Electrocardiographic Monitoring of Myocardial Ischaemia – Novel Methods and Potential Application in Implanted Devices

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Abstract

Implanted devices are well established for the treatment of bradyarrhythmias and life threatening ventricular tachyarrhythmias. A significant proportion of these patients receiving device therapy suffers with coronary artery disease, or has had previous myocardial infarction. With the option to effectively treat these arrhythmias, progression of the underlying heart disease becomes the prime determinant of the patient's prognosis. Multilead bipolar configurations presently available in implanted devices offer a potential source for monitoring myocardial ischaemia.

The major objective of this thesis was to investigate whether myocardial ischaemia can be reliably detected from intracardiac electrograms (EGMs) that are potentially available in implanted devices such as pacemakers and implantable cardioverter defibrillators. It also investigated whether novel parameters of repolarisation (T wave morphology descriptors) can be used as indices to monitor myocardial ischaemia.

The first study investigated the optimal unipole for monitoring myocardial ischaemia (induced by balloon inflation during angioplasty) from a quadripolar intracardiac electrode placed within the right ventricle. This study showed that EGM recordings obtained from unipoles near the distal tip of the electrode are less sensitive in detecting myocardial ischaemia when compared to recordings obtained from more proximal unipoles. Due to the direct contact of the tip electrode with the myocardial wall, the EGM from more distal unipoles are often superimposed by local signals with morphologies similar to local action potentials. Consequently, in order to improve the sensitivity of intracardiac EGM monitoring, the average recording of the two most proximal unipoles within the right ventricular cavity were used as "a single

unipole". This was then used in the subsequent two studies for multilead bipolar EGM reconstruction.

The second and third studies investigated the diagnostic accuracy of detecting myocardial ischaemia using four bipolar leads reconstructed from the unipoles that are potentially available in implanted devices. These studies demonstrated that the absolute ST segment changes during periods of myocardial ischaemia are significantly greater in reconstructed bipolar intracardiac EGM signals compared with surface ECGs. However, when the amplitude of the intracardiac EGMs was normalised relative to that of the surface ECG (to account for the different signal amplitude between the intracardiac EGM and the surface ECG), the ST segment changes had an intermediate detection capability and was inferior to a number of surface ECG leads, particularly leads V2 and V3.

The fourth study investigated the application of novel descriptors of T wave morphology in monitoring myocardial ischaemia. This study demonstrated that abnormalities of these T wave morphology descriptors appear early and continue to evolve temporally during the period of ischaemia. These parameters are more superior to conventional ST segment monitoring from standard surface ECGs. All of these variables can be instantly calculated from digital recordings from standard computer algorithms and with very high reproducibility, from a single ECG beat. Although these T wave morphology descriptors were calculated from the 12-lead surface ECG, there are possibilities of obtaining the same from the intracardiac EGM. Therefore, based on these novel descriptors, the concept of an automatic myocardial ischaemia algorithm in implanted devices is potentially feasible.

In summary, the presented clinical studies demonstrate that monitoring myocardial ischaemia from intracardiac electrodes, analogous to those of implanted cardiac devices is feasible. However current technology limits this detection ability. The development of novel T wave morphology descriptors may improve the diagnostic accuracy of monitoring myocardial ischaemia.

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I am deeply indebted and would like to thank Professor Marek Malik for all is help, encouragement and advice through out this period, and for taking the time to help me prepare this thesis. This work would not have been possible without the assistance of the Dr. David Ward and Dr. Charles Pumphrey who were instrumental in helping me recruit patients and to whom I am extremely grateful. I would also like to thank the staff of the Cardiac Catheter Laboratory at St. George's Hospital, especially Ian Little who helped me record the electrocardiograms. In addition, I thank Dr. Dan Wichterle and Dr. Katerina Hnatkova who wrote the software for data processing and reconstructing the electrocardiograms. I would also like to thank Professor A John Camm whose guidance and support have encouraged me throughout. The studies described were clinical and I should like to record my thanks to the patients who volunteered to participate in these studies.

Lastly, I would like to thank and dedicate this thesis to my wife, Alicia and children Amanda and Alex whose immeasurable support and encouragement helped me through difficult times.

CHAPTER 1

Historical Review and Introduction

Myocardial ischaemia

Despite considerable progress in management over the recent years, coronary artery disease (CAD) remains the leading cause of death in the industrialised world. It is estimated that CAD is responsible for causing 152 000 deaths per year in the United Kingdom and one in eight deaths worldwide [1]. Many of these deaths are attributed to the development of ventricular tachyarrhythmias during periods of myocardial ischaemia or infarction.

The factors leading to the point of partial or complete coronary artery occlusion are multiple and complexly interactive. They include the pathology of early vessel wall abnormalities, interacting with various haemostatic, hormonal, blood factors (lipid fractions, homocysteine, glucose, etc.), inflammatory mediated responses and the cellular constituents of the vessel wall. The end result is the formation and progression of the atherosclerotic plaque.

Coronary artery disease can express itself in two major clinicopathologic forms. The chronic form is caused by progressive atherosclerotic narrowing of the coronary arterial bed and usually presents as angina secondary to ischaemia precipitated by increased myocardial oxygen demand – "demand ischaemia". Treatment consist of pharmacological agents and other measures to reduce oxygen demand, and if inadequate, surgical or catheter based revascularisation. The acute form, on the other hand, results from a sudden reduction in myocardial oxygen supply caused by a thrombus on a fissured or eroded coronary atherosclerotic plaque. This causes "supply ischaemia", which can result in a variety of clinical syndromes, including unstable angina, non-ST elevation and ST elevation myocardial infarction. Treatment

is aimed at rapid reperfusion of the ischaemic area through either administration of thrombolytic agents, percutaneous intervention or occasionally rescue coronary bypass grafting.

The management of patients with chronic coronary artery disease represents one of the critical challenges in cardiology. Any advancement in this field of medicine will certainly impact clinical practice and inevitably mortality and morbidity.

The purpose of this chapter is to review the pathophysiology, biochemical and metabolic changes of myocardial ischaemia and how this translates into the electrophysiology and clinical presentation (symptomatic and asymptomatic angina). Targeting resources to monitor and treat both symptomatic and more commonly asymptomatic angina, will certainly have an impact at alleviating the mortality and morbidity burden associated with ischaemic heart disease.

Supply versus demand and susceptibility to ischaemia

Myocardial ischaemia is defined as the reduction in the supply of oxygen to less than the amount required by myocardial cells to maintain aerobic metabolism. It is a relative condition that depends on the balance among the coronary blood supply, the level of oxygenation of the blood, and the myocardial workload. The molecular, physiologic, and clinical evidence of ischaemia only occur when demand outstrips the supply of oxygen to the myocardium. The reserve on the supply side is large enough to make ischaemia impossible in normal hearts even with the most vigorous level of exercise[2]. However, in the presence of coronary artery disease or abnormal left ventricular hypertrophy, an imbalance between supply and demand may occur

with minimal exercise or even rest. Application of the concept of supply and demand to myocardial oxygen utilisation emphasises and underlines the physiologic parameters that control oxygen delivery and consumption by the heart.

Myocardial Oxygen Supply

The supply of oxygen to the myocardium is determined by the magnitude of coronary flow and the oxygen carrying capacity of the blood. The latter is compromised during clinicopathologic conditions such as anaemia, hypoxia, methaemoglobinaemia, and carbon monoxide poisoning.

By far, the most important determinant of oxygen supply in most clinical situations is the magnitude of coronary blood flow, which is governed by the principles of fluid dynamics. Coronary blood flow is the result of the pressure gradient across the vascular bed divided by the resistance. Aortic root pressure minus right atrial pressure or left ventricular diastolic pressure defines the pressure gradient or coronary perfusion pressure. The regulation of coronary blood flow is a complex process incorporating several factors, the most important of these are:

- metabolic control,
- autoregulation,
- extravascular compressive forces,
- diastolic phase in cardiac cycle,
- endothelial (and other humoral) factors
- neural control.

Metabolic control

Changes in metabolic rate of myocardial cells are closely coupled to coronary blood flow [2]. This coupling mechanism acts within one cardiac cycle with maximal coronary dilation or constriction elicited within 15-20 seconds[3]. This response is called coronary reactive hyperaemia. The mechanisms that link metabolic activity and coronary vascular resistance have been extensively investigated and are believed to include: adenosine, other nucleotides, nitric oxide, prostaglandins, H^+, carbon dioxide, and K^+ as the likely potential mediators[4]. It is likely that these agents do not act singly but in concert to regulate coronary flow in response to metabolic needs.

Autoregulation of coronary blood flow

Blood flow in the coronary arteries remains constant over a range of perfusion pressures (60-160 mmHg)[2,5]. Most patients with demand induced angina have severe stenoses in epicardial coronary arteries but no evidence of a resting perfusion deficit or myocardial ischaemia. Reductions in perfusion pressure distal to stenoses are compensated for by auto regulatory dilation of the resistance vessels (intramural arteries and arterioles). However, in the presence of a critical stenosis, the ability of autoregulation to compensate for the effect of a proximal epicardial obstruction may be compromised by a reduction of aortic pressure. The latter can lower distal perfusion pressure below the critical levels at which autoregulation is no longer effective, thereby lowering myocardial perfusion and intensifying myocardial ischaemia. Chronic hypertension and left ventricle hypertrophy narrow the range of autoregulation, especially in the subendocardium, in which autoregulation is ordinarily more limited than in the subepicardium[6]. Coronary collateral arteries do

not exhibit autoregulation and therefore explains why patients with extensive collateral-dependent segments of myocardium tolerate hypotension poorly.

Although the exact mechanism remains unknown, both myogenic and metabolic control factors have been suggested as the mechanism for autoregulation. The latter shares the principles of metabolic control of blood flow, as discussed above. Namely, maintenance of a set-point concentration of a metabolite/metabolites is the goal of the regulatory system. If the concentration of this substance decreases as a result of increased perfusion pressure and blood flow, vascular smooth muscle constricts and coronary blood flow is limited until the previously established concentration of the metabolite is reached, and vice versa. Arteriolar smooth muscle reacts to increased intraluminal pressure by contracting and to decreased intraluminal pressure by dilating. The consequent augmentation or reduction of resistance tends to return blood flow toward normal. This regulatory mechanism is referred to as myogenic control, and is an important mechanism of autoregulation[7].

Extravascular compressive forces

This refers to the mechanical forces that compress coronary vasculature. It includes the intrapericardial, intramyocardial, and intraventricular pressures during the cardiac cycle. The contribution of the intrapericardial forces to extravascular compressive forces is minimal in most clinical circumstances. The intramyocardial pressure refers to the twisting motion associated with myocardial contraction. Intramyocardial forces exert their maximal effect during systole and the magnitude of these compressive forces decrease from endocardium to epicardium. The intraventricular pressure reaches a peak during systole and has its maximal compressive effect on the

subendocardium. Hence, the summative effect of intramyocardial and intraventricular forces during systole is to maximally compress the subendocardial coronary vasculature. At peak systole, there is a cessation and even reversal of flow in the intramural coronary vessels[8]. This effect is masked by the capacitance properties of epicardial coronary vessels. Approximately 30-50% of total coronary vasculature resistance can be attributed to these forces[2]. At maximal coronary dilation, removal of extravascular compressive forces increases coronary blood flow by 50%[2]. In the presence of coronary artery disease, when distal coronary vasculature beds are maximally dilated, the effects of compressive forces become most pronounced.

During the diastolic phase, the compressive forces are at their minimum and coronary resistance is at its nadir. Coronary blood flow reaches its peak during this phase. The subendocardium receives blood only during this period. Therefore, any factor that shortens this phase (total diastolic phase/minute) during the cardiac cycle such as increasing heart rate or prolonged ventricular systole due to depressed contractility will impair the supply of blood to the subendocardium, rendering this region most susceptible to ischaemia[2]. Changes in the diastolic phase probably have minimal impact on the blood flow to the epicardial layers, which are perfused throughout the cardiac cycle.

The compressive forces exerted by the right ventricle are far smaller than those of the left ventricle and therefore ventricular perfusion is reduced but not interrupted during systole. However, when right ventricular pressure is elevated, the phasic blood flow pattern of the arteries perfusing the right ventricle resembles those of the left ventricle.

Endothelial (and other humoral) factors

Vasoactive agents that influence the tone of large and small coronary vessels can arise from outside the vessel wall; they can circulate in the blood (e.g epinephrine, vasopressin, angiotensin II) or be derived from circulating elements such as platelets (e.g. serotonin, ADP, thromboxaneA2) or from nerve endings (e.g nor epinephrine, vasoactive intestinal peptide). Vasoactive factors such as endothelium-derived relaxation factor, prostacyclin, and endothelin can also be formed in the vascular endothelium. These vasoactive substances complexly interact to modulate coronary arterial tone, atherosclerotic plaque stabilisation and the progression of coronary artery disease.

Neural control

The coronary arteries are richly innervated by sympathetic and parasympathetic fibres, and their activation can exert important influences on coronary vasomotor tone. Generally speaking, α-adrenergic stimulation induces coronary vasoconstriction, whereas β-adrenergic and parasympathetic stimulation induces coronary vasodilatation. However, this simplistic model is influenced by differential regional responses and the presence of coronary artery disease. For instance, depending upon the segment of coronary vasculature, stimulation of α-receptors on epicardial conduit vessels and meta-arterioles with a diameter > 50μm causes vasoconstriction, whereas it has a vasodilatory effect on coronary arterioles < 50μm in diameter[3]. Coronary collateral vessels lack α-adrenergic receptors and therefore the resistance do not alter with α-adrenergic stimulation[3]. In the presence of

coronary artery disease, parasympathetic stimulation may lead to net coronary vasoconstriction[9]. This paradoxical effect may represent a defect in endothelial vasodilator function, and may be important in the pathogenesis of coronary vasospasm[9].

In addition to the regulatory effects of the autonomic nervous system on coronary blood flow, the central nervous system, also has direct effects on coronary resistance. Stimulation of certain areas of the brainstem can cause coronary vasoconstriction[10]. This phenomenon highlights the role of the central nervous system and emotions in modulating coronary resistance.

Myocardial oxygen demand

The heart relies exclusively on aerobic metabolism for energy production under normal conditions. The three most important factors determining myocardial metabolism and oxygen need are:

- heart rate
- systolic wall tension
- myocardial contractility

Heart rate

Heart rate is a prognostic index of cardiovascular risk before, during and after a coronary event[11-13]. Elevated resting heart rate is associated with shortening of diastolic perfusion time and increased myocardial oxygen demand, which may be

critical during ischaemia. Increased heart rate is directly associated with a proportional increase in coronary flow. Because the myocardium is mainly perfused during diastole, peak coronary flow is markedly increased during diastole with reversal during systole. Diastolic endothelial shear stress, as well as pulsatile wall stress, is therefore greater in the coronary arteries compared with most other organs. The increased shear stress stimulates release of vasodilatory peptides and growth hormones from endothelial cells and may explain why the coronary arteries are a target for atherosclerotic disease. Patients with coronary artery disease have a blunted endothelial response to increased flow rates, which may become the nidus for the development of atherosclerotic disease at branching points with high shear stress. The higher diastolic shear stress in coronary arteries may explain the progression of atherosclerosis in these arteries compared to a sparing effect on the internal mammary artery, in the same patient[14]. Increased shear stress also enhances platelet aggregation and the rapid pulsatile changes may cause mechanical stress and increase atheromatous plaque instability, particularly in the shoulder region of the plaque[15].

Elevated heart rate can influence the incremental elastic modulus in large arteries and therefore increase the stiffness in central and peripheral arteries[16]. This may contribute to the loading condition of the heart and further contributes to the energy requirement of the heart and coronary risk.

Systolic wall tension

Myocardial wall tension is proportional to ventricular systolic pressure, ventricular radius, and inversely proportional to ventricular wall thickness. The effects of the preload and after load are incorporated into the above parameters. Preload influences

ventricular radius, whereas afterload dictates the magnitude of systolic pressure generation[2]. Systolic wall tension decreases with increasing ventricular wall thickness. Hence, left ventricular hypertrophy in response to pressure overload is a compensatory mechanism to reduce systolic wall tension.

Myocardial contractility (velocity of contraction dP/dT)

Myocardial contractility refers to the rate of rise in the intraventricular pressure during isovolumetric contraction. It is the third major determinant of myocardial oxygen consumption. In the absence of heart failure, drugs that stimulate myocardial contractility increases the energy costs of enhanced excitation-contraction coupling[17]. The increased energy costs result from the greater and more rapid Ca^{++} uptake by the sarcoplasmic reticulum as well from the increased contractile activity, rather than from a direct stimulating effect on basal myocardial metabolism. In the failing left ventricle, treatment with positive inotropic agents causes an expected increase in oxygen consumption. However, the improved systolic function and consequent decreased end-diastolic volume, wall tension, and oxygen consumption yield a net decline in oxygen demand. Contractility is influenced by the autonomic nervous system, heart rate, blood calcium level, temperature, and other factors.

Biochemical and metabolic changes, and cell death during myocardial ischaemia and infarction

Oxygen is required for the generation of high energy phosphates that form the energy source for all cellular processes (aerobic metabolism). A rapid initial decrease in the free energy of ATP hydrolysis[18]results in a transsarcolemmal redistribution of

potassium resulting in a biphasic increase in extracellular potassium concentration and subsequent depolarisation of the sarcolemma[19]. For a limited period of time, the myocytes can maintain their metabolic competence through anaerobic glycolysis, which results in lactate production and thus acidosis[20]. Other extracellular metabolic changes include: elevated lysophosphoglycerides and adenosine concentrations, increased lactate and carbon dioxide production, acidosis, and catecholamine release[21]. Concomitantly, other intracellular changes include: elevated cyclic adenosine monophosphate (cAMP), and elevated concentrations of calcium, magnesium, and sodium ions[21]. The combined effects of acidosis and accumulation of metabolites result in decreased efficacy of anaerobic glycolysis, and a further metabolic deterioration[22]. These energy-depleted myocytes must uncouple their electrical activation from mechanical contraction and remain in their resting state in order to prolong survival. Thus the area of myocardium that is ischaemic cannot participate in the pumping process of the heart (myocardial stunning). Longer duration of ischaemia results in intracellular calcium overload[23], closure of the gap junctions and rigor[24,25]. Thereafter, cells will loose their membrane integrity, enzymes will leak out of the cell and the cell dies. Myocardial necrosis defines infarction[26].

In the intact heart, ischaemic damage develops heterogeneously[27] and certain parts of the ischaemic zone survive the ischaemic burden. For instance, subepicardium and subendocardium remain viable through diffusion of oxygen and nutrients from surrounding tissues, although active membrane properties change[28].

Sequence of Events in Ischaemia

During an episode of myocardial ischaemia, there is a sequence of pathophysiological events often termed the ischaemic cascade (figure 1)[29]. The first detectable changes associated with heterogeneity of flow to the left ventricle are biochemical followed by a significant perfusion defect. Next, regional myocardial dysfunction, characterized by both abnormal diastolic relaxation and compliance and impaired systolic wall thickening and endocardial motion, occurs in rapid succession (within a few cardiac cycles). Ischaemic ST-segment depression on electrocardiography and clinical angina are relatively late manifestations of ischaemia and are not seen consistently.

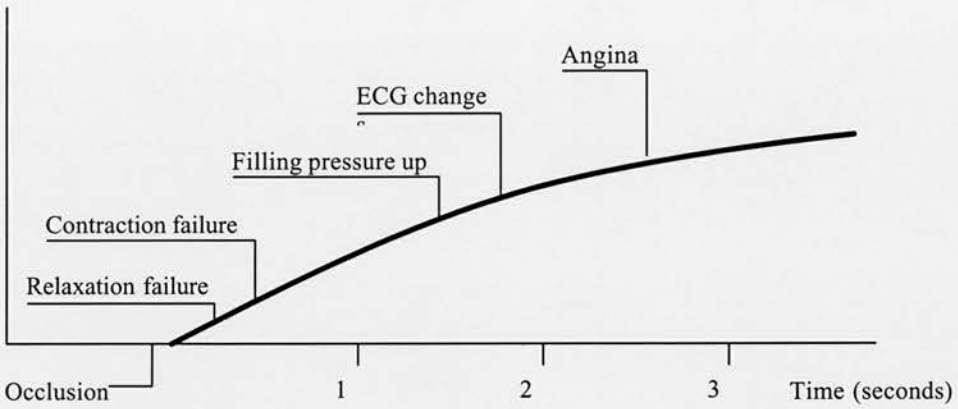


Figure 1. Schematic representation of the sequence of events occurring after balloon occlusion of a coronary artery. (Adapted from Sigwart *et al.* In Silent Myocardial Ischaemia. Edited by Rutishauser W, Roskamm H. Berlin: Springer-Verlag; 1984:29–36.

Ischaemic heart disease presenting as arrhythmias

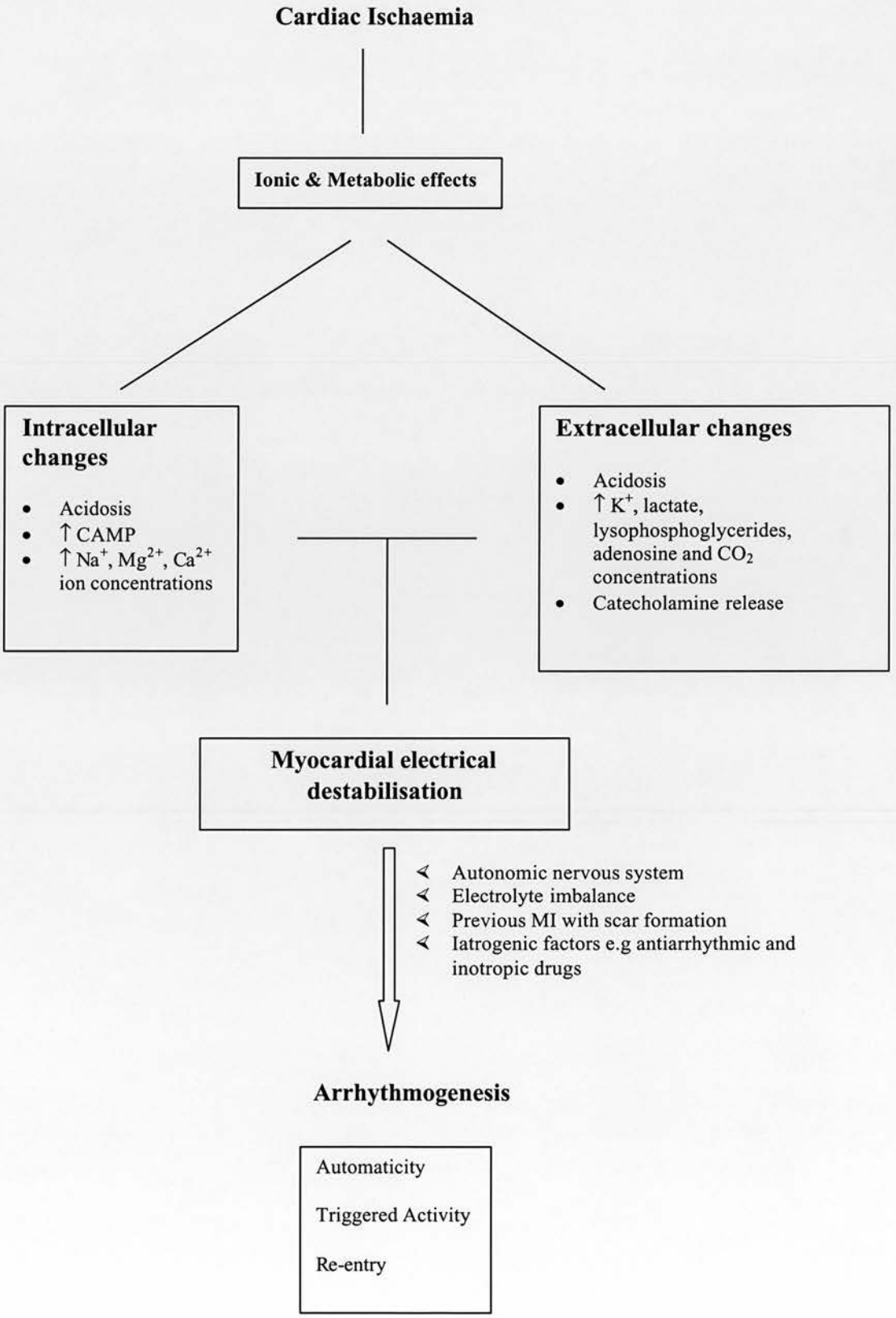
The biochemical and metabolic changes associated with myocardial ischaemia, together with alterations in autonomic tone (table 1), alter inward and outward transmembrane ionic current fluxes, causing profound alterations of the resting membrane and action potential characteristics of the myocyte[30,31]. Changes such as depolarisation of the resting membrane potential (that is a less negative resting membrane potential), diminished upstroke velocity, slowed conduction, decreased excitability, shortening of the action potential duration, altered refractoriness,

dispersion of repolarisation, and abnormal automaticity, can occur[30]. The alterations in the electrical properties of myocardial cells are reliant on the extent and duration of ischaemia. For instance, in the central ischaemic zone, there is prolongation of the refractory period, whereas in the bordering area of infarction, the refractory period shortens. This inhomogeneity is partly caused by diffusion of potassium from the ischaemic areas towards more normal myocardium. These electrophysiological changes do not all occur at once but evolve temporally, providing the electrophysiologic trigger and anatomic substrate necessary to induce and sustain arrhythmias through virtually all known arrhythmogenic mechanisms; automaticity, triggered activity and re-entry (figure 2). A history of a previous myocardial infarction with scar formation further contributes to this arrhythmogenic milieu; the presence of myocardial fibrosis causes slowing of cardiac conduction, resulting in re-entry circuits and subsequent ventricular desynchronisation.

Table 1

Electrophysiological effects of the sympathetic nervous system
• Shifts pacemaker from sinus node to junctional region
• Increases Purkinje fiber automaticity
• Alters P wave morphology and shortens QT interval
• Shortens PR interval
• Increase after-depolarisations (facilitating triggered activity)
• Enhances re-entry during acute myocardial ischaemia
• Decreases ventricular fibrillation threshold

Figure 2. Influence of cardiac ischaemia on arrhythmogenesis



Surface ECG manifestation of myocardial ischaemia, injury and infarction

The ECG changes of myocardial ischaemia and infarction, first described in 1920 by Pardee, are those of ischaemia, injury, and cellular death (necrosis)[32]. Respectively, these pathological processes are, within limits, reflected by T-wave changes, ST-segment displacement, and alteration of the QRS complex (for instance Q waves) (figure 3). Such a clear-cut differentiation, although clinically useful, may be overly simplistic and artificial. For instance, T-wave changes may be due to ischaemia, injury or myocardial necrosis. Similarly, a Q wave may be due to transmembrane ionic fluxes and not necessarily cellular death. Furthermore, ischaemia has complex time-dependent effects on the electrical properties of myocardial cells and therefore the ECG findings vary considerably, depending on the duration and acuteness of the ischaemic process, its extent (transmural versus subendocardial), its location (anterior versus inferior-posterior) and the presence of pre-existing conduction abnormalities (conduction block, Wolff-Parkinson-White syndrome or pacemaker patterns). However, for the purpose of this chapter, T-wave changes, ST-segment displacement, and appearance of a Q wave are assumed to reflect, ischaemia, injury and cell death, respectively.

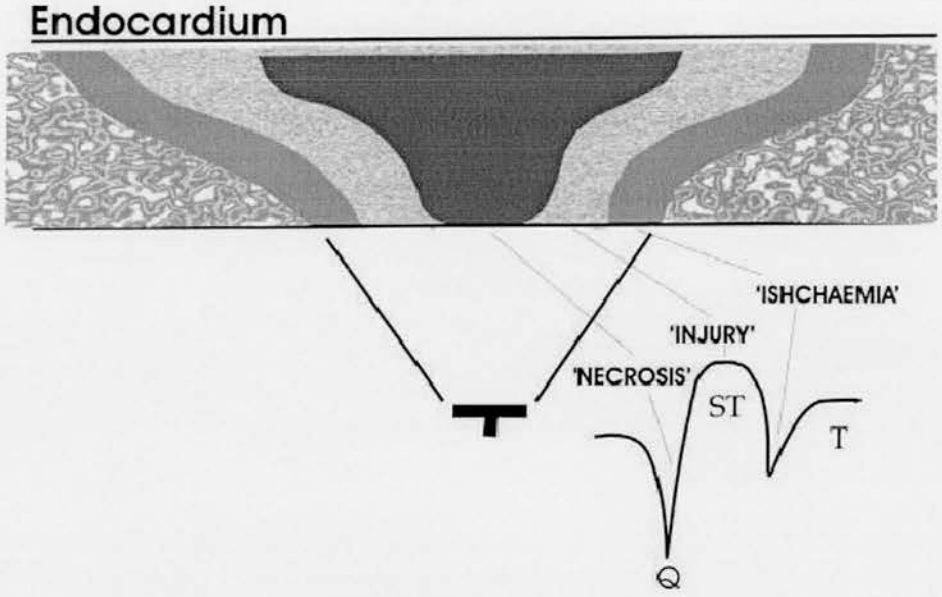


Figure3. The pathological processes and associated ECG changes during transmural myocardial ischaemia and infarction. Necrosis, injury and ischaemia are seen as Q waves, ST segment deviation and T wave inversion, respectively

Myocardial ischaemia and the T Wave

In experimental models, the changes of myocardial ischaemia are noted by the rapid onset of changes in the T wave appearance. Normally the process of repolarisation proceeds from the epicardium to the endocardium, giving rise to an upright T wave (figure 4). Acute ischaemia shortens the duration and decreases the amplitude of the ventricular action potential[33]. This results in the deviation of the T wave vector towards the ischaemic region. Consequently, if the ischaemia is subendocardial, the direction of repolarisation is reversed, proceeding from endocardium to epicardium, and inverted T waves are recorded (figure 4)[33]. Conversely, when myocardial ischaemia is transmural or epicardial, the direction of repolarisation remains unchanged or even augmented, and the polarity of the T wave is upright or

hyperacute. Small changes in the action potential duration (for instance, changes of < 20 ms in the duration of the monophasic action potential) can cause large changes in the configuration of the T wave.

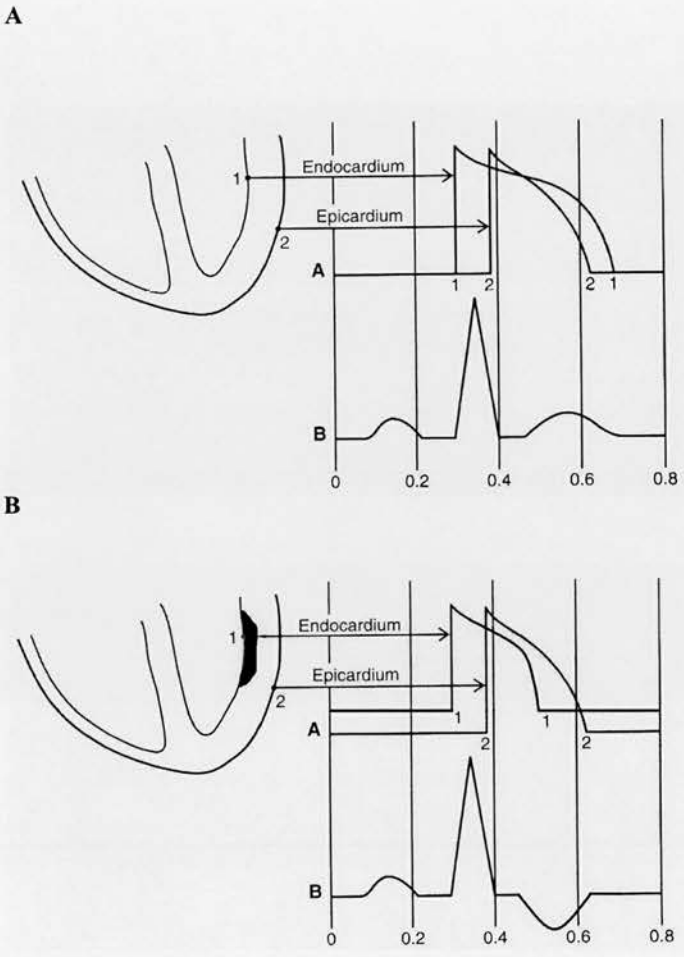


Figure 4. A. Endocardial and epicardial action potentials and the normal electrocardiogram. Note the endocardium is the first to depolarise but the last to repolarise. The epicardium is the last to depolarise but repolarises before the endocardium. This results in an upright T wave. **B**. During subendocardial ischaemia the resting membrane potential depolarises (i.e., less negative) and there is shortening and decreased amplitude of the action potential amplitude. Consequently the endocardium repolarises before the epicardium resulting in a reversal of the direction of repolarisation and T inversion.

Postischaemic T wave abnormalities associated with a prolonged QT interval are attributed to prolongation of action potentials in the ventricular myocardium bordering the infarcted area. These T wave changes evolve independently of the ST segment changes produced by ischaemia[33]. The vector of the abnormal T wave tends to be directed away from the area of abnormal (prolonged) repolarisation; that is, negative T waves in leads I, AVL, and V5-V6 in anterolateral infarction, in right- and midpraecordial leads in anteroseptal infarction, in leads II, III, and AVF in inferior infarction, and tall upright T waves in right praecordial leads in posterior infarction. However, the correlation between then distribution of T wave abnormalities and localisation of myocardial lesions is not as reliable as the correlation between the distribution of Q waves and the region of myocardial infarction. Therefore, it is not advisable to attempt to localise regions of ischaemia or fibrosis based on the T wave vector alone in the absence of QRS abnormalities produced by infarction[34]. Furthermore, T-wave changes alone are both less specific and less sensitive than ST-segment changes for diagnosing myocardial ischaemia as it can occur in other cardiac and noncardiac conditions[35], for example: pericarditis, myocarditis, myocardial contusion, cardiomyoapthies, intracranial pathology (especially subarachnoid haemorrhage), drug induced (digoxin), phaeochromocytoma, hypothyroidism, etc..

Myocardial Injury and the ST Segment

Myocardial injury is reflected electrocardiographically by deviation of the ST segment. The ST segment is deviated towards the surface of the injured tissue. Thus, if the injury is dominantly transmural or epicardial, the ST segment is deviated towards the injured epicardial surface, and a lead orientated towards this surface will

reflect a raised ST segment. Conversely, a lead orientated towards the uninjured surface will reflect a depressed ST segment - "reciprocal changes". With a dominantly subendocardial injury, a lead orientated to the injured subendocardial surface will reflect an elevated ST segment, whereas a lead orientated to the uninjured surface will reflect a depressed ST segment. This subendocardial ischaemia pattern is the typical finding during spontaneous episodes of angina pectoris or during exercise or pharmacological stress testing. Experimental studies have demonstrated that ST segment depression occurred when the normal endocardial to epicardial blood flow ratio of 1.16±0.22 decreased to 0.67 or less, and the magnitude of ST shift correlated with the intensity of flow distribution[36]. Since the myocardial injury in most infarctions is dominantly epicardial with some subendocardial sparing (the most endocardial surface derives its blood supply directly from the ventricular cavity), the manifestation presents electrocardiographically with elevated ST segment in leads orientated to the epicardial surface. The ST segment in the fully evolved phase of the infarction is, in addition, coved or convex-upward.

Therefore, ST segment depression in the praecordial leads reflects a posteriorly directed ST segment vector, which is seen in subendocardial ischaemia/infarction of the anterior wall and by subepicardial ischaemia/infarction of the posterior wall. Whereas, ST segment elevation in the praecordial leads represents an anterior directed ST segment vector, which is seen in the presence of subepicardial injury, infarction, pericarditis, cardiac tumour or transient ischaemia during coronary spasm

The mechanism of these ST segment shifts is believed to be the result of diastolic and systolic current of injury[37]. Myocardial ischaemia results in (1) a shortening and

decreased amplitude of the action potential, and (2) depolarisation, that is less negative resting membrane potential. The shortening and decreased amplitude will cause potential differences during repolarisation, that is electrical systole, and this will result in systolic current of injury. The depolarisation will cause potential differences during electrical diastole that will result in a diastolic current of injury[37].

- *Systolic current of injury*

  The concept of the systolic current of injury proposes that during electrical systole, the normal heart is depolarised, but the injured area undergoes early repolarisation. As a result, a voltage gradient is established between normal and ischaemic myocardium, creating a current of injury vector directed towards the ischaemic region.

- *Diastolic current of injury theory*

  Resting healthy myocardium has an electrically positive surface charge and no difference in electrical potential exist across the myocardium (figure 9). When the heart muscle is stimulated or injured its surface becomes electrically negative. If only part of the muscle strip is injured, the injured part will have a negative surface charge and the healthy muscle will have a positive surface charge. This potential difference between the injured and uninjured tissue creates a continuous negative current in the resting phase (electrical diastole). The injury current vector is directed away from the more negative ischaemic zone towards the more electropositive normal myocardium. As a result, leads overlying the ischaemic zone will record a

negative deflection during electrical diastole and produce depression of the TQ segment. Conventional alternating current electrocardiographs compensate for this baseline shift and therefore the ST segment deviation is not observed on the scalar ECG. When the remainder of the heart is depolarised, a potential difference no longer exists, and the injury current is abolished. As a result, the depressed baseline returns to the normal level giving the impression of a raised ST-segment. Therefore, the ST segment is apparently elevated with respect to the depressed but rectified (isoelectric) diastolic segment and represents an apparent shift (figure 9).

It appears that the major change after coronary occlusion is the diastolic injury current, whereas the systolic injury current makes a smaller contribution to the ST segment displacement[38].

Myocardial Infarction and the Q wave

Myocardial infarction is reflected electrocardiographically by the electrocardiographic parameters of ischaemia, injury and necrosis. The former two has already been discussed. Myocardial necrosis is reflected by a deep and wide Q wave or a QS complex by electrodes orientated towards the necrotic area. An abnormal or pathological Q wave is defined as having a duration > 40 ms and/or the amplitude exceeds 25% of the following R wave. The Q wave develops within 6-14 hours after the onset of symptoms.

Two concepts have been suggested to explain the Q wave. The " Wilson window theory" suggests that the epicardial Q waves are caused by the passive transmission of intracavitary potentials through the electrically inert myocardial tissue.

Alternatively, the loss of voltage results in a new balance of electrical forces, which become orientated away from the regions of complete or partial tissue loss and toward the non-infarcted tissue.

Myocardial Infarction and the ECG

The initial ECG is diagnostic during an acute myocardial infarction in approximately 50% of patients, abnormal but not diagnostic in approximately 40% and normal in about 10%. Serial ECG recordings can increase the sensitivity to close to about 95%. Failure of the ECG to reflect myocardial ischaemia reliably, may stem in part from the facts that leads on the body surface are too distant from the ischaemic subendocardial muscle.

The first change noticed at the onset of a myocardial infarction involves an abnormal T wave. The T wave may be prolonged, increased in magnitude, upright or inverted, as previously discussed. This is followed by ST elevation in leads facing the infarcted area, with reciprocal depression in the opposite leads. Provided it is still upright, the terminal aspect of the T wave may then invert whilst the ST segment is still elevated. The amplitude of the QRS complex may diminish as Q waves evolve. The ST segment returns to baseline and the T waves become inverted and symmetrical. The evolution of the Q wave, T wave and ST segment is summarised graphically in figure 10. The classic evolution of an acute myocardial infarction is documented in approximately one-half to two-thirds of patients.

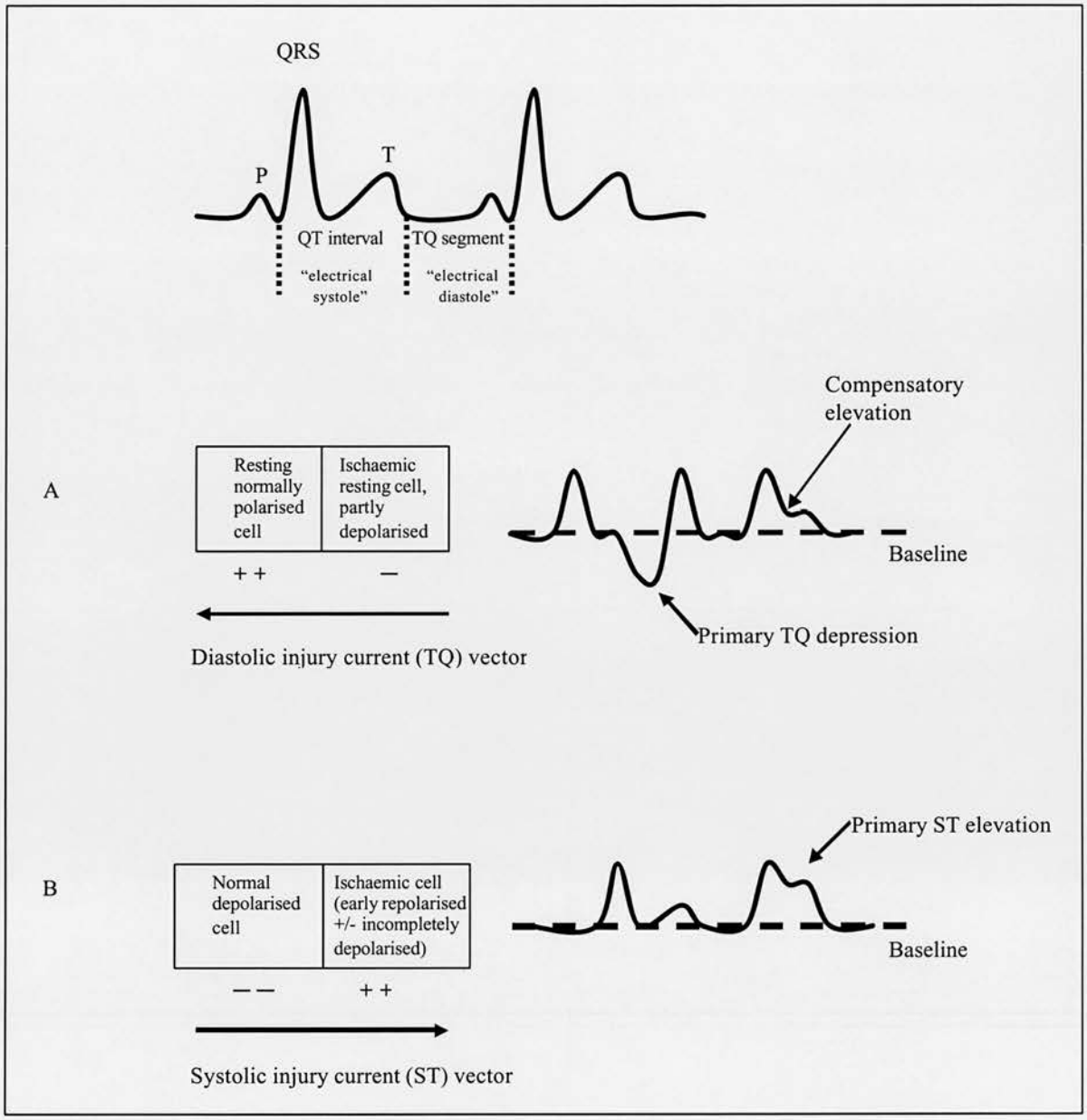


Figure 9. Pathophysiology of ischemic ST elevation. Two basic mechanisms have been advanced to explain the elevation seen with acute myocardial injury. *A, Diastolic current of injury*. In this case (first QRS-T complex), the ST vector will be directed away from the relatively negative, partly depolarised, ischemic region during electrical diastole (TQ interval), and the result will be primary TQ depression. Conventional alternating-current electrocardiograms compensate for the baseline shift, and an apparent ST elevation (second QRS-T complex) results. *B, Systolic current of injury*. In this case, the ischemic zone will be relatively positive during electrical systole because the cells are repolarised early and the amplitude and upstroke velocity of their action potentials may be decreased. This injury current vector will be oriented toward the electropositive zone, and the result will be primary ST elevation. (After Goldberger AL: Myocardial Infarction: Electrocardiographic Differential Diagnosis. 4th ed. St Louis, Mosby-Year Book, 1991)

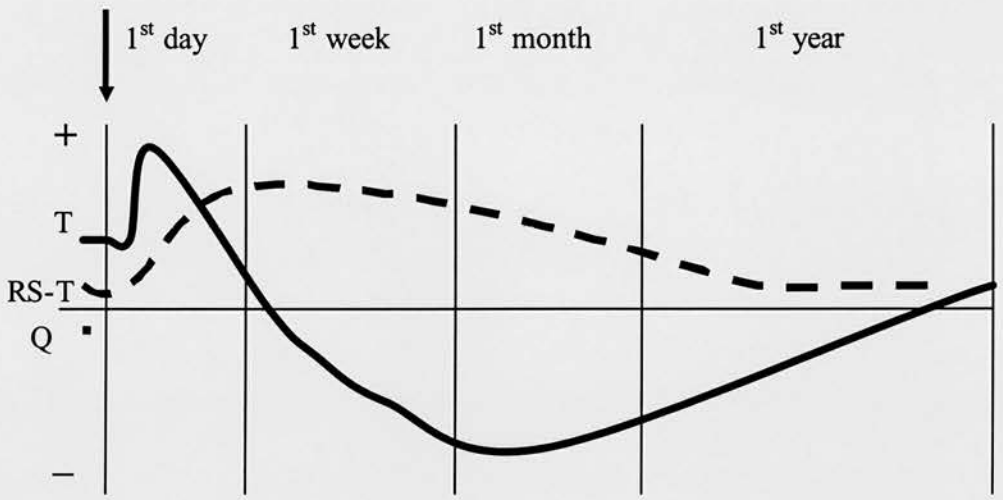


Figure 10. Evolution of the Q wave, T wave and ST segment after myocardial infarction (adapted from Braunwald E. *Heart disease. A textbook of cardiovascular medicine*, 5th ed. Philadelphia: WB Saunders Company, 1997;127-141[4]).

Angina and Silent myocardial ischaemia

Angina

Angina pectoris is regarded as the cardinal symptom of myocardial ischaemia for more than two centuries. It is a clinical syndrome characterized by discomfort in the chest, jaw, arm, or adjacent areas, brought on by exertion, and associated with a disturbance of myocardial function but without myocardial necrosis. It was first described by William Heberden in 1772[39]:

> *"There is a disorder of the breast, marked with strong and peculiar symptoms, considerable for the danger belonging to it.... Those who are afflicted with it are seized, while they are walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast... the moment they stand still all this uneasiness vanishes.... After it has continued some months, it will not cease so instantaneous upon standing still... (most) whom I have seen, who are at least twenty, were men, and almost all above 50 years old, and most of them with a short neck, and inclining to be fat.... But the natural tendency of this illness be to kill the patients suddenly.... The os sterni is usually pointed to as the seat of this malady ... and sometimes there is with it a pain about the middle of the left arm"*

The mechanisms of cardiac pain and the neural pathways involved are poorly understood. It is presumed that angina pectoris results from ischemic episodes that excite chemosensitive and mechanoreceptive receptors in the heart[4]. Stimulation of these receptors results in the release of adenosine, bradykinin, serotonin, lactate and other noxious substances that excite the sensory ends of the sympathetic and vagal

afferent fibers. The afferent fibers traverse the nerves that connect to the upper five thoracic sympathetic ganglia and upper five distal thoracic roots of the spinal cord. Impulses are transmitted by the spinal cord to the thalamus and hence to the neocortex. Within the spinal cord, cardiac sympathetic afferent impulses may converge with impulses from somatic thoracic structures, which may be the basis for referred cardiac pain, for example, to the chest. In comparison, cardiac vagal afferent fibers synapse in the nucleus tractus solitarius of the medulla and then descend to excite the upper cervical spinothalamic tract cells, which may contribute to the anginal pain experienced in the neck and jaw. Anginal pain is typically described as tight, squeezing, like a weight on the chest, or like indigestion; as with any visceral pain the localisation is vague and there is considerable individual variation between patients.

Silent myocardial ischaemia

During an episode of myocardial ischaemia, anginal pain may appear late or not at all, even in the presence of ischaemic changes on the electrocardiogram. Episodes of asymptomatic myocardial ischaemia or even infarction was first recognised by James Herrick in 1912 and formally described by Stern and Tzivoni in 1974[40,41]. Silent myocardial ischaemia is the most common manifestation of coronary heart disease[42]. As many as 70% of daily ischaemic episodes in stable coronary artery disease and 90% of episodes in unstable angina are silent[43]. Even when drug therapy apparently controls symptoms of angina, as many as 40% of patients continue to have silent myocardial ischaemia[44]. Therefore, anginal pain is a poor indicator and underestimates the frequency of significant cardiac ischaemia.

Diagnosing and detecting silent ischaemia

The methods used to detect silent ischaemia may be crucial for the evaluation of the prevalence of the disease in asymptomatic and symptomatic patients, and the different methods used to investigate the epidemiology of silent myocardial ischaemia may be related to the conflicting results reported. The methods used include: electrocardiographic ST changes either during exercise or Holter monitoring; assessing myocardial perfusion (thallium scintigraphy); assessing wall motion abnormalities such as stress echocardiography or isotopic ventriculography; assessing metabolic function (positron emission tomography - PET scans); and most recently electron beam computed tomography (CT). Silent ischaemia is then defined by the development of any of these objective signs of ischaemia, without any awareness or discomfort by the patient.

As previously discussed, the electrocardiographic changes of myocardial ischaemia are manifested by the ST segment injury current, which occurs late. It has been suggested that following the metabolic alterations of the myocardial syncytium during ischaemia, changes in the T wave morphology may occur earlier than ST segment changes[45]. These morphological changes may not be visually recognisable on the surface 12-lead ECG but can be mathematically computed (this is further discussed in chapter 7).

When compared to other tests, exercise testing appears to be the most suitable laboratory diagnostic and screening test to document silent myocardial ischaemia in those with a history of coronary heart disease and in asymptomatic individuals. Test results in the latter group need to be interpreted carefully in view of the low

prevalence of the condition in asymptomatic subjects. Exercise testing is only moderately sensitive and has a low specificity, especially in women[46].

Holter monitoring is the second most frequently used diagnostic test for silent ischaemia. It has the advantage of providing long-term ECG recording of ischemic and arrhythmic events while patients are engaged in routine daily activities out of the hospital. Although it may play a role in symptomatic individuals[44], for reasons mentioned above its use in asymptomatic individuals remains equivocal. Furthermore, it is hindered by its poor reproducibility and there is marked day-to-day variability in the frequency and duration of ST segment depression[47].

It is generally recommended that the presence of myocardial ischaemia detected by ECG changes during exercise testing or ambulatory Holter monitoring should be confirmed by an imaging study, such as myocardial perfusion scintigraphy or a stress echocardiography study, depending on local resources. Previous reports have shown that such an imaging study is not only helpful in confirming the presence of myocardial ischaemia and diagnosis of CAD but also provides additional prognostic information. In general, coronary angiography should be reserved for those with findings suggestive of high-risk CAD on the imaging study. A good deal of caution and restraint is, however, required to avoid unnecessary procedures that might not only be expensive and inappropriate but also have the potential for harm.

Although other tests are available that can be used to diagnose silent ischaemia with higher sensitivity and specificity, with the exception of electron beam CT, they hardly lend themselves to the study of large populations. The following chapters discuss and investigate a novel method of monitoring silent ischaemia in a selected population with implanted devices.

Classification

To evaluate the problem and develop therapeutic strategies for patients with silent myocardial ischaemia, different groups of patients must be identified, particularly because silent ischaemia appears to be a heterogeneous condition associated with all various forms of myocardial ischaemia. It is in this context, that Cohn[48] proposed three categories to classify silent ischaemia: (i) patients who are asymptomatic with no previous history of angina or myocardial infarction, (ii) patients who are asymptomatic after a myocardial infarction but still present ischaemia, and (iii) patients with both symptomatic and asymptomatic episodes of myocardial ischaemia. This group can be further subdivided into patients with stable or unstable angina pectoris.

Epidemiology

Asymptomatic patients (Type 1). Data from epidemiologic studies have reported disparate findings in the prevalence of silent myocardial ischaemia in asymptomatic individuals. This is likely to reflect the differences in methodology used, the population studied, the duration of follow up, and the under reporting of symptoms. Overall, it has been estimated that between 2-4% of apparently healthy asymptomatic middle-aged men have significant coronary artery disease[49]. The data in women are inconclusive because of the higher incidence of false positive electrocardiograms.

Post MI patients (Type II). In the post infarction population, silent myocardial ischaemia is estimated to occur in up to 30% of patients[50,51, 52]

Stable and unstable angina (Type III). The largest number of patients at risk of silent ischaemia are those with stable angina. Among such patients, the prevalence of silent ischaemia is estimated to be between 25-50%[42,44,53,54]. In patients with unstable angina, despite aggressive medical treatment, the prevalence of silent myocardial ischaemia occurs in 30-50% of patients [42,55].

Pathophysiology and mechanism of silent myocardial ischaemia.

It is not clear why some patients with unequivocal evidence of ischaemia do not experience chest pain whereas others are symptomatic. The following factors may be involved:

1. Cardiac autonomic neuropathy. For instance patients with diabetes mellitus are far more likely to have silent myocardial infarction and episodes of silent ischaemia [56].
2. A high pain threshold. Patients with silent ischaemia have been shown to have a high threshold for other forms of pain such as that resulting from electrical shocks, limb ischaemia or cutaneous application of heat[57,58].
3. A defective anginal warning system related to abnormal central nervous system processing. Frontal cortical activation appears necessary to experience cardiac pain, and some evidence indicates that in patients with silent ischaemia, afferent pain messages from the heart are subject to abnormal neural processing centrally[59].
4. Production of high levels of endorphins, which increase the pain threshold[58].
5. Less severe or shorter duration of ischaemia tend to be asymptomatic whereas longer periods are accompanied by angina[60,61].

6. The role of psycosocial factors (denial) in the perception of pain is controversial[62].

Prognosis

During the past two decades, a large number of epidemiologic and prospective observational studies have demonstrated that the presence of myocardial ischaemia, diagnosed by ST-segment depression on exercise testing or during ambulatory Holter monitoring, is associated with adverse clinical outcome in asymptomatic individuals with or without a history of coronary artery disease[49,63-77]. For instance, in the Multiple Risk Factor Interventional Trial (MRFIT), which studied 12,866 asymptomatic middle-aged men with two or more coronary risk factors, there was a relative risk of 3.4 for cardiac death in men with exercise testing-induced silent ischaemia compared to men without ischaemic ST segment changes. More recently, it has been shown that exercise-induced ST segment depression in men without a history of coronary heart disease carries a fourfold-sixfold increase in coronary heart disease mortality in subjects with one of the of the major three risk factors, which include hypercholesterolaemia, smoking and hypertension [78].

In patients post myocardial infraction, the prognostic significance of silent ischaemia is well established. For example, in the study by Theroux et al [79], 210 patients admitted with an acute MI had a pre discharge exercise test. The 1-year mortality rate was 2.1% in patients without ischaemic ST changes during exercise, and 27% in those with ischaemic ST changes ($p < 0.001$). The results were unaltered with or without associated chest pain during exercise testing. Of the 37 patients with ST depression on exercise testing but without angina, 10 died compared with 7 of the 17

with both exercise induced ST depression and angina. De Belder et al[80] studied 262 patients 7 days post MI. Of these, 104 had a positive exercise test, and 67 had silent ischaemia. In the first year after MI, the latter group had a cardiac mortality rate 12 times higher than that of negative responders and twice as high as that in patients with angina and ST depression. There are a number of ambulatory Holter studies performed in patients post MI. These studies have shown a 2 to 4 fold increase in cardiac event rates in patients with silent ischaemia compared with those without [51,77].

In patients with chronic stable angina, Weiner et al[81], using the database of the Coronary Artery Surgery Study Registry, reported on the survival rate in more than 1400 patients with coronary artery disease and silent ischaemia at exercise ECG testing[81]. They observed that the patients with silent ischaemia only had the same survival rate as those who had angina at ECG exercise testing. Falcone et al[82], concluded that patients with exercise-induced silent ischaemia had a similar risk of adverse outcome as did patients with effort angina. Silent ischaemia during ambulatory Holter monitoring carries a 3-fold increase for coronary events and cardiac mortality[44]. Multiple regression analyses comparing several established clinical, ECG, and exercise test parameters revealed that silent ischaemia during ambulatory monitoring was the most powerful, and independent predictor of adverse clinical outcome and cardiac death [44]. A report of 558 patients from the Asymptomatic Cardiac Ischaemia Pilot (ACIP) trial noted that death, myocardial infarction, or hospitalization occurred in 13 percent of patients with silent ischaemia within 12 months. Multivariate analysis indicated that only the number of ischemic episodes on the entry ambulatory ECG monitor predicted outcome, although the effect was small (odds ratio 1.06[83]). An angiographic study from the same trial

found no correlation between the severity of coronary disease or the presence of a complex plaque and adverse outcome at 12 months[84].

Silent ischaemia in patients with unstable angina carries a poor prognosis[55,85,86]. Noorgard et al, have shown that silent ischaemia after an episode of unstable angina has a relative risk of 7.43 for cardiac death or acute MI at 30 days[86]. Combining raised troponin T and continuous ST segment monitoring identified subgroups at high (both positive), intermediate (one positive) or low risk (neither positive) for death or MI (25.8%, 3.1% and 1.7%, respectively[86]).

Possible mechanisms related to adverse prognosis

There are a number of theories proposed to explain the adverse prognosis associated with silent ischaemia:

- Animal studies have shown that intermittent brief episodes of ischaemia have a cumulative effect and can cause myocardial necrosis[87].
- Human studies using tissue biopsies taken during cardiac surgery have demonstrated that repeated episodes of reversible ischaemic injury is associated with abnormalities of nuclei and mitochondria, loss of myocytes, and increased interstitial fibrosis from areas supplied by diseased coronary arteries. The subendocardium was more affected than the subepicardium. These changes were seen in the absence of any gross histological evidence of MI[88]. These findings are interpreted as the morphologic correlate of functional disturbances, especially of hypokinesia of the affected areas.
- Structural alterations of the myocardium (muscle fiber hypertrophy and increased interstitial nonmuscular tissue) appear to be associated with

evidence of ischaemia-induced regional wall motion abnormalities during exercise[89].

Thus, it is possible that repeated episodes of silent ischaemia could lead to progressive fibrosis and the development of left ventricular dysfunction. It is also conceivable that prolonged episodes of silent ischaemia can lead to life-threatening arrhythmias, especially in patients with an electrical substrate for arrhythmias such as a hypertrophied ventricle. There are many experimental and clinical observations now available showing that ventricular tachyarrhythmias are often provoked by acute myocardial infarction and transient ischaemic episodes[30,90]. However the majority of patients who die suddenly, do not have painful ischaemia immediately before the fatal event, and in such patients the onset of ventricular tachyarrhythmias seems related to painless ischaemia. Sharma et al[91], reported the presence of silent ischaemia, detected by ECG exercise testing in 15 survivors of out of hospital ventricular fibrillation. Savage et al[92], showed episodes of transient myocardial ischaemia, just before the occurrence of sudden death in 64% of 14 patients, submitted to ECG Holter monitoring, while Corrado et al [93], reported in 24% of 79 cases of sudden deaths in young adults (18-35 years), the presence of significant coronary atherosclerosis, which was clinically silent.

Treatment options.

Based on the data presented and the pathophysiologic mechanisms associated with myocardial ischaemia, it is clear that silent myocardial ischaemia carries an adverse clinical outcome and presents a rationale for treating. Abolishing silent ischaemia

can improve quality of life, preserve ventricular function, lower arrhythmogenic risk and probably improve prognosis.

In post MI patients (type 1) or patients with stable or unstable angina (type II), an aggressive therapeutic approach appears justified. However, treatment options in totally asymptomatic patients (type I) are more difficult to establish. The first approach is to address any modifiable risk factors, such as smoking cessation, blood pressure control, cholesterol reduction, weight loss, programmed exercises, and dietary changes.

The ideal pharmacological approach for any condition should be based upon its underlying pathophysiology. Increased myocardial oxygen demand appears to be the primary reason for the development of silent ischaemia. Thus, beta-blockers and heart rate reducing calcium channel blockers are the logical therapeutic agents since these drugs decrease myocardial oxygen demand. Many reports indicate that medical therapy with beta-blockers, calcium channel blockers, nitrates or various combinations of these drugs, is effective in reducing the incidence and duration of silent myocardial ischaemia[94-97].

There are only limited data evaluating the efficacy of coronary revascularisation in the treatment of silent ischaemia[97-99] . The available data suggest that revascularisation may improve patient outcomes. This was illustrated in the Asymptomatic Cardiac Ischaemia Pilot (ACIP) trial, which randomised 558 patients to one of three treatment strategies: angina-guided medical therapy; ischaemia-guided medical therapy; or revascularisation with CABG or PTCA. At 12 weeks, CABG more effectively suppressed ischaemia than PTCA both on the ambulatory

ECG (70 versus 46 percent of patients) and on ETT (46 versus 23 percent[99]). At two years, total mortality was significantly lower with revascularisation compared to ischaemia-guided or angina-guided medical therapy (1.1 versus 4.4 and 6.6 percent[100]). The composite end point of death, MI, or recurrent cardiac hospitalization was also reduced.

In patients with silent ischaemia, the only appropriate indication for revascularisation is to improve prognosis since revascularisation cannot improve symptoms. The choice of revascularisation and of the procedure are dependent upon coronary anatomy, left ventricular function, and the presence or absence of diabetes.

At present, although there is not enough evidence to confirm the hypothesis that suppressing myocardial ischaemia would favourably affect prognosis, the available data suggest that this may indeed be the case. Further randomised controlled studies are needed to confirm these findings.

CHAPTER 2

Concept and Aims of This Thesis

Role of intracardiac electrograms (EGMs) for monitoring myocardial ischaemia

Measurement of ST-segment deviation on the surface electrocardiogram is the most common clinical technique for the diagnosis of myocardial ischaemia. Long-term monitoring for ST-segment deviations can detect both symptomatic and asymptomatic ischaemia, thus offering important clinical potential for improved risk stratification, clarification of the aetiology of arrhythmias or non-specific chest pain, and/or characterization of response to anti-ischemic therapy. However, practical application of long-term monitoring for ST-segment deviations has been limited, due in part to the inconvenience of external monitoring equipment and the prevalence of false positive ST-segment deviations as a result of noise, postural changes, or artefacts. Furthermore, the injury current that leads to deviation of the ST segment on the ECG is influenced greatly by the distance from the recording electrode to the region of ischaemia. Thus an electrode on the body surface distant from a region of ischaemia would be expected to record less ST segment deviation than an electrode placed on the surface of the heart, near the ischaemic area.

In contrast, by virtue of the proximity of intracardiac electrodes to regions of potential ischaemia, it is plausible to expect that intracardiac electrograms (EGMs) may be more sensitive and better indicators of transient myocardial ischaemia than the standard ECG recorded from the body surface. Intracardiac EGMs avoid the insulating effects and increased bioimpedance of the lungs and thorax, and therefore have 5-10 times larger signal amplitude than surface ECG. Noise and signal artefacts are greatly reduced in the EGM by avoiding the electrode-skin interface. The location of implanted electrodes is convenient, consistent and permanent.

Additionally, the intracardiac location of electrodes may provide improved sensitivity to inferior and posterior ischaemia - known limitations of standard 12 lead ECG.

Previous studies

The heart can be depicted as a dipole (an electrical source consisting of an asymmetrically distributed electrical charge) in a volume conductor because one position of the myocardium is depolarized while the remaining regions are still in their resting state at any instant during the spread of a wave of depolarization (see chapter 1, figure 9). An electrocardiogram measures the variations in voltage that are produced by depolarization and repolarization of the myocardium either at the surface of the body using electrodes (ECG) or from within the heart from an intracardiac electrode. Unipolar recordings measure the potential difference between one point of the body with respect to a second point, called the ground potential or Wilson's central terminal (arithmetic zero of the surface leads I, II, III). Unipolar leads therefore record voltages at one point relative to zero. Bipolar leads detect variations in electrical potential between two electrodes, neither of which is at zero potential.

In the standard surface ECG, the detection of ischaemia is usually not difficult since each of the unipolar praecordial leads maps a specific region of the ventricular myocardium and localised ischaemia episodes result in characteristic ST segment changes in at least one lead[42,101,102]. The situation with intracardiac recordings, and especially with right ventricular (RV) recording, is much less clear[103,104]. The impact of chronic myocardial ischaemia on endocardial electrograms is known but it

is not very specific or sensitive[105,106]. Acute ischaemia is easily detectable in monophasic action potential recordings (decrease of the maximum up-stroke velocity, shortening of the plateau duration, decrease in amplitude, etc) but these recordings are not suitable for chronically implanted devices[107-109].

Several small studies have investigated intracardiac EGMs during ischaemia induced by balloon inflation or artery legation[110-116]. As early as 1978, Varriale and Niznik reported ≥ 1.5 mV ST segment displacement in right ventricular unipolar electrograms signals, in patients studied within 12 hours of the occurrence of acute myocardial infarction[113]. A seminal animal study by Siegel et al, investigated graded occlusion of the circumflex and left anterior descending coronary artery[114]. Compared with the surface ECG, more dramatic and earlier ischemic changes in all left ventricular EGMs, 71% of RV EGMs, and 90% of bipolar EGMs recorded in the coronary sinus, were reported[114]. Nabel et al, investigated the detection of pacing induced myocardial ischaemia by endocardial EGMs, in humans[116]. They reported that unipolar endocardial EGMs were more sensitive than surface ECG for detection of ischaemia induced by rapid atrial pacing. More recent animal studies have found similar results and observed changes in RV EGMs very shortly after artery ligation[117,118].

Human data are restricted to very small and non-systematic studies of both left and RV endocardial recordings during elective angioplasty. For instance, a study of left ventricular EGMs in 11 patients found a decrease of amplitude and increase of duration of the EGMs after 90 s of balloon occlusion of left anterior descending artery with a return to baseline values after 30 – 120 s of balloon deflation[110]. Intra-

coronary EGMs were also studied in 25 patients during angioplasty[119]. ST segment elevations were found in 72% of stenoses being dilated appearing much more quickly during balloon inflation and disappearing during balloon deflation. It has been also reported that these changes are more sensitive than the standard ST segment changes in the surface ECG.

Probably the most principal problem encountered in these studies is the character of intracardiac recordings[120]. Compared to the standard surface ECGs, both unipolar and bipolar intracardiac EGMs are much more local signal driven, masking the global far-field ECG by magnified near-field signal reflecting the focal activity of the tissue close to the tip of the electrode. To a lesser extent, the focal activity affects the coronary sinus EGMs since, compared to the screwed-in intracardiac leads, the coronary sinus electrodes are in a less direct contact with the active myocardium. This suggests that special electrode configurations are needed to detect ischaemia remote from the electrode implantation site. For the purposes of this study, the use of special electrode configurations is proposed that are able to record electrograms of 'global' far-field dipoles not polluted by the near-field local signals.

Objective of this thesis.

Implanted devices are well established for the treatment of bradyarrhythmias and life threatening ventricular tachyarrhythmias. A significant proportion of these patients receiving device therapy suffers with coronary artery disease, or has had previous myocardial infarction. With the option to effectively treat these arrhythmias, progression of the underlying heart disease becomes the prime determinant of the patient's prognosis. Multilead bipolar configurations presently available in

implanted devices offer a potential source for long term monitoring of myocardial ischaemia.

The thesis is aimed at investigating whether myocardial ischaemia can be reliably detected from reconstructed right-sided bipolar intracardiac EGMs. A real-time ischaemic ST segment monitoring algorithm can then be incorporated into implanted devices to monitor for silent or symptomatic myocardial ischaemia. The potential clinical application of a commercially available device to monitor myocardial ischaemia is enormous and includes the following:

I. In patients with unstable angina, episodes of silent ischaemia are approximately 10 fold more frequent than the episodes of symptomatic ischaemia[42,101,102]. Moreover, all episodes of symptomatic ischaemia are preceded by a silent phase, which lasts in a substantial proportion of symptomatic episodes, for tens of seconds to minutes. Prolonged ischaemic episodes, including the silent ones, contribute to disease progression and decrease myocardial viability. Even brief ischaemia episodes can induce arrhythmia through virtually all known arrhythmogenic mechanisms including focal re-entry, in-homogeneity of conduction velocity, increased repolarisation dispersion, and triggered activity[121]. The danger of arrhythmogenesis increases with the duration of ischaemia episodes. Consequently, if an implantable device was to detect episodes of silent ischaemia quickly, the device could then be used to facilitate the application of anti-ischaemic therapies. For instance, the implanted device can be programmed to give the patient a warning by a specific sensation (e.g. vibration of the can of the device). The patient could then react appropriately, either by changing physical and/or psychological workload or by taking a fast

acting nitrate preparation. Alternatively, automatic ischaemia detection can be linked to an implanted system delivering drug or neural stimulation therapy. In pacing dependent patients, the pacemaker can be programmed to pace at a slower heart rate therefore minimising oxygen consumption and demand.

II. Early warning to patients or physician of an impending acute coronary syndrome. For instance, ST segment duration of unusual duration and amplitude can alert the attending physician to arrange urgent cardiac catheterisation and/or intervention

III. The ability to objectively compare signs of myocardial ischaemia with the subjective and non-specific symptoms reported by patients. Patients can activate EGM storage by application of an external device such as a magnet.

IV. Monitoring and classification of chest pain syndromes and coronary artery stenosis of indeterminate haemodynamic severity.

V. Classifying ischaemic versus non-specific substrates of arrhythmias. By analysing the EGM prior to the onset of the arrhythmias, the mechanism of arrhythmogenesis can be determined and treated appropriately with revascularisation strategies. Thereby avoiding unnecessary ICD insertion with its associated costs and morbidity.

VI. Improving the therapeutic algorithms of ICDs. Ischaemia can negatively affect the efficacy of a device anti-tachycardia therapy, e.g. by increasing defibrillation and pacing threshold[122,123]. Acute ischaemia can also change

the morphology of endocardial electrocardiograms making them unrecognisable by the arrhythmia device, thus causing device failure[110]. Hence, if an anti-tachycardia implantable device were equipped with the possibility of detecting ischaemia episodes, the low and high energy therapy algorithms and programming could be changed, e.g. by changing the sensitivity of arrhythmia detection and classification, and by increasing the voltage of pacing stimuli and the energy of defibrillation shocks.

For all the above reasons, an automatic detection of myocardial ischaemia by an implanted device is desirable. Unfortunately, it is not obvious whether a practically feasible device could have a sufficiently high sensitivity and specificity for ischaemia detection making the practical application plausible. Consequently, before the development of an implantable ischaemia monitor is attempted and/or the possibility of adapting the pacing and defibrillation algorithms for ischaemia researched, a comprehensive pilot study needs to be conducted confirming that the detection of ischaemia from right-sided intracardiac electrodes (suitable for chronic implantation) can be achieved speedily (within the silent phase) with an acceptable accuracy. The project proposed is aimed at undertaking this investigation.

CHAPTER 3

Methodology and General Conduct of The Study

Introduction

The studies undertaken in this thesis were part of an overall programme aimed at modelling the detection of myocardial ischaemia by an implanted device. It also investigated whether novel T wave morphology descriptors can be used as indices to monitor myocardial ischaemia. The goal of this thesis was therefore accomplished by conducting the following studies:

- To define the optimal unipole for monitoring myocardial ischaemia from within the right ventricle (chapter 4).
- The diagnostic accuracy of detecting myocardial ischaemia using the *absolute* electrical activity detected from four bipolar leads reconstructed from the optimal unipoles that are potentially available in implanted devices (chapter 5).
- The diagnostic accuracy of detecting myocardial ischaemia using *normalised* electrical activity detected from the four bipolar leads (chapter 6).
- Monitoring myocardial ischaemia by the application of novel descriptors of T wave morphology, potentially available in implanted devices (chapter 7).

All the studies shared the same patient population and electrocardiographic protocol. In this chapter, patient selection, the electrocardiographic procedure, signal processing, ethical issues and the general conduct of the study are discussed.

Subjects

The study investigated patients electively admitted for percutaneous transluminal coronary angioplasty (PTCA)/stenting. The following patients were excluded:

- patients with a previous myocardial infarction in the area at risk during PTCA
- patients with occluded coronary arteries
- bundle branch block,
- atrial fibrillation
- leads with noisy recordings
- patients with contrast induced ST changes

All patients studied were in normal sinus rhythm. The patients were classified according to the artery on which the procedure was being performed and to those with single and multiple vessel disease. The study was approved by the Local Research Ethics Committee and all subjects provided written informed consent (see appendix).

Electrocardiogram protocol

The following ECG recordings were recorded before, during and after PTCA:

1. The standard surface 12-lead ECG. High quality surface electrodes (Medicotest Blue Sensor disposable electrodes type R-00-S; Medicotest A/S, Rugmarken 10, DK-3650 Olstykke, Denmark) were used.
2. Four surface high quality surface electrodes were placed at the left pre-pectoral region (expected site of a monitoring device implant), which simulated an active can of a hypothetical implanted device. These four electrodes were combined to form a single output lead.
3. In all patients, a multipolar cardiac electrode was positioned at the right ventricular apex (figure 2.1). This allowed unipolar recordings to be obtained

from the right atrium and within the right ventricle. The initial electrode used was a Cordis Webster Inc. Porterfield hexapolar electrode;

6 unipoles (4 ventricular and 2 atrial).

9-pin connector

Deflectable tip

Total length: 115 cm

Spacing of unipoles: 4,13,4,100,4 mm

Unfortunately there were three cases of cardiac tamponade and following the local research ethics committee review, the electrode was changed to a Cordis Avail electrode (A-Josephson Type);

4 unipoles

Size 6 F

10-pin connector

Fixed curve

Total length: 115 cm

Spacing of unipoles: 5 mm

4. In 9 patients, a Cordis Quadripolar deflectable tip electrode was positioned in the coronary sinus (figure 2.1b and c) as distal as possible or to the level of the great cardiac vein;

4 unipoles

Size 6F

Plug connector

Deflectable tip

Total length: 92 cm

Spacing of unipoles: 2, 5, 2 mm

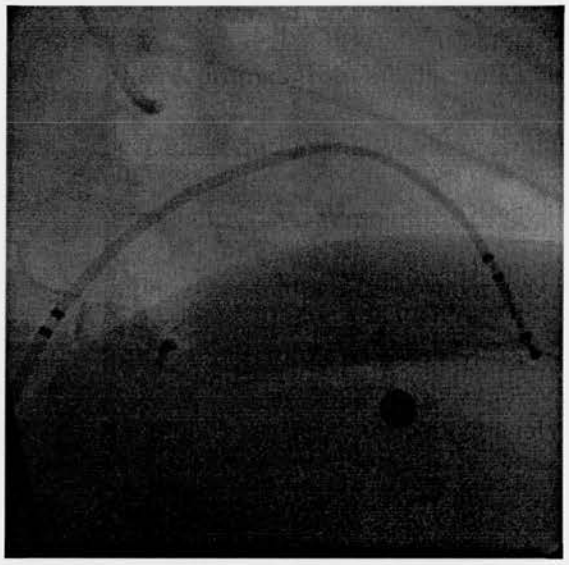
In order to obtain reasonable baseline characteristics, the recording were started a few minutes prior to the induction of the angioplasty balloon and finished several minutes after completion of the PTCA/stenting and removal of the balloon. The overall electrocardiographic recording protocol for the project in addition to the standard preparation for the PTCA procedure can therefore be summarised as follows:

- Patient in catheter lab
- 12-lead ECG and left pectoral recording
- Intracardiac electrodes
- Baseline recording
- Routine angioplasty / stenting
- Balloon, guidewire and guide catheter removal
- Final control recording
- End of study

} Continuous 12-lead ECG and intracardiac EGM recording

The recordings from all electrodes present were performed continuously on a beat-to-beat basis during the whole procedure. The target vessel that was revascularised, the introduction and removal of the balloon, and each moment of balloon inflation and deflation were precisely recorded. The timings of balloon induction/removal and inflation/deflation were used to identify the appropriate sections of the ECG recordings used for subsequent analysis.

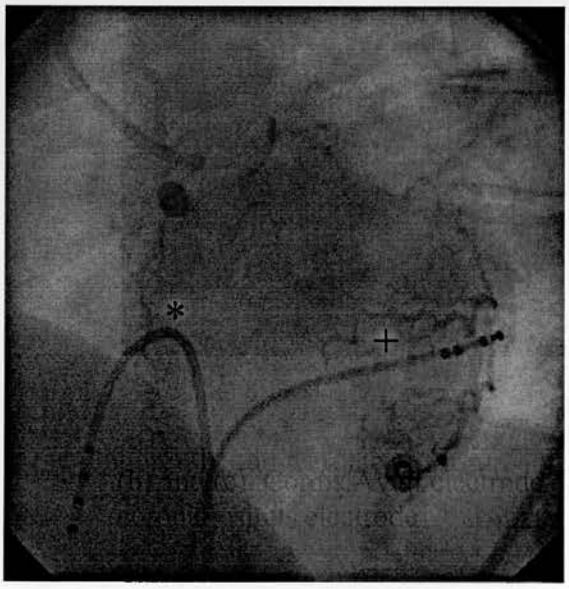
Figure 2.1. Intracardiac electrodes.



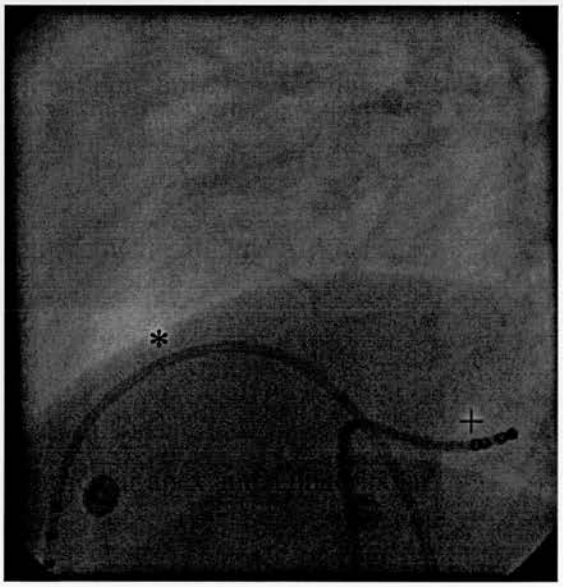
(a) RAO view. Cordis Porterfield hexapolar electrode positioned in the right ventricular apex. Four unipoles are within the right ventricle and two unipoles are within the right atrium.

(b) and (c). Cordis Avail electrode* positioned in the right ventricular apex and a quadripolar coronary sinus electrode+

(b) LAO view



(c) Lateral view



Electrocardiogram recording and storage protocol

All unipolar recordings were sampled at 1 kHz and stored digitally on the magneto-optical disc of the EP Med Systems EP Work Mate. This is a computer based electrocardiographic recording and monitoring system designed for efficient capture, display and retrieval of surface and intracardiac signals during cardiac electrophysiology studies. The system contains a fully automated software waveform detector, which performs on-line recognition of cardiac activation on pre-selected leads. Temporal interval measurements are computed on a beat-to-beat basis on multiple channels and dynamically posted on the real time display. The hardware configuration consist of four 21" high resolution display monitors, a Pentium processor, 2 Gbyte hard disk drive, 1.44 Mbyte industry standard floppy disk drive (3.5"), 4.6 Gbyte Optical (MO) drive, 4 Gbyte Digital Audio (DAT) tape dive, TI 34020 Advanced Graphics Coprocessor, 74-138 channel analog-to-digital (A/D) signal conditioning data acquisition module with integrated pressure/marker interface, catheter interface box, EP-3 integrated stimulator, and HP LaserJet 6 series printer.

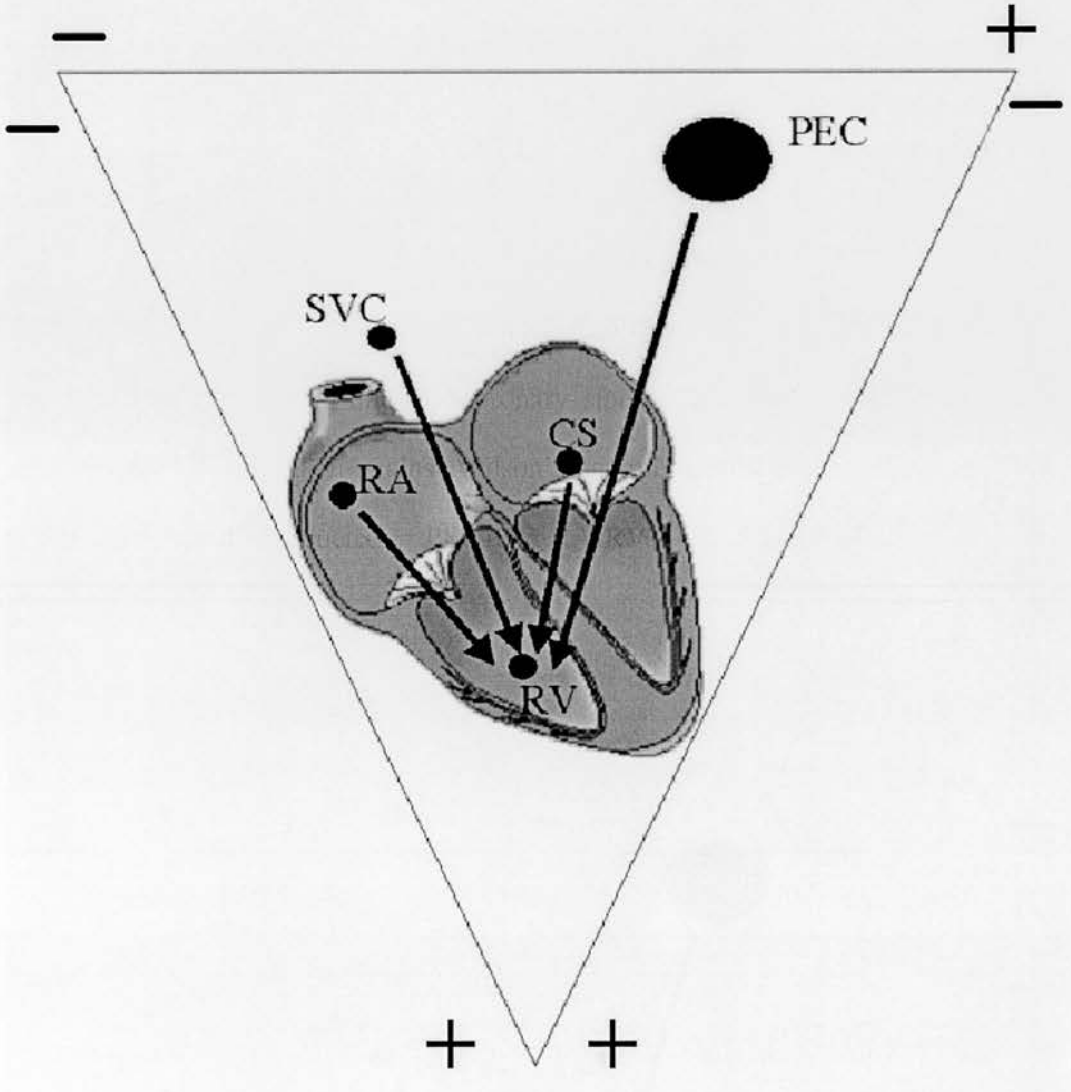
Electrocardiogram signal processing

The digital data (sampling frequency of 1000 Hz and voltage resolution of 1.0 μV) was exported from EP Work Mate (EP MedSystems, Inc.) using an IOmega zip external disk drive (250 MB) and transferred to a dedicated personal workstation for off line processing using purpose-written software. Surface and intracardiac ECG leads were stored in separate data files. Recording of each patient consisted of ≥ 1 sessions and each session was analysed separately.

Availability of ECG leads

Besides the standard surface ECG leads (I, II,III,AVR,AVL,AVF,V1-V6), the following leads were recorded: pectoral lead (PEC), 4 unipolar right ventricular unipolar leads (RV1-4, from distal to proximal), 4 unipolar coronary sinus leads (CS1-4, from distal to proximal), 2 unipolar right atrial leads (RA1-2). The pectoral lead and all intracardiac EGMs were recorded in a unipolar configuration against Wilson's central terminal (arithmetic zero of the surface leads I, II, III) as the standard indifferent electrode (figure 2.2).

Figure 2.2. The standard surface ECG leads, a pectoral lead (PEC - simulating an implanted device) and unipolar EGMs were recorded from: the right ventricle (RV), superior vena cava (SVC) and the coronary sinus (CS). The pectoral lead and all unipolar EGMs were taken against Wilson's central terminal. The following bipolar EGMs were then reconstructed: = PEC-RV, RA-RV, SVC-RV, CS-RV.



Definition of potentially "device-related" ECG unipoles and dipoles

Unipoles were defined as follows:

1) mean right atrial unipole RA = (RA1 + RA2) / 2

2) superior vena cava unipole SVC = (PEC + 2 * RA) / 3

3) mean coronary sinus unipole CS = (CS1 + CS2) / 2

4) mean right ventricle unipole RV = (RV3 + RV4) / 2

From the unipolar digital data, bipolar leads were reconstructed by calculating the algebraic sum of the potential between two unipoles. The following bipolar leads were reconstructed:

1) dipole between PEC and RV

2) dipole between RA and RV

3) dipole between SVC and RV

4) dipole between CS and RV

Definition of ECG segments

Special multichannel ECG-viewer with incorporated timing database was used to identify the appropriate sections of the ECG recordings used for subsequent analysis. Specifically, pre-procedural segment with baseline ECG record was identified and timing of individual coronary procedures (times of balloon inflation/deflation) was entered. The information regarding the angioplastied artery was also provided.

Identification of QRS complexes

In order to minimize the influence of white noise (the term used to describe noise within measured signals that has no preferential frequencies and is thus of random background nature), baseline shifting, and movement artefacts, the "best" of all surface leads was selected for the detection of QRS complexes. The QRS complexes were detected using combination of threshold and derivative method[124]. The signal-averaged sinus QRS template was created and correlation between all QRS complexes and the signal-averaged template of sinus QRS was used to adjust the exact position of QRS fiducial points. The QRS fiducial point is a reference to QRS complex timing. Specifically, as each QRS complex has a non-zero width, the measurement of the time interval of a cardiac cycle can only be precise if each QRS complex is recognised at a standardised point within the complex.

Classification of QRS complexes

QRS complexes and corresponding RR intervals were sorted into specific sequences according to a) QRS morphology, b) RR interval length, and c) difference of consecutive RR interval length. Both tails of all these sequences (most probably containing the QRS complexes of non-sinus origin or artefacts) were visually inspected and all QRS complexes were appropriately classified. Ten categories of QRS complexes were used: normal sinus, supraventricular premature complexes, ventricular premature complexes, atrial escape complexes, ventricular escape complexes, aberrantly conducted complexes, fused complexes, other abnormal wide

QRS complexes, noisy sinus, unclassified morphologies. Only narrow, non-distorted QRS complexes of sinus origin with normal AV conduction were used for the calculation of sinus RR intervals.

Calculation of ST deviation

The signal averaged ECG template of PP interval was created and reference point in the middle of PQ segment and J-point were manually defined. For each normal sinus RR interval, the mean voltage was calculated in the interval ± 5 msec around the PQ-reference-point and in the interval 75-85 msec after J-point within ST segment. ST deviation was defined as the absolute value of difference between mean voltages in PQ and ST segment.

Analysis of ST deviation trend

Two alternative methods were used for the analysis of ST trend during coronary procedures:

Correction of ST trends

Trends of ST deviation in individual leads were smooth-averaged in such a way that ST deviation in each PP interval was replaced by the average of ST deviations within interquartile range of ST deviations in the interval of ±5 seconds surrounding this PP interval. Trends of ST deviations during coronary procedures were corrected for spontaneous oscillation of ST deviations at baseline (i.e. divided by standard deviation of mean ST deviation at baseline segment). Finally, ST deviation at any time of

procedure was expressed as an absolute difference to the ST deviation at the time of balloon inflation.

Pairwise comparison of ST trends

The advanced manual editing of ECG signal including baseline and procedural segments was performed to exclude all PP intervals with excessive noise. Mean ST deviation was calculated in the sequence of 5 s windows with 2.5 s overlap. Average ST deviation in corresponding windows of baseline and procedural segments were used for the statistical testing.

T wave morphology Assessment

Recently, a fundamentally new concept for analysis of the abnormalities of ventricular repolarisation that can be obtained from a single ECG beat has been proposed. It is based on analysis of the morphology of the three-dimensional T loop[125,126]. However, unlike classical vectorcardiography, the T loop is analysed in a mathematically derived three-dimensional space, after separating the components of the T wave representing the three-dimensional movement of the ECG dipole from the non-dipolar components. The non-dipolar components, termed T wave residua, most likely reflect regional heterogeneity of myocardial repolarisation. The separation of T wave residua represents the first successful attempt to quantify regional information about ventricular repolarisation from the standard 12-lead ECG. The proportion of T wave residua within all dipolar and non-dipolar components was shown to differ significantly between normal subjects and patients with hypertrophic cardiomyopathy,

dilated cardiomyopathy and acute myocardial infarction[127]. In a recent prospective evaluation, increased proportion of T wave residua predicted independently in multivariate analysis adverse outcome in 813 male patients (70% with coronary artery disease) followed-up for 10.4±3.8 years[128].

After separating the non-dipolar components and reconstructing the ECG in a 3-dimensional space containing only the dipolar components, the T loop is described by a set of parameters. One of them measures the angle between the main QRS and T vectors (total cosine between the R and T vectors, TCRT). In effect, it quantifies the difference between the main direction of the wavefront of depolarisation and of repolarisation. This parameter revives the classical concept of the ventricular gradient (VG), proposed in the 1930's by Wilson et al[129]. They calculated the algebraic sum of the areas under the ventricular deflections of the electrocardiogram (the net QRST area) and believed that this vector parameter was independent of the sequence of ventricular activation, as long as the ventricular recovery properties remained constant. Therefore, it was considered that VG might help to distinguish T wave changes following changes in the activation pattern ('secondary' T wave changes) from those due to myocardial damage ('primary' T wave changes). The concept did not evolve into a clinically useful tool mainly due to technical difficulties with the measurement of ECG areas[130,131]. In the last decade the concept was largely forgotten.

The TCRT has been demonstrated to be more reproducible and to separate normal from abnormal ECGs better than conventional repolarisation parameters, such as QT interval and QT dispersion[126]. More recently, TCRT was also shown to predict

independently in multivariate analysis mortality and arrhythmic complications after myocardial infarction[128].

The other parameters or descriptors of T-wave morphology include: T-wave loop dispersion, which reflects variability of the T-wave vector loop; the normalized T-wave loop area, which measures the heterogeneity of the principal components of the T wave within its loop; and T-wave morphology dispersion, which expresses morphological heterogeneity within the 12-lead ECG.

Analysis of T-wave morphology trend

For the analysis of T-wave morphology similar approach as described in the Section 7.2 was applied. Instead of mean, median of repolarisation waveforms was used. A detailed description the T wave morphology descriptors used are discussed in Chapter 7.

General Conduct of The Study

Patient recruitment

Patients' names were obtained from the elective PTCA/stenting waiting list and their notes examined to ensure that they met the inclusion criteria. Patients were contacted via the telephone several weeks (minimum of one week) before their elective date for admission. The study was briefly explained. An information sheet (see appendix) together with the consent form (see appendix) was then mailed to them. The patients were advised not to consent until they had read the information sheet and fully understood the objective and reason for conducting the study. For patients who were uncontactable over the telephone, a covering letter (see appendix) was also enclosed and mailed.

The patient was then met the evening before or the morning of the procedure to answer any queries and obtain final informed consent.

In total 120 patients were contacted. Twenty-four (20%) refused to participate. Twenty-one (17.5%) were cancelled due to no beds. Four were (3.3%) cancelled due to time pressure (unable to perform the procedure within the working day). In two patients the target vessel was considered too small for intervention. In two patients there were no available electrodes or connectors. One patient was asymptomatic and the lesion was considered not significant. In one patient there were difficulties cannulating the femoral vein. In one patient the target vessel was occluded (previously patent with a 90% stenosis) and the area it supplied was well collateralised. In one patient the risk-benefit ratio was considered too great, as the vessel was unprotected.

One patient developed left bundle branch block whilst waiting to be admitted. One patient was cancelled due to no perfusionist for surgical cover. One patient was admitted in pulmonary oedema and was therefore cancelled. Ten recordings were noisy or unsuitable. At the end, a final cohort of forty-eight patients with suitable ECG and EGM recordings were obtained.

Patient characteristics

The demographics and characteristics of the 48 patients that were studied are summarised in table 1.

Table 1. Demographics and characteristics of the 48 patients studies

Name	Sex	age	Intracardiac Recordings	Artery angioplastied/stented
Patient 1	f	58	RV, CS	LAD
Patient 2	m	63	RV, Atrial	LAD
Patient 3	m	57	RV, CS	LAD
Patient 4	m	75	RV, Atrial	RCA
Patient 5	m	58	RV, Atrial	RCA
Patient 6	m	55	RV, CS	RCA
Patient 7	m	71	RV, Atrial	Cx
Patient 8	m	51	RV, Atrial	LAD, D, OM
Patient 9	m	61	RV	RCA
Patient 10	m	67	RV	LAD
Patient 11	m	59	RV, Atrial	LAD
Patient 12	m	60	RV	RCA
Patient 13	m	68	RV, Atrial	LAD
Patient 14	m	68	RV	RCA
Patient 15	m	64	RV, Atrial	Cx, LAD
Patient 16	m	56	CS	Cx
Patient 17	m	56	RV, Atrial	LAD
Patient 18	m	49	RV	RCA
Patient 19	m	65	RV, Atrial	RCA
Patient 20	m	61	RV, Atrial	LAD
Patient 21	m	64	RV, Atrial	LAD
Patient 22	m	62	RV, Atrial	LAD
Patient 23	m	71	RV, Atrial	LAD, RCA
Patient 24	m	51	RV, Atrial	LAD, RCA
Patient 25	m	70	RV, Atrial	LAD, OM, D
Patient 26	m	74	RV, CS	OM, SVG-LAD graft
Patient 27	m	79	RV	RCA
Patient 28	m	69	RV, Atrial	LAD
Patient 29	m	51	RV, Atrial	Cx, LAD
Patient 30	m	70	RV, Atrial	D
Patient 31	m	57	RV, CS	OM, LAD
Patient 32	m	54	RV, Atrial	RCA
Patient 33	f	68	RV, CS	OM, Cx
Patient 34	m	43	RV, Atrial	RCA
Patient 35	m	53	RV, Atrial	RCA, OM
Patient 36	m	42	RV, Atrial	LAD, Cx, RCA
Patient 37	m	56	RV, CS	RCA
Patient 38	m	55	RV, CS	Cx

Table 1 (continued). Demographics and characteristics of the 48 patients studies

Name	Sex	age	Intracardiac Recordings	Artery angioplastied/stented
Patient 39	m	60	RV, Atrial	RCA
Patient 40	m	49	RV, Atrial	RCA
Patient 41	m	76	RV, Atrial	RCA
Patient 42	m	64	RV, Atrial	LIMA/LAD anastamosis
Patient 43	m	78	RV, Atrial	RCA, Cx
Patient 44	f	70	RV	RCA
Patient 45	m	60	RV, Atrial	LAD, RCA
Patient 46	m	49	RV, CS	RCA
Patient 47	m	59	RV, Atrial	RCA
Patient 48	m	42	RV	LAD

Male= m, female= f. All patients had a 12-lead surface ECG and an electrode placed in the left prepectoral region (expected site of an implanted device). RV= recordings from the right ventricular electrodes, Atrial = recordings from the atrial electrodes, CS= recordings from the coronary sinus electrodes. LAD= left anterior descending artery. RCA= right coronary artery, Cx= circumflex artery, D= diagonal artery, OM= obtuse marginal artery, SVG= saphenous vein graft, LIMA= left internal mammary artery.

Adverse events

Unfortunately, during EGM recordings, there were three cases of cardiac tamponade after electrode placement in the right ventricular apex by two senior operators.

Patient1. Approximately 2 hours after the angioplasty/stenting procedure, the patient became acutely unwell with hypotension and dyspnoea. Echocardiogram confirmed a pericardial effusion, which was treated by pericardiocentesis and a drain insertion. He made a good recovery and was discharge 2 days later.

Patient 2. Approximately 15 minutes after angioplasty/stenting the patient did not feel well and became bradycardic and hypotensive. He later had an EMD arrest, which required brief cardiopulmonary resuscitation. There were no electrocardiographic changes to suggest stent re-occlusion. He was intubated by the anaesthetist and an echocardiogram showed a large circumferential pericardial effusion. A pericardial drain was inserted, which drained approximately 480 mls. of blood. His blood pressure then normalised and repeat echocardiogram showed a small effusion. At approximately 13:20 he again became hypotensive and bradycardic requiring 1mg of adrenaline. At this stage his case was discussed with the cardiothoracic surgeon who arranged for surgical repair. At sternotomy a bleeding point at the right ventricular apex was identified and oversewn. The patient was finally discharged 6 days later.

Patient 3. About one hour after angioplasty/stenting, the patient became hypotensive and an echocardiogram demonstrated a 2 cm pericardial effusion. Pericardiocentesis -

and a drain insertion were carried out. The pericardial drain was removed the following day and the patient was discharged 2 days later.

The study was temporarily discontinued after the first two cases whilst the Local Research Ethics Committee (LREC) reviewed the study. It was then decided to restrict the placement of intracardiac electrodes by consultants only. After the third incidence, the study was again stopped. Following the LREC review, the study was allowed to continue with the proviso that the intracardiac electrode was changed to one which is commonly used, and with a proven safety and experience record. This was done and there were no further complications.

CHAPTER 4

Monitoring Myocardial Ischaemia Using Right Ventricular Unipolar Intracardiac Electrograms

INTRODUCTION

A number of previous studies have investigated the use of unipolar electrograms (EGMs) from within the right ventricle during myocardial ischaemia[110,113,114,132]. However, there has been no systematic study of the ideal location from within the right ventricle for monitoring myocardial ischaemia. As subsequent studies in this thesis are dependent on investigating the reconstruction of bipolar leads using RV unipoles, it is imperative to ensure that the ideal or most sensitive RV unipole is used. The aim of this study is to investigate the optimal unipole for monitoring myocardial ischaemia from a multipolar intracardiac lead placed at the right ventricular apex.

PROTOCOL

Study Subjects, Surface Electrocardiograms (ECGs), Intracardiac Electrograms and Signal processing

Eleven patients were investigated who were undergoing elective percutaneous transluminal angioplasty (PTCA). After obtaining informed consent, each patient had a Cordis Webster Porterfield 7F electrode inserted at the right ventricular apex. As previously discussed in Chapter 2, the Porterfield electrode had 4 ventricular unipoles. The first unipole (RV1) was situated at the tip of the electrode with the subsequent unipoles being 4 mm (RV2), 17 mm (RV3), and 21 mm (RV4) from the electrode tip. Continuous 12-lead surface ECG and intracardiac EGM recordings were recorded at baseline, during, and following angioplasty, using the EP Workmate Med Systems. Offline ST segment processing and analysis have been fully discussed in Chapter 2. In

short, the amplitude of the ST segment was measured in all sinus complexes relative to the PQ segment, 75-85 ms after the J point. ST deviation was defined as the absolute value of difference between mean voltages in PQ and ST segment.

Statistical analysis

The surface ECG lead with the most prominent ST change during balloon inflation was selected for each patient. Pearson's correlation coefficient was then calculated between this surface lead and the four ventricular unipoles. Differences between intracardiac unipoles, and between intracardiac unipoles and the surface leads were tested using the paired t-test. A p value <0.05 was considered as statistically significant. Statisca for Windows version 5.1 was used for all statistical analysis.

RESULTS

In total 10 men and 1 woman were investigated during normal sinus rhythm. Mean age = 62.9 (± 7.7) years (standard deviation). Tables 4.1 summarises the target coronary arteries that were revascularised and the surface ECG lead with the maximum ST deviation during balloon inflation. Figure 4.1 illustrates an example of the 12-lead surface ECG and intracardiac EGM at baseline and during balloon inflation for a patient undergoing distal right coronary artery intervention (patient 5). Pearson's correlation coefficient between the best surface ECG lead and the four ventricular unipoles (RV1-RV4) are also summarised in Table 4.1. The accuracy to detect dynamic ST segment deviation progressively increased the further the distance

from the endocardial tip (RV1 versus RV4, p= 0.03). With the exception of lead V2, there was no significant difference between the surface ECG leads and RV4 (table 4.2).

Table 4.1. Demographics and Pearson's correlation coefficient between the best surface ECG lead for monitoring myocardial ischaemia and the respective right ventricular unipoles (RV1-4).

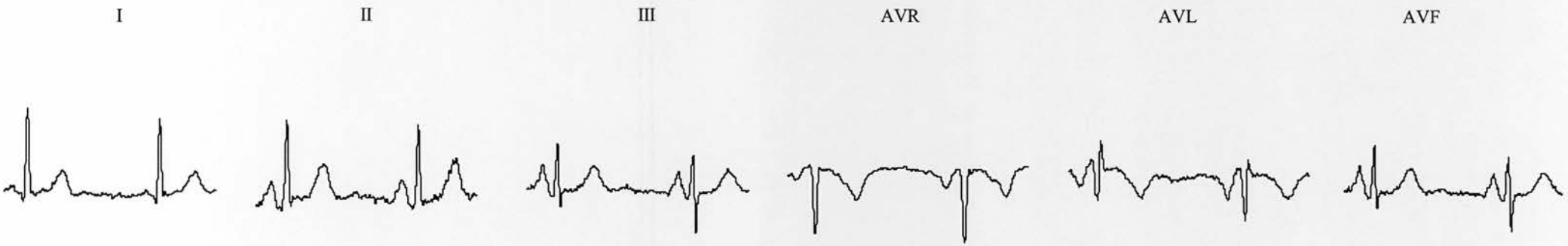
	Age	Sex	PTCA ARTERY	Surface ECG lead with max. ST deviation	Pearson's correlation coefficient between the best surface ECG lead and the respective RV unipoles			
					RV1	RV2	RV3	RV4
Patient 1	63	m	LAD	V2	0.14	0.08	0.60	0.64
Patient 2	55	m	RCA	AVF	0.10	0.18	0.20	0.37
Patient 3	67	m	LAD	V2	0.37	0.72	0.74	0.71
Patient 4	59	m	LAD	V4	0.17	0.28	0.44	0.65
Patient 5	60	m	RCA	AVF	0.38	0.37	0.42	0.44
Patient 6	68	m	LAD	V4	0.06	0.02	0.08	0.01
Patient 7	65	m	RCA	III	0.15	0.17	0.03	0.20
Patient 8	51	m	LAD	V3	0.07	0.01	0.07	0.08
Patient 9	79	m	RCA	AVF	0.52	0.51	0.36	0.39
Patient 10	57	m	OM,LAD	V3	0.01	0.33	0.45	0.39
Patient 11	68	f	OM,CX	III	0.20	0.26	0.03	0.24

Table 4.2. Results of paired t-test for dependent samples between RV4 and surface ECG leads. With the exception of V2, there was no significant difference between RV4 and the surface ECG leads. Paired t-test between RV1 and RV4, $p = 0.03$.

	I	II	III	AVR	AVL	AVF	V1	V2	V3	V4	V5	V6
RV4	0.81	0.20	0.45	0.63	0.15	0.57	0.45	0.046	0.15	0.41	0.24	0.18

Figure 4.1. Surface 12-lead ECG and intracardiac EGM before and during balloon inflation during distal right coronary angioplasty (patient 5). Note the improved signal to noise ratio in the intracardiac EGM compared with the surface ECG. Maximum ST elevation during the procedure occurred in leads AVF and RV4 amongst the surface ECG and intracardiac EGMs, respectively.

Before inflation



During inflation

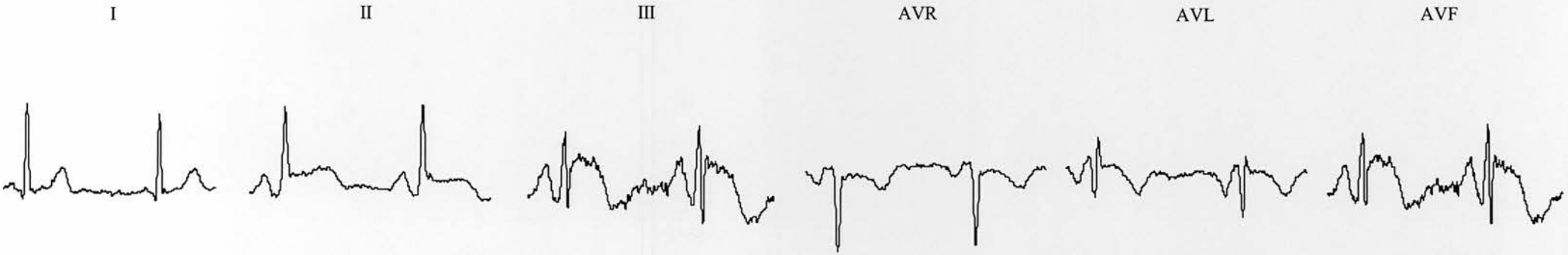
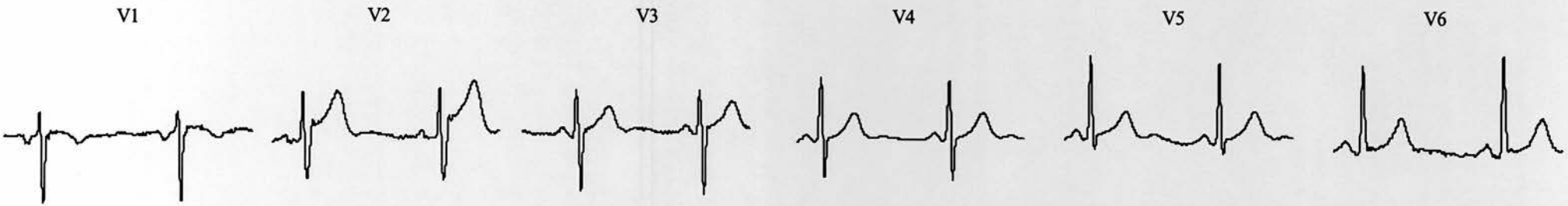


Figure 4.1. **Continued.**

Before inflation



During inflation

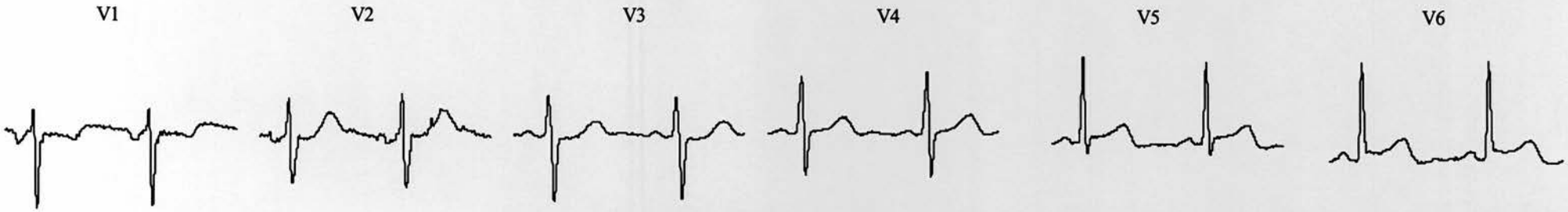
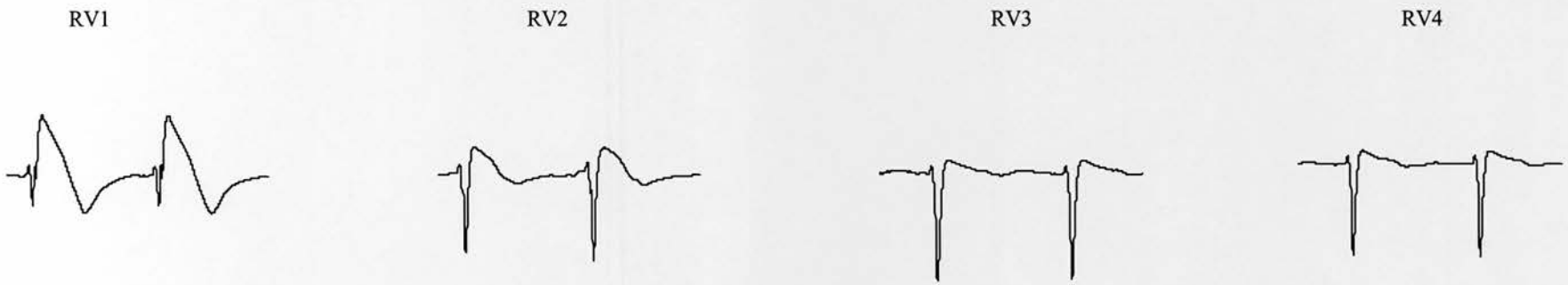


Figure 4.1. Continued.

Before inflation



During inflation

DISCUSSION

Right ventricular cavity potential varies considerably depending on its precise intraventricular location. This study demonstrates that right ventricular intracavitary recordings obtained from unipoles at or near the distal tip of the electrode are less sensitive in detecting myocardial ischaemia when compared to recordings obtained from more proximal unipoles.

This is the first systematic study that investigated the optimal site for unipolar recordings from within the right ventricular cavity for monitoring cardiac ischaemia. Previous studies randomly place electrodes at the right ventricular apex and obtained recordings from 1 or 2 distal unipoles[113,116,132]. Electrode contact with the endocardium generates a variable ST segment elevation termed current of injury[133]. The ST segment remains isoelectric if the electrode position is free of endocardial contact. This current of injury may pollute unipolar signals at or close to the tip of the electrode, thereby masking regional and farfield electrophysiological changes that occur during myocardial ischaemia. Although the current of injury may play an influential role in the acute setting of electrode placement, it does not apply to chronically implanted electrodes, since ST segment returns to baseline in one to three weeks[134]. Therefore it is reasonable to speculate that with time there may be no significant differences between proximal and distal unipolar recordings.

The clinical relevance of using the proximal unipoles becomes important during the construction of bipolar multilead configurations using the RV unipoles as discussed in the subsequent chapters. In order to improve the sensitivity of intracardiac EGM

monitoring, the average recording of RV3 and RV4 recordings will be used as a single unipole.

A limitation of the study is that a quadripolar catheter was used in the right ventricle. An electrode with more unipoles may have better defined the most optimal unipole for monitoring myocardial ischaemia. For instance, there may be a transition point within the right ventricular cavity whereby more proximal recordings are less sensitive. In addition, the optimal unipole in a patient will vary in relation to right ventricular cavity size. Multipolar monitoring in implanted devices is impractical in view of battery consumption.

CONCLUSION

EGM recordings obtained from unipoles near the distal tip of the electrode are less sensitive in detecting myocardial ischaemia when compared to recordings obtained from more proximal unipoles. Therefore, for far-field global myocardial ischaemia monitoring, intracardiac electrodes should obtain recordings from a more central or basal location within the right ventricular cavity.

CHAPTER 5

The Detection of Myocardial Ischaemia Using Four Bipolar Leads Reconstructed From The Unipoles That Are Potentially Available In Implanted Devices

INTRODUCTION

Compared to the standard surface ECGs, unipolar intracardiac EGMs are much more local signal driven, masking the global far-field ECG by magnified near-field signal reflecting the focal activity of the tissue close to the tip of the electrode. To a lesser extent, the focal activity affects the coronary sinus EGMs since, compared to the passive or screwed-in intracardiac leads, the coronary sinus electrodes are in a less direct contact with the active myocardium. Therefore, multilead bipolar configurations may improve the detection of myocardial ischaemia remote from the electrode implantation site. For the purposes of this study, the use of special electrode configurations is proposed that are able to record electrograms of 'global' far-field dipoles not polluted by the near-field local signals.

The aim of this study is to investigate the diagnostic accuracy of detecting myocardial ischaemia using four bipolar leads reconstructed from the unipoles that are potentially available in implanted devices.

PROTOCOL

Study Subjects, Surface Electrocardiograms (ECGs), Intracardiac Electrograms (EGMs) and Signal processing

Forty-eight patients were investigated who were undergoing elective percutaneous transluminal angioplasty (PTCA)/stenting. Inclusion and exclusion criteria as well as the electrocardiographic (surface ECGs and intracardiac EGMs) and ST segment analysis protocol are fully discussed in chapter three. The standard 12-lead ECG was

compared with the reconstructed bipolar recordings: pectoral-right ventricle (PEC-RV), superior vena cava and RV (SVC-RV), right atrium-RV (RA-RV) and coronary sinus-RV (CS-RV).

Statistical analysis

In view of the skewed distribution of the data, Wilcoxon matched pairs test was used to compare surface ECGs with intracardiac EGMs. A p value <0.05 was considered as statistically significant. Statisca for Windows version 5.1 was used for all statistical analysis.

RESULTS

In total 48 patients (45 males, 3 females, age 60.8 ± 9.3 [standard deviation] years) were studied during normal sinus rhythm (see chapter three, table 1). Tables 5.1 and 5.2 summarise the coronary arteries that were dilated as well as the total number of balloon inflations in each respective coronary artery. There were a total of 194 balloon inflations involving 23 left anterior descending, 2 diagonals, 8 circumflex, 5 obtuse marginal and 23 right coronary arteries.

Figure 5.1(A-C) illustrate the surface ECG and unipolar pectoral and intracardiac EGMs in a patient undergoing LAD intervention (patient 36). Figure 5.2 illustrates the reconstructed bipolar EGMs of the same patient (PEC-RV, SVC-RV, RA-RV). Figure 5.3 illustrates the reconstructed bipolar EGM (CS-RV and PEC-RV) in another

patient (patient 1) during LAD intervention to demonstrate the bipolar EGMs obtained from using the unipolar coronary sinus recordings.

Table 5.3 summarises the maximum, median and standard deviation of the ST deviation (75-85 milliseconds after the j point) relative to the PQ segment during balloon inflation.

Figures 5.4 - 5.8 display the graphs obtained by plotting the median of ST segment deviation from baseline (mm) in the respective leads during the first 40 seconds of balloon inflation, for all arteries.

Compared with the two best surface ECG leads (V2, V3), the bipolar leads were superior in detecting ischaemic ST changes, for all combinations; $p<0.0001$, Wilcoxon matched pairs test.

Table 5.1. Targeted coronary arteries during elective angioplasty.

ELECTIVE ANGIOPLASTY IN 48 PATIENTS	
Coronary artery	***Number***
Left Anterior Descending artery	23
Diagonal Artery	2
Circumflex Artery	8
Obtuse Marginal Artery	5
Right Coronary Artery	23

Table 5.2. Total number of balloon procedures during angioplasty and surface ECG and EGM recordings.

	All	**LAD**	**DIA**	**RCA**	**CX**	**OM**
Surface ECG	194	78	5	68	30	13
PEC-RV	160	70	5	57	15	13
SVC-RV	90	45	5	24	10	6
RA-RV	90	45	5	24	10	6
CS-RV	51	22	0	17	5	7

Figure 5.1. Patient 36 during LAD angioplasty/stent insertion. Panels A-C illustrate the surface ECG and unipolar pectoral (PEC) and intracardiac EGMs at baseline and during inflation.

(A)

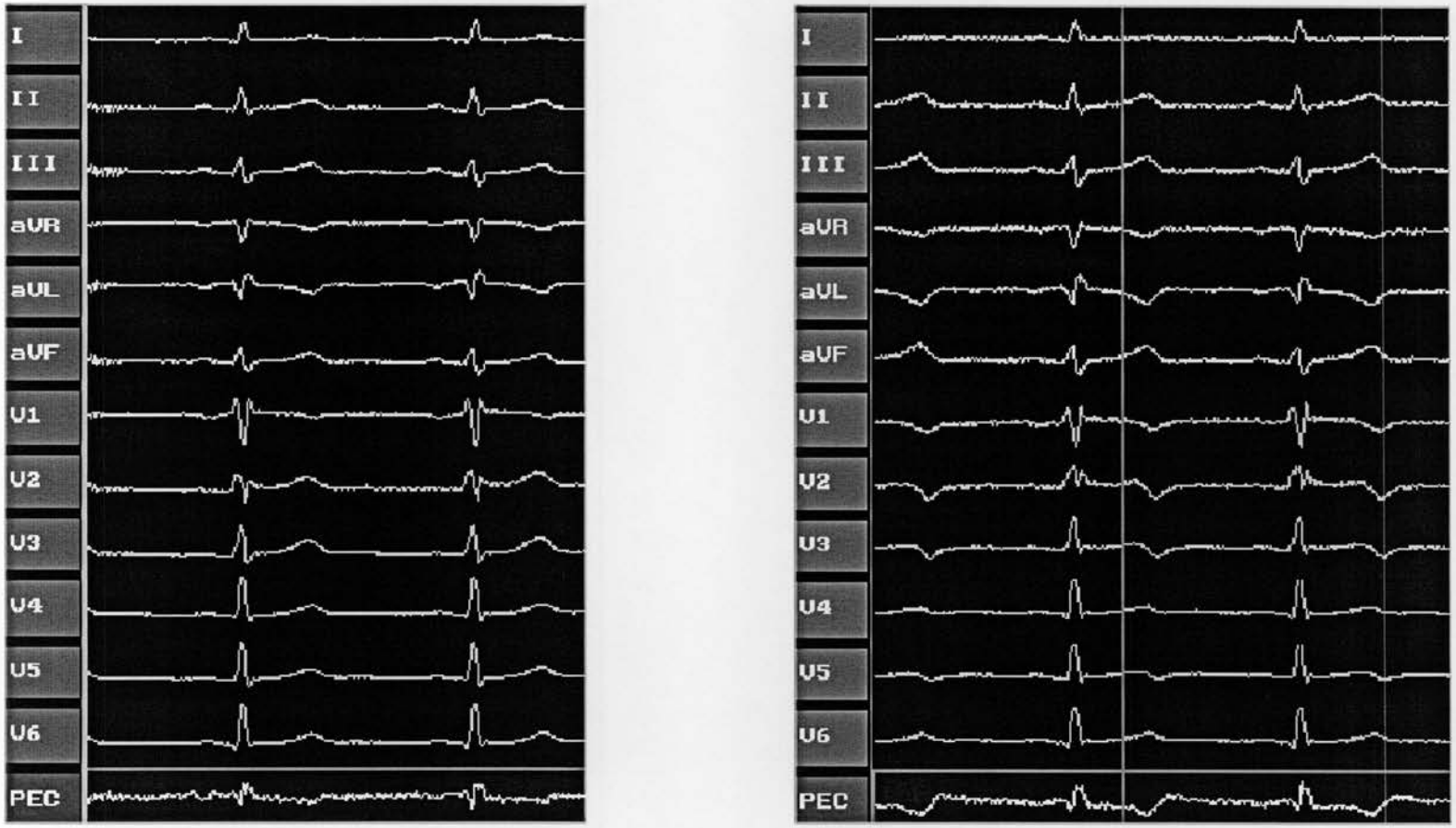
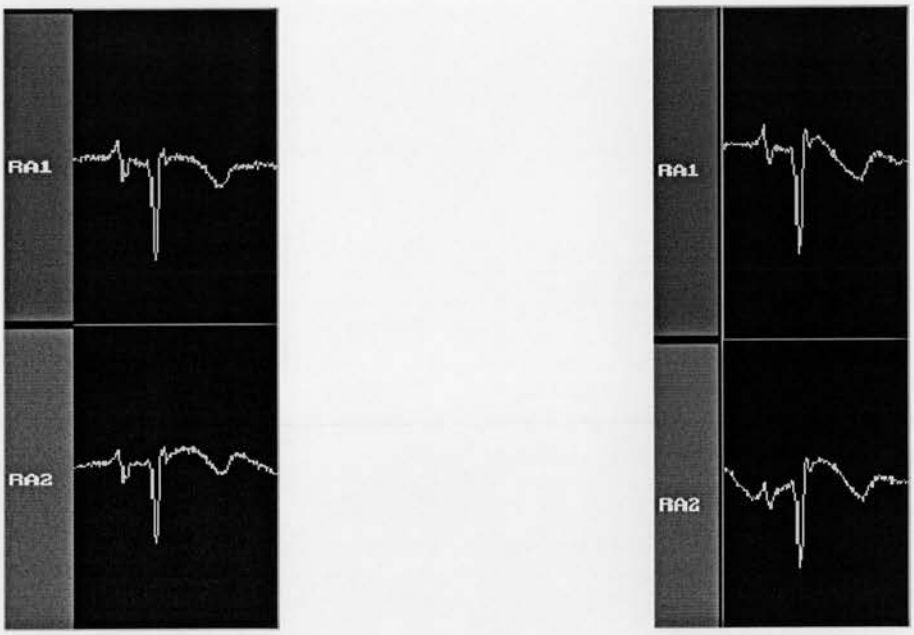


Figure 5.1. Continued

Baseline Inflation

(B) Atrial unipolar EGMs



(C) Right ventricular EGMs

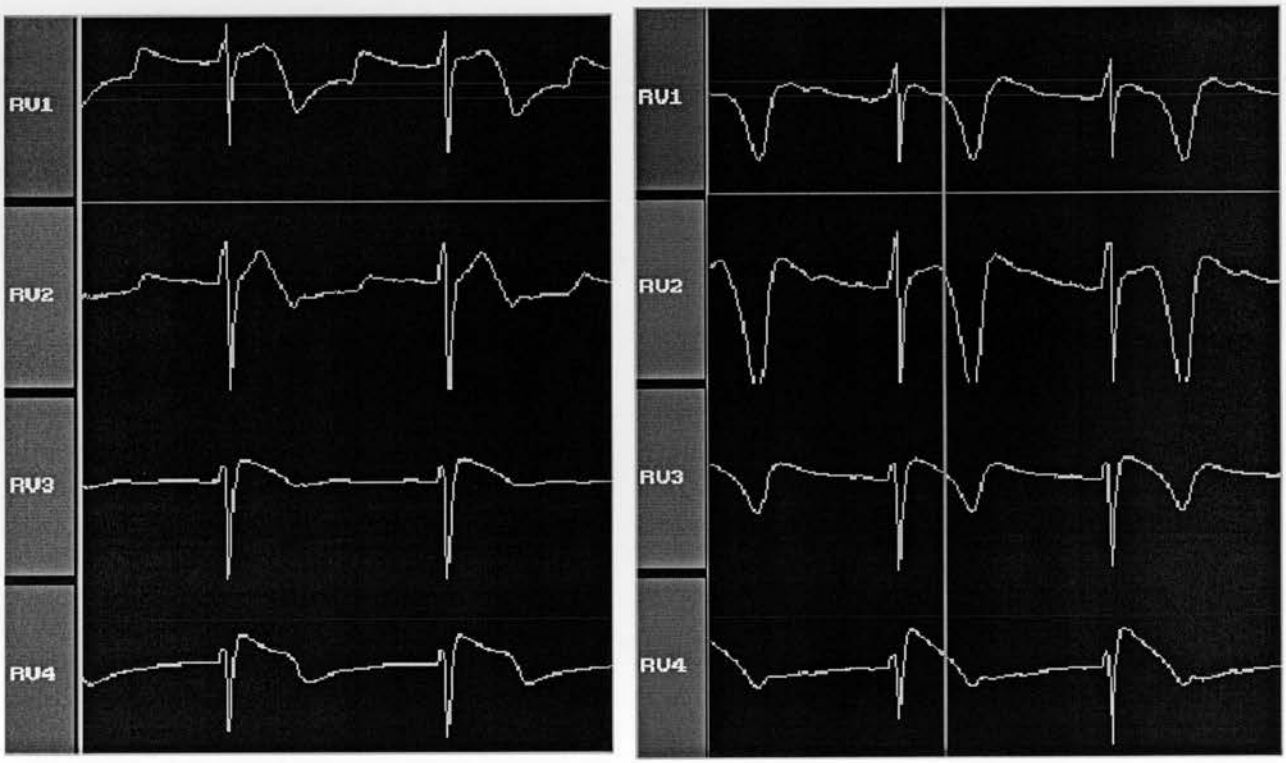


Figure 5.2. Reconstructed bipolar EGM of the same patient as in figure 5.1(patient 36) during LAD angioplasty/stent insertion

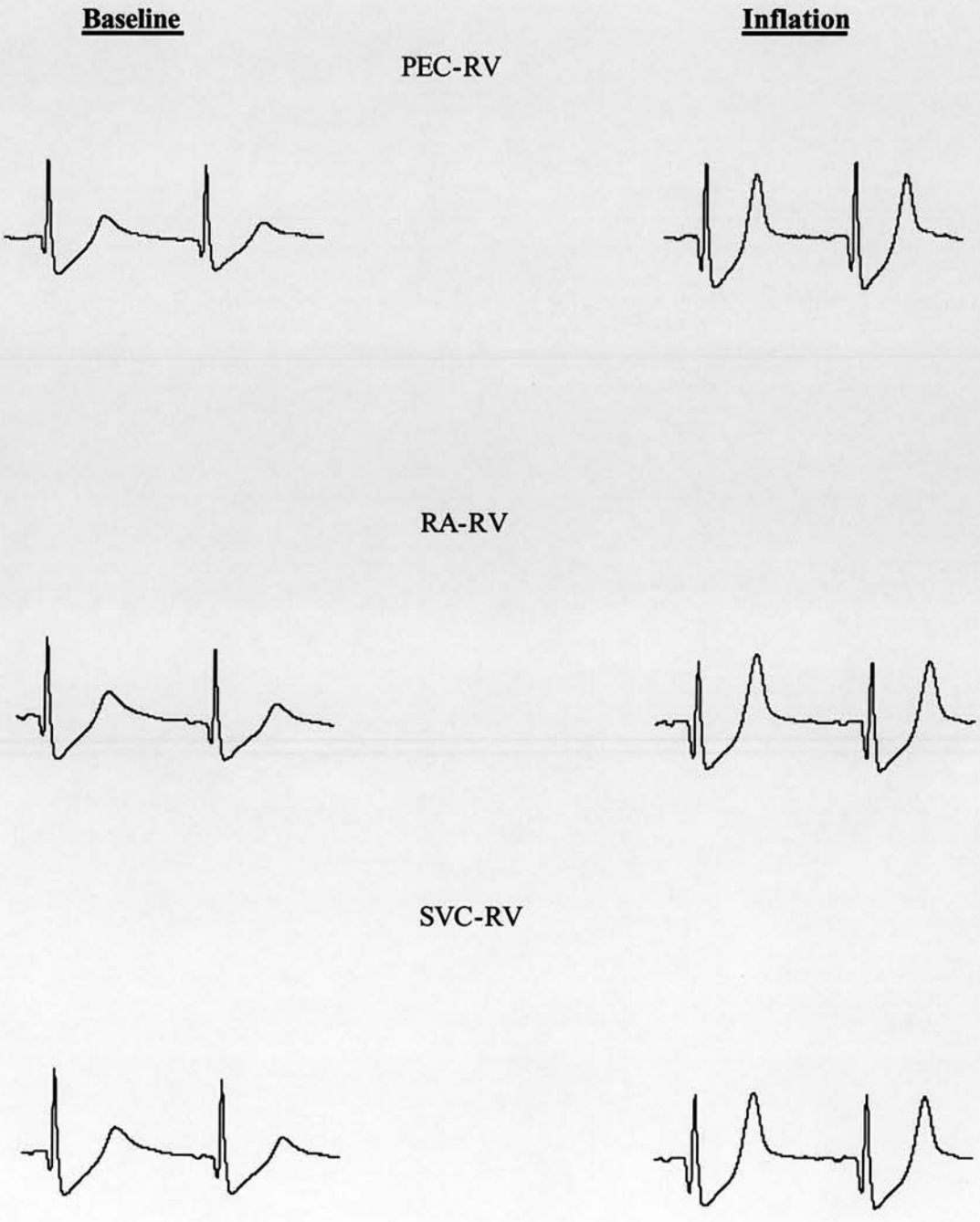


Figure 5.3. Reconstructed bipolar EGM in another patient (patient 1) during LAD intervention to illustrate the bipolar EGM obtained from using the coronary sinus recordings.

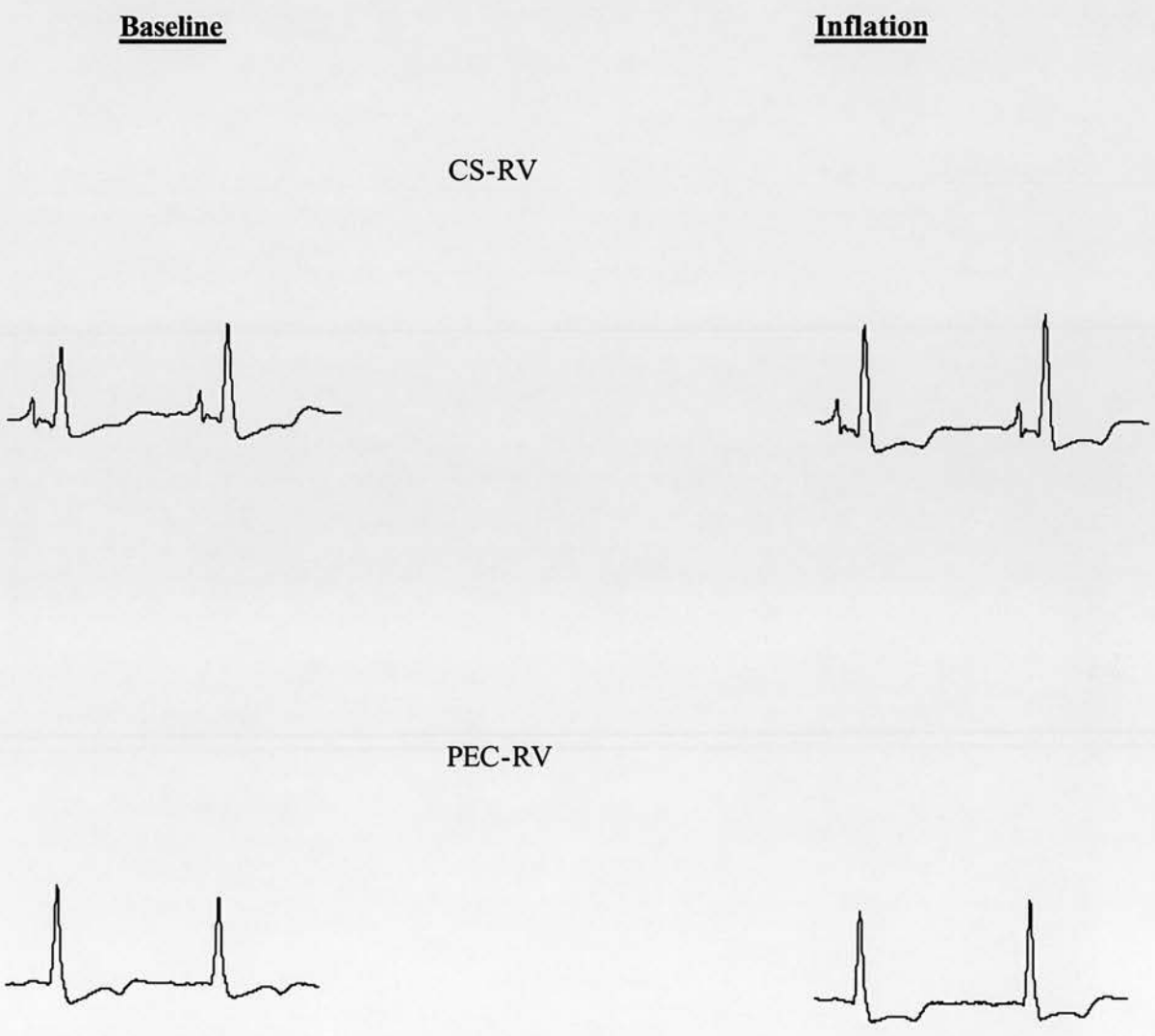


Table 5.3. The maximum (max), median (med) and standard deviation (SD) of the ST deviation (expressed in mV, 75-85 milliseconds after the j point) relative to the PQ segment during balloon inflation. LAD = left anterior descending artery, D = diagonal artery, C = circumflex artery, OM = obtuse marginal artery, RCA = right coronary artery.

		I	II	III	AVR	AVL	AVF	V1	V2	V3	V4	V5	V6	PEC-RV	RA-RV	SVC-RV	CS-RV
LAD	Max	1.39	1.55	2.62	0.87	1.21	1.19	2.46	5.13	6.84	5.69	1.69	0.96	11.76	9.14	9.15	7.78
	Med	0.07	0.09	0.1	0.07	0.05	0.05	0.08	0.09	0.12	0.1	0.09	0.08	0.42	0.48	0.52	0.4
	SD	0.13	0.18	0.20	0.11	0.10	0.10	0.29	0.64	0.93	0.68	0.25	0.15	1.02	1.25	1.23	1.14
D	Max	0.94	1.11	1.64	0.69	0.81	0.81	1.05	0.76	1.96	1.36	0.91	0.95	2.53	2.44	2.47	ND
	Med	0.09	0.07	0.11	0.06	0.07	0.07	0.12	0.1	0.11	0.06	0.07	0.09	0.33	0.41	0.34	ND
	SD	0.15	0.21	0.32	0.10	0.16	0.16	0.18	0.14	0.39	0.23	0.16	0.15	0.47	0.47	0.46	ND
C	Max	1.4	2.12	1.62	1.42	0.75	0.76	3.71	3.21	1.89	1.99	2.75	2.3	6.11	5.65	4.88	7.38
	Med	0.07	0.14	0.13	0.08	0.07	0.065	0.12	0.16	0.23	0.2	0.14	0.12	1.1	1.395	1.34	0.65
	SD	0.16	0.30	0.30	0.18	0.15	0.14	0.32	0.38	0.40	0.41	0.32	0.29	1.25	1.42	1.22	1.99
OM	Max	0.97	1.41	0.85	1.19	0.39	0.39	1.22	1.38	1.51	2.19	2.23	1.09	2.84	17.54	11.68	3.44
	Med	0.08	0.09	0.11	0.06	0.06	0.06	0.14	0.22	0.19	0.12	0.08	0.08	0.58	0.37	0.49	0.62
	SD	0.16	0.23	0.16	0.19	0.08	0.08	0.22	0.25	0.29	0.36	0.32	0.16	0.55	3.17	2.07	0.86
RCA	Max	1.31	2.53	2.95	1.35	1.47	1.49	1.59	3.33	2.62	2.78	1.21	0.93	10.05	18.67	11.97	3.05
	Med	0.07	0.1	0.11	0.06	0.06	0.06	0.08	0.12	0.1	0.09	0.07	0.07	0.69	1.06	1.18	0.38
	SD	0.15	0.34	0.39	0.17	0.19	0.19	0.20	0.39	0.32	0.31	0.17	0.13	1.01	3.38	2.45	0.66

Figure 5.1. Surface 12-lead ECG versus PEC_RV

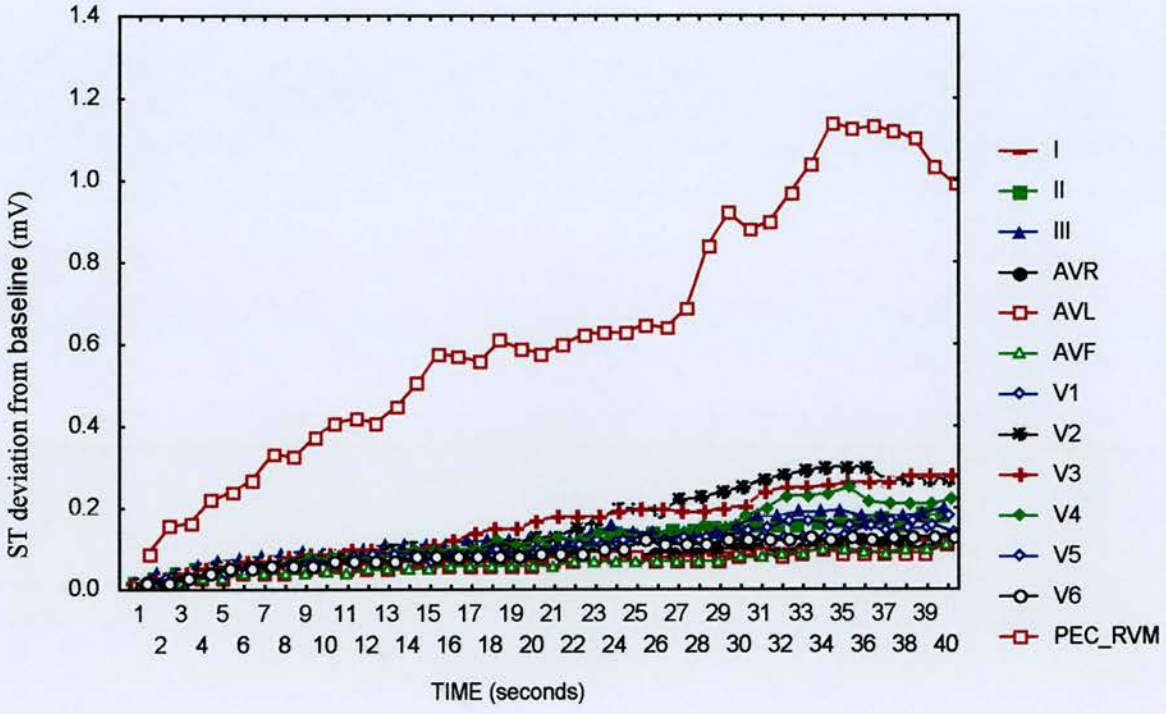


Figure 5.2. Surface 12-lead ECG versus RA_RV

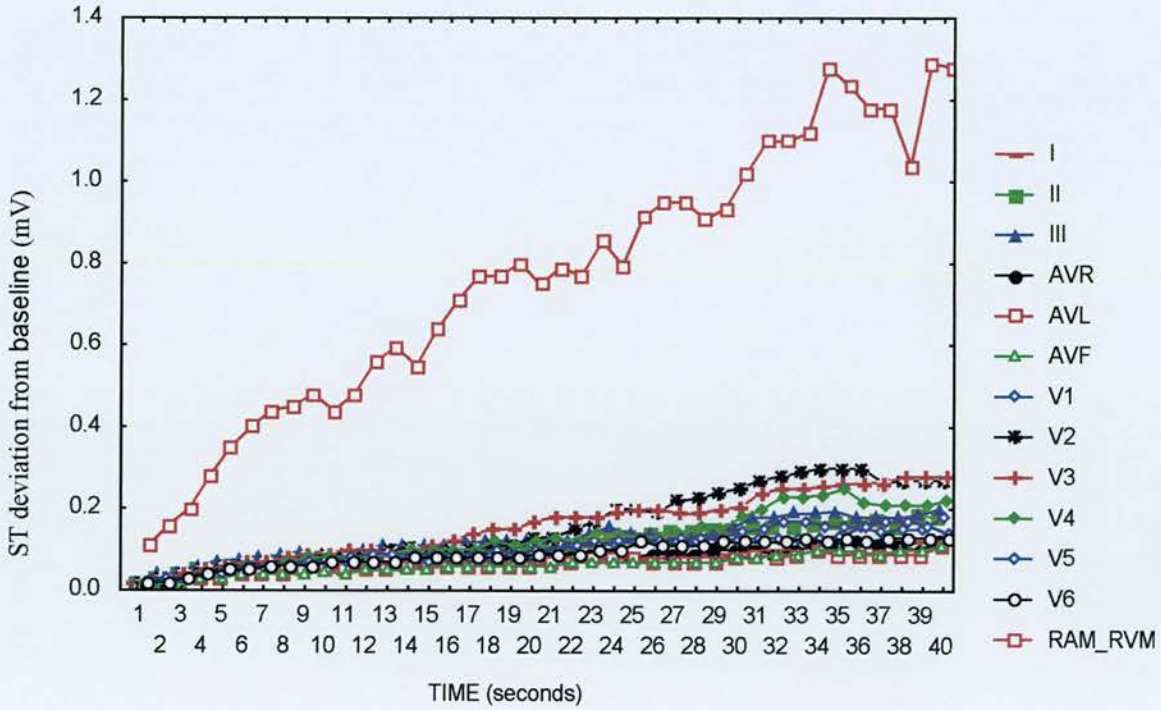


Figure 5.3. Surface 12-lead ECG versus SVC_RV

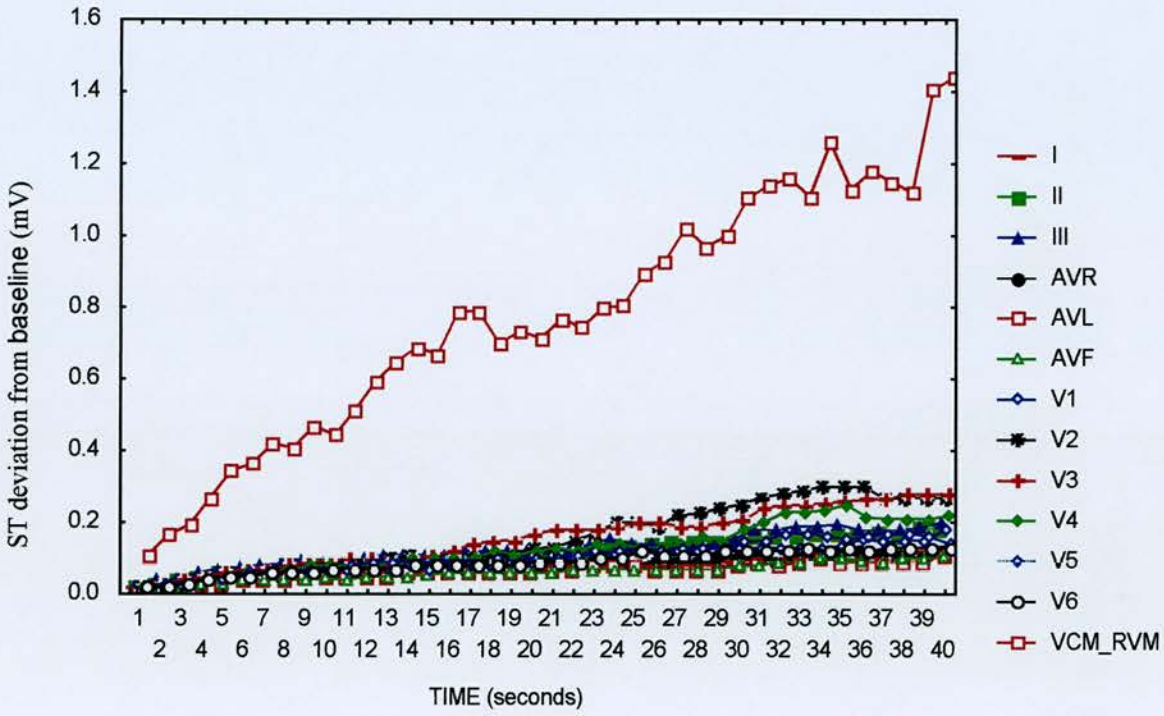


Figure 5.4. Surface 12-lead ECG versus CS_RV

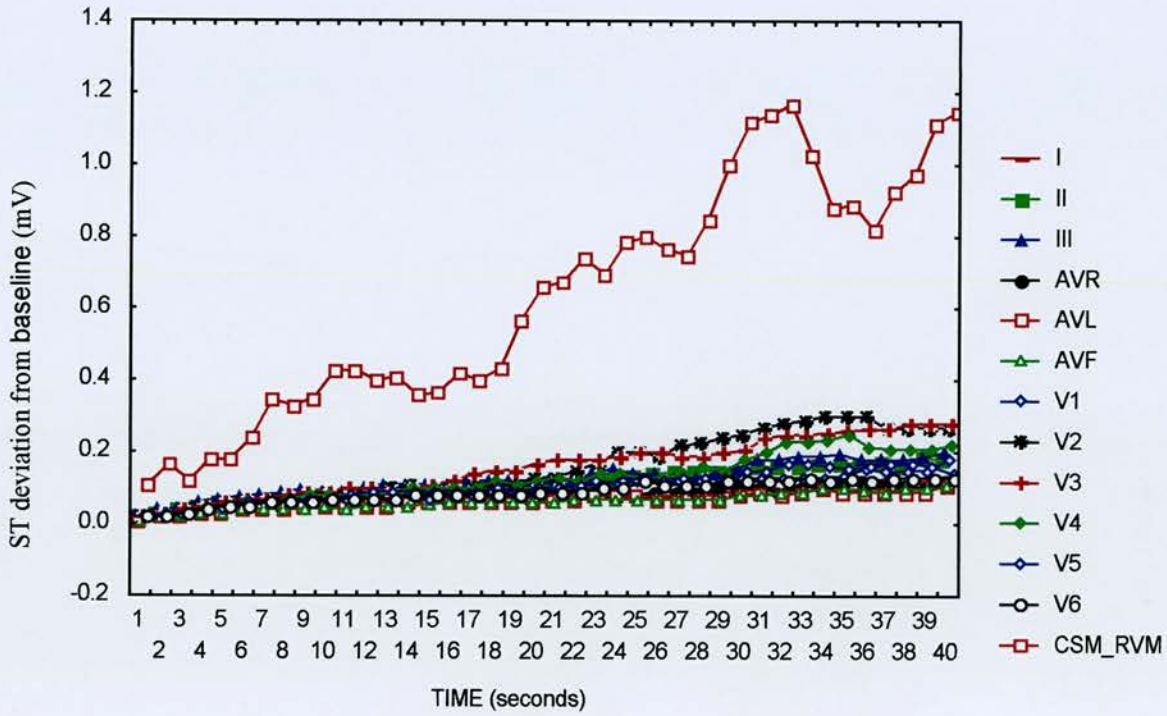
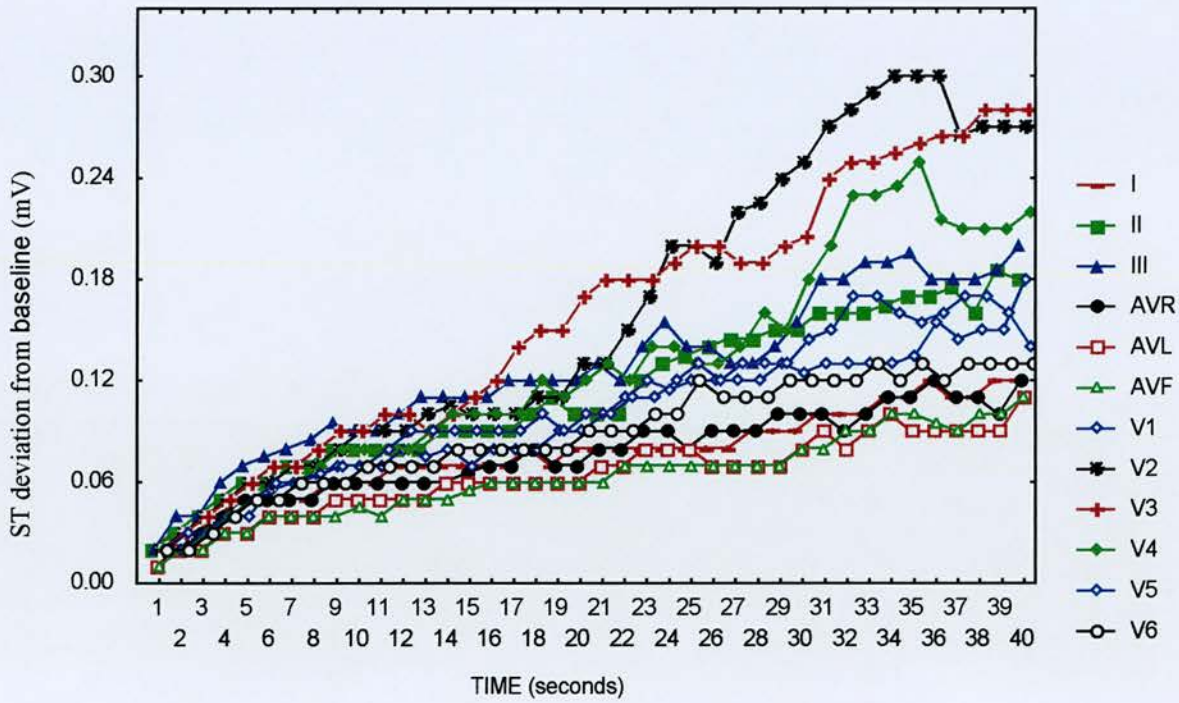


Figure 5.5. Surface 12-lead ECG.



DISCUSSION

This study demonstrates that ST changes during periods of myocardial ischaemia are significantly greater in reconstructed bipolar intracardiac EGM signals compared with surface ECGs.

The observation of greater ischaemic ST segment changes in EGM than in ECG is consistent with several small studies that investigated unipolar intracardiac EGMs during myocardial ischaemia induced by balloon inflation or coronary artery ligation[110-116]. Unfortunately, these studies suffered with the limitations of using isolated myocardial specimens[111,112], left-sided ventricular recordings[110,114,116] or changes in the monophasic action potential[115]. The latter two are obviously not suitable for chronic lead implantation. Furthermore, unipolar recordings are more local signal driven (reflecting the focal electrical activity of the tissue close to the tip of the electrode) and therefore mask a more global far-field ECG. By maximising the distance between the dipole, using multiple bipolar lead configurations, an EGM that is capable of recording a more "global" far-field dipole can be obtained. Indeed, this was the case. Similar results were recently reported by Theres et al who also compared intracardiac bipolar EGMs with three surface ECG leads (I, II, V2) during transient coronary artery occlusion[135].

The analysis included all balloon inflations during the procedure. It is likely that ischaemic preconditioning can affect subsequent electrocardiographic changes[110]. Nevertheless, the maximum change in ST deviation was considered at each inflation

step and the maximum ST deviation for that targeted vessel was then used in the analysis.

The pectoral ECG recording used in this study was not an ideal model simulating recordings from an implanted device. The pectoral electrode was a combination of four electrodes with a single output lead. This was done to improve the signal to noise ratio. However, in reality, recordings from an implanted device is significantly superior to those obtained form the pectoral electrode as it avoids the skin-electrode interface.

As a first step in evaluating intracardiac multiple lead configuration in monitoring global myocardial ischaemia, patients with bundle branch block were excluded from the study. As patients with implanted devices often have antibradycardic pacing therapy (usually seen as left bundle branch block on the surface ECG), it would be useful to assess the effects of ischaemia during intracardiac monitoring in the presence of these conduction disturbances.

The atrial unipole was at a fixed 121 mm from the electrode tip. This, together with the fact that the electrode was placed via the femoral route, would imply that the atrial recordings in our study would be different from those obtained using the standard right atrial appendage placement for implanted devices. Furthermore, the electrodes were placed acutely and may differ in response from those that are chronically implanted.

The study was conducted in the cardiac catheter laboratory with the patient lying flat. Whether similar findings will be found in patients with an actual implanted device capable of ST segment monitoring in an ambulatory setting remains unknown.

CONCLUSION

Irrespective of the epicardial artery, monitoring regional myocardial ischaemia using the absolute change in ST segment deviation from right-sided intracardiac electrodes is feasible, and has the potential to be incorporated into the algorithms of implanted devices.

CHAPTER 6

Diagnostic accuracy of monitoring myocardial ischaemia from normalised bipolar intracardiac recordings during percutaneous coronary angioplasty

INTRODUCTION

In Chapter 5, it was demonstrated that absolute changes in ST segment deviation (ΔST) in intracardiac leads are more prominent when compared to the standard 12-lead ECG, during periods of myocardial ischaemia. The signal amplitudes from intracardiac leads are inherently bigger than surface ECGs (figure 6.1), and therefore the expression of ΔST in absolute terms can sometimes lead to larger values. To account for these differences a process of normalisation should be used to create uniformity in the amplitude of the ECGs and EGMs, so that it is less sensitive to differences in amplitude and more sensitive to differences in electrogram morphology. Furthermore, normalisation reduces the effects of random variability, white-noise, baseline shifts, movement artefacts, and can therefore improve the signal to noise ratio. This study investigated the diagnostic accuracy of monitoring myocardial ischaemia from normalised bipolar intracardiac recordings during percutaneous coronary angioplasty.

PROTOCOL

Study Subjects, Surface Electrocardiograms (ECGs), Intracardiac Electrograms (EGMs) and Signal processing

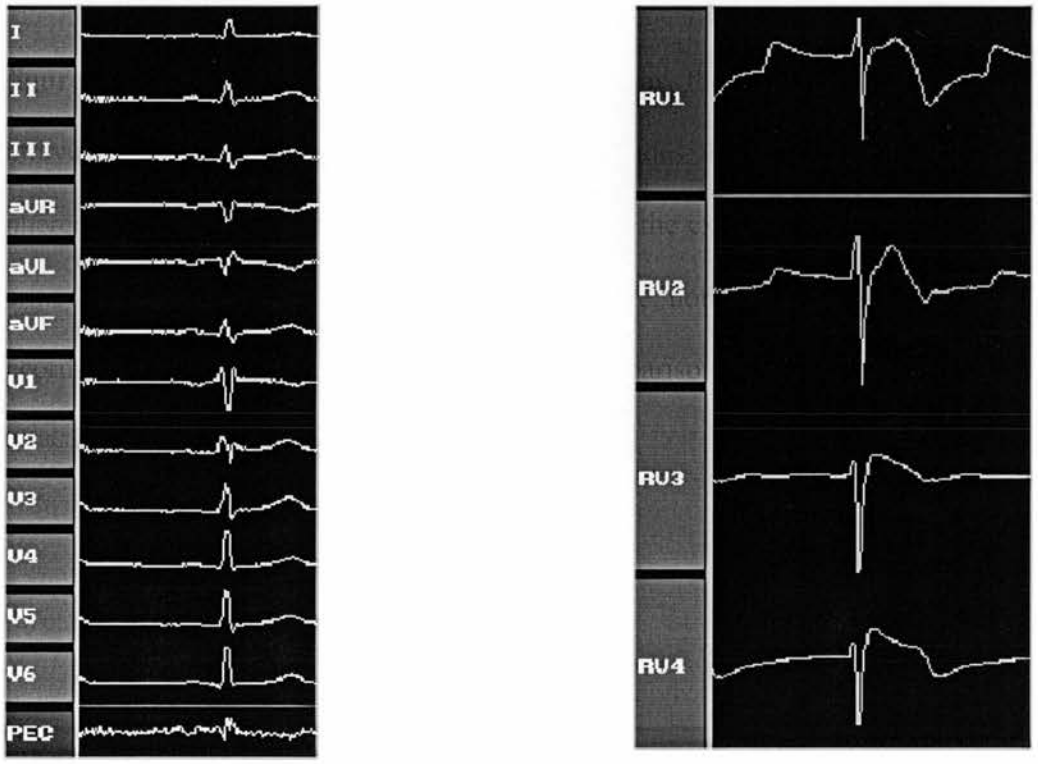
The same patient population as discussed in Chapter three and four was studied during percutaneous transluminal angioplasty/stenting. Following reconstruction of the bipolar leads, the intracardiac ΔST EGMs were normalised by multiplying the absolute change in ST-segment deviation (ΔST) in the intracardiac EGMs by the ratio of the average QRS amplitudes in the surface leads to the QRS amplitude of the

intracardiac EGM (normalisation factor). For instance, the normalised ΔST in the RA-RV bipole is calculated as follows:

$$\text{Normalised } \Delta ST \text{ RA-RV} = \Delta ST \text{ RA-RV} \times \left(\frac{\frac{\sum \text{QRS amplitude I,II...V5,V6}}{12}}{\text{QRS amplitude RA-RV}} \right)$$

This normalisation formula was chosen as it is straightforward, can be easily calculated and each patient served as his or her control. The standard 12-lead ECG was compared with the normalised ΔST in the following reconstructed bipolar EGMs: pectoral-right ventricle (PEC-RV), superior vena cava and RV (SVC-RV), right atrium-RV (RA-RV) and coronary sinus-RV (CS-RV).

Figure 6.1. Examples of raw waveforms from the surface ECG and right intraventricular (RV) EGM. The signal amplitudes from intracardiac leads are inherently bigger than surface ECGs and therefore the expression of ΔST in absolute terms will inevitably lead to larger values. Therefore, normalisation of the intracardiac recordings is necessary to allow an accurate comparison between surface ECGs and intracardiac EGMs



Statistical analysis

Wilcoxon matched pairs test was used to compare surface ECGs with intracardiac EGMs. A p value <0.05 was considered as statistically significant. Statisca for Windows version 5.1 was used for all statistical analysis.

RESULTS

The total number of patients and the target coronary arteries that were revascularised are summarised in Chapter 4.

Table 6.1 summarises the maximum, median and standard deviation of the ΔST (75-85 milliseconds after the j point) relative to the PQ segment during balloon inflation.

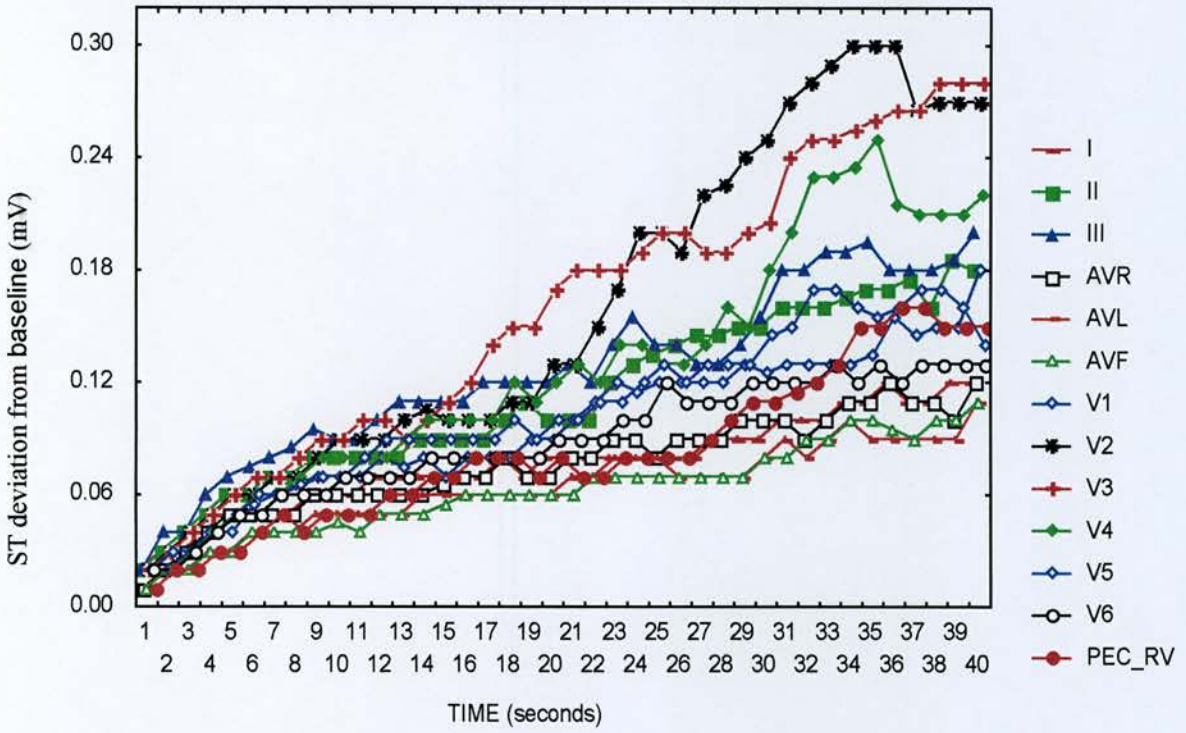
Figures 6.1-6.4 display the graphs obtained by plotting the median of ST segment deviation from baseline (mV) in the respective leads during the first 40 seconds of balloon inflation, for all arteries.

The table below each graph summarises the p value between the surface ECGs and the intracardiac EGMs. Compared to the two best (V2, V3) and two worse (AVL, AVF) surface ECG, the intracardiac EGMs have an intermediate detection capability compared to the standard 12-lead surface ECG ($p<0.0001$).

Table 6.1. The maximum (max), median (med) and standard deviation (SD) of the ST deviation (expressed in mV, 75-85 milliseconds after the j point) relative to the PQ segment, during balloon inflation. LAD = left anterior descending artery, D = diagonal artery, C = circumflex artery, OM = obtuse marginal artery, RCA = right coronary artery.

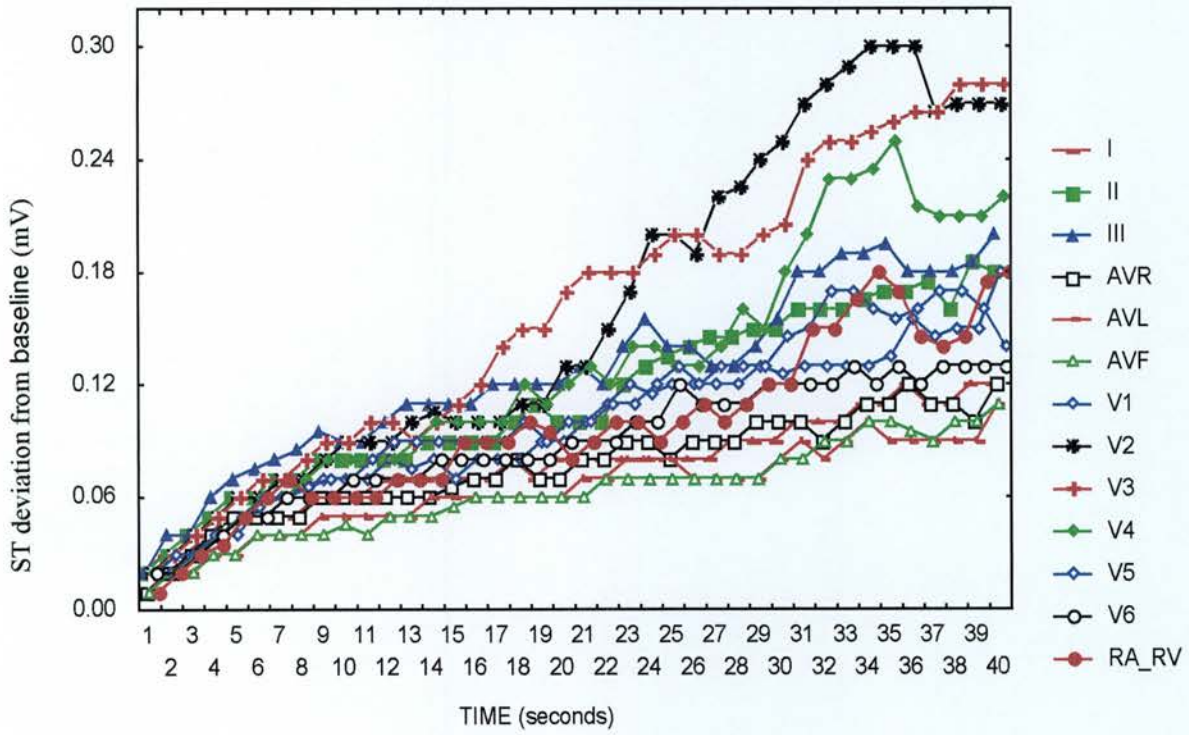
		I	II	III	AVR	AVL	AVF	V1	V2	V3	V4	V5	V6	PEC-RV	RA-RV	SVC-RV	CS-RV
LAD	Max	1.39	1.55	2.62	0.87	1.21	1.19	2.46	5.13	6.84	5.69	1.69	0.96	2.46	2.53	2.51	0.68
	Med	0.07	0.09	0.1	0.07	0.05	0.05	0.08	0.09	0.12	0.1	0.09	0.08	0.06	0.07	0.08	0.05
	SD	0.13	0.18	0.20	0.11	0.10	0.10	0.29	0.64	0.93	0.68	0.25	0.15	0.21	0.26	0.26	0.11
D	Max	0.94	1.11	1.64	0.69	0.81	0.81	1.05	0.76	1.96	1.36	0.91	0.95	0.19	0.23	0.21	ND
	Med	0.09	0.07	0.11	0.06	0.07	0.07	0.12	0.10	0.11	0.06	0.07	0.09	0.02	0.04	0.03	ND
	SD	0.15	0.21	0.32	0.10	0.16	0.16	0.18	0.14	0.39	0.23	0.16	0.15	0.04	0.05	0.04	ND
C	Max	1.40	2.12	1.62	1.42	0.75	0.76	3.71	3.21	1.89	1.99	2.75	2.30	0.59	0.78	0.64	0.82
	Med	0.07	0.14	0.13	0.08	0.07	0.07	0.12	0.16	0.23	0.20	0.14	0.12	0.13	0.20	0.18	0.08
	SD	0.16	0.30	0.30	0.18	0.15	0.14	0.32	0.38	0.40	0.41	0.32	0.29	0.13	0.20	0.16	0.23
OM	Max	0.97	1.41	0.85	1.19	0.39	0.39	1.22	1.38	1.51	2.19	2.23	1.09	0.33	0.11	0.13	0.30
	Med	0.08	0.09	0.11	0.06	0.06	0.06	0.14	0.22	0.19	0.12	0.08	0.08	0.05	0.03	0.04	0.06
	SD	0.16	0.23	0.16	0.19	0.08	0.08	0.22	0.25	0.29	0.36	0.32	0.16	0.06	0.03	0.03	0.08
RCA	Max	1.31	2.53	2.95	1.35	1.47	1.49	1.59	3.33	2.62	2.78	1.21	0.93	0.86	0.77	0.64	0.38
	Med	0.07	0.10	0.11	0.06	0.06	0.06	0.08	0.12	0.10	0.09	0.07	0.07	0.10	0.14	0.13	0.05
	SD	0.15	0.34	0.39	0.17	0.19	0.19	0.20	0.39	0.32	0.31	0.17	0.13	0.15	0.14	0.13	0.08

Figure 6.1. Surface 12-lead ECG versus PEC-RV. The table below summarises the p values obtained from Wilcoxon matched pairs test between surface ECGs and the normalised PEC_RV bipole.



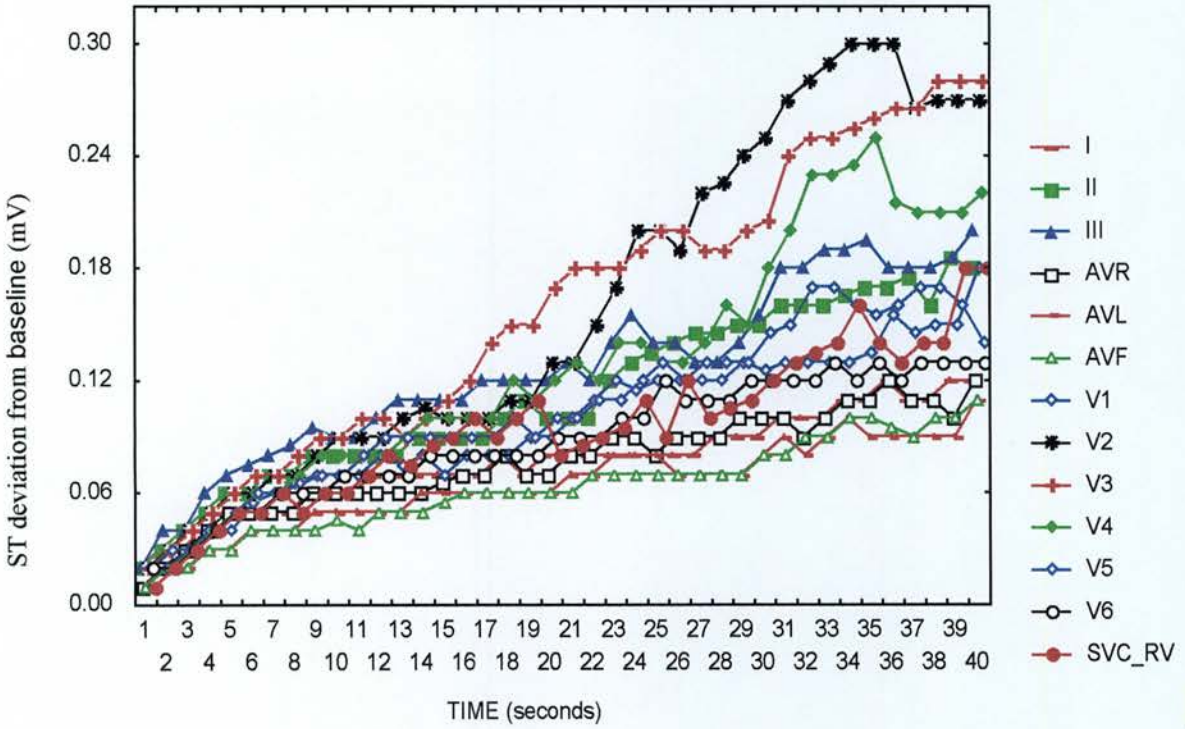
	I	II	III	AVR	AVL	AVF	V1	V2	V3	V4	V5	V6
PEC_RV	P = 0.22	P = 0	P = 0	P =0.001	P< 0.0001	P< 0.0001	P = 0	P = 0	P = 0	P = 0	P = 0	P = 0.027

Figure 6.2. Surface 12-lead ECG versus RA-RV. The table below summarises the p values obtained from Wilcoxon matched pairs test between surface ECGs and the normalised RA_RV bipole.



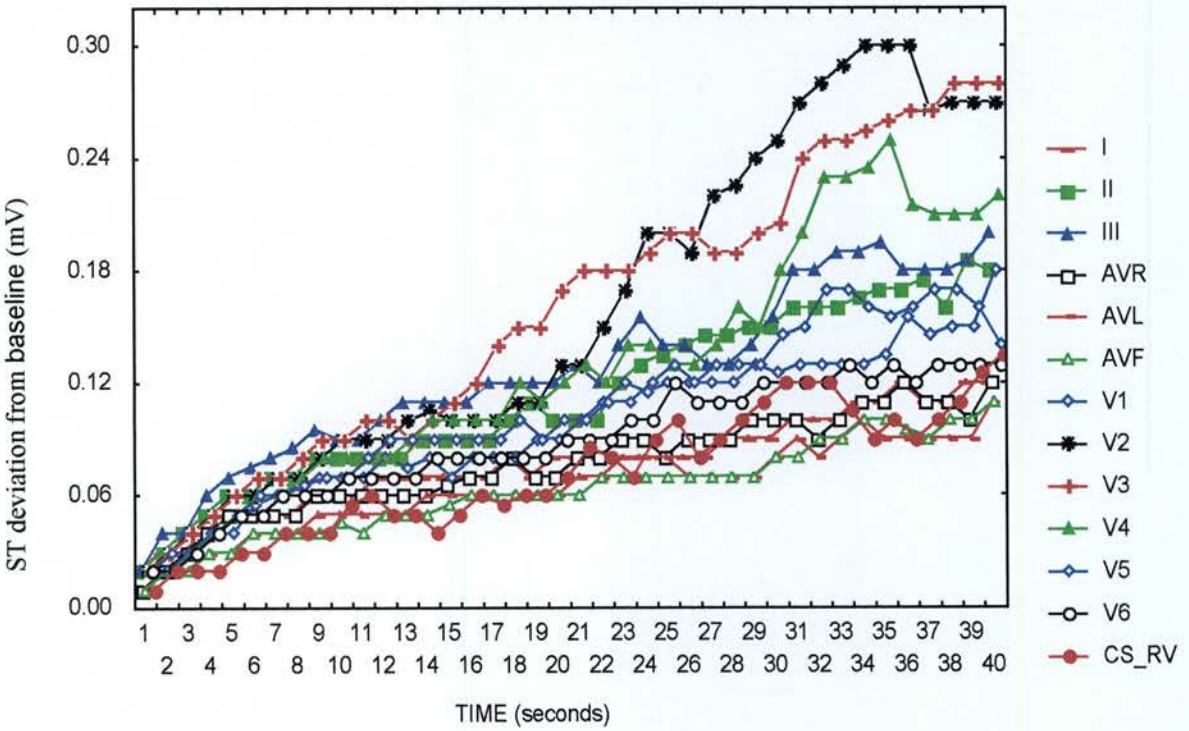
	I	II	III	AVR	AVL	AVF	V1	V2	V3	V4	V5	V6
RA_RV	P< 0.0001	P< 0.0001	P = 0	P< 0.0001	P< 0.0001	P< 0.0001	P< 0.0001	P = 0	P = 0	P = 0	P< 0.0001	P< 0.0001

Figure 6.3. Surface 12-lead ECG versus SVC-RV. The table below summarises the p values obtained from Wilcoxon matched pairs test between surface ECGs and the normalised SVC_RV bipole.



	I	II	III	AVR	AVL	AVF	V1	V2	V3	V4	V5	V6
SVC_RV	P< 0.0001	P = 0	P = 0	P=0.0005	P< 0.0001	P< 0.0001	P< 0.0001	P = 0	P = 0	P = 0	P< 0.0001	P = 0.0612

Figure 6.4. Surface 12-lead ECG versus CS-RV. The table below summarises the p values obtained from Wilcoxon matched pairs test between surface ECGs and the normalised CS_RV bipole.



	I	II	III	AVR	AVL	AVF	V1	V2	V3	V4	V5	V6
CS_RV	P< 0.0001	P = 0	P = 0	P< 0.0001	P< 0.0001	P< 0.0001	P< 0.0001	P = 0	P = 0	P = 0	P< 0.0001	P< 0.0001

DISCUSSION

In Chapter 4, it was demonstrated that absolute ST segment changes during periods of myocardial ischaemia are significantly greater in reconstructed bipolar intracardiac EGM signals compared with surface ECGs. However, when the amplitude of the intracardiac EGMs was normalised relative to that of the surface ECG, the ST segment changes were comparable and had an intermediate detection capability. Therefore, much of the difference in ST segment changes between the absolute intracardiac EGM and surface ECG signals appears to be related to the larger amplitude of EGM signals.

Acute myocardial ischaemia leads to a number of electrophysiological changes that result in a current flow between ischaemic and nonischaemic regions[37]. It is this current flow that leads to deviation of the ST segment in the ECG/EGM. Of note, the magnitude of such "currents of injury" is influenced greatly by the distance from the recording electrode to the region of ischaemia[136]. Thus an electrode on the body surface distant from the region would be expected to record less ST segment deviation than an electrode placed on the surface of the heart relatively closer to the ischaemic region. Indeed, as discussed in Chapter 6 together with a number of earlier studies[104,110,113,114,116,132], it was thought that intracardiac EGMs were better than the surface ECG for monitoring myocardial ischaemia. However, none of these studies normalised the EGM signals. Our study demonstrates that intracardiac EGMs have a modest detection capability for monitoring myocardial ischaemia and is significantly inferior to a number of surface ECG leads, particularly leads V2 and V3. Our findings concur with those of the recently published study by Theres et al who

also compared normalised bipolar intracardiac EGMs with three surface ECGs leads (I, II, V2)[135].

Nabel et al, reported that left ventricular endocardial unipolar EGMs were more sensitive than surface ECGs for detection of myocardial ischaemia induced by rapid atrial pacing in humans[116]. To enhance detection of subendocardial ischaemia, the unipolar recordings were obtained from the tip of a guide wire positioned against the endocardial surface of the potentially ischaemic regions. For instance, the guide wire was positioned against the anteroseptal or anterior wall when the left anterior descending artery was the study vessel, the lateral or posterolateral wall for study of the left circumflex artery and the inferior or inferoapical wall for the right coronary artery. For obvious clinical reasons, chronic lead implantation in the left ventricle is not possible and once the lead is deployed it remains fixed. In our study, intracardiac recordings were obtained from the coronary sinus as a surrogate for the left ventricle. The electrode was positioned as distal as possible, although this was not always feasible. It is reasonable to speculate that multiple bipolar lead configurations from EGMs obtained from the lateral, anterolateral or great cardiac vein would perhaps be more sensitive. Since the advent of cardiac resynchronisation therapy for heart failure[137,138], it is becoming standard practice to place electrodes in the cardiac veins of the left ventricular free wall and therefore recordings from these distal sites would not be difficult to obtain.

It was originally proposed to conduct a feasibility sub-study to retrospectively analyse the original EGM data to simulate the signal practically available in an implanted device (recordings of 50 Hz and 100Hz sampling were to be reconstructed from the

original 1kHz data). However, given the limited diagnostic performance of the bipolar EGMs, it was not considered of clinical practical value to pursuit this sub-study. The limitations of this study are similar to those as discussed in Chapter 6.

CONCLUSION

It was hypothesised at the beginning of the study that multiple bipolar lead configurations would facilitate monitoring regional and global myocardial ischaemia, irrespective of the coronary artery, and can potentially be used in implanted devices. Although this is feasible, it has an intermediate detection capability compared to the standard 12-lead surface ECG.

CHAPTER 7

The Application of Novel T-Wave Morphology Descriptors In Monitoring Myocardial Ischaemia

INTRODUCTION

Early identification of patients with myocardial ischaemia is a primary goal in the evaluation of emergency department patients with chest pain. At present, ECG changes during myocardial ischaemia in clinical practice are confined to visual inspection of the QRS complex, and the ST-T wave segments. Despite being initially promising, automatic ST segment trend analysis monitoring does not have robust data to substantiate an evidence base guideline practice for prolonged monitoring of myocardial ischaemia, in patients presenting with chest pain[139]. Consequently an alternative index that is clinically practical, easily applicable and reproducible is needed.

Surface ECG changes and symptomatic angina are late manifestations of myocardial ischaemia. It has been suggested that following the metabolic alterations of the myocardial syncytium during ischaemia, changes in the T wave morphology may occur earlier than ST segment injury current changes[45]. These morphological changes may not be visually recognisable on the surface 12-lead ECG. The ability to objectively monitor and assess these subtle changes will therefore be of great practical value.

As discussed in chapter 3 (T wave morphology assessment), Acar et al, recently developed a set of novel repolarisation descriptors that quantifies the variations in T wave morphology by extending the concept into a 3 dimensional model and applying more sophisticated mathematical analysis[125,126]. These descriptors are highly reproducible and are independent of the problematic time domain measurements such

as the detection of the T wave offset. Furthermore, these descriptors can be easily calculated from a single ECG beat, from all 12 leads. These measures include: (1) T wave residua, which characterise the nondipolar contents of the 12-lead ECG T wave and represent true heterogeneity of ventricular repolarisation. (2) T wave morphology dispersion, which expresses the morphologic heterogeneity within the 12-lead ECG. (3) Normalised T wave loop area, which is a measure of the heterogeneity of the principal components of the T wave. (4) The total cosine R to T (TCRT) descriptor, which is a measure of the vector deviation between the depolarisation and repolarisation waves by calculating the cosines between the three dimensional vectors of the R wave and T wave loop within the optimised decomposition space. (5) Finally, T wave loop dispersion, which measures spatial irregularities of the T wave loop during its time course (figure 7.1).

As a first step in developing an automatic algorithm for monitoring myocardial ischaemia based on these novel parameters, it is first necessary to investigate how these parameters behave during periods of myocardial ischaemia. The aim of this study is therefore to investigate the application of these novel descriptors of T wave morphology in monitoring myocardial ischaemia during angioplasty. Although these T wave morphology descriptors were calculated from the 12-lead surface ECG, there are possibilities of obtaining the same from the intracardiac EGMs. If these novel descriptors are sensitive enough to diagnose myocardial ischaemia then an automatic algorithm in implanted devices is potentially feasible.

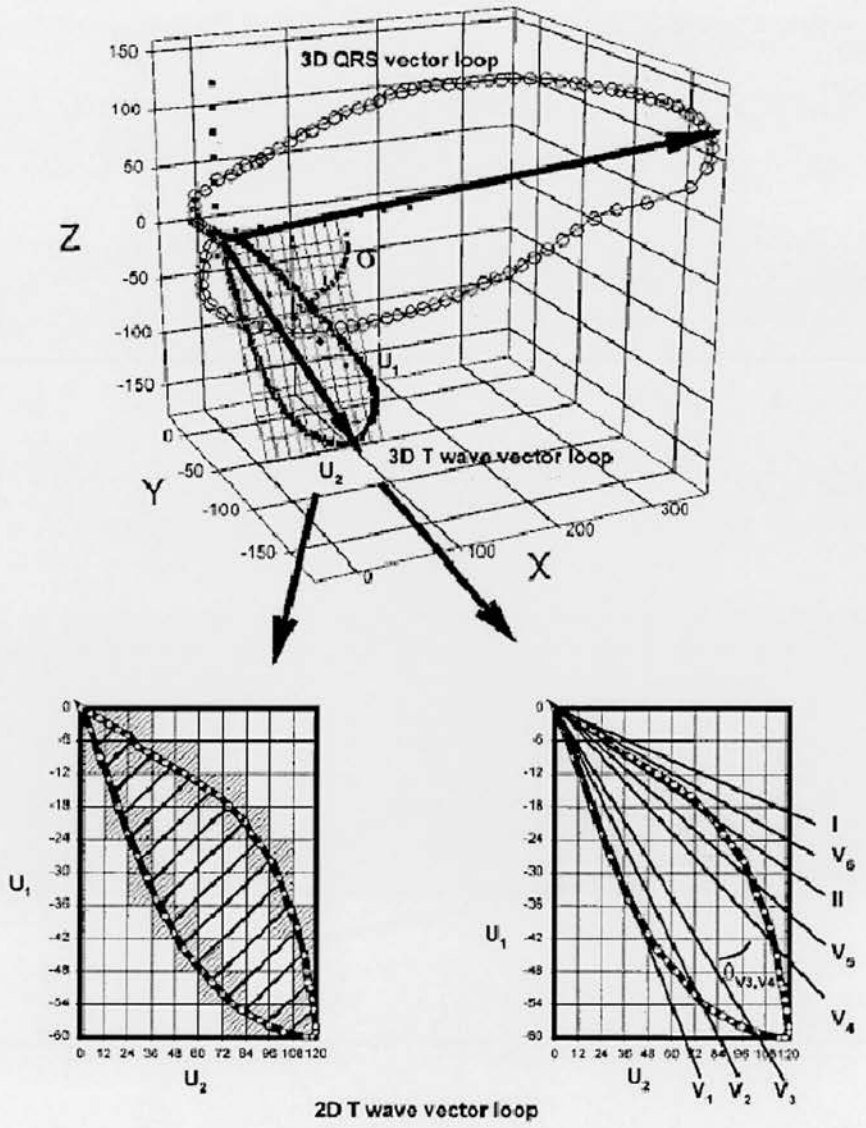


Figure 7.1. Schematic 3-dimensional view of QRS and T-wave vector loops. Main vectors of 2 loops are depicted by arrows, and angle between them is shown (determines TCRT). Bottom left, T-wave loop is shown in 2-dimensional plane with axes U1 and U2. A rectangle encompasses loop in this plane and is divided into 100 subdivisions. In this example, loop passes 35 marked subdivisions; thus, T-wave loop dispersion is 35. Normalized T-wave loop area is calculated as fraction of loop area (marked by stripes) of encompassing rectangle. Bottom right, reconstruction vectors of different ECG leads onto T-wave loop. T-wave morphology dispersion is calculated by averaging angle between all possible reconstruction vector pairs. Angle between V3 and V4 reconstruction vectors is shown in figure. See Methods for more detailed explanation. Adapted from Zabel et al. Circulation 2000;102:1252-1257

PROTOCOL

Study Subjects and Surface Electrocardiogram (ECG) Recordings

Forty-eight patients were investigated who were undergoing elective percutaneous transluminal angioplasty (PTCA)/stenting. Inclusion and exclusion criteria, as well as the 12-lead electrocardiographic protocol and ST segment analysis are fully discussed in chapter three. Tables 4.1 and 4.2 in chapter 4, summarise the coronary arteries that were dilated as well as the total number of balloon inflations in each respective coronary artery. In short, there were a total of 194 balloon inflations involving 23 left anterior descending, 2 diagonals, 8 circumflex, 5 obtuse marginal and 23 right coronary arteries.

T-wave Morphology Descriptors Analysis

Analysis of the digital 12-lead ECG recordings was performed in a fully automatic manner with a custom-developed software implemented on a personal computer[126]. In brief, the 8 independent leads of the ECG are subjected to singular value decomposition and after that the ECG is reconstructed in an orthogonal 8-lead system. In this system, the ECG signal in the first three leads encompasses the energy of the three-dimensional ECG vector (the ECG dipole). The energy of the remaining 4 to 8 leads corresponds to the non-dipolar components of the 12-lead ECG. The non-dipolar components were quantified by calculating the proportion between the non-dipolar components in leads 4 to 8 within the T wave, and the total power of the T

wave signal in leads 1 to 8 (dipolar + non-dipolar components). This parameter is the normalised T wave residua and is unitless.

Based on the decomposition, several descriptors were calculated of spatial and temporal variations of T-wave morphology and repolarisation wavefront direction. (1) The so-called normalized T-wave loop area describes the shape and irregularity of the T-wave loop by expressing its area as a fraction of the rectangle that encompasses the loop. The variable is unitless. (2) The so-called TCRT measures the vector deviation between the depolarisation and repolarisation waves by calculating cosine values between the 3-dimensional R- and T-wave loop vectors within the optimised decomposition space. Negative values correspond to large differences in the orientation of the 2 loops. The variable is unitless. (3) The so-called T-wave morphology dispersion expresses the dissimilarities between the T-wave shapes in individual leads, based on the differences between reconstruction vectors of individual ECG leads created from the 3-dimensional T-wave loop. It is calculated as the average of angles between all possible pairs of reconstruction vectors. A small value indicates that reconstruction vectors are close to each other, indicating similar T-wave morphology between leads.

Statistical analysis

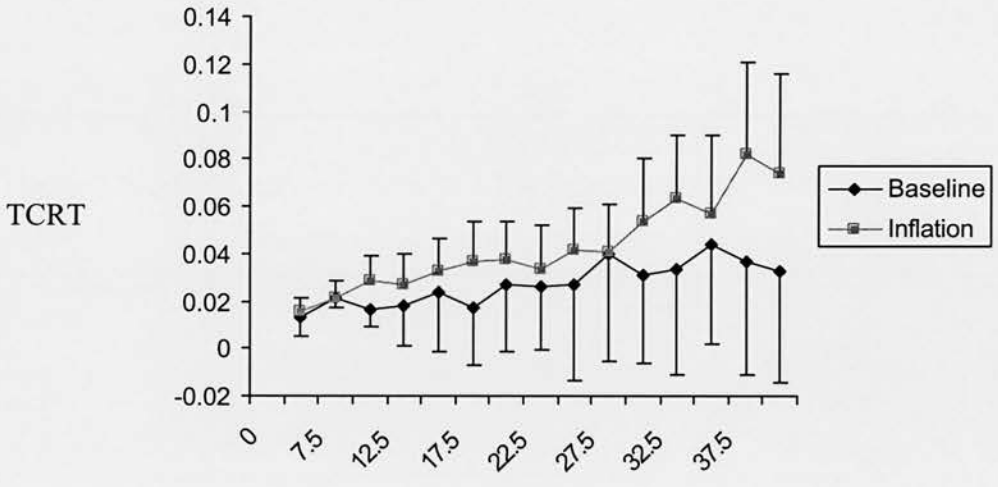
T-wave morphology descriptors were calculated at baseline (the time period before the start of percutaneous intervention, see chapter 3, methodology) and during the time of balloon inflation, to determine the effects of myocardial ischaemia. Similar measures were obtained for ST segments in the individual leads of the ECG. Differences in these parameters between baseline and balloon inflation values were

assessed by Wilcoxon matched pairs test. A p value <0.05 was considered as statistically significant. Statistica for Windows version 5.1 was used for all statistical analysis.

RESULTS

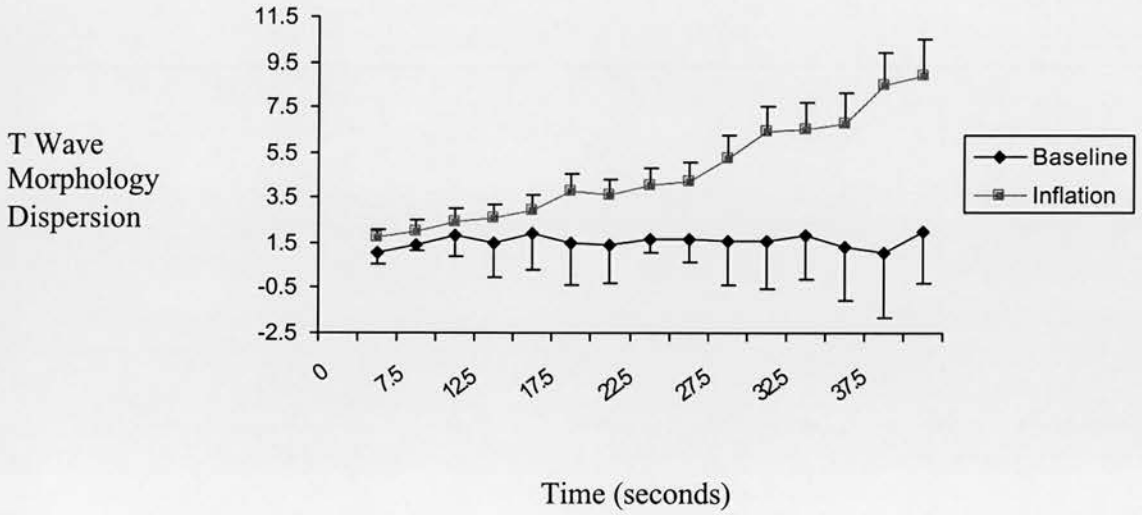
Changes in T wave morphology descriptors (TCRT, T wave morphology dispersion, T wave loop dispersion, normalized T wave loop area and normalized T wave residuum) as well as ST segment shifts in the individual leads of the 12-lead ECG, during balloon inflation are graphically illustrated in figures 7.2 A-P. Corresponding p values at each point in time during balloon inflation are also shown. All of the T wave morphology descriptors significantly changed as the time interval of balloon inflation increased. These changes appear to occur earlier (within 9 seconds) when compared to the two best surface ECG leads (V2 and V3).

Figure 7.2A. Difference between TCRT at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



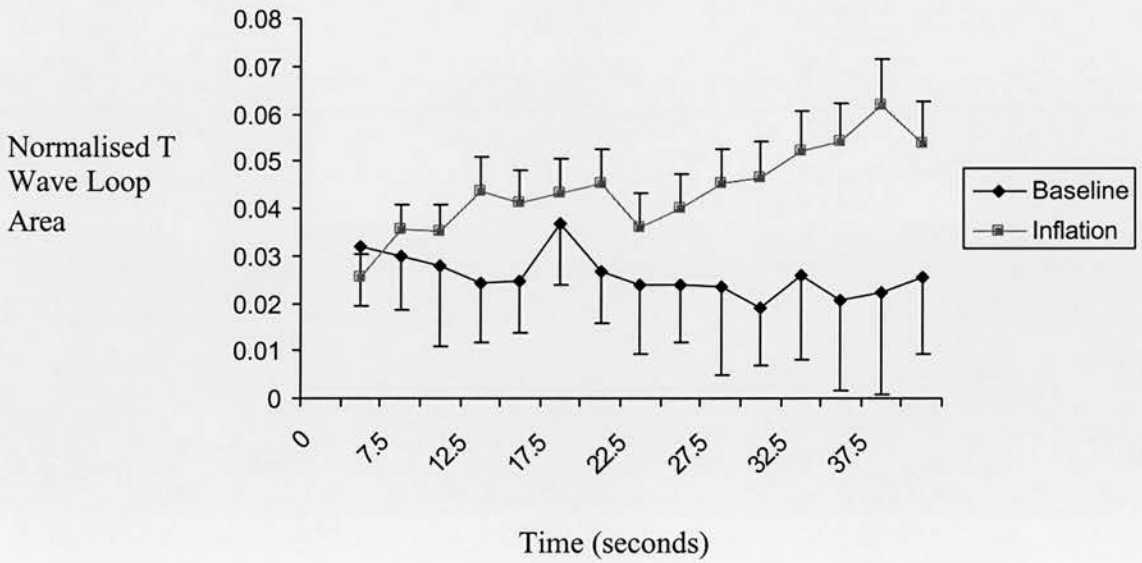
Time during balloon inflation (seconds)	P value
5	0.06
7.5	0.002
10	< 0.0001
12.5	0.032
15	< 0.0001
17.5	< 0.0001
20	< 0.0001
22.5	0.003
25	< 0.0001
27.5	0.17
30	0.0009
32.5	0.0028
35	0.022
37.5	0.001
40	0.01

Figure 7.2B. Difference between T wave morphology dispersion at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



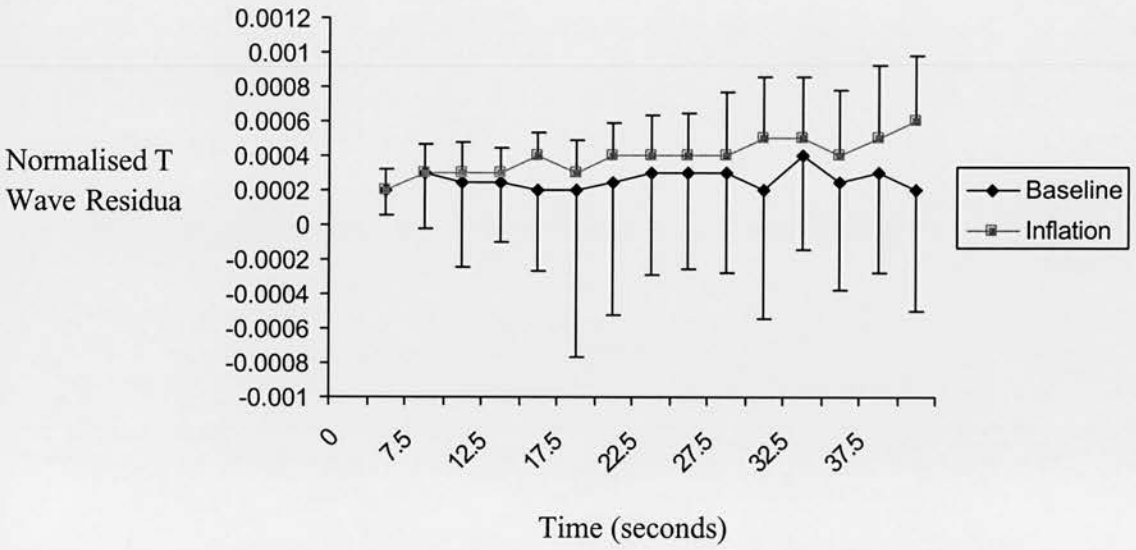
Time during balloon inflation (seconds)	P value
5	p < 0.0001
7.5	p < 0.0001
10	p < 0.0001
12.5	p < 0.0001
15	p < 0.0001
17.5	p < 0.0001
20	p < 0.0001
22.5	p < 0.0001
25	p < 0.0001
27.5	p < 0.0001
30	p < 0.0001
32.5	p < 0.0001
35	p < 0.0001
37.5	p < 0.0001
40	p < 0.0001

Figure 7.2C. Difference between normalised T wave loop area at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



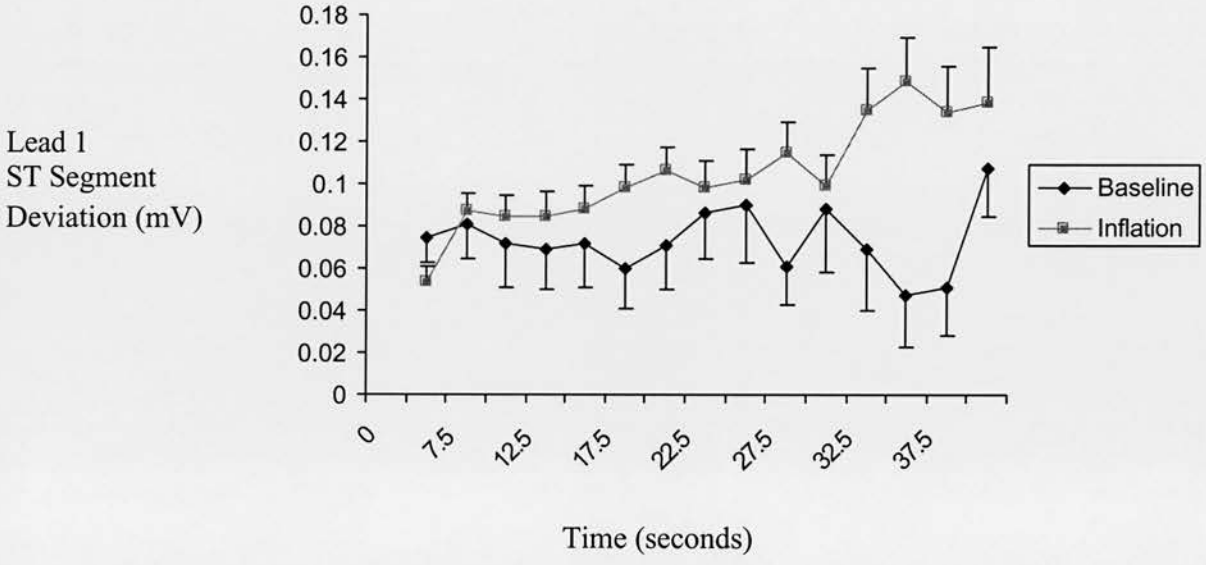
Time during balloon inflation (seconds)	P value
5	0.68
7.5	0.96
10	0.74
12.5	p < 0.0001
15	p < 0.0001
17.5	0.001
20	p< 0.0001
22.5	p < 0.0001
25	p < 0001
27.5	0.0006
30	p < 0.0001
32.5	0.0007
35	0.0024
37.5	0.27
40	0.032

Figure 7.2D. Difference between normalised T wave residua at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



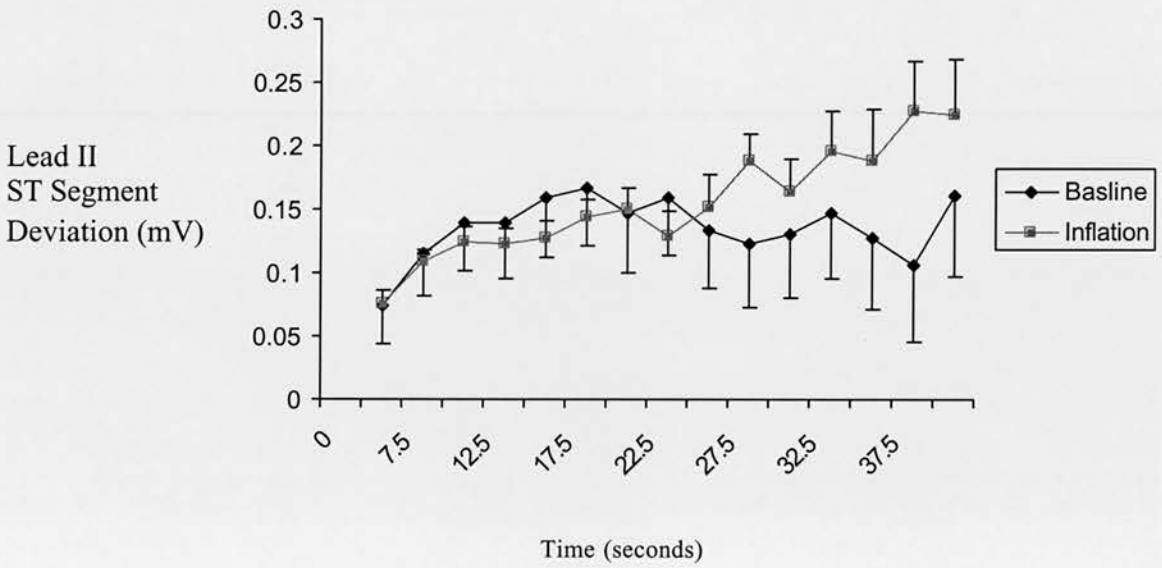
Time during balloon inflation (seconds)	P value
5	0.004
7.5	0.005
10	0.0003
12.5	0.049
15	0.00066
17.5	0.077
20	0.38
22.5	0.022
25	0.0003
27.5	0.0005
30	0.0031
32.5	0.0005
35	0.0003
37.5	0.022
40	0.013

Figure 7.2E. ST Segment Deviation (mV) in lead I at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



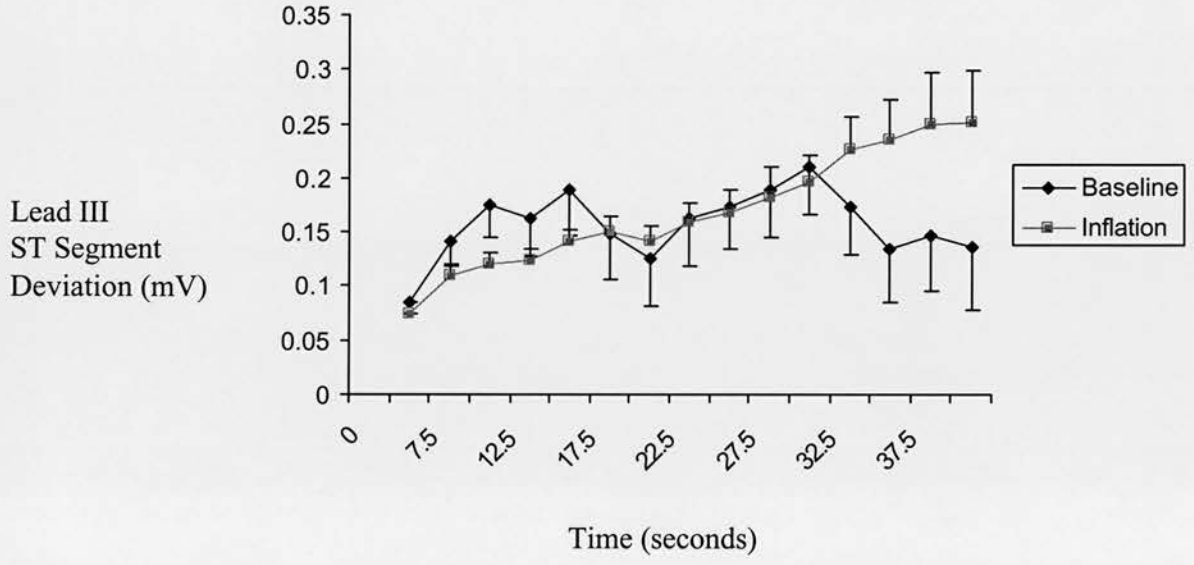
Time during balloon inflation (seconds)	P value
5	0.1
7.5	$p < 0.0001$
10	$p < 0.0001$
12.5	0.001
15	$p < 0.0001$
17.5	$p < 0.0001$
20	0.01
22.5	0.03
25	0.14
27.5	$p < 0.0001$
30	0.13
32.5	$p < 0.0001$
35	$p < 0.0001$
37.5	0.0003
40	0.11

Figure 7.2F. ST Segment Deviation (mV) in lead II at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



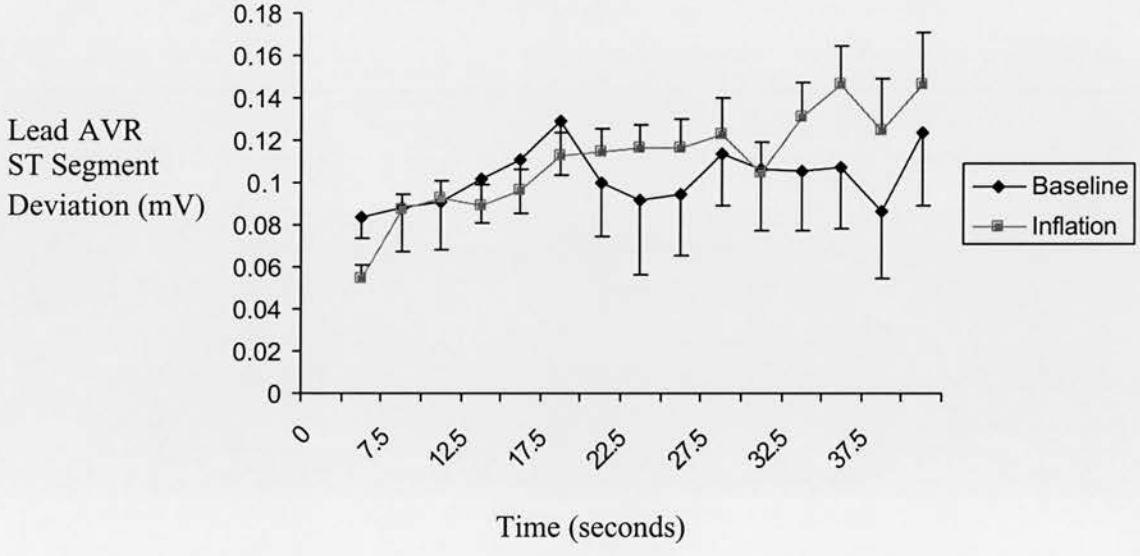
Time during balloon inflation (seconds)	P value
5	0.62
7.5	0.5
10	0.14
12.5	0.91
15	0.3
17.5	0.67
20	0.076
22.5	0.73
25	0.066
27.5	0.056
30	0.059
32.5	0.053
35	0.28
37.5	0.041
40	0.06

Figure 7.2G. ST Segment Deviation (mV) in lead III at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



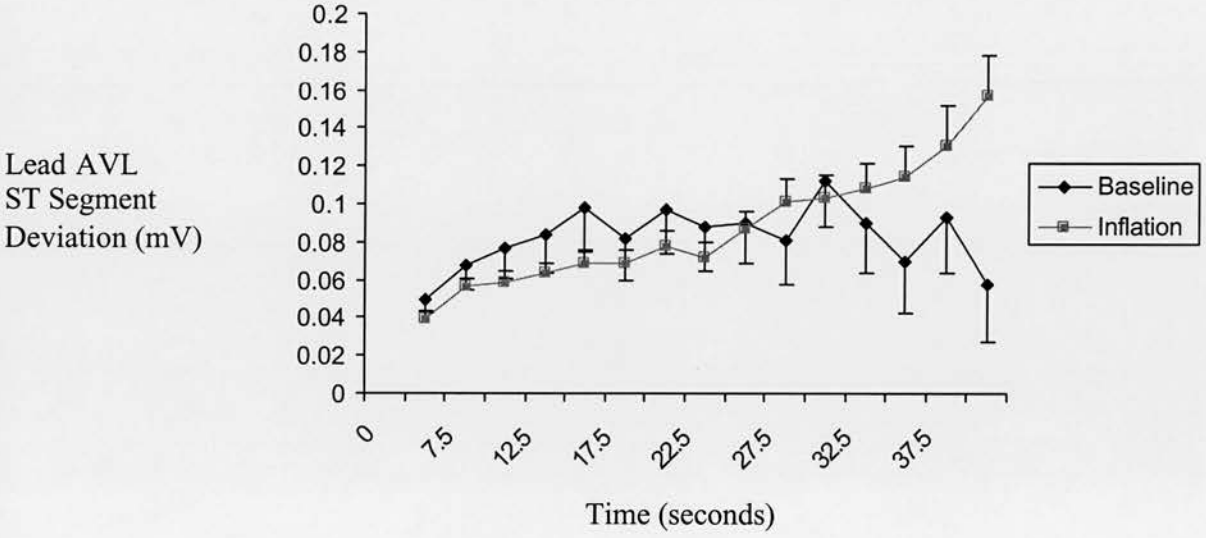
Time during balloon inflation (seconds)	P value
5	0.33
7.5	0.09
10	0.001
12.5	0.0001
15	0.01
17.5	0.29
20	0.13
22.5	0.62
25	0.38
27.5	0.65
30	0.91
32.5	0.14
35	0.71
37.5	0.23
40	0.05

Figure 7.2H. ST Segment Deviation (mV) in lead AVR at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



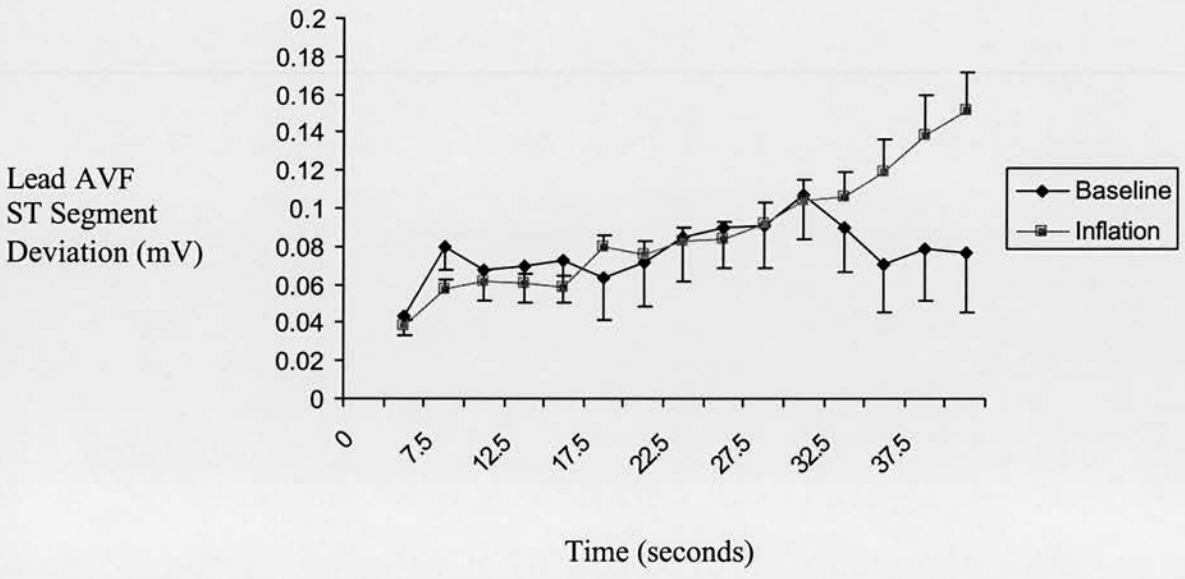
Time during balloon inflation (seconds)	P value
5	0.74
7.5	0.46
10	0.18
12.5	0.85
15	0.2
17.5	0.066
20	0.021
22.5	0.0021
25	0.18
27.5	0.018
30	0.27
32.5	0.051
35	0.12
37.5	0.35
40	0.38

Figure 7.2I. ST Segment Deviation (mV) in lead AVL at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



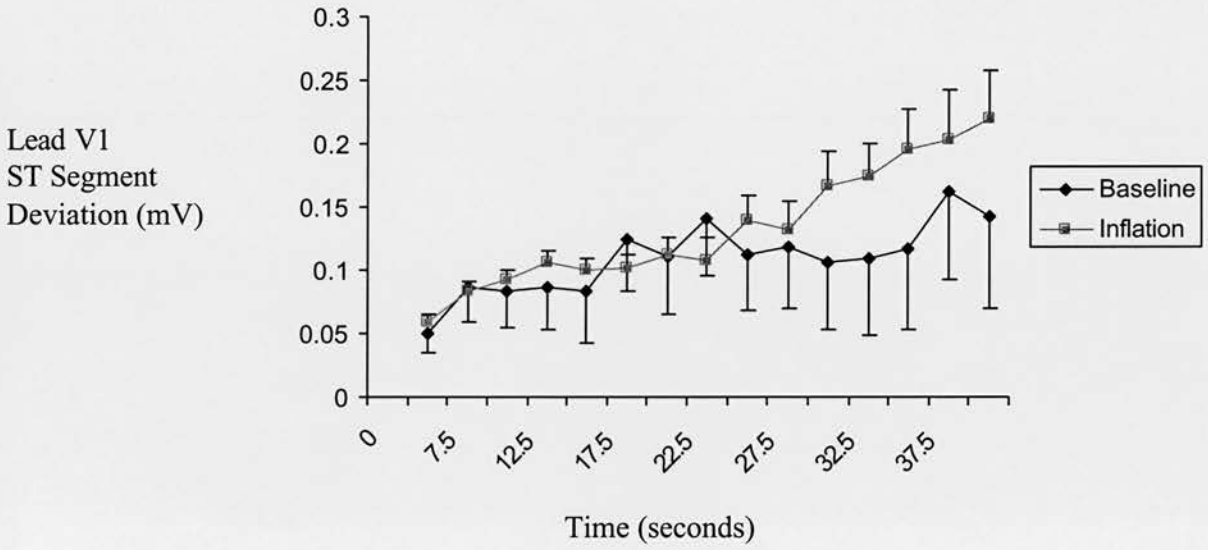
Time during balloon inflation (seconds)	P value
5	0.63
7.5	0.007
10	0.007
12.5	0.01
15	0.031
17.5	0.61
20	0.93
22.5	0.31
25	0.92
27.5	0.38
30	0.98
32.5	0.2
35	0.83
37.5	0.54
40	0.1

Figure 7.2J. ST Segment Deviation (mV) in lead AVF at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline..



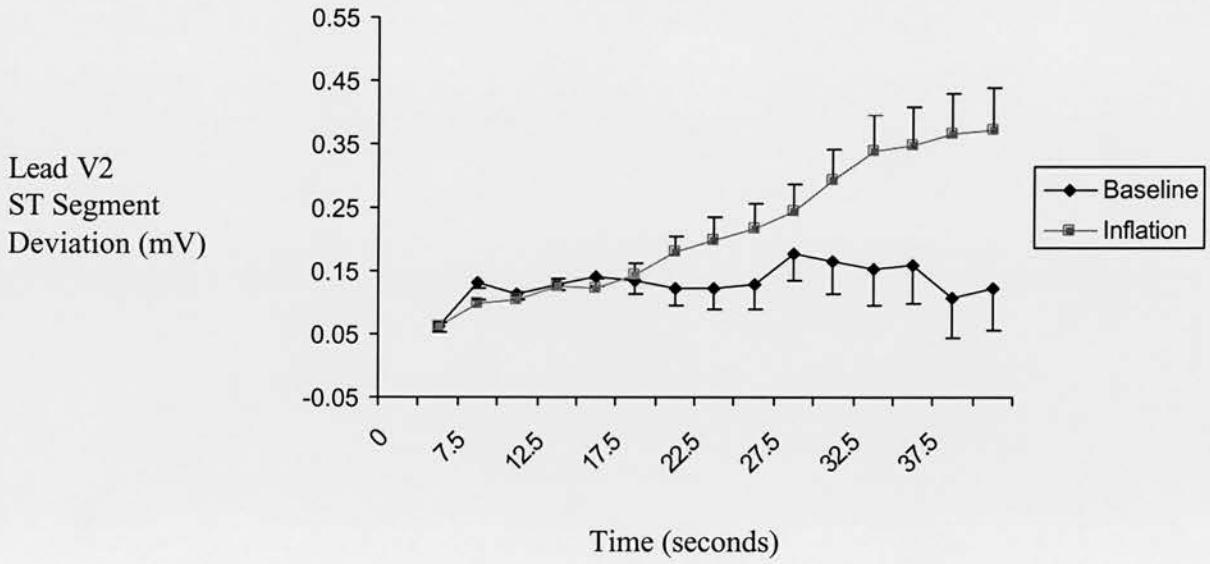
Time during balloon inflation (seconds)	P value
5	0.17
7.5	0.22
10	0.35
12.5	0.08
15	0.25
17.5	0.16
20	0.13
22.5	0.92
25	0.44
27.5	0.74
30	0.77
32.5	0.09
35	0.91
37.5	0.4
40	0.09

Figure 7.2K. ST Segment Deviation in lead V1 (mV) at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



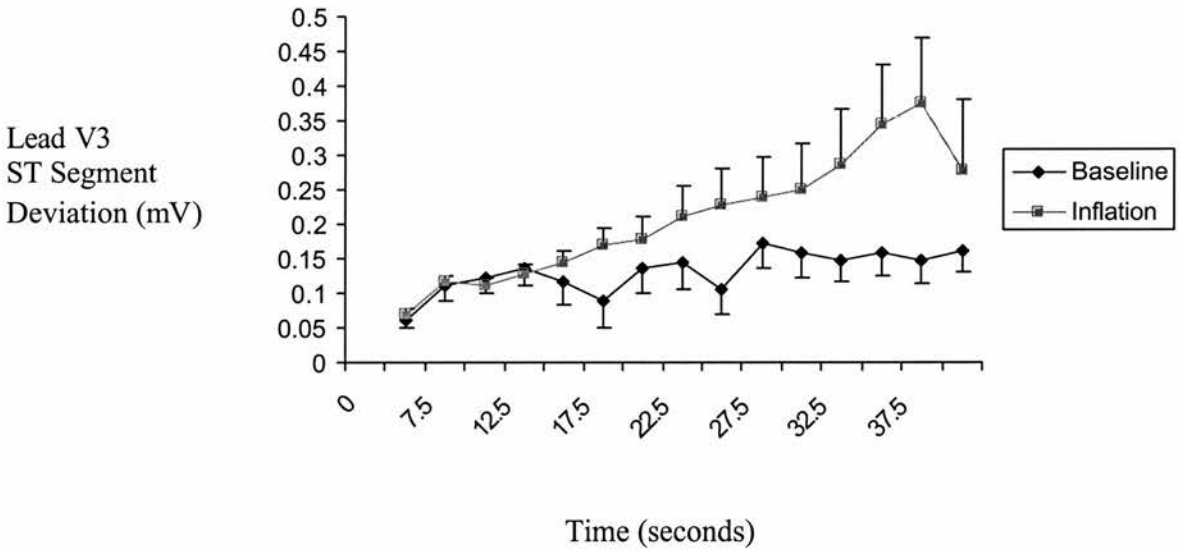
Time during balloon inflation (seconds)	P value
5	0.11
7.5	0.72
10	0.05
12.5	0.05
15	0.01
17.5	0.83
20	0.78
22.5	0.65
25	0.17
27.5	0.01
30	0.03
32.5	0.03
35	0.01
37.5	0.03
40	0.02

Figure 7.2L. ST Segment Deviation (mV) in lead V2 at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



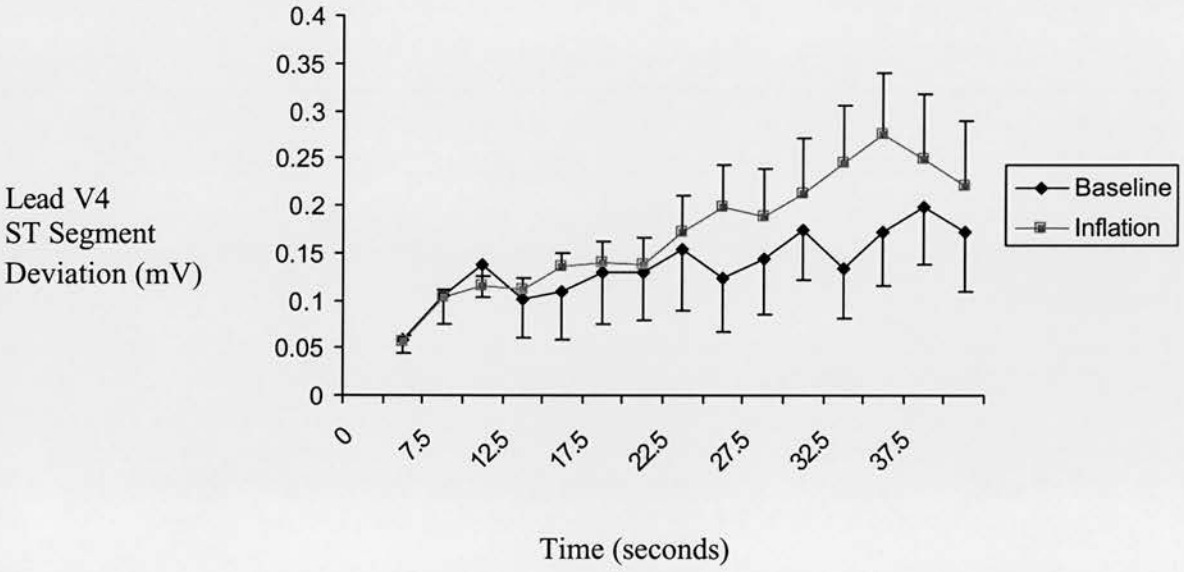
Time during balloon inflation (seconds)	P value
5	0.94
7.5	0.001
10	0.21
12.5	0.63
15	0.15
17.5	0.15
20	0.04
22.5	$p < 0.0001$
25	0.001
27.5	0.02
30	0.0002
32.5	$p < 0.0001$
35	$p < 0.0002$
37.5	0.0004
40	0.0007

Figure 7.2M. ST Segment Deviation (mV) in lead V3 at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



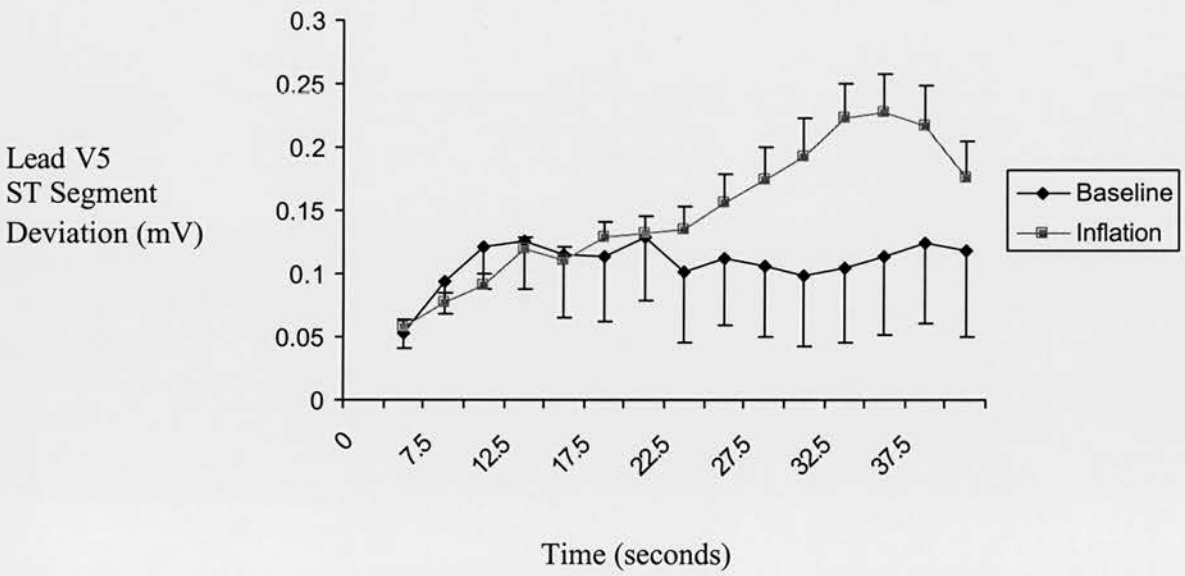
Time during balloon inflation (seconds)	P value
5	0.05
7.5	0.64
10	0.15
12.5	0.17
15	0.004
17.5	0.0002
20	0.0005
22.5	p < 0.0001
25	p < 0.0001
27.5	0.11
30	0.02
32.5	0.0003
35	p < 0.0001
37.5	0.001
40	0.001

Figure 7.2N. ST Segment Deviation (mV) in lead V4 at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



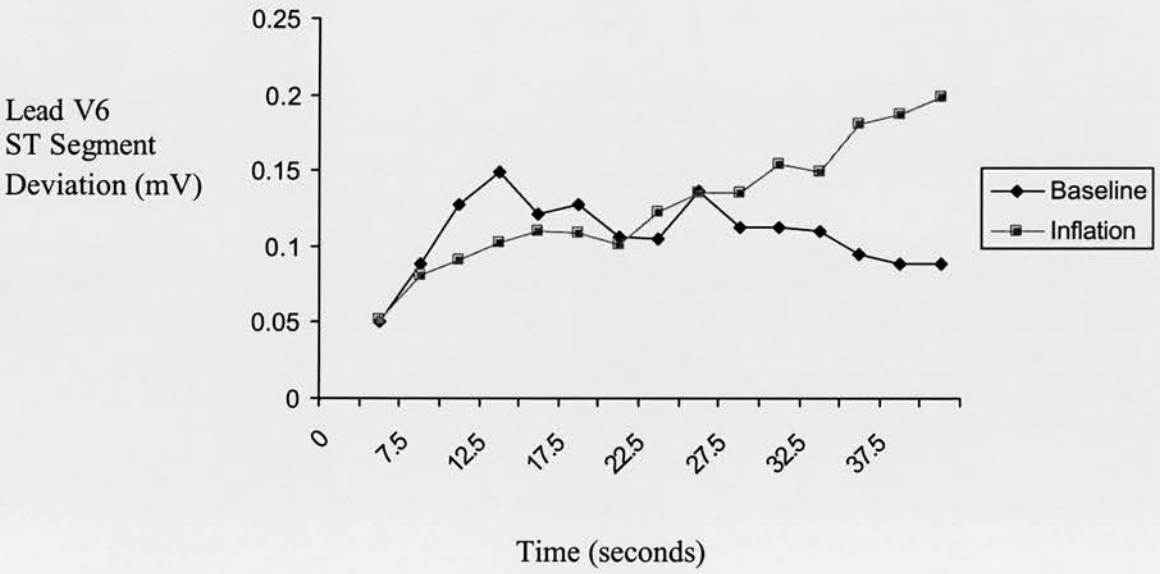
Time during balloon inflation (seconds)	P value
5	0.005
7.5	0.03
10	0.84
12.5	0.61
15	0.31
17.5	0.5
20	0.32
22.5	0.07
25	0.0003
27.5	0.43
30	0.07
32.5	0.002
35	0.006
37.5	0.07
40	0.41

Figure 7.2O. ST Segment Deviation (mV) in lead V5 at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



Time during balloon inflation (seconds)	P value
5	0.04
7.5	0.02
10	0.14
12.5	0.53
15	0.98
17.5	0.31
20	0.88
22.5	0.03
25	0.005
27.5	0.004
30	0.01
32.5	0.01
35	0.001
37.5	0.004
40	0.01

Figure 7.2P. ST Segment Deviation (mV) in lead V6 at baseline (40 seconds before percutaneous intervention) and during time of balloon inflation. Data presented are median ± standard error of mean. The table below summarises the p value obtained from Wilcoxon matched pairs test at various points in time during balloon inflation and corresponding time period at baseline.



Time during balloon inflation (seconds)	P value
5	0.01
7.5	0.75
10	0.6
12.5	0.001
15	0.15
17.5	0.36
20	0.27
22.5	0.003
25	0.1
27.5	0.37
30	0.19
32.5	0.04
35	0.11
37.5	0.09
40	0.03

DISCUSSION

This is the first study to investigate the use of novel T wave morphology descriptors during periods of myocardial ischaemia. Overall, abnormalities in these T wave morphology descriptors appear early and continue to evolve temporally for the duration of myocardial ischaemia. T wave morphology dispersion appear to be the best index for monitoring myocardial ischaemia with abnormal changes occurring as early as 5 seconds during balloon inflation. Although deviation in the ST segment in the surface ECG leads also occurred during balloon inflation, these usually appeared later. Furthermore, during the early periods of myocardial ischaemia, there was a paradoxical overlap between ST segment deviation at baseline and during balloon inflation in leads I, AVR, AVL, AVF, V1 and V6. This may reflect noise or ST segment baseline drift, although care was taken to avoid or filter out noisy signals. Furthermore, in the presented study, trends of ST deviations during coronary procedures were normalised to spontaneous oscillation of ST deviations at baseline (that is, divided by the standard deviation of mean ST deviation at baseline segment – see chapter 3, signal processing). The variability in the ST segment may account for the failure of ST segment trend analysis to provide an accurate assessment of prolonged myocardial ischaemia monitoring. Fully automatic processing of T wave morphology descriptors has been shown to have 99.7% reproducibility of all variables for any given ECG and within the same subject[126]. Reproducibility in this patient population was not assessed.

The prognostic value of T wave morphological assessment has been restricted to mortality prediction in patients with cardiovascular disease and in the post myocardial

infarction population[128,140]. Given the enhanced capability to detect repolarisation changes during myocardial ischaemia, it is plausible to suggest that these novel T wave morphology descriptors can be used risk stratify patients presenting with acute coronary syndrome. Particularly, patients presenting with chest pain and having no significant visual ECG changes and/or normal troponin. It may also improve the diagnostic accuracy of exercise tolerance testing.

As discussed in chapter 6, ST segment monitoring from bipolar right-sided intracardiac EGMs (available in implanted devices) has a modest detection capability for monitoring myocardial ischaemia and was significantly inferior to leads V2 and V3. As T wave morphology descriptors appear more superior to standard surface ECG leads, it is feasible to speculate that by incorporating automatic T wave morphology assessment algorithms in implanted devices, the diagnostic accuracy for monitoring myocardial ischaemia can be improved. This will require additional ring electrodes in chronically implanted leads and special electrode configurations, which can easily be accomplished.

This study excluded patients with bundle branch block, which is not infrequently found in patients with ischaemic heart disease. It has been previously demonstrated that TCRT is influenced by the presence of left bundle branch block; however, it still retains its prognostic value[140]. Other T wave morphology variables are not significantly influenced. It would be useful to know the effect of myocardial ischaemia on these T wave morphology descriptors in patients with pre-existing left bundle branch block. This will be most relevant if T wave morphology assessment algorithms are incorporated in implanted devices, particularly patients who are paced

from the right ventricle. Right bundle branch block appear to have little effect on T wave morphology variables[140].

CONCLUSION

This is the first study to investigate the use of novel T wave morphology descriptors during periods of myocardial ischaemia. Abnormalities of these indices appear early and continue to evolve temporally as long as ischaemia continues. These T wave morphology descriptors are more superior to conventional ST segment monitoring from standard surface ECGs. All of these variables can be instantly calculated from digital recordings from standard computer algorithms and with very high reproducibility, from a single ECG beat. The clinical implications of these findings are enormous and may improve the diagnosis, risk stratification, and early treatment of patients presenting with chest pain and acute coronary syndromes. Although these T wave morphology descriptors were calculated from the 12-lead surface ECG, there are possibilities of obtaining the same from the intracardiac EGM. This has the potential to expand the use of these novel descriptors into automatic algorithm for monitoring myocardial ischaemia in implanted devices.

CHAPTER 8

Concluding Remarks

Summary

The injury current that leads to deviation of the ST segment on the ECG is influenced greatly by the distance from the recording electrode to the region of ischaemia. Thus an electrode on the body surface distant from a region of ischaemia would be expected to record less ST segment deviation than an electrode placed on the surface of the heart, near the ischaemic area. By virtue of the proximity of intracardiac electrodes to regions of potential ischaemia, it is plausible to expect that intracardiac EGMs may be more sensitive and better indicators of transient myocardial ischaemia than the standard ECG recorded from the body surface. This thesis investigated whether myocardial ischaemia can be reliably detected from intracardiac electrograms (EGMs) that are potentially available in implanted devices such as pacemakers and implantable cardioverter defibrillators. It also investigated whether novel parameters of repolarisation (T wave morphology descriptors) can be used as indices to monitor myocardial ischaemia.

The first study investigated the optimal unipole for monitoring myocardial ischaemia from a multipolar intracardiac lead (a quadripolar electrode) placed within the right ventricle. This study showed that EGM recordings obtained from unipoles near the distal tip of the electrode are less sensitive in detecting myocardial ischaemia when compared to recordings obtained from more proximal unipoles. Due to the direct contact of the tip electrode with the myocardial wall, the EGM from more distal unipoles are often superimposed by local signals with morphologies similar to local action potentials. Therefore, for far-field global myocardial ischaemia monitoring, intracardiac electrodes should obtain recordings from a more central or basal location

within the right ventricular cavity. Consequently, in order to improve the sensitivity of intracardiac EGM monitoring, the average recording of the two most proximal unipoles within the right ventricular cavity were used as "a single unipole". This was then used in the subsequent two studies for multilead bipolar EGM reconstruction.

The second and third study investigated the diagnostic accuracy of detecting myocardial ischaemia using four bipolar leads reconstructed from the unipoles that are potentially available in implanted devices. These studies demonstrated that the absolute ST segment changes during periods of myocardial ischaemia are significantly greater in reconstructed bipolar intracardiac EGM signals compared with surface ECGs. However, when the amplitude of the intracardiac EGMs was normalised relative to that of the surface ECG, the ST segment changes were comparable and had an intermediate detection capability. Therefore, much of the difference in ST segment changes between the absolute intracardiac EGM and surface ECG signals appears to be related to the larger amplitude of EGM signals. It was therefore concluded that intracardiac EGMs have a modest detection capability for monitoring myocardial ischaemia and is significantly inferior to a number of surface ECG leads, particularly leads V2 and V3. It was originally proposed to conduct a feasibility sub-study to retrospectively analyse the original EGM data to simulate the signal practically available in an implanted device (recordings of 50 Hz and 100Hz sampling were to be reconstructed from the original 1kHz data). However, given the limited diagnostic performance of the bipolar EGMs, it was not considered of clinical practical value to pursuit this sub-study.

The fourth study investigated the application of novel descriptors of T wave morphology in monitoring myocardial ischaemia. This study demonstrated that abnormalities of these T wave morphology descriptors appear early and continue to evolve temporally during the period of ischaemia. These parameters appear to be more superior compared to conventional ST segment monitoring from standard surface ECGs. All of these variables can be instantly calculated from digital recordings from standard computer algorithms and with very high reproducibility, from a single ECG beat. The clinical implications of these findings are enormous and may improve the diagnosis, risk stratification, and early treatment of patients presenting with chest pain and acute coronary syndromes. Furthermore, automatic T wave morphology assessment algorithms can potentially be incorporated in implanted devices to improve the diagnostic accuracy of monitoring myocardial ischaemia.

In summary, the presented clinical studies demonstrate that monitoring myocardial ischaemia from intracardiac electrodes, analogous to those of implanted cardiac devices is feasible. However current technology limits this detection ability. The development of novel T wave morphology descriptors may improve the diagnostic accuracy of monitoring myocardial ischaemia.

Technical considerations

In addition to software algorithms, there are a number of technical issues that need to be considered before an implanted device can continuously and automatically monitor for myocardial ischaemia. Inclusion of ST segment monitoring algorithms into implanted devices will have a further impact on battery consumption. If, as with

current implanted devices, the EGM signals are used only to document arrhythmias, current drain can be decreased by using reduced EGM sampling rates, bits of resolution per sample, and signal bandwidth[141]. If implantable ST-segment algorithms are to record the same signal quality as the standard surface ECG, then significant developments must be made, which can greatly increase current drain. A second major component of current drain is use of the microprocessor. Continuous ST monitoring will increase the duty cycle of the implanted microprocessor and adversely affect the longevity of the device.

Future studies and conclusion

Detection of myocardial ischaemia from intrathoracic farfield EGMs appear promising. Advances in pacemaker and ICD technology have evolved to allow more sophisticated devices with improved storage capacity and longevity. Digitally acquired signals with better sampling frequency (1KHz) will enhance EGM resolution and ST segment analysis. These technological advances, together with new sites for multiple bipolar lead configurations, for instance between the right ventricle the anterolateral or great cardiac vein (left ventricle) may provide a more global farfield EGM for monitoring myocardial ischaemia. Lastly, the prospective assessment of these novel T wave morphology parameters calculated from intracardiac EGMs potentially available in implanted devices will help establish its clinical utility for automatic ischaemic monitoring.

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Appendix

Publications and presentations arising from this work

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Abstracts

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St. George's Hospital Medical School

Patient Information Sheet

Automatic Intracardiac Detection of Myocardial Ischaemia during angioplasty

Introduction

You have been scheduled to undergo angioplasty to alleviate your symptoms of angina. Angina occurs when there is a narrowing in one or more of the coronary (heart) arteries. Angioplasty is really an extension of coronary angiography, which you have previously had to assess the sate of the coronary arteries. During angioplasty, a wire (called a catheter) with a deflated balloon attached to it is passed across the narrowing in the artery. The balloon is then inflated, stretching the artery and compressing the material blocking it. When the balloon is deflated and removed, an enlarged channel remains which permits improved blood flow to the heart muscle. Your cardiologist will have already discussed the risks and benefits of angioplasty with you.

In patients with coronary artery disease, episodes of silent angina are approximately 10 fold more frequent than episodes of symptomatic angina. Prolonged episodes of angina including silent ones may lead to the development of a heart attack, a decrease in the function of the heart and a predisposition to life threatening abnormal heart rhythms. If we were able to detect episodes of silent angina then we will be able to develop an implantable device (like a pacemaker) which can detect these episodes and warn the patient to alter his/her activity or take their medication earlier. It can also be used to assess whether your medication is working effectively or whether the chest pain, which you are experiencing, is truly angina.

Before we can do this we need to take recordings from inside the chambers of the heart. These recordings are similar to the ones we frequently perform using the surface of your chest and limbs ("an ECG"). The only difference is that this time it will be done from inside your heart and only one or two catheters (called electrodes) will be used. We would be grateful if you would consider assisting in our medical research project. It is sometimes necessary to insert such an electrode during angioplasty whether or not you participate in the study. This study is voluntary and requires your consent. Refusing to participate in the study will not alter the treatment you will receive.

What is required in the study?

During your planned angioplasty study we will insert one or two electrodes into your heart and obtain recordings before, during and after balloon inflation.

What inconvenience and risks are involved?

Whilst the electrodes are being placed, you might experience some palpitations (an increased awareness of your heart beat) which normally settles with time. If these palpitations do not settle, then we will remove the electrode and consider discontinuing the procedure. You will still have your angioplasty as arranged. The amount of extra X-ray used is very small in comparison with that which will be administered routinely. As you may be aware, coronary angiography carries a small risk of bruising at the site where we gain access to the arteries and veins (usually in the groin area). Should bruising occur, we will limit its extent by applying pressure to the area. The electrodes being used have a good safety record and have used before in the department. Participation in the study requires you to stay in the EP lab about 15 minutes longer than usual and will not affect the time you will be discharged home. Refusal to participate in the study will not affect your treatment in any way. If, having agreed to participate in the study and you would like to stop the study at any time, for whatever reason, you have the right to do so without affecting your treatment.

Confidentiality

Data collected during the trial will be available only to investigators in charge. No details about you or your condition will be available to people other than your doctors except in an anonymous form.

Thank you for taking the time to read this and we hope you feel able to help.
If you feel there are any questions, which are left unanswered, then please contact me:

Contact details:
Dr. Azad Ghuran,
Department of Cardiological Sciences,
St. George's Hospital Medical School
Cranmer Terrace, London
SW17 0RE
Tel. 0208-725-5894 (direct to office)
Tel. 0208-672-9944 (switchboard), Page number 7013.

The Local Research Ethics Committee has seen and approved the above statement. Protocol No.:

Dr. A. Ghuran
Clinical Research Fellow

Dr. D. Ward
Consultant Cardiologist

Professor M Malik
Professor of Cardiac Electrophysiology

Professor A J Camm
Professor of Cardiology

Chairman of the Local Research Ethics Committee
Canon I. Ainsworth-Smith

Informed Consent Form
for the
participation in the study

"Intracardiac Detection of Myocardial Ischaemia"

Name: .....

Date of Birth: .....

Hospital Number .....

Date: .....

I, ..., consent to participate in the study described above. The study procedures and the study objectives have been carefully explained to me and my questions answered.

Signed,

.....
(patient)

..... Print Name .....
(witness)

St George's Healthcare

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Blackshaw Road, London SW17 0QT
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Our Ref: IAS/avm/99.6.7
2nd December, 1999
Dr. Azad Ghuran
Research Fellow
Department of Cardiological Sciences
St. George's Hospital Medical School.

Dear Dr. Ghuran,

Re: Automatic Intracardiac Detection of Myocardial Ischaemia - 99.6.7

Further to your letter of 11th November, 1999 and our subsequent discussion yesterday, I confirm that due to the report of a further study related life threatening adverse event, involving a patient at this centre, the above-named study should be immediately suspended.

We would remind you that any unexpected adverse event should be reported to the Committee immediately the incident occurs and in particular, when the incident involves a patient at this centre, the Chairman or Vice-Chairman should be contacted and informed immediately. The procedure to be followed is explained in the LREC Guidelines for Investigators- Appendix 3. (Copy enclosed).

The Committee wish to be kept informed of the condition of the patient and any further details regarding the incident and will certainly wish to discuss this at their meeting on the 15th December. In the meantime, I would appreciate as full a report as possible on the circumstances of this adverse event and any possible cause.

Yours sincerely,

Ian Ainsworth-Smith

Canon Ian Ainsworth-Smith
Chairman
Local Research Ethics Committee
c.c. Dr.D.Ward, Prof.M Malik.

Please Note: All research should be conducted in accordance with the guidelines of the Ethical Committee; the reference number allocated to the project should be used in all correspondence with the Committee and the Committee should be informed:

(a) when the project is complete.
(b) what stage the project is at one year from today's date.
(c) if any alterations are made to the treatment or protocol which might have affected ethical approval being granted.
(d) all investigators whose projects have been approved by this Committee are required to report at once any adverse experience affecting subjects in the study.

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Our Ref: IAS/jlr/99.6.7

20 December 1999

Dr Charles Pumphrey
Consultant Cardiologist
Dept. of Cardiological Sciences
St George's Hospital Medical School

Dear Dr Pumphrey,

Automatic Intracardiac Detection of Myocardial Ischaemia - 99.6.7

The Local Research Ethics Committee of 15 December 1999, considered the correspondence between Dr Ghuran and Canon Ian Ainsworth-Smith relating to two serious adverse events that occurred in subjects volunteering for the above study. Members felt that two almost identical adverse reactions of a technical nature suggests that the 'operator' introducing the electrodes (Dr Baig) may not have sufficient experience in this area to ensure minimum risks. With this in mind members asked that for the time being you, in person, introduce the electrodes. It will be for Dr Baig to be 'retrained' in electrodes introduction and when this has occurred he could restart being involved in the procedure. Although the letter from Dr Azad Ghuran emphasises that 'Dr Baig is very experienced', members felt that caution was necessary.

With best wishes,

Yours sincerely

Ian Ainsworth-Smith (Chairman)
pp.
Professor Joe Collier
Vice-Chair/Clinical Secretary
Local Research Ethics Committee

cc. Dr. Azad Ghuran.

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Our Ref: IAS/it/99.6.7

15 June 2000

Dr A Ghuran
Research Fellow
Department of Cardiological Sciences
St George's Hospital Medical School

Dear Dr Ghuran

Re: Automatic Intracardiac Detection of Myocardial Ischaemia - 99.6.7

Thankyou for your letter of 14 June 2000 and for your very full details of the adverse event concerning Mr Walters.

I am pleased to know that he seems to have suffered no long term ill effects.

The best thing would be for me to place your letter on the agenda for our meeting on 28 June 2000. I think you have given us full enough details, so we would not require your attendance. But I will hope to have a brief conversation with you before the meeting.

With all good wishes,

Canon Ian Ainsworth-Smith
Chairman
Local Research Ethics Committee

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Our Ref: JC/kl/99.6.7

29 June 2000

Dr Azad Ghuran
Research Fellow
Department of Cardiological Sciences
St. George's Hospital Medical School

Dear Dr Ghuran

Re: Automatic Intracardiac Detectionof Myocardial Ischaemia - 99.6.7

The Local Research Ethics Committee of 28 June 2000 considered your letter to Canon Ainsworth-Smith dated 14 June 2000, reporting a recent adverse event relating to the placement of the experimental electrode. Members felt that such a serious event, occurring in three patients out of less than fifteen, constituted a hazard of such seriousness that required that the study is stopped. Members asked that modifications are made to the project and that you submit a new application which will need approval before the project continues. Members will be looking for an application which ensures less risk to participants and to that end would expect you to revise the protocol, or use a new device or technique.

One important role of the Local Research Ethics Committee is to protect the interests of participants and with so many of your subjects put at risk, the approach we have chosen would seem inevitable.

I look forward to receiving a new protocol if that is your wish.

Yours sincerely

pp.
Professor Joe Collier
Vice-Chair/Clinical Secretary
Local Research Ethics Committee

PS
Members asked for confirmation as to who was placing the wire initially that led to the most recent perforation? Members remember making stipulations as to who should undertake placement.

Dr Azad Ghuran
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E mail: aghuran@totalise.co.uk

11/7/00

Professor J Collier
Vice-Chair/Clinical Secretary
Local Research Ethics Committee,
St. George's Hospital Medical School

Dear Professor Collier, **Re. Automatic Intracardiac Detection of Myocardial Ischaemia – 99.6.7**

Thank your for your correspondence dated 29th June 2000. We fully agree with the decision of the committee and we would like to resubmit the project for ethical approval.

Specifically, we have changed the electrode to a smaller, less stiff, flexible one (the Avail electrode). It is not steerable like the Porterfield electrode (which contributed to its stiffness) and has an excellent safety profile. I have enclosed correspondence (e-mail) from Biosense Webster, which confirms the absence of any negative feedback. Additionally, the electrode has been used on a number of occasions at the catheter laboratory at St. George's Hospital without any complications.

In response to several issues mentioned in your letter, I would like to clarify the following. There were three complications out of thirty-three patients and not three out of fifteen. Nevertheless, the event rate was clearly still too high to continue. You also asked for confirmation as to who placed the wire in initially. My letter dated 14/6/00 (enclosed) to Canon Ainsworth-Smith clearly described the procedure. Dr. R. Crook initially inserted the electrode to the right ventricular apex. As we were not obtaining good signals, the electrode was recited by Dr. Pumphrey. Dr. Crook is one of the senior intervionalist and was recently appointed as a consultant cardiologist at York district Hospital, York. Prior to the procedure, permission was requested from the LREC to allow Dr. Crook to insert the electrode (letter enclosed).

Should there be any queries please don't hesitate to contact me. I would be happy to attend and answer any questions the committee may have at their next meeting.

I look forward to the committee's decision regarding our project.

Yours sincerely,

Azad Ghuran

St George's Healthcare

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Our reference: JC/it/99.6.7

1 August 2000

Dr. Azad Ghuran
Research Fellow
Department of Cardiological Sciences
St George's Hospital Medical School

Dear Dr Ghuran,

Re: Automatic Intracardiac Detection of Myocardial Ischemia (modification of previous study, reference 99.6.7)

At its meeting last night the Local Research Ethics Committee considered your application for the above study. Several issues need to be raised before approval can be given.

1. Has the new electrode you plan to use been approved by the Medical Devices Agency (MDA)

2. The Committee wants to know the name of those who would be placing the electrode were approval to be given.

3. In your original application you planned to study around 150 patients. We note that in the current application the figure is down to 50. What has changed in the methodology to permit this reduction? Members wondered whether this reduction was acceptable to your grant giving body.

4. Members recalled that tamponad occured in around 3 of 12 patients studied. In this current application the figure is given as 3 of 33. Could you explain the discrepancy? Perhaps the larger figure is taken from studies at other centres. If that is so, the members wondered whether the serious adverse events (tamponade) was operator, rather than catheter, error.

5. Could you please redo the Patient Information Sheet to include the possible risks of the procedure. These risks should relate to known risks occurring with the new catheter.

6. When you redo the Patient Information Sheet could you include a note to the effect that the study is of no therapeutic value to the participants.

7. Members of the Committee felt it was inappropriate to seek approval for the study once the patient was admitted. The issue of consent should be tackled in outpatients.

8. If we were to approve this study we would expect to have an interim report on the outcome of each intervention after the first ten patients had been investigated.

I look forward to receiving your response to the above points

Yours sincerely

Professor Joe Collier
Vice-Chair/Clinical Secretary
Local Research Ethics Committee

Dr Azad Ghuran
Research Fellow
Department Of Cardiological Sciences,
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London
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Ext. 5894
Page No. 7013

06/9/00

Canon Ainsworth-Smith
Chairman
Local Research Ethics Committee
St. George's Hospital
Blackshaw Rd.
London SW17 0QT

Dear Canon Ainsworth-Smith,

Re: **Automatic Intracardiac Detection of Myocardial Ischaemia (modification of previous study) – 99.6.7**

With regards to your letter dated 1/8/00, I would like to answer the issues raised by the Local Ethics Research Committee. I shall answer the committee in the same order as the issues were raised.

1. I have contacted the representative from Biosense Webster who has sent me a copy of their CE Certificate, which covers all their electrophysiological products and demonstrates compliance for the British Standards Institution. (enclosed)
2. Dr. Ward will be responsible for the placement of all electrodes.
3. I have spoken to Dr. Anthony Woods, Scientific Officer at the Wellcome Trust when he came to St. George's Hospital on the 13th March for a site visit. I explained to him the previous complications and the reduction of elective angioplasty admissions. I told him that we were realistically aiming for a recruitment figure of approximately 50 patients (and not 150, as previously stated). He did not mind the exact number of patients studied, provided we were able to produce something from the study.
4. In this day and age of "Governance in NHS Research" an accurate account of all patients studied is mandatory. Out of 33 cases studied there were 3 cases of cardiac tamponade. I am not who has informed the LREC an erroneous figure of 3 out of 12. I am happy to justify my figures.
5. The Patient Information Sheet has been amended to include the possible risks of the procedure and the lack of any therapeutic benefit.
6. See above.
7. Acknowledged and will be instituted.
8. Acknowledged and will be instituted.

I hope these answers satisfy your queries and approval for my project can be granted. I look forward to the LREC's response.

Yours sincerely,

Azad Ghuran

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Our Ref: IAS/kj/99.6.7

8 September2000

Dr A Ghuran
Research Fellow
Department of Cardiological Sciences
St George's Hospital Medical School

Dear Dr Ghuran

Re: Automatic Intracardiac Detection of Myocardial Ischaemia - 99.6.7

Thank you for your letter of 6 September 2000 together with enclosures. We note the points you make in response to our letter and I would appreciate discussing point 4 of your letter briefly with you before giving final ethical approval for you to proceed. Please could you possibly give me a ring on Ext. 3398 or Ext. 3071.

Yours sincerely

Canon Ian Ainsworth-Smith
Chairman
Local Research Ethics Committee

Please Note: All research should be conducted in accordance with the guidelines of the Ethical Committee; the reference number allocated to the project should be used in all correspondence with the Committee and the Committee should be informed:

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(b) what stage the project is at one year from today's date.

(c) if any alterations are made to the treatment or protocol which might have affected ethical approval being granted.

(d) all investigators whose projects have been approved by this Committee are required to report at once any adverse experience affecting subjects in the study and at the same time state the current total number of Serious Adverse Events that have occurred.

Page No. 6211

St George's Healthcare NHS
NHS Trust

Our Ref: IAS/kj/99.6.7

11 September 2000

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Dr A Ghuran
Research Fellow
Department of Cardiological Sciences
St George's Hospital Medical School

Dear Dr Ghuran

Re: Automatic Intracardiac Detection of Myocardial Ischaemia - 99.6.7

Thank you for coming to see me today. I confirm that the figures you showed me are of a cardiac tamponade rate of 3 in 33 cases. Approval is therefore given for the above named study to proceed. We shall be pleased to receive an interim report on your study in due course.

Yours sincerely

Canon Ian Ainsworth-Smith
Chairman
Local Research Ethics Committee

Please Note: All research should be conducted in accordance with the guidelines of the Ethical Committee; the reference number allocated to the project should be used in all correspondence with the Committee and the Committee should be informed:

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(d) all investigators whose projects have been approved by this Committee are required to report at once any adverse experience affecting subjects in the study and at the same time state the current total number of Serious Adverse Events that have occurred.

Dr Azad Ghuran
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Page No. 7013

13/10/00

Canon Ainsworth-Smith
Chairman
Local Research Ethics Committee
St. George's Hospital
Blackshaw Rd.
London SW17 0QT

Dear Canon Ainsworth-Smith,

Re: **Automatic Intracardiac Detection of Myocardial Ischaemia (modification of previous study) – 99.6.7**

In keeping with the LREC request, I am writing to inform the committee that we have successfully conducted 2 cases
without any problems.

Yours sincerely,

Azad Ghuran