% CI. 71, 81), NPV was 86% (95% CI. 81, 90), +LR was 4 (95% CI. 3, 5) and -LR was 0.2 (95% CI. 0.1, 0.2).

In individuals with TOF the screening tool sensitivity was 77% (95% CI. 64, 87), specificity was 76% (95% CI. 68, 83), PPV was 60% (95% CI. 48, 71), NPV was 88% (95% CI. 80, 93), +LR was 3 (95% CI. 2, 4) and -LR was 0.3 (95% CI. 0.2, 0.5).

In individuals with TGA the screening tool sensitivity was 83% (95%. 73, 90), specificity was 76% (95% CI. 66, 84), PPV was 75% (95% CI. 65, 83), NPV was 84% (95% CI. 74, 91), +LR was 3 (95% CI. 2, 5) and -LR was 0.2 (95% CI. 0.1, 0.3).

In individuals with SVP the screening tool sensitivity was 90% (95% CI. 82, 95), specificity was 86% (95% CI. 76, 93), PPV was 89% (95% CI. 81, 94), NPV was 87% (95% CI. 77, 93), +LR was 6 (95% CI. 4, 11) and -LR was 0.1 (95% CI. 0.06, 0.2).

The diagnostic and discriminative values of the screening tool for the three leads and six postures are given in Table 30.

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

Table 29: Subcutaneous ICD screening tool sensitivity, specificity using S-ICD sensing algorithm as a reference.

	Sensitivity % (95% CI %)	Specificity % (95% CI)	Positive predictive value % (95% CI)	Negative predictive value % (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	McNemar p value
All	86 (81, 90)	79 (74, 82)	73 (68, 77)	89 (86, 92)	4 (3, 5)	0.2 (0.1, 0.2)	
Normal	95 (83, 99)	79 (70, 85)	59 (47, 70)	98 (93, 99)	4 (4, 6)	0.06 (0.01, 2)	
TOF	77 (64, 87)	76 (68, 83)	60 (48, 71)	88 (80, 93)	3 (2, 4)	0.3 (0.2, 0.5)	★0.001
TGA	83 (73, 90)	76 (66, 84)	75 (65, 83)	84 (74, 91)	3 (2, 5)	0.2 (0.1, 0.3)	*0.03
SVP	90 (82, 95)	86 (76, 93)	89 (81, 94)	87 (77, 93)	6 (4, 11)	0.1 (0.06, 0.2)	*0.002
Lead III	88 (80, 93)	72 (63, 80)	79 (72, 85)	83 (74, 90)	3 (2, 4)	0.2 (0.1, 0.3)	
Lead II	83 (73, 90)	78 (72, 85)	68 (58, 77)	90 (83, 94)	4 (3, 6)	0.2 (0.3, 0.6)	□1
Lead I	89 (78, 95)	83 (76, 88)	68 (58, 77)	94 (89, 97)	5 (4, 7)	0.1 (0.07, 0.3)	□0.004
Supine	79 (64, 89)	83 (72, 89)	76 (61, 86)	86 (75, 92)	5 (2, 8)	0.2 (0.1, 0.4)	
Standing	86 (73, 94)	84 (73, 91)	80 (67, 89)	89 (78, 95)	5 (3,9)	0.2 (0.1, 0.3)	§0.1
Sitting	85 (71, 93)	80 (69, 89)	74 (60, 85)	89 (79, 95)	4 (3, 7)	0.2 (0.1, 0.4)	§1
Left lateral	92 (79, 97)	73 (61, 83)	70 (57, 80)	93 (82, 98)	3 (2, 5)	0.1 (0.04, 0.3)	§1
Right lateral	88 (74, 96)	71 (60, 80)	63 (50, 75)	92 (80, 97)	3 (2, 4)	0.2 (0.1, 0.4)	§0.6
Prone	89 (76, 96)	82 (71, 90)	76 (62, 96)	92 (82, 97)	5 (3, 8)	0.1 (0.05, 0.3)	§0.1

*McNemar p value derived in comparison to individual with normal heart morphology.

[□]McNemar p value derived in comparison to Primary Lead III.

[§]McNemar p value derived in comparison to supine posture.

Subcutaneous ICD screening tool sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and McNemar p value for comparison of different categories.

7.4 DISCUSSION

The sensing algorithm of the S-ICD depends on the surface (subcutaneous) ECG morphology, specifically the R-wave amplitude, T-wave amplitude, R/T ratio, QRS duration and QT interval. A pre-implant screening tool has been developed by the manufacturers (Boston Scientific) taking into account these ECG parameters (153). The screening tool is used in all patients under consideration for S-ICD implantation; to select individuals with ECG morphology that is offering an appropriate signal configuration to satisfy the requirements of the S-ICD sensing algorithm critical for appropriate delivery of ICD therapy (153). In this study, the performance of the screening tool was compared against a gold standard (sensing algorithm prepared by the manufacturers (Boston Scientific) in Matlab®.

Our study demonstrated sensitivity and specificity of the S-ICD pre-implant screening tool in individuals with normal cardiac morphologies that is compatible with patient selection for subcutaneous ICD therapy and an expectation of delivery of appropriate therapy. However, the sensitivity and specificity of the screening tool were significantly lower in individuals with CHD ($p=0.001$) compared with normal controls. The screening tool was developed using data from adults with normal cardiac morphologies, accounting for the higher sensitivity in this group. The sensitivity and specificity of the screening tool were highest in Lead I, followed by Lead III; there was no statistically significant difference between Lead II and Lead III. There were no statistically significant differences in sensitivity and specificity of the screening tool between the six postures.

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

The first non-randomised clinical trial of S-ICD was conducted by Bardy et al. demonstrating successful sensing and termination of induced arrhythmias at the time of implant and during 10±1 month follow up (131). In this study, at the time of implant, the VF was appropriately detected in 100% of 137 induced episodes. The device terminated VF twice-in 58 out of 59 patients (98%) with 65-J shocks at the time of implant. In this study, 55 subjects were closely followed up for a mean duration of 10±1 months. During which the S-ICD successfully detected and treated 12 spontaneous episodes of VF. During the follow up the complications of S-ICD included two pocket infections, four lead revisions, and 9% inappropriate sensing. Although this is the first landmark study introducing the clinical use of S-ICD in humans, in this particular study the number of participants were small, and the sensing and the shocking ability of the S-ICD was mainly evaluated at the time of implant, while patients were in the supine posture. The mean follow up duration was also relatively short (131).

Dabiri et al. published a single centre registry of the first 31 patients who had the S-ICD implant in their centre (141). At the time of implant, 52 sustained episodes of VF were induced in 29 patients, which were all appropriately

sensed and treated with standard polarity in 29 patients. The mean time to therapy was 13.9 ± 2.5 seconds (range 11-21.6 s). In the mean follow-up duration of 9 months, lead migration occurred in 2 patients. Spontaneous ventricular arrhythmias were observed in four patients, with accurate detection of all episodes. Inappropriate therapy was observed in five patients (16%) requiring reconfiguration of S-ICD setting.

Jarman et al. (142) reported another single centre experience of S-ICD involving sixteen patients; all patients were relatively younger with a median age of 20 years (range 10-48 years). 12 out of 16 patients had S-ICD implanted for primary indications due to arrhythmic diseases, while 4 patients had CHD. No perioperative complications were reported. At the time of implant, induced sustained VF was successfully sensed and terminated in all cases. The median follow-up duration was 9 months (range 3-15 months), 3 out of 16 patients required re-operation. During the follow-up, 6 patients received 18 shocks therapies. 10 out of 18 shocks in four patients were inappropriate due to T-wave over-sensing. The rest of the 8 shocks were appropriate (including 3 for VF, however, there was a delay of 24 and 27 seconds from detection to therapy in 2 patients.

Aydin et al. (143) reported the clinical experience of three German institutions involving a cohort of non-randomised 40 consecutive patients (age 42 ± 15 years; body mass index, 27 ± 6 kg/m; left ventricular ejection fraction, 47 ± 15%; 28 men). The S-ICD was used for primary prevention in 17 patients and secondary prevention in the rest of 23 patients. Defibrillation testing failed in 1 patient at the time of implant. During a median follow-up of 7.6 months (interquartile range, 3.8-10 months), 21 spontaneous ventricular arrhythmias

occurred in 4 patients, for which appropriate shocks were delivered. Mixed logistic regression modelling revealed a shock efficacy of 96.4% (95% CI, 12.8-100). The efficacy of first shocks, however, was only 57.9% (95% CI, 35.6-77.4). Inappropriate sensing and shock therapies were observed in two patients on four occasions.

Olde Nordkamp et al. (145) reported a Dutch multicentre experience of the first 118 S-ICD implantation (75% males, mean age 50 years). At 18 months follow-up, 45 appropriate shocks were recorded in 8 patients with a 98% conversion to patient's own rhythm with the first shock. During this follow up period no death occurred. Inappropriate shocks were observed in 15 patients (13%), further assessment revealed T-wave over-sensing, it was reported that this problem was solved by a software upgrade and changing the sensing vector of the S-ICD. Overall complications were observed in 16 patients (14%). In this study, complications were more frequent in the first 15 S-ICD implants per centre compared to the subsequent procedures (inappropriate shocks 19% vs. 6.7%, p = 0.03; complications 17% vs. 10%, p = 0.10), which highlights the importance of learning curve.

Köbe et al. (144) reported a case control study of S-ICD and conventional TV-ICD conducted in three German centres. Sixty-nine patients had S-ICD implantation (72% male, mean age 45.7±15.7 years) and 69 sex and age matched patients who had conventional TV-ICD were used as a control. The S-ICD was used for primary prevention in 41 patients (59%). ICM was the underlying cardiac pathology in 11 patients (15%), DCM in 25 (36.2%), and HCM in 10 (14.5%). The mean procedure time reported for S-ICD was 71 ± 28 minutes (P = 0.398). Intraprocedure induced VF was terminated in 89% with 65

J (15-J safety margin) and 95% including reversed shock polarity in the S-ICD group. In control TV-ICD group induced VF was terminated successfully in 91% (10-J safety margin, device dependent) (P = 0.815). There was no difference in the procedural complications between the two groups. The mean follow-up duration was 7±4 months, during which appropriate S-ICD therapies were observed in 3 patients. However, 3 inappropriate therapies were delivered in 3 patients (5.2%), with similar rate (2 patients) of inappropriate sensing and therapies in TV-ICD group due to rapidly conducted AF (P = .745). Pericardial effusion occurred in 1 patient with TV-ICD, haematoma, requiring evacuation occurred in 1 patient with S-ICD, a revision was required in 2 patients with S-ICD, and inappropriate shocks were delivered in 2 patients with TV-ICD and 5 patients with S-ICD.

For appropriate S-ICD sensing, it is vital to identify suitable candidates, to reduce the chances of inappropriate shocks and sensing failure. There are limited published data regarding the performance of the pre-implantation screening tool, especially in patients with structural abnormality due to congenital heart disease. The START study directly compared transvenous and subcutaneous devices, by assessing their respective abilities to discriminate between arrhythmias (138). This study showed that all ICDs tested had >99 % appropriate detection for ventricular tachyarrhythmias, but the discrimination of supraventricular arrhythmias was markedly higher for S-ICDs (98%) than for two of three transvenous devices tested (76.7% and 68%) (138). Similarly, further clinical studies demonstrated the excellent ability of the S-ICD for rhythm discrimination (141-143, 152). However, most of these studies on the rhythm discrimination were performed immediately after implantation of S-ICD

with patients in a supine posture; therefore, this poses questions regarding "real life" performance of S-ICD sensing. Additionally, recent clinical studies have reported inappropriate therapies in as many as 13% of therapy deliveries at one-year follow-up in patients having had S-ICD implantation (144, 145, 150). In the majority of these cases, the inappropriate therapies were due to sensing algorithm failure rather than mechanical factors, such as subcutaneous lead displacement (145). The recently published EFFORTLESS S-ICD registry of 472 patients with follow-up at 558 days, reported a 360-day inappropriate shock rate of 7% with the vast majority occurring due to T-wave oversensing of cardiac signals (237). We speculate that the relatively low specificity of the screening tool may have allowed patients with ECGs that were not appropriate for the S-ICD to have received the device; resulting in inappropriate sensing and therapies.

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

7.5 LIMITATIONS

Our study has several limitations. Firstly, the sample sizes are small, due to limited resources, time constraints, and the relative difficulty of finding appropriate patients, having the relevant structural cardiac defects, for inclusion in the four categories. However, all data were collected by a single investigator to reduce variation, and furthermore, the sample size for the

current study was selected to mimic preclinical drug safety studies (239). Secondly, since ECGs were collected from individuals in sinus rhythm at rest, there is the possibility of variation in the morphologies of ECGs during exercise and arrhythmia. However, in this study, the Boston Scientific S-ICD pre-implant screening method was followed, which recommends collection and analysis of resting surface ECGs. More recently, screening is also performed on ECGs acquired during exercise (153). Considering the patient population who are likely to receive an ICD, the congenital heart disease cohort sampled was limited to three groups – Tetralogy of Fallot, transposition of the great arteries and single ventricle physiology. However, these conditions represent the most complex congenital structural abnormalities (117). Although such defects are rare, they do represent patients who have a high burden of ventricular arrhythmias and the risk of sudden death (117). Also, the number of complex C-CHD patients attached to any single centre is small and therefore difficult to recruit. Compounding factors were reduced by recruiting 10 near age and sex matched subjects from normal control, TOF, TGA and SVP patients.

7.6 CONCLUSIONS

The screening tool plays a vital role in the selection of appropriate candidates for S-ICD implantation. In this study, the screening tool proved to be highly sensitive in identifying S-ICD patients without CHD and would satisfy the requirements of the detection algorithms, but it was too non-specific in that it also selected patients who would not. Additionally, the screening tool is significantly less sensitive in patients with CHD. We propose the use of a device with a real-time sensing algorithm for screening purposes that would

allow testing of the potential sense vector through the virtual sensing algorithm in patients considered for S-ICD and so permit a more rigorous assessment of patient suitability; with the aim of reducing inappropriate shock therapies.

CHAPTER 8

DISCUSSION AND FUTURE RESEARCH

8 GENERAL DISCUSSION AND FUTURE RESEARCH

8.1 DISCUSSION BSM DELTA MAP STUDIES

8.1.1 Principle findings:

- These studies have successfully confirmed the feasibility of using novel BSM Delta map in the patients with unstable IHD presenting to ED with acute MI and in patients requiring out patients investigation for the screening and diagnosis of stable IHD.
- These studies have demonstrated excellent sensitivity and specificity of the novel BSM Delta map for the diagnosis of ACS and stable angina using the current standard diagnostic tools as a reference standard.
- These studies have successfully validated the application of the various thresholds for the ST shift as a marker of TRMI, making the result more accurate, rapid and easy to interpret.
- These studies have successfully validated the application of new protocols for the Interpretation of BSM Delta map.
- These studies have successfully validated the novel concept of ischaemic burden (IB), which is a numerical description of the extent of myocardial ischaemia.

8.1.2 Detail discussion BSM Delta map studies

These studies have successfully demonstrated the feasibility of using BSM Delta map in two different clinical settings with excellent results for identifying TRMI in patients with acute chest pain and also in patients with stable chest pains. BSM Delta map has superior sensitivity and specificity in comparison to standard 12 lead ECG for the diagnosis of both stable and unstable IHD. BSM Delta map technique is a more intuitive form of the BSM and makes the assessment of IHD easier and rapid, with a minimal training requirement. However, the potential of BSM Delta map for clinical use needs to be explored with further larger studies.

8.1.2.1 Future research, possible study models for BSM Delta map

Bossuyt and colleagues have proposed a framework for new test evaluation that may help guide future research of BSM Delta map (252). This framework divides the new diagnostic tests into the following three categories:

- Potential replacement.
- Triage test.
- Add-on tests.

BSM Delta map can be a replacement test for ETT in the diagnosis of TRMI in patients with a history of suspected stable angina and ACS in ED instead of 12 lead ECG. Bossuyt argues that in order to determine if a new test can replace an existing one, the diagnostic accuracy of both tests need to be compared in the same patient sample since the sensitivity and specificity of a test can vary

across subgroups. Furthermore, the new tests should be compared to existing tests using the same reference standard. The paired test evaluation that is used to determine performance characteristics has advantages over a randomised controlled trial (RCT) design, including a requirement of fewer subjects than an RCT and allowing head-to-head comparison. I adopted this method in the above pilot and feasibilities studies; however, these findings need to be confirmed with larger studies, according to appropriate sample size calculation, which is now possible with the results from above studies.

In our studies, BSM Delta map demonstrated higher sensitivity than the standard 12-lead ECG. This suggests that BSM Delta map could potentially serve to complement the findings from the standard 12-lead ECGs as “add-on” tests. Add-on tests can be used in the subgroup of patients where diagnosis needs clarification. For example, BSM Delta map could be used as an add-on test to further evaluate a patient who presents with cardiac sounding chest pain and normal ECG. This may help clarify whether or not such a patient is having chest pain due to cardiac aetiologies that are undetected by the 12-lead ECG. Further studies to evaluate BSM Delta map as an add-on test are attractive because this would allow calculating the number of extra patients with cardiac chest pain missed on the standard 12-lead ECG. However, this design would not account for the standard 12 lead ECG false positives and the BSM Delta map false negative. Therefore, the add-on test strategy can potentially increase the sensitivity of the existing testing standards, but possibly at the expense of specificity.

8.1.2.2 Observational (before and after) study

The BSM Delta map can be implemented into clinical practice. An observational study design would show the change in the way that patients with chest pain are treated in the department and observe their eventual disposition. Such a stud y would require a comparison with a period before the implementation of the BSM unit. The earlier period would serve as a reference period.

The principle outcome measures in such a study would be a change in the number of patients identified as having myocardial disease +/- infarction.

The advantages of observational studies are that they are easy to conduct and it is possible to see how patterns of care and clinical care change with the introduction of new technologies.

The potential biases include, difficulty to account for the passage of time between the two observed periods and with this design there is a risk of misclassification. Additionally, patients in the two groups may differ in their baseline characteristics thereby affecting the results.

8.1.2.3 Randomised controlled trial

Randomised controlled trial has been suggested as an appropriate method for the evaluation of diagnostic tests (253, 254). This design would allocate patients randomly into two different groups, one group treated in the usual manner and another group treated with the addition of the BSM Delta map information. Such a study could yield information on the clinical benefits of BSM Delta map. Outcomes could be expressed in terms of patient outcomes

(e.g., mortality) or proxy measures such as time to intervention, or final diagnosis).

The randomised controlled design can only be considered if the ability of the diagnostic intervention is known to be accurate at identifying the target condition. In addition, the use of a diagnostic test in an RCT trial within a department may lead to biased results due to the Hawthorne effect (increasing staff awareness of ECG criteria outside the 12 lead ECG may result in additional leads being taken on patients not enrolled in the BSM study arm).

The impact of BSM Delta map on the diagnostic decision-making or patient outcomes can be evaluated by RCTs. Depending on the specific question, a number of trial designs could be considered, including a clinical trial of test positive patients, with clinicians randomised to disclosure of test results. Another alternative would be a trial that randomises patients to a test strategy that uses conventional testing versus a test strategy that uses BSM Delta map. Finally, another but less direct approach would be to link evidence on test performance to evidence to the effects of interventions (e.g., antianginals or PCI) in the population of interest. The United States Preventive Services Task Force for evaluation of screening tests sometimes employs this final example. This less direct approach is more subject to bias due to the underlying assumptions that are inherent in creating these linkages.

The advantages of RCTs include the ability to investigate both groups together. It allows direct comparisons between groups, and the effect of additional information gained is easy to see.

The potential biases include spill over of information to the non-BSM group (i.e., if additional MIs found on the BSM group this will raise awareness of potential misses in other group leading to change in behaviour).

Broad patient selection would require stratified randomisation. The accuracy of BSM Delta map needs to be established with appropriate investigations before RCT to avoid unnecessary invasive investigations.

8.1.2.4 Diagnostic cohort study

When the purpose of the study is to determine the ability of the new diagnostic test to identify the target disorder accurately the RCT, and observational studies are not indicated. A better design is to use a paired diagnostic test study to measure the ability of the new diagnostic intervention to identify the target disorder.

The outcome of such a study is to quantify the sensitivity and specificity of the new diagnostic intervention.

A classical diagnostic test study follows a cohort of patients from presentation to a gold standard diagnosis. The new diagnostic test is evaluated by comparison with its ability to match the gold standard diagnosis. In this way, we can be certain that the ability of the test is not affected by differences in the baseline groups (unlike the observational or RCT designs).

The advantages of this model include, (I) blinded comparison against the gold standard, (ii) no changes are required in the clinical practice, (iii) the possibility of a focused design to quantify the performance of the diagnostic test.

The potential biases include, (i) inability to test the effect of the findings on patient care, (ii) the results are limited to "can it diagnose" rather than "what use is the additional information," (iii) this design does not account for the superiority of the new test.

Both the randomised controlled trial and diagnostic cohort designs can be considered for further evaluation of BSM Delta map. However, a well-conducted diagnostic cohort is most likely to reduce bias to a minimum and achieve the study aim. Now with the results of our studies, it is possible to conduct a diagnostic cohort study with an appropriate number of patients by calculating study power. This cohort study can be followed by RCT and outcomes could be expressed in terms of patient outcomes (e.g., mortality) or proxy measures such as time to intervention, or final diagnosis).

8.2 DISCUSSION OF S-ICD SENSING STUDIES

8.2.1 Principle findings:

- These studies have successfully demonstrated that the individuals with C-CHDs fulfill the screening criteria for the S-ICD implant.
- These studies have successfully confirmed the effect of posture, cardiac morphologies, electrodes location and gender on the surface ECG parameters of S-ICD sensing algorithm. These studies showed that the amplitude of the R wave varies with posture and sensing electrode position, the amplitude of the T wave varies with cardiac morphology, and the QRS duration varies with gender and cardiac morphology. These variations are likely to have important implications in relation to the sensing ability of monitoring devices. Therefore, care is required when selecting patients for S-ICD as R waves and T waves are dynamic, and changes may affect the sensing quality by the S-ICD.
- These studies showed no significant impact of posture, cardiac morphology, sensing electrode position and gender on the surface ECG's markers of ventricular arrhythmias such as R/T ratio, QTc interval, Tpeak-end duration. Therefore, it would be feasible to develop an algorithm for S-ICD in order to raise a pre-alert to ventricular tachyarrhythmia based on surface ECG markers of malignant arrhythmias (QTc and Tpeak-end duration).
- These studies successfully showed that although the screening tool is highly sensitive in identifying S-ICD patients without CHD and would satisfy

the requirements of the detection algorithms; however, it was too non-specific in that it also selected patients who would not. Additionally, the screening tool is significantly less sensitive in patients with CHD.

- Based on these studies, I proposed a device with a real-time sensing algorithm for screening purposes. Such a device would allow testing of the potential sense vector through the virtual sensing algorithm in patients considered for S-ICD to permit a more rigorous assessment of patient suitability. This would reduce inappropriate shock therapies. This led to the development of such a device and is currently in clinical use.
- In these studies, Lead III, which represents S-ICD primary sensing vector, demonstrated less variation with changes in posture. Lead III is derived from two electrodes, one placed at the left lower sternal edge, 1cm left lateral to *manubrium sterni* and the second one at the S-ICD generator at the mid-axillary line in the fifth and sixth intercostal space. Therefore, anatomically, this lead is derived from two electrodes, which are placed horizontally on the body. In terms of S-ICD sensing vectors, this means that sensing vectors horizontal on the thorax are less likely to suffer changes from postural variation. This finding can be further exploited by placement of electrodes at various angles to derive multiple vectors at several angles to determine the optimal placement of the sensing electrode that would suffer less variation with changes in the posture.

8.2.2 Detail discussion S-ICD studies

These studies have laid a foundation for further improvement in the sensing configurations of S-ICD and have provided insight into the factors that have an impact on current sensing algorithms, potentially causing sensing failure. These studies have provided a platform for improved methods for patient selection through a screening device with sensing algorithm leading to the development of a new screening device and development of a better sensing vectors designs and leads with multiple vectors.

These studies have demonstrated the feasibility of further investigation and development of S-ICD sensing algorithm through non-invasive body surface mapping and virtual sensing algorithm programs.

8.2.2.1 S-ICD and patients with congenital heart disease

The study of potential eligibility of CHD for S-ICD using the pre-implant screening criteria showed no significant differences in the suitability of CHD patients in comparison to individuals with a structurally normal heart, using both six and two postures criteria (Section 8.2).

Using the pre-implant screening criteria, the analysis of drop out rate for S-ICD based on six postures demonstrated 10% of subjects with structurally normal hearts, 20% of patients with TOF, 10% of patients with TGA, and 20% of patients with SVP (All p=>0.05), were not suitable for S-ICD sensing and implant. At two postures 0% of patients with structurally normal hearts, 20% of

patients with TOF, 0% of patients with TGA, and 20% of patients with SVP were not suitable for S-ICD sensing and implant (All p=>0.05). (Section 8.2)

8.2.2.2 Surface electrocardiogram signals variation with posture

The study of surface electrocardiogram signals variation with posture in normal adults and in adults with congenital heart disease showed variation in the R-wave amplitude in postures as shown in Figure 38. The postural variation was significant only between left lateral and right lateral postures. However, it is possible that variation that is statistically insignificant may also have an impact on the sensing algorithm because even slight variation in the borderline cases would affect the sensing ability of S-ICD. Therefore, to avoid inappropriate sensing, we suggest that every patient is screened in six postures with the method described below. There were no statistically significant variations in the mean T-wave amplitude, R/T ratio, QTc interval, Tpeak-end duration in six postures.

8.2.2.3 Cardiac morphologies and surface ECG signals

The assessment of CHD patients in comparison to individuals with normal cardiac morphologies showed no significant difference in the R-wave amplitude and the variation with posture change. However, the mean T-wave amplitude in individuals with TOF was significantly greater than individuals with normal cardiac morphology (p=0.013) and SVP (p=0.005). The mean QRS duration in individuals with normal cardiac morphology was significantly smaller than

individuals with TOF (p=0.0001) and SVP (p=0.006). There were no statistically significant differences in the mean R/T ratio, QTc interval, and Tpeak-end duration between individuals with CHD and normal heart morphology (All p>0.05).

8.2.2.4 Surface ECG signals and electrodes position on thorax

The analysis of differences of sensing parameters in the three leads (Lead I, Lead II, and Lead III) showed that the mean R-wave amplitude was significantly smaller in Lead I than Lead III (p=0.025). However, there was no significant difference between Lead I and Lead II (p=>0.05). There were no statistically significant differences in the mean T-wave amplitude, R/T ratio, QTc interval, Tpeak-end duration between the three leads (p>0.05).

Lead III, which is considered a primary sensing vector for S-ICD demonstrated less variation with changes in posture. One possible explanation for this could be that Lead III is derived from two bipolar electrodes, one placed at the left lower sternal edge, 1cm left lateral to manubrium sterni and the second one at the S-ICD generator at the mid axillary line in the 5th and sixth intercostal place. Therefore geographically this lead has relatively horizontal course, which means that the sensing lead horizontal on the thorax is less likely to suffer changes from postural variation. This finding can be further exploited by designing multiple vectors at several angles to determine the optimal placement of the sensing electrode (arrays) (Section 9.4).

8.2.2.5 Screening tool sensitivity and specificity

The study on screening tool sensitivity and specificity showed that the screening tool sensitivity was 86% (95% CI. 81%, 90%), specificity was 79% (95% CI. 74%, 82%), positive predictive value was 73% (95% CI. 68%, 77%) and negative predictive value was 89% (95% CI. 86%, 92%) in all patients. The sensitivity of the screening tool was excellent in individuals with normal cardiac morphology, however this was significantly lower in individuals with CHD in comparison to individuals with normal heart morphology ($p < 0.05$) (TOF $p=0.001$, TGA $p=0.03$, SVP $p=0.002$), and in Lead I in comparison to primary Lead III ($p=0.004$). However there was no significant difference in Lead II in comparison to Lead III, and six postures in comparison to supine posture (all $p>0.05$). The screening tool displayed high sensitivity but comparatively lower specificity across all the study groups, leads, and postures. Therefore screening tool effectively identifies suitable patients for S-ICD implantation (true positive) but is also liable to be deemed unsuitable for patients as suitable (high false positives), which could explain the high incidence of inappropriate shocks reported in the literature. Therefore we propose a device with the S-ICD sensing algorithm as a pre-implant screening tool, to reduce false exclusion and selection and hence possible inappropriate shocks.

8.2.2.6 Screening at two and six postures

This study showed more patients suitable at two postures in comparison to six postures, although this difference was not statistically significant. However, at the same time we have observed variations in the R-wave amplitude with

postural changes, and additionally, keeping in mind the higher rate of inappropriate shocks, we would propose screening at six postures.

8.2.3 S-ICD sensing and future research

These studies have provided greater insight into the S-ICD sensing algorithm. On the basis of lessons learned from these studies future research can be undertaken into the following areas:

8.2.3.1 Studies on a larger cohort of patients

Similar studies can be undertaken on a larger number of populations for reconfirmation of these findings.

8.2.3.2 Vectors design

The findings of these studies can be used to design sensing vectors with minimal interference from postural changes. For example in this study Lead III, which is considered a primary sensing vector for S-ICD demonstrated less variation with changes in posture. Therefore, this finding can be further exploited by designing multiple vectors at several angles to determine the optimal placement of the sensing electrode (arrays).

8.2.3.3 Lead design and the use of more than three sensing vectors

This study has demonstrated that there is significant variation in the ECG morphologies depending on the sensing vectors bipolar electrode position on the thorax. In future studies, leads with multiple sensing electrodes can be designed to have a more robust system of rhythm discrimination. The templates from these vectors can be saved to the device and in the case of abnormal rhythm detection; the device would have the ability to confirm the findings through several rapid checks through each one of these vectors channels before deployment of therapy, which will reduce the chances of delivering inappropriate shocks.

8.2.3.4 Development of algorithms for detection of ECG markers of arrhythmias

VT storm is a major problem; patients usually suffer multiple distressing shocks, which requires hospital admission and pharmacological modification of arrhythmogenesis, which is successful in most of the cases and a minority of patients may require VT ablation. However, with developing multiple sensing arrays the S-ICD sensing algorithm can be armed with ability to predict arrhythmia development before its onset through virtue of known markers of life threatening arrhythmias, e.g., QTc duration, QT peak-end dispersion, and QRS duration and as our studies demonstrated there was no significant effect of posture change, cardiac morphologies and electrode positions on these parameters.

8.2.3.5 Proposal for changing screening method

Recent clinical studies have reported 13% inappropriate therapies during one-year follow-up of patients who had S-ICD implantation (144, 145, 150). Although in a small number of patients the inappropriate shocks were due to mechanical reasons, like subcutaneous lead displacement. However, in the majority of the cases, the inappropriate therapies were due to sensing algorithm failure (145). Therefore, it would not be unreasonable to speculate upon the contribution of the low specificity of the screening tool to the failure of S-ICD sensing ability.

Based on these studies, as published in the literature (255), I propose the use of a device with sensing algorithm for screening purposes that led to the development of such a device, which is currently in the clinical use.

APPENDICES

APPENDIX 1: ED STUDY PATIENT INFORMATION SHEET AND CONSENT FORM

PATIENT INFORMATION SHEET

Cardiothoracic Directorate

Department of Cardiology E Level,

East Wing, Mail point 46

Southampton General Hospital

Tremona Road Southampton

SO16 6YD

Study Title: An Investigation into the ability of the PRIME® ECG body surface mapping system to detect transient regional myocardial ischaemia using a novel colour map display

Lay Title: The use of a novel ECG device to detect restrictions in the blood supply to heart muscle

Dear Sir/Madam,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part

PART 1

What is the purpose of the study?

We are interested in studying a type of ECG machine called PRIME® ECG to investigate restrictions in the blood supply to the heart muscle (coronary artery disease). Currently, when patients are being investigated for chest pain, an electrical recording of the heart called an ECG is performed. When chest pain occurs due to restrictions in heart muscle blood supply, this is often reflected in changes that can be seen on this electrical tracing.

The conventional ECG machine has a number of limitations, which means in some cases it is unable to pick up problems relating to heart muscle blood supply. PRIME® ECG uses an 80-electrode “vest” that records electrical information from the heart. By covering a greater proportion of the chest and back, it gathers information over a wider distribution than the conventional ECG. Furthermore, this information is displayed in a different way. Instead of electrical waveforms printed on a strip of paper as with the conventional ECG, the new device displays the electrical signals as a colour map projected on to a diagram of a torso. The areas of colour correspond to areas with impaired blood supply in the heart.

Our study is designed to look at patients presenting to hospital with chest pain of unknown cause. We want to see if this device can provide diagnostic information about whether the cause of the chest pain is due to impairment in

heart muscle blood supply (myocardial ischaemia) or not. If this device is able to help distinguish cardiac from non-cardiac chest pain, it may represent an additional useful tool in the management of patients presenting to hospital with chest pain.

Why have I been chosen?

You have come to hospital because of chest pain and will be undergoing investigations to try and elucidate the cause of your pain to allow it's effective treatment. It is possible that your chest pain could be caused by problems with your heart muscle blood supply and this needs to be investigated. All such patients presenting to A&E at Southampton are eligible to help with this study.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

When you arrive at hospital with your chest pain, you will have a conventional ECG performed as part of your routine investigation. In addition, we will perform an extra PRIME® ECG recording.

In order to do this, we will fix a series of sticky recording electrode strips to your chest and back, in much the same way that the conventional 12 lead electrodes are attached. We can record electrical data at the push of a button

on the PRIME® ECG recording console. The normal treatment of your chest pain will not be affected in any way by undergoing a PRIME® ECG recording.

Once your chest pain has resolved completely, a second PRIME® ECG recording will be obtained. The recording electrodes will then be removed.

Sometimes your pain will have settled by the time you get to hospital. If that is the case, we would still perform a PRIME® ECG recording while you are pain free, and only perform a second recording in the event of you developing further chest pain. It does not matter in which order the recordings are performed, as long as we have 2 recordings to compare – one when you have chest pain and one when you are pain free. A comparison of the "in-pain" and "pain-free" recordings may provide important diagnostic information about the likelihood of your pain being cardiac in origin. You're on going investigation and management will not in any way be affected by taking part in the study.

What are the other possible disadvantages and risks, and what are the possible benefits of taking part?

There are no disadvantages or risks to you and similarly no possible benefits to you as a result of this study, but we do believe that the results may help us develop a better way of diagnosing coronary artery disease in patients similar to you in the future.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2

Will my taking part in the study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2

Contact for further information: Dr Mehmood Zeb Clinical Cardiology Research Fellow and Dr Nick Curzen, Consultant Cardiologist 023 8079 4972

This completes Part 1 of the Information Sheet. If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

PART 2

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time, but we will need to use any data collected up to the time of your withdrawal. It is important to note that your normal treatment is not affected in any way by the taking part or withdrawal from this study.

Complaints

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. They can be contacted via the Clinical trials Unit. The contact person is: Sue Kitt (0)23 8079 8538, email sue.kitt@suht.swest.nhs.uk

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Harm

In the unlikely event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against Southampton University Hospitals NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

Involvement of your General Practitioner

Your GP will not be informed about your involvement with the study. As involvement with the study does not alter your normal treatment in any way, your GP will not be required to take any action as a result of your participation.

What will happen to the results of the research study?

Results of the study will be published in peer-reviewed medical journals. You will not be identified in any report or publication.

Who is organising and funding the research?

This research is being organised by the Coronary Research Group in association with The Wellcome Trust Clinical Research Facility. The researchers are not being paid for including you in the study. Heartscape Ltd is providing the PRIME® ECG hardware for the purposes of the research study. Charitable grants have been applied for to help with the running costs and costs of consumables used during the study.

Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by the Southampton and South West Hampshire Research Ethics Committee

Thank you for considering taking part and for taking the time to read this sheet.

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: An Investigation into the ability of the PRIME® ECG body surface mapping system to detect transient regional myocardial ischaemia using a novel colour map display

Please initial box

1. I confirm that I have read and understand the information sheet (Version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

_____ _____ _____

Name of Patient Date Signature

_____ _____ _____

Name of Person taking consent Date Signature

_____ _____ _____

Researcher Date Signature

PRIME® ECG study: patient consent

Version 2, REC reference number: 06/Q1702/49

1 copy for patient; 1 for researcher; 1 for hospital notes

PRIME® ECG ED study form

Study number:

Date of study:

Demographic Data

Name:

Hospital Number:

Sex:

Date of Birth:

Occupation:

Indication For Referral:

CHEST PAIN? Y N

Location:

Time of Onset:

Precipitants:

Relievers:

Severity:

Past Medical History:

Hypertension: Diabetes:

Heart Disease:

Asthma: COPD: Hypercholesterolaemia:

Smoker:

Alcohol:

Exercise Habits:

Family History:

Drug History:

Allergies:

List of medications currently being taken:

Previous Cardiac Investigations:

Date:

Findings:

On Examination:

GENERAL:

Pale

Cold

Clammy

Sweaty

Nausea

Vomiting

Height:

Weight:

Calculated BMI:

Waist:

Hip:

WHR:

ECG Findings:

PRIME®:

Nitrates given: Yes / No

Time of Pain Free Study:

Study done by:

Time of Pain Study:

Study done by:

Blood Tests:

Troponin:

Lipid Profile:

Angiographic Findings

Date:

Operator:

Findings:

Analysis

Date:

Performed by:

In Pain Analysis:

Without pain Analysis:

APPENDIX 2: PRIME® NUCLEAR MEDICINE STUDY PATIENT INFORMATION SHEET AND CONSENT FORM

PATIENT INFORMATION SHEET

Study title: An Investigation into the ability of the PRIME® ECG body surface mapping system to detect transient regional myocardial ischaemia using a novel colour map display

Lay title: The use of a novel ECG device to detect restrictions in the blood supply to heart muscle

Dear Sir/Madam,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part

PART 1

What is the purpose of the study?

We are interested in studying a type of ECG machine called PRIME® ECG to investigate restrictions in the blood supply to the heart muscle (coronary artery disease). Currently, when patients are being investigated for chest pain, an electrical recording of the heart called an ECG is performed. When chest pain occurs due to restrictions in heart muscle blood supply, this is often reflected in changes that can be seen on this electrical tracing.

The conventional ECG machine has a number of limitations, which means in some cases it is unable to pick up problems relating to heart muscle blood supply. PRIME® ECG uses an 80-electrode “vest” that records electrical information from the heart. By covering a greater proportion of the chest and back, it gathers information over a wider distribution than the conventional ECG. Furthermore, this information is displayed in a different way. Instead of electrical waveforms printed on a strip of paper as with the conventional ECG, the new device displays the electrical signals as a colour map projected on to a diagram of a torso. The areas of colour correspond to areas with impaired blood supply in the heart.

It may be that the extra information collected by this device coupled with this novel method of displaying it, leads to improved diagnostic accuracy and a more intuitive way of visualising the problem. Our study is designed to test this device against currently used investigations for coronary artery disease, including cardiac perfusion scanning, to see whether or not this it is able to reliably detect problems with heart muscle blood supply. If so, it could lead to the widespread use of this device in the diagnosis of coronary artery disease.

Why have I been chosen?

You have been referred to the hospital for further assessment and investigation of symptoms that may relate to coronary artery disease. All such patients at Southampton are eligible to help with this study.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

As part of your routine cardiac perfusion scan, you will have a conventional 12 lead ECG test done. After this is completed, we would apply the PRIME® ECG electrodes and do a baseline PRIME® rest study. In order to do the PRIME® ECG recordings we will fix a series of sticky recording electrode strips to your chest and back in much the same way as the conventional ECG electrodes are attached. We can record electrical data at the push of a button on the PRIME® ECG recording console. As is usual with the cardiac perfusion scanning, you will then be given an infusion of a drug through a drip in your arm to make the heart beat faster and work harder to mimic exercise or stress. This infusion takes nine to twelve minutes to be administered and during this time we would take a PRIME® ECG recording midway and again at the end of the infusion. This in no way affects the cardiac perfusion scans which are done one hour after

the infusion is given. Once we have completed the PRIME® ECG recording at the end of the infusion, the recording electrodes will be removed.

Any further investigations and treatment will be determined in the normal way by the doctor reviewing you in the clinic, in conjunction with your cardiac perfusion scan results. Your treatment will not be affected in any way by the results of the PRIME® ECG test. There will be no extra follow-up visits as a result of taking part in this study.

What are the other possible disadvantages and risks, and what are the possible benefits of taking part?

We will not be changing the usual protocol for cardiac perfusion scanning so there are no disadvantages or additional risks to you. Similarly, there are no possible benefits to you as a result of this study, but we do believe that the results may help us develop a better way of diagnosing coronary artery disease in patients similar to you in the future.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2

Will my taking part in the study be kept confidential?

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PART 2

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Complaints

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. They can be contacted via the Clinical trials Unit. The contact person is: Sue Kitt (0)23 8079 8538, email sue.kitt@suht.swest.nhs.uk

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Involvement of your General Practitioner

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What will happen to the results of the research study?

Results of the study will be published in peer-reviewed medical journals. You will not be identified in any report or publication.

Who is organising and funding the research?

This research is being organised by the Coronary Research Group in association with The Wellcome Trust Clinical Research Facility. The researchers are not being paid for including you in the study. The PRIME® ECG hardware is being provided by Heartscape Ltd. for the purposes of the research study. Charitable grants have been applied for to help with the running costs and costs of consumables used during the study.

Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by the Southampton and South West Hampshire Research Ethics Committee

Thank you for considering taking part and for taking the time to read this sheet.

Study Arm:

Patient Identification Number for this trial:

CONSENT FORM

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Please initial box

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3. I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

_____ _____ _____

Name of Patient Date Signature

_____ _____ _____

Name of Person taking consent Date Signature

(if different from researcher)

_____ _____ _____

Researcher Date Signature

PRIME® ECG study: patient consent

Version 2, REC reference number: 06/Q1702/49

1 copy for patient; 1 for researcher; 1 for hospital notes

Nuclear Medicine Heart Scan
Preparation Required before your Stress Appointment

PATIENT NAME

STRESS APPOINTMENT DATE

Medication checked by

Before your Stress appointment it is very important that you do the following:

1. DO NOT TAKE THESE MEDICATIONS FOR 24 HOURS BEFORE YOUR STRESS TEST (ie after)

   Take all your other medication as usual.

2. YOU MUST BRING YOUR INHALERS WITH YOU

3. DO NOT HAVE ANY CAFFEINE FOR 24 HOURS BEFORE YOUR STRESS TEST (ie after)

   This includes tea, coffee, green tea, hot chocolate, coke, red bull and most decaffinated products.

   Some flu and cold preparations contain caffeine.

   You may drink lemonade, squash, milk, horlicks, herbal and fruit infusions, red bush tea as well as water.

   You should eat as normal.

If you have any queries later, please contact the department on 02380 796627

Feb '11

For staff use only

PHARMACOLOGICAL STRESS TEST

NAME: DOB NUC MED NO:

WEIGHT:

ASTHMA: YES / NO

MEDICATION TO STOP: DRUGS CHKD BY

? MEDICATION STOPPED CAFFEINE STOPPED:

STRESS DRUG ADMINISTERED

BATCH NO: CHECKED:

SYMPTOMS DURING TEST:

ECG CHANGES:

MINUTES TO RECOVERY:

TIME	0'					
STAGE	0	1	2	3	4	RECOVERY
BP						
HR						

TOTAL DOSE ADMINISTERED: OVER: MINS

STRESSED BY: DATE

PRIME® Nuclear Medicine Screening Form

Patient PRIME® Number:

Date of consent:

Date of study:

Demographic Data

Name:

Hospital Number:

Sex:

Date of Birth:

Occupation:

Indication For Referral:

CHEST PAIN? Y N

Location:

Time of Onset:

Precipitants:

Relievers:

Severity:

Past Medical History:

Hypertension: Diabetes:

Heart Disease:

Asthma: COPD: Hypercholesterolaemia:

Smoker:

Alcohol:

Exercise Habits:

Family History:

Drug History:

Allergies:

List of medications currently being taken:

Previous Cardiac Investigations:

Date:

Findings:

On Examination:

GENERAL:

- Pale
- Cold
- Clammy
- Sweaty
- Nausea
- Vomiting

Height:

Weight:

Calculated BMI:

Waist:

Hip:

WHR:

ECG Findings:

PRIME®:

Study Time	**Time from start of Infusion**	**Study done by**	**HR**	**BP**
Pre-infusion	N/A	MRR		

Target HR:

Dobutamine infusion stopped at:

Radioactive dye injected at:

Blood Tests:

Troponin:

Lipid Profile:

Nuclear Medicine Findings:

Angiographic Findings

Date:

Operator:

Findings:

Appendix 3: Collection of Surface Electrocardiogram (ECG) for assessment of potential configurations of Subcutaneous Defibrillators

Southampton University Hospitals NHS Trust

EP Research Office, Mail point 46

Southampton General Hospital

Tremona Road Southampton

SO16 6YD

023 8079 8487

Patient Information Sheet

Study title: Collection of Surface Electrocardiogram (ECG) for assessment of potential configurations of Subcutaneous Defibrillators

Lay title: EGG collection to assess subcutaneous defibrillator configurations

Dear Sir/Madam

You are being invited to take part in a study. Before you decide to be a voluntary participant it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.

- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

Part 1

WHAT IS THE PURPOSE OF THE STUDY?

ICDs (Implantable Cardioverter Defibrillators) are electronic devices, which are implanted to detect and treat potentially life threatening abnormal heart rhythms. Conventionally these require leads, which go into the heart to detect and-treat the heart rhythm.

Device companies are currently developing systems, which will avoid the use of the leads to the heart, using a fully subcutaneous (under the skin) system instead. The aim is to simplify the implant procedure and lower the complications associated with a traditional device. There are broad ranges of potential configurations of a subcutaneous system, with multiple electrodes placed around the chest to detect the heart rhythm. To date there have not been any studies assessing the detection function of such systems, particularly in the Congenital Heart Disease population, which is a target population for these devices. This study is looking at the detection of the heart rhythm from different positions on the chest. An understanding of electrogram characteristics (which reflect electrical activity of the heart) from a variety of patients will result in useful information to identify issues in choosing a

set up for the electrode configuration to allow detection of different heart rhythms. This study is being performed as part of a thesis for a Doctorate in Medicine addressing this key aspect of subcutaneous defibrillation devices.

WHY HAVE I BEEN CHOSEN?

You have been invited to take part as you are a patient being assessed under the cardiothoracic directorate. We are looking to collect ECGs (electrocardiograms) from a broad spectrum of heart disease, so as to reflect the range of signals that a device would have to interpret in order to function appropriately. This study will include approximately 100 patients at this hospital.

DO I HAVE TO TAKE PART?

It is up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. If you decide to take part you are free to withdraw at any time without giving a reason. This would not affect the standard of care you receive

WHAT WILL HAPPEN TO ME IF I TAKE PART?

You will be participating in the research for the time it takes to collect the additional electrocardiograms for the study (approximately 10 minutes), with no need for additional visits for this research. Information will be collected from your notes about previous history and any diagnoses and review of heart imaging. We would also collect information on your height / weight which would be taken as routine during both out and in-patient attendances. The study requires attaching multiple skin electrodes in order to collect electrocardiograms, which we will aim to do whilst

you are having your routine investigations. This data will be analysed further using a computer. No further monitoring or follow-up is required.

WHAT WILL I HAVE TO DO?

You will have to be prepared to have short-term adhesive skin electrodes attached, sometimes requiring preparation of the skin in the form of shaving. This will allow for collection of representative heart tracings. This will require additional time (approximately 10 minutes) and will not affect your management.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS, AND WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

There are no disadvantages or risks to you beyond the extra time taken to collect the data, as your care will be the same whether you choose to participate or not. Similarly, there are no direct benefits from participating in this study but the results may help in establishing the challenges for heart rhythm detection with this new developing technology.

CONTACT FOR FURTHER INFORMATION

Please discuss with your doctor any questions or concerns you may have regarding your rights as a research subject, research-related injury, and general questions or concerns pertaining to your participation in this clinical study. If you have any question, please contact Professor John Morgan, Cardio-thoracic Centre, E Level, Mail point 46, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD. Tel: 023 8079 8487

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

WHAT IF THERE IS A PROBLEM?

If you have a concern about any aspect of this study, you should ask to speak with the researcher who will do their best to answer your questions, Professor Morgan Tel 023 8079 8487.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure, details of which can be obtained from the hospital.

In the unlikely event that something goes wrong and you are harmed during the research study and this is due to someone's negligence, you may have grounds for a legal action for compensation against Southampton University Hospitals NHS Trust, but you may have to pay your legal costs. Agreeing to participate in this study and signing the consent form does not take away any of your legal rights.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

All information, which is collected, about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed, so that you cannot be recognised from it.

Individuals from regulatory authorities may also inspect the quality of data collected in this study, requiring access to the relevant sections of your medical notes.

INVOLVEMENT OF YOUR GENERAL PRACTITIONER (GP)

Your GP will not be informed about your participation in this study. This because involvement does not alter your normal treatment in any way and your GP will not be required to take any action.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

After the study is completed, all results will be examined and a report may be published in a medical journal. You will not be identified in any report or publication.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

This research is being organised by Professor Morgan. He is not paid for including you in the study.

WHO HAS REVIEWED THE STUDY?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Southampton & South West Hampshire NHS Research Ethics Committee and the hospital's Research & Development department.

Thank you for taking the time to read this information sheet. You will be given a copy of it (3 pages) and a copy of the consent form (1 page) to keep. It is suggested that you retain these documents for your reference and personal record.

CONSENT FORM

ECG collection to assess subcutaneous defibrillator configurations

Please initial box

1. I confirm that I have read and understand the information sheet (version 1.2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

Print Name of Patient (Surname/First Name) Date (DD/MM/YY)

Signature

Print Investigator Name Date (DD/MM/YY)

Signature

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