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MONITORING OF POSTOPERATIVE MYOCARDIAL ISCHEMIA AND INFARCTION WITH CONTINUOUS ECG MEASUREMENTS

Master of Science thesis

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ABSTRACT

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Postoperative myocardial ischemia leading to myocardial infarction (PMI) after a non-cardiac surgery is shown to be common in selected population and is associated with increased mortality and morbidity in-hospital and long term. Primary and a relatively sensitive detection rate can be achieved using assays of a biomarker called cardiac troponin in order to indicate myocardial injury. However, for troponin concentration to rise an injury must have already occured. Electrocardiography(ECG) changes on the other hand are known to be present in the setting of myocardial ischemia immediately after diminished or restricted blood flow. In addition major part of the postoperative ischemic events are asymptomatic thus further stressing the importance of ECG monitoring. Despite the abundant clinical evidence supporting these facts the standard of practice in many hospitals does not include routine troponin assays or even routine ECG monitoring after non-cardiac surgery. Thus in order to increase the likelihood of timely detection of ischemic events continuous ECG monitoring in parallel with regular troponin assays should be performed to prevent the ischemia developing further in the first place. At the same time this should be done efficiently with minimal burden for the patient. Recent advances are driving patient monitoring towards wireless approach which suits the needs placed by this scenario as well. In this thesis the ischemic events of patients undergoing a non-cardiac vascular surgery were studied in the Helsinki university central hospital. ECG was measured using a Holter ECG system in order to imitate the wireless monitoring setting. The monitoring time was 72 hours after a noncardiac vascular surgery. Additionally standard 12-lead snapshot ECG's were measured for comparison to determine the benefits of continuous ECG monitoring. The performance of the continuous measurements was used to assess the quality of the measurements for future development of ischemia monitoring. A literature review of the relevant

background of the topic and the current state of ischemia monitoring is given as well. Additionally a custom software analysis tool was developed in order to visualize and utilize the data in an orderly manner. The tool was used in visual annotations and post-processing of the data. From the study group of 56 patients, 19 were diagnosed to have ischemia. Out of the 19 patients, 5 were diagnosed to have myocardial infarction during the postoperative monitoring. All ischemia appeared as depression of the ST-segment. After analysing the data the ECG lead sensitivities were found to be consistent with similar studies and clinical guidelines. Moreover the ischemic burden revealed by continuous monitoring was considerable and increased cumulatively during the monitoring. The thesis shows evidence that continuous realtime ECG monitoring of certain postoperative patients would reduce the total ischemic burden of patients.

TIIVISTELMÄ

JOONAS VANHATALO: Postoperatiivisen sydänlihasiskemian ja sydäninfarktin jatkuva-aikainen monitorointi
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Postoperatiivisen sydänlihasiskemian kehittyminen sydäninfarktiksi ei-sydänkirurgisten verisuonileikkausten jälkeen tiedetään olevan yleistä tietyissä potilasryhmissä ja se yhdistetään kohonneeseen kuolleissuuteen ja sairastavuuteen sairaalassa oloaikana ja sen jälkeen. Yleisesti käytetty ja suhteellisen sensitiivinen tapa havaita sydänlihasvaurio on käyttää sydänlihasperäisen troponiinimerkkiaineen kohonnutta arvoa indikoimaan sydänlihasvauriota. Troponiinipitoisuuden kohoaminen kuitenkin vaatii jo tapahtuneen sydänlihasvaurion. Elektrokardiografiaan(EKG) rajoittuneen tai katkenneen sydänverenkierron tiedetään sen sijaan vaikuttavan välittömästi sydänlihasiskemian aikana. Tämän lisäksi postoperatiiviset iskeemiset kohtaukset ovat pääasiassa oireettomia, mikä edelleen lisää EKG-seurannan tärkeyttä. Huolimatta suuresta määrästä kliinisiä todisteita, monen sairaalan hoitokäytännöt ei-sydänkirurgisen leikkauksen jälkeen eivät sisällä troponiinimittauksia tai edes rutiininomaista EKG-seurantaa. Hyödyntämällä jatkuva-aikaista EKG-seurantaa sekä samanaikaisesti seurannan aikana tehtäviä troponiinimittauksia, sydänlihasiskemian kehittyminen pidemmällä voitaisiin estää ja iskemia voitaisiin diagnosoida normaalia aiemmin. Iskemian toteaminen täytyisi lisäksi pyrkiä tekemään tehokkaasti ja kuormittamatta potilasta liiaksi. Potilasmonitoroinnin kehittyminen yhä enemmän langattomaksi tukee myös tämänkaltaista hoitomuotoa. Tutkimuskohteena tässä diplomityössä olivat potilaat, joille oli tehty ei-sydänkirurginen verisuonileikkaus Helsingin seudun yliopistollisessa keskussairaalassa. Potilailta mitattiin EKG käyttämällä Holter EKG -järjestelmää, millä pyrittiin imitoimaan langatonta monitorointiympäristöä. Seuranta-aika oli 72 tuntia ei-sydänkirurgisen verisuonileikkauksen jälkeen. Tämän lisäksi potilaille tehtiin standardi 12-kytkentäinen näyte EKG-mittaus, jotta langattoman EKG-mittauksen hyödyt voitaisiin tunnistaa. Lisäksi jatkuva-aikaisten mittausten suorituskyky arvioitiin, jotta tietoa voidaan hyödyntää iskemiamonito-

roinnin jatkokehitykseen. Työ sisältää myös kirjallisuuskatsauksen aiheen taustasta, nykytilasta ja tutkimuksesta. Koko 56 potilaan tutkimuspopulaatiosta, 19 potilaalla todettiin sydänlihasiskemia. Näistä 19 potilaasta, viidellä diagnosoitiin sydäninfarkti seurannan aikana. Kaikki diagnosoitu iskemia todettiin EKG:ssä ST-tason laskuna. Data-analyysin jälkeen EKG:n kytkentöjen sensiivisyyden todettiin olevan linjassa muiden samankaltaisten tutkimusten tulosten kanssa sekä kliinisten suositusten kanssa. Lisäksi jatkuva-aikasessa seurannassa paljastunut iskemiakuorma oli merkittävä ja kasvoi kumulatiivisesti seurannan aikana. Työssä esitetään todisteita siitä, että tiettyjen potilasryhmien jatkuva- ja reaaliaikainen EKG-seuranta vähentäisi iskemiakuorman kokonaismäärää potilailla.

PREFACE

This thesis was written at GE Healthcare Finland Oy. The thesis was done as a part of a project focusing on future development of ischemia monitoring in the clinical environment. I want to thank my Engineering manager Rene Coffeng for giving me this great opportunity to work in this project and be a part of the study group conducting the clinical study.

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LIST OF ABBREVIATIONS AND TERMS

AACN	American Association of Critical-Care Nurses
ACS	Acute Coronary Syndrome
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
AMI	Acute Myocardial Infarction
AP	Action Potential
AV	Atrioventricular
BPM	Beats Per Minute
CAD	Coronary Artery Disease
CBF	Coronary Blood Flow
CCU	Cardiac Care Unit
cTn	Cardiac Troponin
ECG	Electrocardiography
ESC	European Society of Cardiology
ESA	European Society of Anaesthesiology
GE	General Electric
GUI	Graphical User Interface
HR	Heart Rate
HRS	Heart Rhythm Society
LAD	Left Descending Artery
LA	Left Arm (electrode)
LBBB	Left Bundle Branch Block
LCX	Left Circumflex artery
LL	Left Leg (electrode)
LPHB	Left Posterior HemiBlock
LVH	Left Ventricular Hypertrophy
MI	Myocardial Infarction
MIT	Massachusetts Institute of Technology
NP	Natriuretic Peptide
NSQIP	National Surgical Quality Improvement Program
NSTEMI	Non ST-elevation Myocardial Infarction
PMI	Postoperative Myocardial Infarction
PDA	Posterior Descending Artery
RBBB	Right Bundle Branch Block
RCA	Right Coronary Artery
RCRI	Revised Cardiac Risk Index

RA	Right Arm (electrode)
RL	Right Leg (electrode)
SA	Sinoatrial
SQI	Signal Quality Index
STEMI	ST-elevation Myocardial Infarction
TnI	Troponin I
TnT	Troponin T
TPA	Tissue-type Plasminogen Activator
UA	Unstable Angine

1. INTRODUCTION

Myocardial infarction (MI) occurs when blood flow is significantly reduced or blocked to a part of the heart, i.e. it becomes ischemic, which then leads to permanent damage of the heart muscle. It has a major impact on the mortality and morbidity worldwide. Postoperative myocardial infarction (PMI) after noncardiac surgery have been recognized as a common and serious cardiac complication and it has been associated with increased 30-day mortality [74, 37]. The estimates of in-hospital economic burden caused by PMI have been reported up to $12 billion annually. Moreover the elevation of a cardiac biomarker, troponin T (TnT), released during myocardial injury, have been shown to have a strong association with noncardiac surgery [41] as well as with mortality within one year after the surgery [11]. In the year 2009, the estimated number of major surgeries was 230 million worldwide and this number is expected to increase as the advances in treating diseases result in a more aged population who are in a more high-risk group to undergo surgery [33].

The detection of PMI is challenging as the common symptoms, such as chest pain, are not felt by the patient due to postoperative pain medication. This complicates making the conventional clinical diagnosis of MI as according to current criteria a second piece of evidence is needed. [20] To fulfill the clinical criteria of MI an ischemic symptom, imaging finding or ECG finding is required [69]. It seems obvious that continuous ECG monitoring following noncardiac surgery would be a simple and convenient tool for detecting the second piece of evidence for the MI diagnosis. However, continuous postoperative ECG, or rather monitoring the ST-segment of the ECG waveform, has not yet become a standard of practice although it has been suggested to be such [15]. It has been reported that only half of critical care use ST-monitoring. Although a standard of taking sample 12-lead ECG's is frequently used, the dynamic nature of the ischemic events cause this static snapshot to miss important information and does cover the underlying trend. [62]

Only a few studies have examined the incidence of PMI events after noncardiac surgery simultaneously while studying the sensitivity of different ECG leads for these events. These studies have all used conventional wired technology.[34, 30]. Although providing valuable information, these studies reveal little about the contrast between

continuous monitoring and performing snapshot ECG measurements. In addition a moving patient has not been considered in these studies. It is evident that new trends in long-term health care and thus in patient monitoring, are transforming towards a more wireless environment. The advances in other fields of technology have enabled the health care industry to look for wireless solutions as well but this new monitoring environment poses several challenges. These challenges include for instance power management issues and the effect of movement to physiological measurements.[68]

2. THEORY AND BACKROUND

The heart is the most vital organ when it comes to providing oxygen and nutrients for the human body. It works tirelessly throughout human life beating over two billion times in an average human lifetime. The importance of the heart and the cardiovascular system also reflects to the statistics as cardiac diseases is the largest cause of morbidity and mortality in developed countries as well as in undeveloped countries [59].

2.1 Anatomy and Physiology of the Heart

The heart is located in the thorax, in a compartment called mediastinum just above the diaphragm. Located slightly on the left side of the body, the heart is covered by a double-layered sac, the pericardium. The pericardium is divided into fibrous and serous pericardium. The outer fibrous pericardium protects the heart, attaches the heart to the surrounding structures and prevents overfilling of the heart. The inner part, the serous pericardium, can be further divided into the parietal pericardium and the visceral pericardium, from which the latter is the outermost layer of the actual heart. The visceral pericardium is also called the epicardium. In between these two pericardia lies the pericardial cavity containing pericardial fluid. This thin layer of fluid allows the heart to pump without notable friction. [9]

The mass of the heart consists mainly of cardiac muscle tissue, better known as myocardium. The cardiac muscle fibers are connected by intercalated discs which have gap junctions, which are specialized intercellular connections. Gap junctions have a very low resistance which makes conduction of the signals between the cells faster. Another structurally important part is the fibrous cardiac skeleton of the heart which is a single structure of connective tissue anchoring and strengthening the different parts of the heart. It also acts as electrical insulation between the atria and the ventricles. [9].

Structurally the inner heart consists of four separate chambers: two atria and two ventricles. The deoxygenated blood first enters the right atrium through the superior and inferior vena cavae. The right atrium has the thinnest walls of all the chambers.

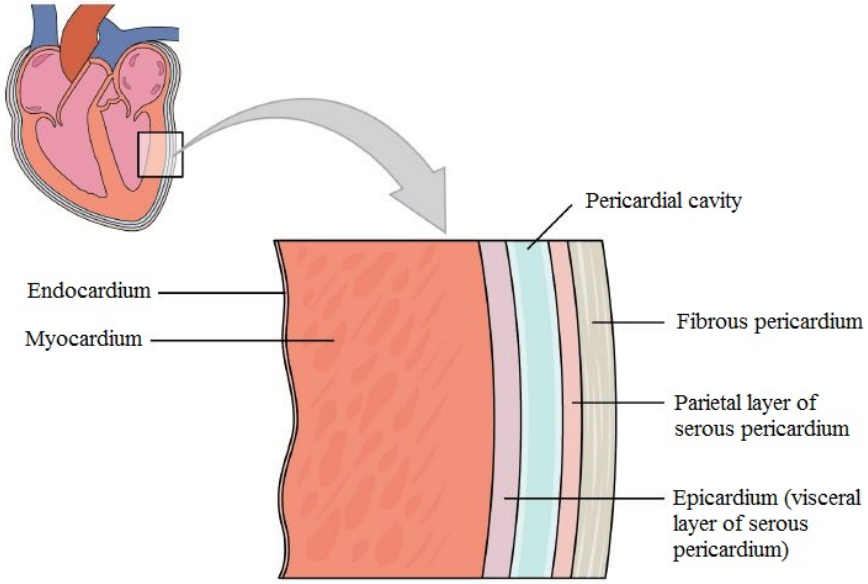

Figure 2.1 *Cross-section of the different layers of the heart [9]*

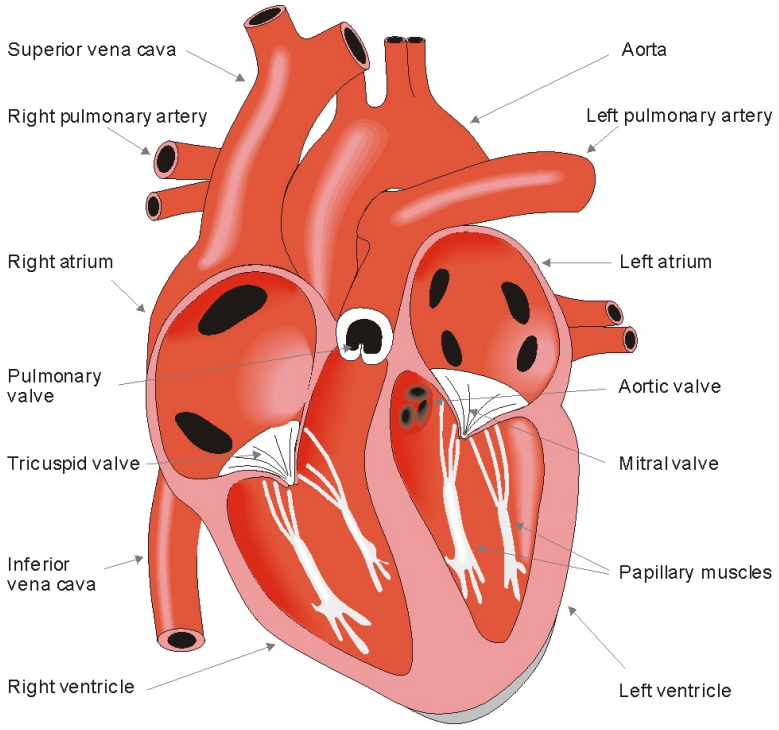

Figure 2.2 *Basic anatomy of the heart [43, Ch. 6]*

During ventricular diastole the blood enters the right ventricle through the tricuspid valve. The right ventricle forms largely the anterior surface of the heart. Next, during ventricular systole, blood is pumped to the pulmonary circulation through the pulmonary valve.

The left atrium, which forms the base of the heart, receives oxynated blood from four pulmonary veins and ejects the blood further to the left ventricle as a preparation to the ventricular ejection. The valve between the left atrium and the ventricle is called the mitral valve. The left ventricle has the thickest walls among the four chambers, roughly three times thicker than the right ventricle. These muscular walls are required to overcome the vascular resistance in the systemic circulation. The atria are separated by the interatrial septum and the ventricles by interventricular septum. [70]

2.1.1 Coronary Circulation

The heart is supplied with blood by the coronary circulation. The two main coronary arteries, the right (RCA) and the left coronary artery (LCA), branch from the aorta as it arises from the left ventricle. The LCA is responsible for supplying blood to the left side of the heart, mainly to the left atrium and ventricle and to the interventricular septum. The LCA quickly branches into the circumflex artery (LCX) and left anterior descending artery(LAD). The LCX continues left along the coronary sulcus to the posterior side of the heart. Quickly it gives off branches called obtuse marginal branches. The LAD in turn follows the anterior interventricular sulcus downwards. The LAD gives off branches called diagonal branches that are used to segment the LAD into different parts using these branches as boundaries. Additionally the LAD also gives off branches called septal branches which supply the interventricular septum. The RCA runs to the right, along the coronary sulcus.

An important artery on the posterior side of the heart is the posterior interventricular artery or posterior descending artery (PDA) which also follows the interventricular sulcus, but on the posterior side. All of these mentioned larger coronary arteries give rise to smaller branches that spread all over the heart to secure a steady blood supply to all parts of the heart. Additionally anastomoses, i.e. vessel interconnections, are formed between the branches. In a case of a narrowing or blockage in some coronary artery, blood supply can be sustained with a favourable anastomosis supplying the same area. However a blockage of a larger coronary artery is harder to overcome and is more likely to lead into lack of oxygen and nutrients. [9, p. 789] The main coronary arteries and veins are illustrated in figure 2.3.

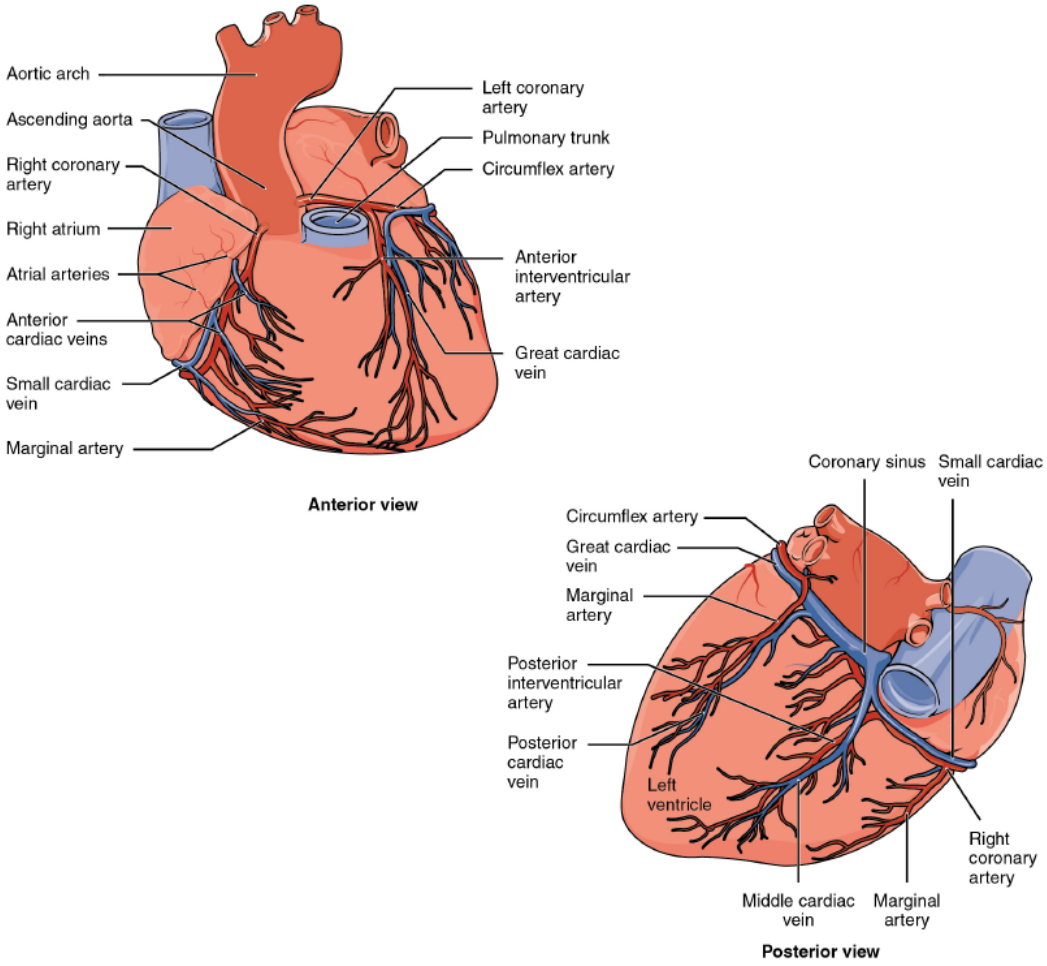

***Figure** 2.3 Main coronary arteries and veins [9]*

2.1.2 Electrophysiology of Myocardial Cells

A cardiac muscle cell or myocyte is an excitable cell capable of carrying an electrical signal to its adjacent cells. At rest the membrane potential of a cardiac myocyte is approximately -85 mV. In case of no external stimulus this potential remains stable.

The cell membrane potential is formed mainly due to combination of concentrations of the following three ions: potassium (K^+), sodium (Na^+) and calcium (Ca^{2+}). A balance between the electro-chemical gradient formed by the concentrations of these ions determines the resulting potential which is defined as the resting state of the cell membrane.

An action potential (AP) is fired when a certain threshold voltage is exceeded due to an external stimulus voltage, while any stimulus voltage below this threshold does not induce an action potential. Between cardiac myocytes this activity is relayed efficiently, which has led to the common concept of a propagating wavefront within

the myocardium. Unlike in skeletal muscle cells with an AP duration of 2-5 ms, cardiac muscle cell has an AP duration significantly longer of 300 ms.

Five phases can be distinguished on the occurrence of an action potential. In these phases the membrane conductance varies for different ions, due to the activation and inactivation of different types of passive and active membrane channels.

In **phase 0** the cell depolarizes rapidly. Once the threshold voltage is exceeded the membrane conductance for sodium increases significantly. As the concentration of sodium is considerably larger outside the cell membrane, the ionic inflow current initiates the depolarization making the membrane rapidly less negative until the potential reaches approximately +20 mV.

Phase 1 is a phase of rapid repolarization during which the membrane conductance for sodium decreases and for potassium increases. In like manner as in the previous case of inflow of sodium, a concentration difference drives a potassium outflow from the cell providing the most repolarization charge. Though minor ones, other ionic currents also occur at this phase.

In **Phase 2** or action potential plateau more slower membrane conductance changes take place. Inward calcium (Ca^{2+}) current and outward potassium current are the two separate currents that are mainly contributing to the potential change during this phase. The balance of these opposing currents determine whether the membrane potential remains still or even makes a brief depolarization, which is possible in some cells.

Phase 3 is called the final repolarization phase, in which the calcium conductance decreases leaving only the potassium currents in effect. Therefore the membrane potential continues to repolarize.

Phase 4 or diastolic phase is the resting phase of the cell. At this time the membrane potential is at its resting potential until the next external stimulus. [24]

The different action potential phases and the corresponding ion movements across the cell membrane are illustrated in figure 2.4.

2.1.3 Conduction of Action Potential

An AP is conducted throughout the heart via a specialized conduction system. For this conduction task the heart has myocardial conduction cells in addition to the contracting myocardial cells responsible for the pumping action. The origin of a

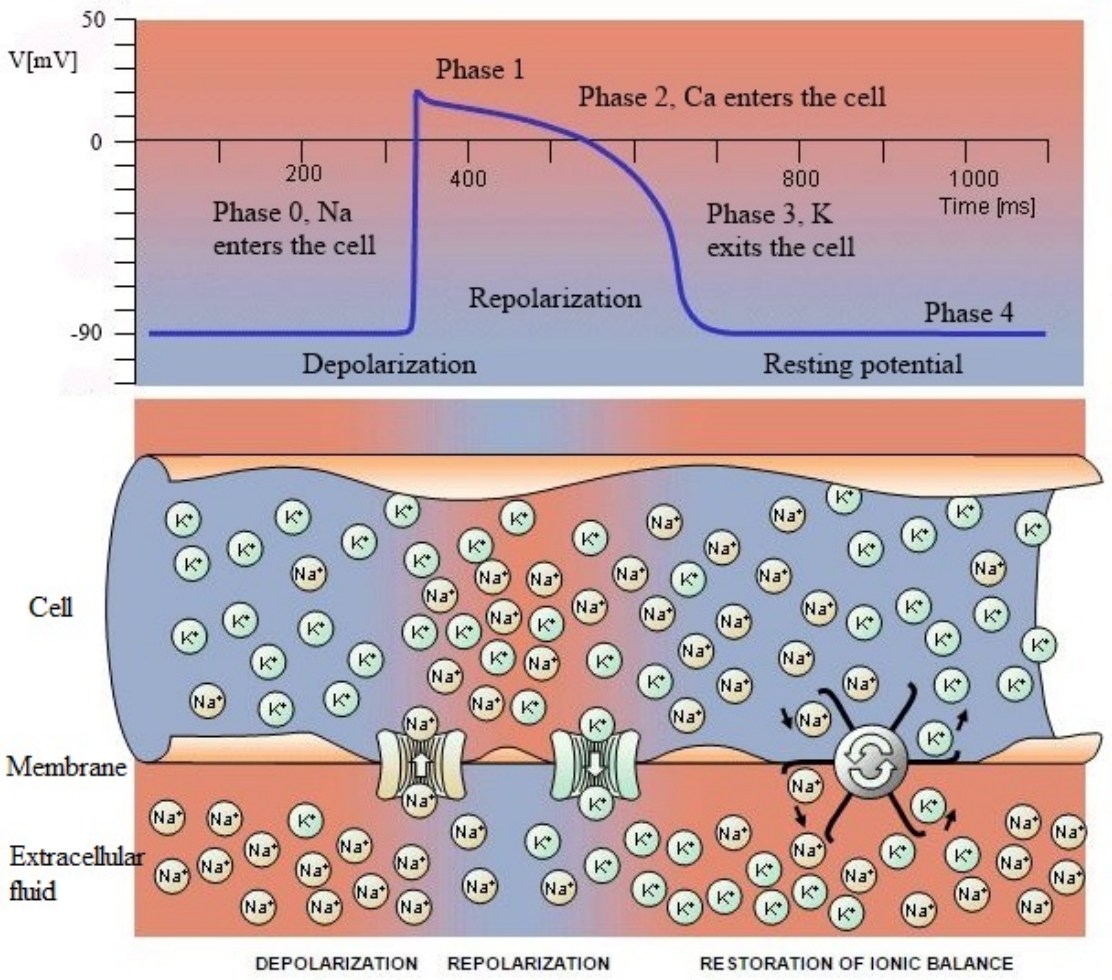

Figure 2.4 *Cardiac action potential phases and the corresponding ion movements across the cell membrane (modified from [43, Ch. 6]*

normal cardiac rhythm is the sinoatrial (SA) node localized in the superior and posterior corner of the right atrium. It consists of special pacemaker cells capable of producing a fixed rate of spontaneous action potentials. This rhythm is referred as the sinus rhythm and without external stimulus it produces 70 AP's per minute [43, ch. 6]. However, this rate is regulated by the nervous and endocrine systems, which adjust the rate to be convenient in each situation.

First the AP wavefront, initiated by the SA or sinus node located in top of the right atrial wall, is propagated through the atria via internodal pathways to the atrioventricular (AV) node. This takes a relatively long time, approximately 50 ms. The action potential is propagated to the left atrium through Bachmann's bundle. The AV node is located between the atria and ventricles in the atrioventricular septum and it also consists of pacemakers cells. The base rhythm of about 50 AP's per minute of the AV node is slower than in the SA node and thus it only serves

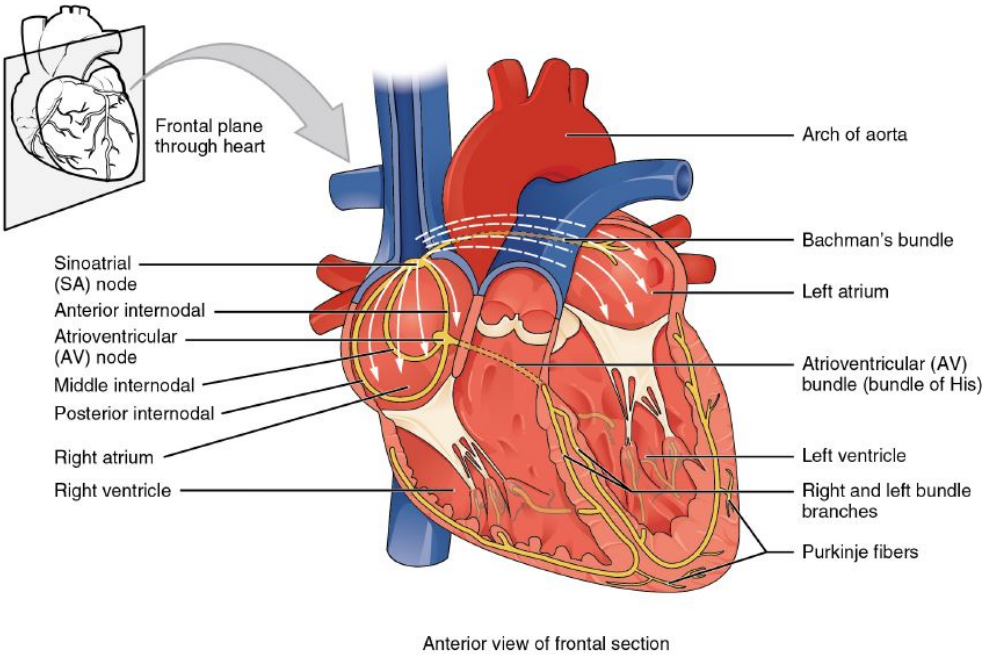

Figure 2.5 *Parts of the heart conduction system [9]*

as pathway for the higher frequency of action potentials from the SA node. In case of a failure in the connection from the atria to the AV node, the AV node will take over the place of SA node as the primary pacemaker for the heart rhythm. In case the AP is initiated normally in the SA node the AV node is only causing a delay to the signal propagation. More specifically at the AV node it takes the signal 100 ms to pass through it. During this time blood has enough time to pass from the atria to the ventricles before the ventricles contract.

Proximally following the AV node is the bundle of His, which separates quickly into two atrioventricular bundle branches labeled as the left and right bundle branch. Both bundle branches run down towards the apex of the heart along the interventricular septum until they are spread along as Purkinje fibers. The Purkinje fibers conduct the signal exceptionally fast and spread the signal further to the ventricles. Following the conduction of the signal, the contraction sequence of the contractile cells is directed from the atria to the inner ventricle walls and finally to the outer ventricle walls. [9, p. 814] The different parts of the conduction system are presented in figure 2.5.

2.2 Electrocardiography

2.2.1 Theory of ECG

The electrical activity of the heart can be recorded from the surface of the thorax with electrodes. This process is called electrocardiography (ECG). The interpretation of the surface potential leans on an assumption that numerous cardiac sources, i.e. cardiac myocytes, are modelled as a single electric dipole which is situated in the center of a sphere, the thorax, that is in turn modelled as an infinite homogenous volume conductor. In this simplification the volume conductor does not take into account any boundaries or inhomogenities within the thorax and the single dipole is a sum of all the cardiac sources, having three direction variables (x, y, z), an orientation and a magnitude.

The underlying theory of measuring ECG can be deduced when solving the inverse problem: What is the source given the measured field on the conductors surface? Although this problem does not have a unique solution, a reasonable estimation can be made using the assumptions presented as well as using theoretical approaches and knowledge of the anatomy and physiology of the heart. Important theories contributing to the formation of ECG include the concepts of resultant vector of the electrical activity of the heart, lead vector and lead field.

The electrical activity of the heart, the single dipole, can be thought as a total vector of the microscopic dipole sources. The vector presents the mean magnitude and direction of the electrical activity and this way the mean direction of the depolarization wavefront. This vector can be estimated with the lead vector. The total electrical activity vector can be projected along different lead vectors through function of time. This is done when forming the different lead signals in ECG. The relation between the electrical axis vector and the ECG-waveform is further discussed in the following section.

The concept of lead vector is used to estimate the detected signal on the conductor surface. It defines a relationship between a point dipole source and how it affects a point potential within or on a volume conductor relative to a reference potential. The general equation for lead vector is presented in equation 2.1.

$$V = \bar{c} \cdot \bar{p}, \tag{2.1}$$

where $\bar{c}$ is the lead vector and $\bar{p}$ the bipolar leads $P_i - P_j$, and V is their scalar product.

The lead field is the field of lead vectors on the surface of the volume conductor. With lead field, it is possible to determine the sensitivity distribution of a lead, i.e. a fixed electrode pair, on the volume conductor. The propagating activation wavefront is seen in the ECG signal as shown in equation 2.2.

$$V_L = \frac{1}{\sigma} \bar{J}_L \cdot \bar{J}^i dv, \tag{2.2}$$

where V_L is the lead voltage, $\bar{J}_L$ is the lead field and $\bar{J}^i$ is the source distribution, i.e. dimensions of dipole moment per unit volume. [43, ch. 11]

2.2.2 Formation of ECG

The depolarization wavefront in cardiac tissue propagate to areas still at rest, depolarizing the adjoining cells along the way and thus carrying the depolarization wavefront forward. The depolarization wavefront forms a charge separation or a layer of dipoles between the two sides of the wavefront, forming a double layer with depolarized cells in the middle and resting cells around it. Taking a negative derivative of the double layer gives the direction where the wavefront is propagating. For depolarization the dipole polarity is to the direction of the propagating depolarization wave. In the case of repolarization the dipole polarity is opposite and thus opposite to the direction of the propagation of the repolarization wave. However, one must note that repolarization is only thought as a propagation wave, when in reality it is not, as is the case in depolarization. Repolarization occurs because the action potential of a single cell has a limited duration and the cell repolarizes spontaneously. Additionally the action potentials of cardiac cells are of different duration depending on their location: The action potential duration in the epicardial cells is shorter than in the endocardial cells which results to a repolarization wave direction from endocardium to epicardium. [43, ch. 15]

If two electrodes are placed on opposite sides of a conductor the signal detected is positive when a depolarization wave is propagation toward the positive electrode, and negative if it is propagating away from the positive electrode. In contrast the signal is positive if a repolarization wave is propagation away from the positive electrode and negative when the wave is propagation towards it. The potential difference between two electrodes is referred as a lead. Using the single resultant vector for all the dipole sources eases the interpretation of the ECG waveform and distinct phases can be identified in the waveform. Figure 2.6 illustrates how the electrical resultant vector changes during a single cardiac cycle and how it is seen

when projected to three lead vectors.

Different Waveforms

As described earlier on section 2.1.3, the initial depolarization occurs in the SA node, and the atria are the first to depolarize. This forms the **P-wave**. Next the depolarization continues downward and left to the AV node where a short delay occurs. After this the depolarization moves down to the interventricular septum where the ventricular depolarization begins. The depolarization of the left side of the septum results in a leftward resultant vector and formation of the **Q-wave**. As the depolarization propagates further down the interventricular septum and reaches finally the left ventricle. This forms the large **R-wave**, first initiated by apical repolarization, peaking during left ventricular depolarization and recovering during late left ventricular depolarization. A negative deflection can be seen after the R-wave in some leads. This is called the **S-wave**. The previous three waves form the so called **QRS-complex**.

Ventricular repolarization start from the base of the ventricles moving to the opposite direction as in depolarization. The resultant vector still points to the same direction. The ventricular repolarization forms the **T-wave** after which the potential returns to baseline. The atria repolarize during the QRS-complex and because of their small electrical contribution, the repolarization is masked by the QRS-complex. [43, ch.15][23] **The U-wave** is a low amplitude deflection following the T-wave and sometimes it merges partially into the T-wave. Most of the time it is virtually undetectable, but in some people it can be seen. Also when applying proper baseline correction it can be seen in most people. It is believed the potentials responsible for U-wave are originating from the relaxation of the ventricular myocardium. [40, Ch. 5]

Mean Electrical Axis

The **mean electrical axis of the heart** is the total sum of all electrical vectors generated in the heart. The mean electrical axis is sometimes called the mean spatial vector. This idea of several vectors can be further applied when defining a mean QRS vector as well as a mean T- or ST-vector. These are, essentially, the resultant vector at a specific time instant of the cardiac cycle, i.e. during the QRS-complex, T-wave or ST-segment. The deflections seen in a particular ECG lead are simply the result of the changing magnitude and direction of the resultant vectors

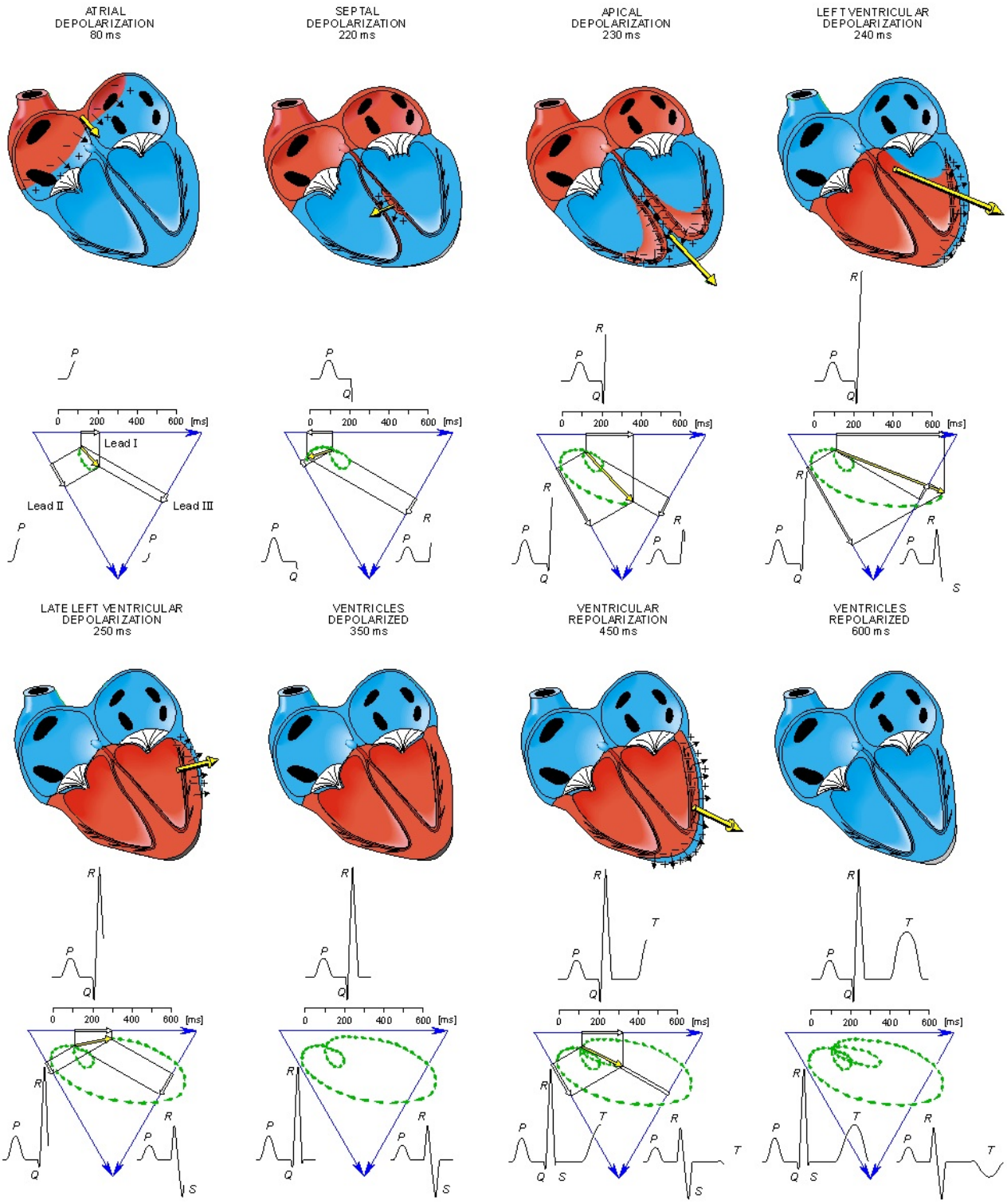

Figure 2.6 *Dipole resultant vector and how the signal is projected to different lead vectors (modified from [43, Ch. 6])*

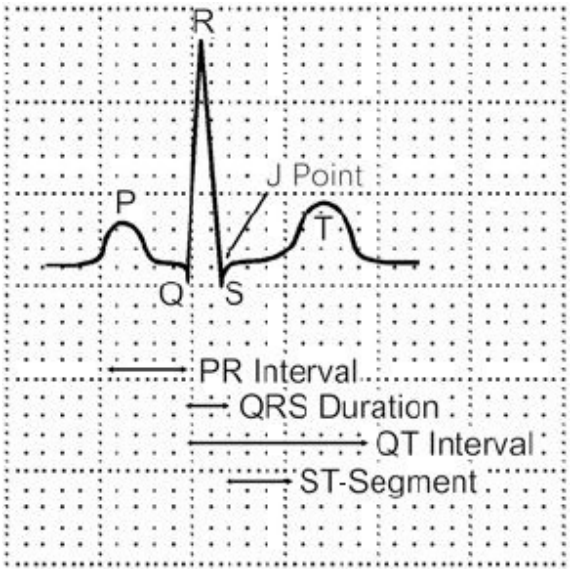

Figure 2.7 *ECG waveforms and segments [17]*

projected along that lead vector. An example of a full cardiac cycle can be seen in figure 2.6. The figure illustrates the behaviour of the mean electrical axis in 2 dimensions and projected to three different lead vectors. Furthermore, these vectors can be, for a more accurate representation, drawn as spatial vectors, visualizing them in three dimensions. However in clinical environment the electrical axis is mainly examined in the frontal plane. In ECG interpretation and analysis, these concepts are useful when detecting abnormalities in the heart function and localizing the affected area. [19]

ST-segment

The **ST-segment** is the time between the end of ventricular depolarization to the onset of ventricular repolarization. Normally the ST-segment is isoelectric, i.e. it denotes resting membrane potentials. The point where the QRS-complex ends and the ST-segment starts, is called the **J-point** (Junction point). It is a point used to denote the end of excitation. [17, p. 5-11] The isoelectricity of the ST-segment is generated when the epicardial and endocardial potentials of an entire ventricle are momentarily in the same potential, thus no current is formed intercellulary, and no voltages are observed. [40] Abnormalities of the ST-segment are caused for example because of ischemia, bundle branch blocks, myocarditis, drugs or ectopic and paced ventricular complexes. [57] Still, abnormalities are seen in completely healthy people as well as other variation between different groups of people, for example between races and gender. [17, p. 9]

Q-wave

Pathological Q-waves are often associated with previous MI and are not an early sign of ischemia. Usually once a Q-wave has formed, the tissue damage is permanent, since the Q-wave corresponds to the electrically silent dead tissue. However it is still possible that the tissue recovers and the Q-wave disappears, if the tissue has not been damaged severely enough. MI cannot be excluded if a Q-wave is not present. [69]

TP-segment

The **TP-segment** is the plateau phase between the end of T-wave and the beginning of the next cardiac cycles P-wave. It is generally electrically silent and gives the baseline voltage to which the ST-segment voltage is referenced to get the ST-deviation. As ST-segment should be electrically silent as well, the TP-segment can be used as a reference. [40, Ch. 17]

2.2.3 Standard 12-lead ECG

The lead system, i.e. combination of lead vectors, almost exclusively used today was first developed by Willem Einthoven. In 1912, he hypothesized the 'Einthoven's triangle' which describes the mathematical relations between the magnitude and direction of the deflections recorded by a set of three limb leads, where electrodes are connected to the left arm(LA), right arm(RA) and left leg(LL). Additional electrode is added to the right leg (RL) to act as ground. The resulting leads are referred to as the bipolar limb leads I, II and III. Bipolar since two actual electrodes are used to measure the potential difference.

There are also three additional limb leads commonly used, called the unipolar augmented leads. Where the bipolar limb leads are measured as potentials between the different limb electrodes, the augmented leads use a potential difference from a limb electrode and a reference point derived from the average of the two other limb leads. The reference point is an application of the Wilson central terminal. Developed by Frank Normal Wilson in the early 1930's, the Wilson central terminal aimed for the definition of unipolar leads. This was achieved by connecting a large resistance to each limb electrode and then connecting the wires into a single point, thus creating an average of the limb potentials. [43, ch. 15]

The term "augmented" originated in 1942 when E. Goldberger found out that omitting the electrode examined from the central terminal augments the amplitude of the

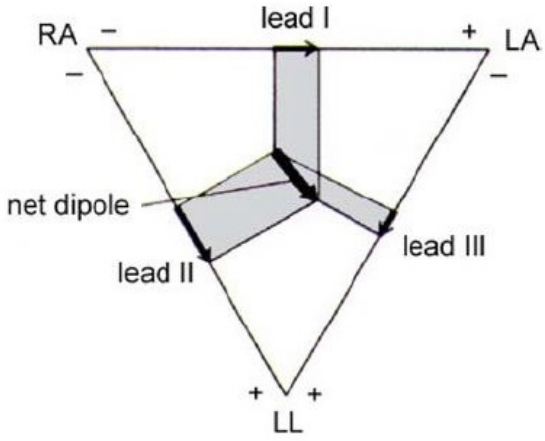

Figure 2.8 *The Einthoven's Triangle, where the electrode positions are as follows: RA = Right Arm, LA = Left Arm and LL = Left Leg. An example electrical heart vector is shown in the middle of the triangle. [48]*

signal by 50 %. These leads are named aV_R, aV_L and aV_F, "a" denoting augmented, and they can be derived from the bipolar limb leads I, II and III. [65]

In the 12-lead ECG system, there are also six additional leads referred to as the chest or precordial leads, with their own dedicated electrode locations. The precordial leads are also unipolar, and measure the hearts activity in the frontal plane, unlike the six limb leads, which measure the activity in the traverse plane. They use a reference point similar to the augmented leads, but in case of the precordial leads the reference point is an average from all the limb leads. This reference point is the same as the one utilized in deriving the augmented limb leads, namely the Wilson central terminal. [23]

The 12-lead ECG electrode configuration illustrated in figure 2.10 is the most common electrode configuration used. As figure 2.9 demonstrates, this configuration provides a three dimensional view of the heart. Several different lead and electrode configurations have been developed, but only a few have been clinically adopted. The Mason-Likar configuration, however, is commonly used in exercise testing and in ambulatory ECG measurements. It differs from the conventional 12-lead ECG in the positioning of the limb electrodes, as they are moved from the wrist and ankles to the torso. Usually the right arm and left arm electrodes are placed to a point in the infraclavicular fossa medial to the border of the deltoid muscle and slightly under the clavicle. The right and left leg electrode are usually placed near the right and left lower rib cage, respectively. [40, p. 411-412] The modified electrode location of the Mason-Likar configuration are also illustrated in 2.10. The Mason-Likar configuration was used in the data collection during making of this thesis.

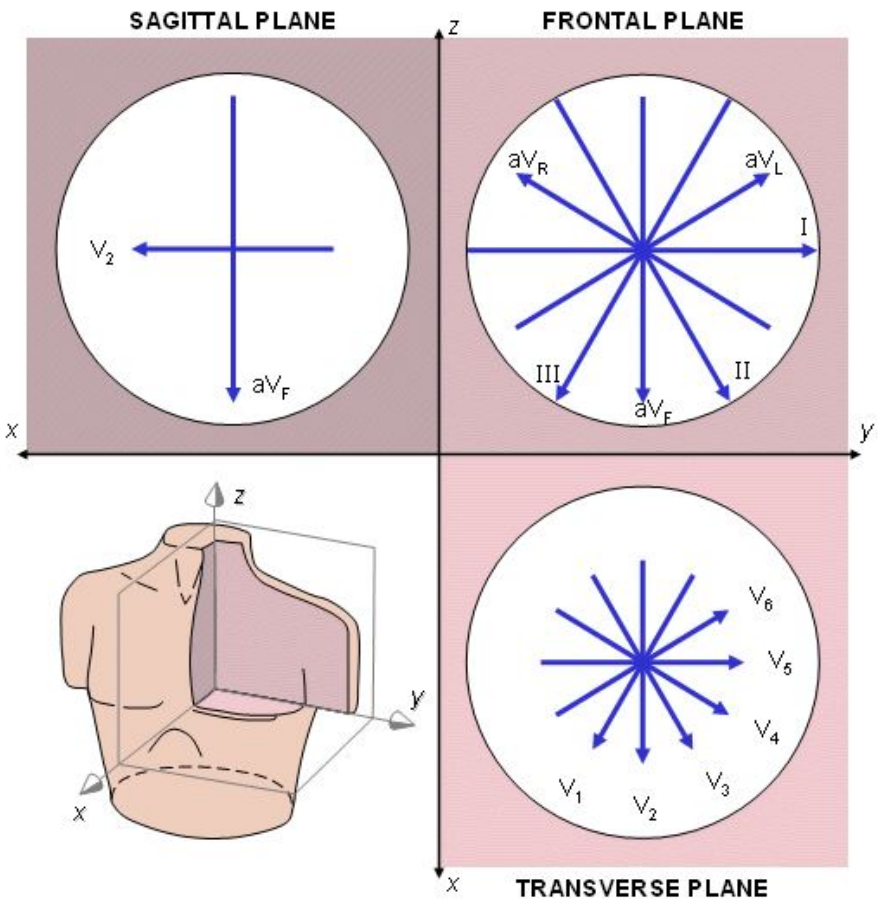

Figure 2.9 *Bipolar (I, II, III) and unipolar (aV_R, aV_L,aV_F) limb leads and the precordial leads V_1 to V_6 give a 3-dimensional view of the heart. [43, Ch. 15]*

2.2.4 Holter ECG Monitoring

Holter ECG recording is an ambulatory form of ECG measurements first introduced by Norman Jefferis Holter in 1961 [22]. Traditionally Holter recordings have been used for detecting arrhythmias and ST-T-changes. A Holter system consist of a ambulatory ECG recorder, which is a small lightweight device that can at its most record 12-lead ECG, and of a analysis system used to analyze the recorded signal. [40, p. 1421-1422] The difference between Holter ECG monitoring to realtime wireless ECG monitoring, is that Holter recordings are analyzed retrospectively. Thus in Holter ECG, timely inverventions are not possible if such are needed. In the data collection of this thesis, the Holter measurements are merely a way of imitating a wireless ECG measurement environment.

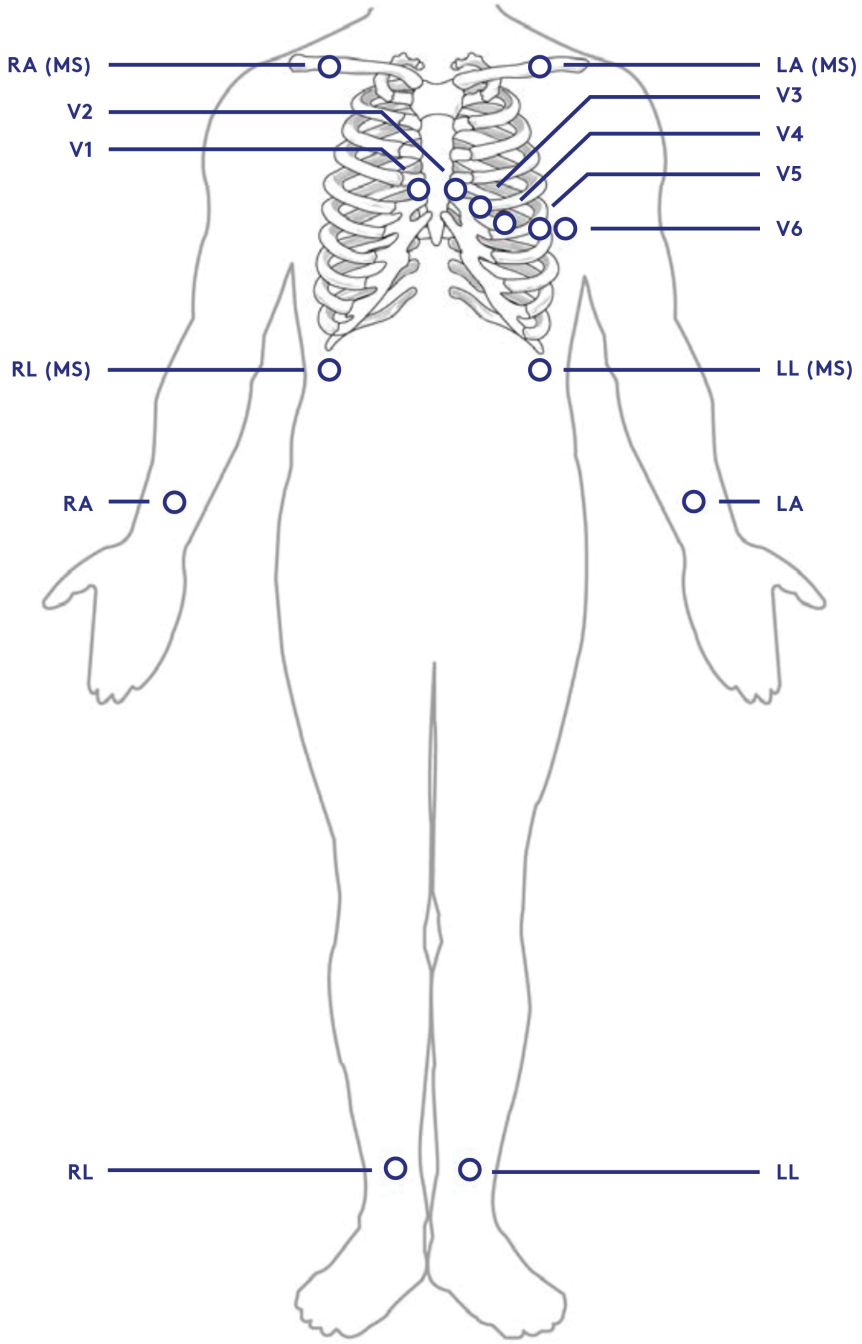

Figure 2.10 *12-lead ECG lead positioning: Traditional configuration and the Mason-Likar configuration. Abbreviation 'MS' denotes limb lead electrode positions of the Mason-Likar configuration.*

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3. MYOCARDIAL ISCHEMIA AND INFARCTION

Cardiovascular diseases, and more specifically Coronary Artery Disease (CAD) continue to be the main cause of death in western countries and in this context myocardial infarction has a key role when assessing the total burden of heart diseases. Although the long-term trend has declined, it has been analyzed that the increase in life expectancy is caused in parallel with the postponement of CAD deaths until older age. [59]

3.1 Pathology and Risk Assessment on Myocardial Ischemia and Infarction

3.1.1 Pathology

While heart only constitutes 0.5 % of the body mass, it uses 7 % of the whole body oxygen consumption. Myocardial oxygen consumption (MVO_2) is closely related to the coronary blood flow (CBF). MVO_2 is affected by the heart rate, stroke work, afterload and the inotropic state of the myocardium. [23]

The lack of oxygen and nutrient supply for the myocardium results in myocardial ischemia. The shortage in this supply is caused by a partial or complete obstruction of one or several coronary arteries, usually resulting from atherosclerosis of the larger coronary arteries. In atherosclerosis, plaques of lipids, cholesterol and fatty acids build up inside the vessel wall narrowing the vessel, thus reducing blood flow. Other mechanisms reducing blood flow are blood clots that obstruct the blood flow and coronary spasm, where the muscles in the artery walls contract narrowing the artery reducing blood flow. [9, p. 809]

At the beginning of an ischemic event the heart tries to compensate the lack of oxygen by reducing the contractile function and increasing glycolysis. However this is an unsustainable situation eventually leading to cell necrosis, i.e. infarction. Different ischemic syndromes are categorized based on whether the myocardial damage is

reversible or not and what is the mechanism of the possible recovery of the myocardial function. [23] For the recovery to happen, a reperfusion of the area is required. However, this can paradoxically lead to a so called reperfusion injury, in which prolonged myocardial dysfunction, limited perfusion and even cell death can occur after the reperfusion. [72]

Myocardial ischemia can be referred as "supply ischemia" or "demand ischemia" depending on whether the supply of oxygen has decreased or the demand of oxygen has increased significantly in the myocardium. [46]

3.1.2 Criteria for Diagnosis Myocardial Infarction

The criteria for diagnosing a myocardial infarction is defined based on the detection of cardiac biomarkers above a significant value in the setting of myocardial ischemia. This setting might include symptoms of ischemia, ECG changes or imaging findings. For initial assessment of MI, ECG is considered to be in a vital role, guiding the first therapeutic interventions done in the emergency room (ED) [73]. The cardiac biomarker preferred today is a protein called cardiac troponin (cTn) due to its high tissue specificity and clinical sensitivity. Despite the high-performance of these biomarkers, a common weakness of them is that they are released after cell death and are in that sense too late of an indicator. Changes in ECG on the other hand can be seen almost instantly after diminished blood flow. The common symptoms of myocardial ischemia may include chest pain (angina pectoris) that radiates to the left arm (in males) and lower jaw, nausea, shortness of breath (dyspnea) and palpations. However studies have shown, that up to 83% of the ischemic events are asymptomatic, and usually referred to as silent ischemia [8, 5, 2]. This fact, quite clearly, increases the significance of ECG-monitoring as an early indicator for ischemia.

High levels of cardiac troponins, namely cardiac troponin I (TnI) and T (TnT), are released during a myocardial injury. [69] It has been shown that a peak TnT value within 3 days after the surgery has a strong link with 30-day mortality [11]. It is noteworthy that other conditions can also cause troponin release such as pulmonary embolism or sepsis [71]. A biomarker called natriuretic peptide (NP) have recently been researched as a predictor of postoperative cardiovascular complications and studies suggest it to be an independent predictor for 30 to 180 day mortality. This further suggests that NP might be a potential biomarker candidate for diagnosing postoperative cardiac complications. [58]

3.1.3 Risk Assessment and Literature Review on Postoperative MI

In general the main risk factors for myocardial infarction are age, smoking, obesity, high cholesterol, diabetes and high blood pressure. [10] In this thesis, however, the focus is in postoperative MI (PMI) rather than in nonoperative MI (acute MI) and these two are believed to have a different pathophysiology. [12, 60] Due to this fact, a different approach to risk assessment is adopted.

The definition of MI gives three types of acute coronary syndromes (ACS): ST-elevation MI (STEMI), non-STEMI (NSTEMI) and unstable angina (UA) with the latter two having the difference of elevated cardiac troponin; in NSTEMI the possibility of cardiac injury is greater as indicated by troponin elevation and without this elevation, the patient is considered to have UA. These designations are used to guide the treatment, as the type of ACS determines the treatment protocol. [3]

Perioperative myocardial ischemia has been under surveillance for over 30 years and in particular postoperative ischemia after major non-cardiac surgery has been strongly associated with increased 30-day mortality, essentially due to myocardial infarction [11]. The occurrence of MI is not significantly high in an unselected patient population ($\sim 0.5\%$), but can increase to over 10 % in a high risk patient population. Several studies have been conducted to form a group of factors associated to the high risk patients. [28, 20, 21] It is well known that surgery invokes stress response in the human body, in which hormonal and metabolic changes occur in a complex manner. Changes include for instance an increased release of cytokines promoting an inflammatory response, increased oxygen consumption and increased coagulability. To sustain adequate oxygen delivery, cardiac output has to go up to increase the arterial oxygen content. [7] A study made by Frank et al. [18] demonstrated the link between heart rate and ST-depression ischemia using Holter recordings. Heart rates as low as 80-85 beats per minute (BPM) were found to induce ischemia.

Patients with reduced cardiac functionality are understandably in higher risk as well as patients with coronary vasculopathy, i.e. CAD. The stress response can continue after the surgery for several days and different types of surgery have a different effect and magnitude in terms of surgical stress. Table 3.1 shows estimates of cardiac risks caused by different surgeries.

Other factors involved in the preoperative cardiac risk assessment include age as a continuous factor as well as patients comorbidities. Comorbidities such as respiratory disease, former ischemic heart diseases, diabetes and heart arrhythmias increase

Table 3.1 *Cardiac estimates for specific surgeries [47]*

High risk (5 %)	**Interm. risk (1-5 %)**	**Low risk (1%)**
Open aortic	Elective abdominal	Breast
Major vascular	Carotid	Dental
Peripheral vascular	Endovascular aneurysm	Thyroid
Urgent body cavity	Head and neck	Ophthalmic
	Major neurosurgery	Gynaecological
	Arthroplasty	Reconstructive
	Elective pulmonary	Minor orthopaedic
	Major urology	Minor urology

the risk of adverse cardiac events, especially myocardial infarction. [47]

A comprehensive overview of the risk involved in patients undergoing noncardiac surgery along with recommendations, are given by American College of Cardiology (ACC) and American Heart Association (AHA). [16] Other factors affect to the total risk of PMI as well. It is possible to estimate the risk by calculating risk models. There are several risk models available, from which the Lee's Revised Cardiac Risk Index (RCRI) and the Gupta risk calculator are the most frequently used. Both of them are simple scoring systems indicating the risk of adverse outcomes after surgery. From these two systems the Gupta risk calculator has been more recently validated using the National Surgical Quality Improvement Program-database (NSQIP) which contains data from over 180000 non-cardiac operated patients. The Lee index has been validated with patient data from the beginning of the 90's, which poses a weakness to the index. [61]

There are two main mechanisms that may lead to an infarction through preceding myocardial ischemia. In the first mechanism, referred to as the type I PMI or acute myocardial infarction (AMI), ischemia leading to infarction is caused because of an rupture in a flow restricting unstable atherosclerotic plaque, which leads to coagulation of blood at that point, suddenly reducing or blocking blood flow. This may be caused by shear stress, which may in turn be caused by tachycardia or hypertension, causing the plaque to rupture. Type II PMI is on the other hand caused by the imbalance between increased demand of oxygen by the myocardium and decreased ability to supply that demand. According to two review articles most of the PMI's are type II. [61, 33] A review article also speaking out on this matter by Priebe [56] states that while there is pathological evidence in some cases which support the type I PMI, the combination of heart rate increase, ST-depression, non-Q-wave infarctions and lack of angiographic evidence in many patients after PMI suggests that type II PMI is likely the major cause of PMI. These two types of PMI mechanisms are illustrated in figure 3.1.

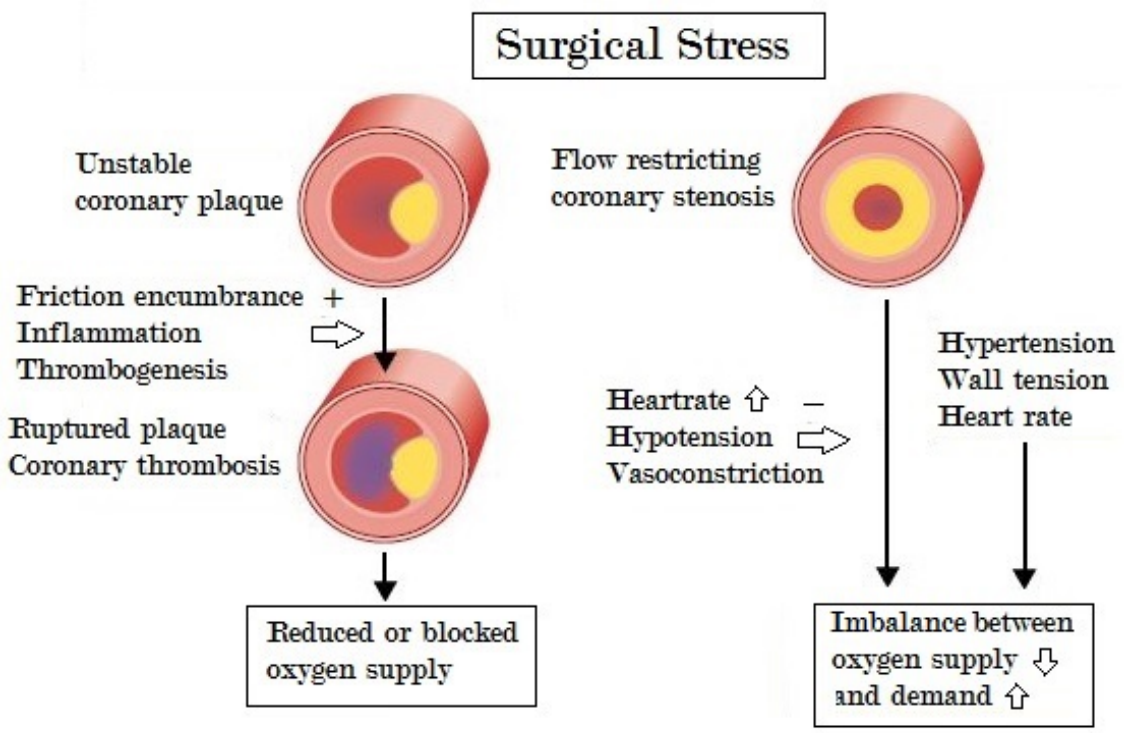

Figure 3.1 *Different modes of origin for PMI (modified from [61]).*

3.2 Ischemia Detection: Effect on ECG Waveforms

When an area of a heart becomes ischemic, voltage gradients are produced between the ischemic and the nonischemic areas during the resting phase and the plateau phase. This gives rise to the flow of so called injury currents which can be seen in the ECG's ST-segment, which makes it a favourable part of the ECG to search for ischemic changes. [29] Other changes in the waveform occur as well as the condition evolves. Still, as the next section explains the first indications of myocardial ischemia can be identified in the ST-segment. However, it is important to understand that ST-segment abnormalities similar to MI can be caused by several other conditions such as hypertrophy, changes in the serum potassium, acute myocarditis and cardioactive drugs. [73] The different mechanisms causing ST-segment variations, i.e. repolarization abnormalities, are discussed later in this section 3.2.3.

3.2.1 Serial ECG Changes of Evolving MI

An acute myocardial infarction is a progressive phenomenon and can be classified into four phases which each have distinct ECG characteristics, that describe the ischemia, infarction and healing of the infarction. These phases are hyperacute,

acute, subacute and completed phase. In the beginning of the hyperacute phase the emerged coronary occlusion can be seen as peaking of the T-wave followed by ST-elevation, when the current of injury points outward from the epicardium from the region affected. Both of these changes usually happen within minutes from the onset of the infarction. In the acute phase the amplitude of the end part of the T-wave and early part of the QRS-complex begin to decrease. As the infarction progresses abnormal Q-waves begin to form and R-wave is attenuated, suggesting that the injury of current have shifted away from the affected region. These changes usually last for 6-8 hours from the onset of the infarction. In the last phase the QRS-changes become stable, ST-segment recover nearly to a normal state and T-wave has usually been inverted. At this point the myocardium is irreversibly damaged.[40, p. 688-689]

3.2.2 The Location of the Infarction Based on the ST-segment

Identifying the location of the myocardial infarction from ECG helps to perform early treatment to the patient and is thus important. The two types of PMI's considered in section 3.1.3 are however different when it comes to localization. In a review article it is stated that type II PMI usually is more global and affects more than one coronary artery making the localization considerably more difficult [56]. In addition a review article by Landesberg [32] states that exercise-induced ST-depression cannot be used to determine the site of the occlusion. Type I PMI or AMI on the other hand usually affects mostly one coronary artery. Thus the localization is more straightforward and covered more thoroughly in literature. The basic idea of locating infarctions is still seen important and is thus covered shortly next.

When considering AMI the location and size of the infarcted area are related to the location and range of the occluded coronary artery's perfusion bed. The displacement ST-vector points outward from the region of infarction and thus leads parallel to this vector are elevated. The magnitude and displacement of this vector is again related to the severity and location of the occlusion. The necrosis of the myocardium also makes it electrically silent, which leads to the loss of current dipoles from the region involved. Diagnosing the location of a MI is based on analysis of the spatial vector of the ST-segment shift, which is again based on careful analysis of the elevation and depression of the ST-segment in different leads. The 3-D representation of heart in figure 3.2 illustrates which section of the heart each lead monitors.

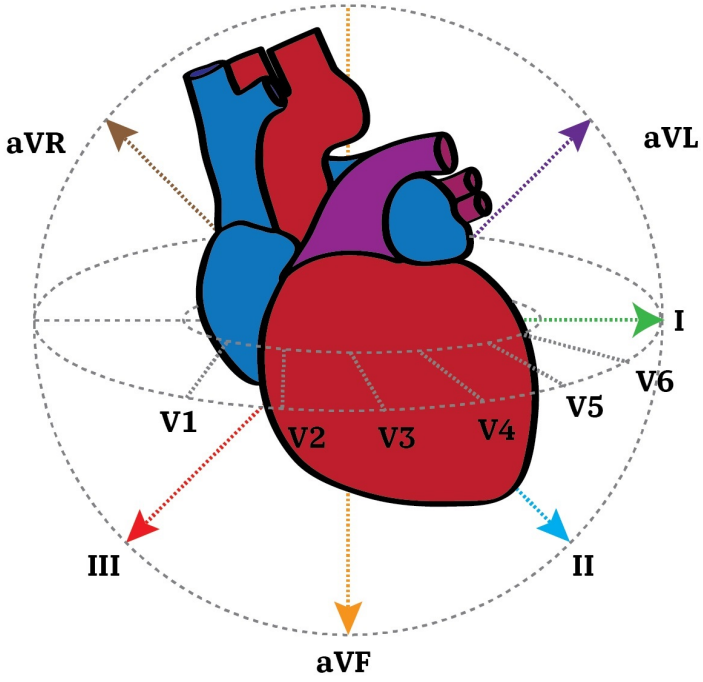

***Figure** 3.2 3D mapping of leads to the surface of the heart*

Localization	ST-elevation	ST-depression	Occluded coronary artery
Anterior MI	V1-V6		LAD
Lateral MI	I, aVL,V5,V6	II, III, aVF	LCX or MO
Inferior MI	II, III, aVF	I, aVL	RCA or RCX
Posterior MI	V7-V9	V1-V3	RCX
Septal MI	V1-V4		

***Table** 3.2 Location of AMI seen in 12-lead ECG; MO = Marginal obtuse artery (or Obtuse marginal)*

Locating Principles

Elevation in particular leads ST-segment usually has a reciprocal ECG lead, whose positive pole is approximately 180° away from the first lead, and has depression present. Such reciprocal leads are for example lead aVL and lead III. However, in the standard 12-lead ECG, all of the leads do not have a reciprocal lead, since by convention no leads are placed on the body surface to record these reciprocal changes. Still, analysis of the ST-segment changes accompanied by the results of coronary angiography has enabled a more precise localization of the MI based on ST-segment shift analysis. Ideally the principles of ST-depression and ST-elevation summarized in table 3.2 can be used in localizing the infarction. [40, p. 653]

3.2.3 Primary and Secondary Repolarization Abnormalities

Ideally the ST-segment of the ECG-waveform lacks significant potential differences and is thus flat. The ECG can be derived theoretically from the difference of two AP's, the first and last ventricular fiber to depolarize during a QRS-complex.

ST-segment abnormalities can be classified into two different categories, primary repolarization abnormalities and secondary repolarization abnormalities. A primary repolarization abnormality is independent of changes that occur in the depolarization phase and thus can indicate ischemia, however ischemia is not the only possible cause. For example myocarditis, toxins, pericarditis (heart muscle inflammation) and electrolyte imbalances may have an effect on the shape and duration of the repolarization. Additionally a normal variant referred to as early repolarization causes changes in the ST-segment.

In case of ischemia the changes in the repolarization are caused by injury currents presented in section 3.2. These currents are generated when potential differences develop between the healthy and the ischemic myocardium. Two types of injury currents exist: systolic injury current and diastolic injury current. In systolic injury current the electrical current runs towards the ischemic myocardium as the healthy myocardium is in a more positive potential. In diastolic injury current the resting membrane potential in the healthy myocardium is more negative, which generates a injury current from the ischemic myocardium towards the healthy myocardium.

Depending on the area and location of the ischemic region, different ECG leads show ST-elevation or depression. Transmural ischemia/infarction is the cause of ST-elevation while subendocardial ischemia/infarction causes ST-depression. The main cause for ST-elevation in transmural ischemia is the depression in the baseline, i.e. TP-segment, which is caused by the reduced electropositivity at the surface of the ischemic region and on the contrary the leads measuring this area are in a region of electronegativity. This TP-segment depression is interpreted as ST-elevation. In subendocardial ischemia the situation is opposite: the leads facing the ischemic area are in a area of electropositivity and thus because of an upward deflection that causes TP-segment elevation, this is interpreted as ST-depression. The two types of injury currents can been seen in figure 3.3). [26, p. 496-497]

In a secondary repolarization abnormality the repolarization changes are caused by changes in the depolarization phase. In essence there is a prolongation between the duration of the first and last fiber AP during ventricular depolarization, which lengthens the QRS-complex. This causes the potential differences to be enhanced causing some of the depolarized fibers to enter the rapid repolarization phase (phase

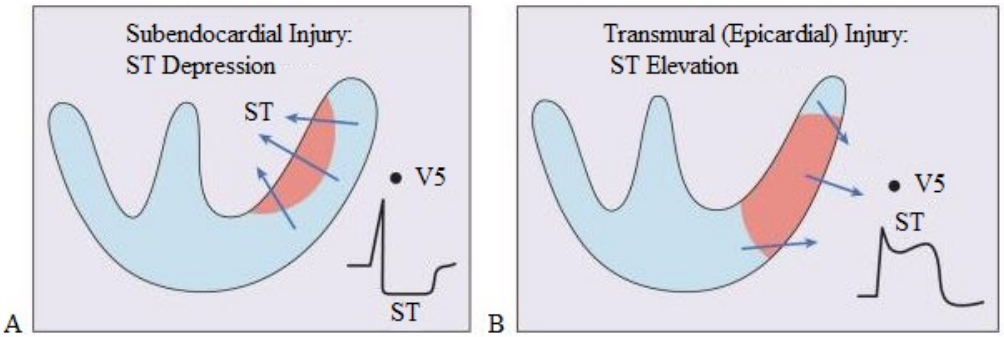

Figure 3.3 *ST-elevation and ST-depression caused by ischemic injury currents. Figure 3.3 A illustrates the transmural ischemia and 3.3 B the subendocardial ischemia. [38]*

3) while some lagging fibers are still in the plateau phase (phase 2). For this reason the ST-segment deviates from the baseline. [40, p. 750-752] Medical conditions causing secondary repolarization abnormalities include for example right and left bundle branch blocks (RBBB and LBBB) and ectopic and paced ventricular complexes. The RBBB and LBBB are conditions where there is a conduction failure of the electrical activation in either in the right or left bundle branch, respectively.

A combination of of primary and secondary repolarization abnormalities can occur concurrently [73]. Figure 3.4 describe the potential differences of the first and the last ventricular AP in the discussed repolarization abnormalities.

Secondary repolarization abnormalities are fairly easily recognised during ventricular hypertrophy and bundle branch blocks. In these cases T-wave vector is opposite to the terminal QRS-vector. In LBBB the T- wave is usually opposite to the QRS axis. In addition the morphology of the QRS-complex have distinguished characteristics in case of bundle branch blocks. Identifying the common secondary repolarization abnormality causes is relatively straightforward, but in the case of concurrent secondary and primary repolarization abnormalities it is hard to distinguish the two causes from each other. [40, 749-767]

3.2.4 ST-segment Criteria for MI

The importance of ST-segment in ischemia detection has been emphasized thus far. Therefore in traditional ischemia monitoring the point of interest is in the ST-segment. This is due to the fact, that the earliest changes caused by the lack of oxygen, can be seen in the ST-segment. There are two basic scenarios where MI can occur: operative and non-operative situation and they usually mean PMI and AMI, respectively. From here on PMI signify type II PMI. The reason for this

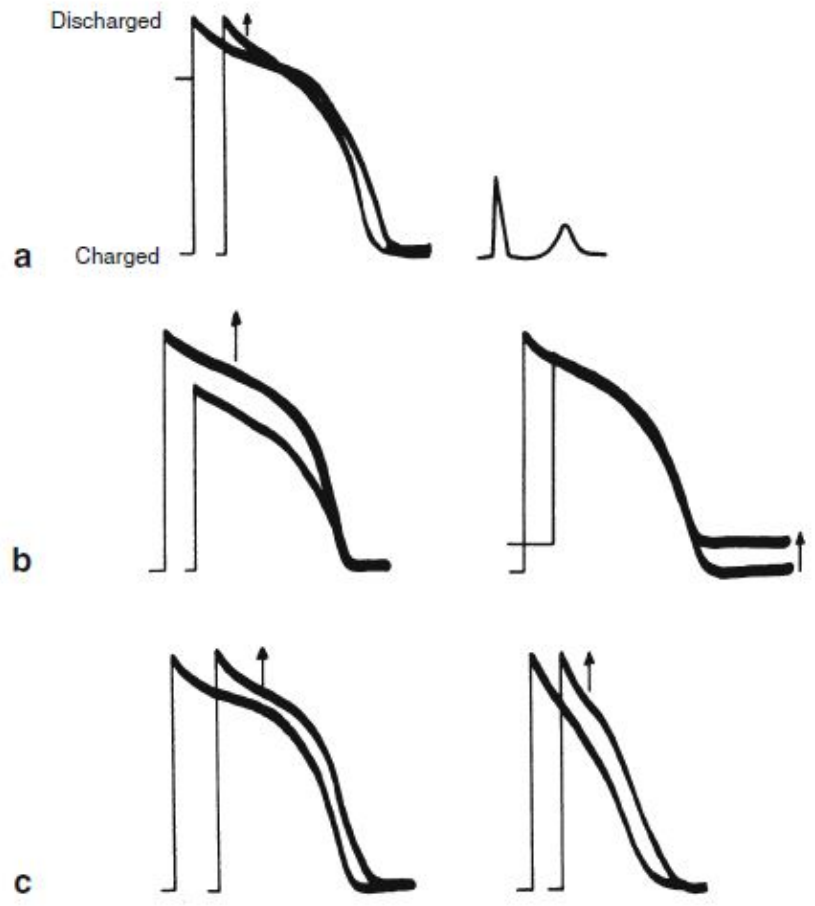

Figure 3.4 *The potential difference of two ventricular AP's. (a) normal potential differences throughout QRST-segment. (b) potential differences caused by primary repolarization abnormalities. (c) potential differences caused by secondary repolarization abnormalities. [40]*

differentiation is the very different characteristics seen on the ECG depending on which type of MI is occuring. This has also lead to different diagnostic criteria for PMI and AMI.

The main changes associated with AMI are ST-level elevation and/or depression, and the corresponding amplitude is usually measured from J-point + 60 ms (J_{60}) or 80 ms (J_{80}), using the isoelectric baseline as a reference. The exact J-point is sometimes used as well. The rationale to measure the deviation after the J-point is that at this point all ventricular fibers are expected to be depolarized, while at the J-point some potential differences may still occur. Current guidelines define AMI to be diagnosed from ECG when ST elevation or ST depression changes can be seen in two anatomically contiguous leads and they exceed the established limits: According to the recommendations of AHA, American College of Cardiology Foundation (ACCF)

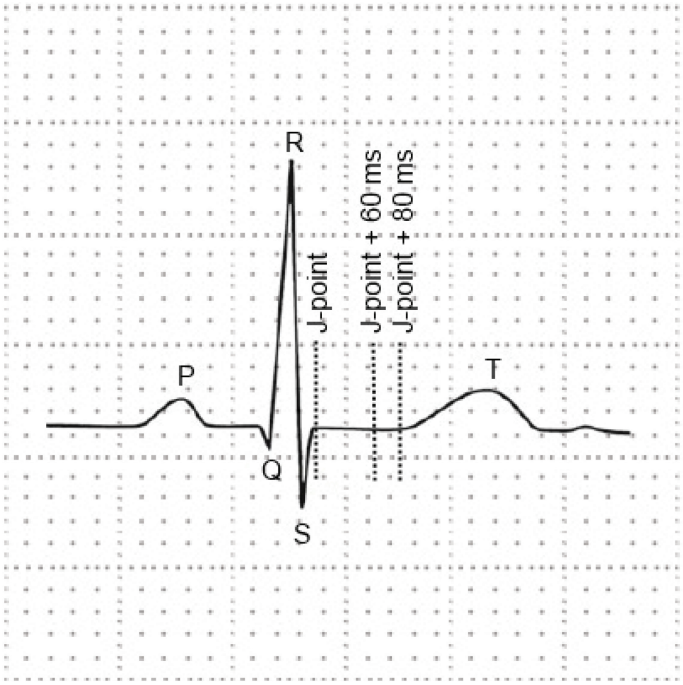

Figure 3.5 *Different measurement points for achieving descriptive ST-values*

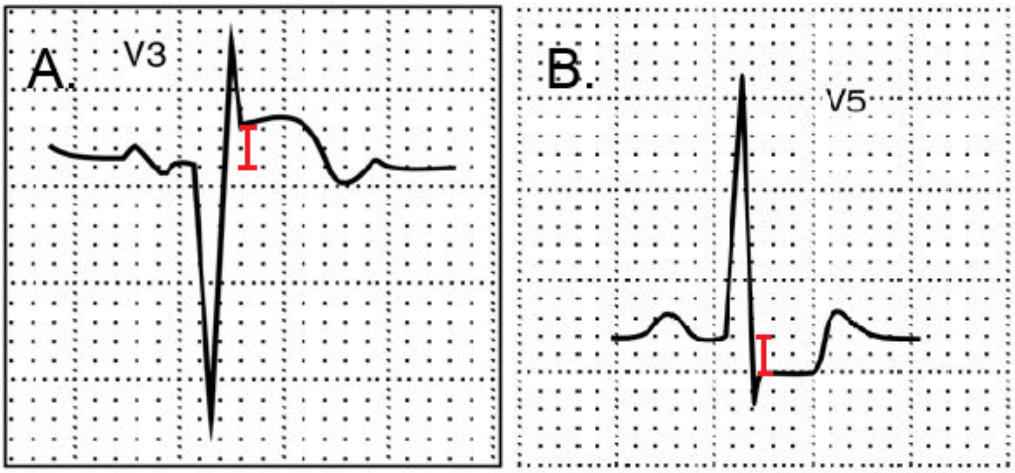

Figure 3.6 *A. ST-elevation B. ST-depression*

and Heart Rhytm Society (HRS), the limits defined as significant change are based on the age and gender of the patient as well as which lead is considered. For over 40 year old men the abnormal elevation in leads V_2 and V_3 is $\geq$0.2 mV (2mm) and $\geq$0.1 mV (1mm) in rest of the leads, whereas for women the recommendation for V_2 and V_3 is $\geq$0.15 mV (1.5mm) of elevation, and again $\geq$0.1 mV (1mm) in rest of the leads. Abnormal depression in turn is defined as $\leq$-0.05 mV (-0.5mm) in V_2 and V_3 and $\leq$-0.1 mV (-1mm) in other leads, independent of age and gender. [73]

Postoperatively, however, prolonged ST-depression has been reported to be the main indication of cardiac complications correlating with peak troponin elevations. [33] The POISE-study concluded that ST-depression infarctions (31.3%) are more common in a postoperative situation exceeding the amount of Q-wave infarctions (12.3%) and STEMI's (10.5%). [13]. Although the criteria for PMI are less comprehensively covered in the literature and standards, there is a suggestion to use the same ECG criteria for PMI as is used in cardiac stress-testing for MI. This criteria is also suggested for ischemia detection using Holter measurements. The aforementioned suggested criteria state that a significant ST-depression indicating ischemia is a depression of $\geq$0.1 mV in the J-point remaining depressed to J_{80} in at least 3 consecutive beats in at least one lead. Furthermore if a pre-operation ECG is available, a reference ST-level is set for each lead. This results in a criteria of $\geq$0.1 mV ST-change relative to the reference, instead of absolute ST-deviation of 0.1 mV. [32] Here absolute ST-deviation means comparing strictly to the reference baseline set, without considering ST-deviation caused from reasons other than ischemia or infarction. For example if the initial ST-depression for lead V_5 is -0.03 mV, a significant ST-deviation for the particular patient and lead would be $\leq$-0.13 mV rather than $\leq$-0.10 mV which without a reference value would be significant.

Criteria in Setting of Comorbidity

In the presence of LBBB, the criteria for MI diagnosis are defined separately, since LBBB causes secondary ST-segment and T-wave abnormalities making the general criteria invalid. In the setting of LBBB the criteria include ST-segment elevation in leads with positive QRS-complex to be greater or equal to 0.1 mV (1mm) and depression greater or equal to 0.1 mV (1mm) in leads V_1 to V_3. In leads with a negative QRS-complex the elevation should be greater or equal to 0.5 mV (5mm). Still, diagnosing MI in this setting have been demonstrated to yield low sensitivity. [63]

When the patient is having RBBB simultaneously with suspected MI, making the diagnosis significantly easier than in the case of LBBB. Theoretically RBBB does not have an effect on the repolarization phase and thus diagnosis of MI could be made normally. However, in the precordial leads V_1-V_3 (even V_4) the ST-elevation might be masked, and thus it is suggested that only V_5 and V_6 are used to diagnose possible MI using the normal criteria. [14]

Left ventricular hypertrophy (LVH), meaning the enlargement of the cardiac muscle of the left ventricle, is also a common cause of secondary repolarization abnormalities and as such can cause ST-deviation without ischemia. [4] In practice diagnosing MI

with LVH includes taking into account the initial ST-deviation before assessing the deviation caused by MI. For a proper diagnosis a non-ischemic ECG measurement is needed, where only LVH is present, so the inital ST-deviation can be measured.

3.3 Clinical Significance and Adoption of Ischemia Monitoring

Monitoring the ST-segment is inexpensive, non-invasive and capable of detecting ischemic events prior to MI. The monitoring can be continuous or can consist of multiple individual snapshot ECG's. For a proper diagnosis, an ECG previous to the care episode is usually necessary. This was shown in the previous section for a MI in the setting of LVH. The latest ACC/AHA/ESC (European Society of Cardiology)/ESA (European Society of Anaesthesiology) guidelines recommend ischemia monitoring to be used for patients suspected of ACS or patients having a major non-cardiac surgery [3].

Sandau et al. [62] demonstrate in their review article the importance of continuous ST-segment monitoring. The article points out, that although no definite study has been done showing that ST-monitoring has a direct link to better patient outcome, there has been several studies showing a indirect benefit from continuous ST-monitoring. For example ST-segment elevation detected with continuous ST-monitoring was an independent predictor of mortality in a study, where utilization of streptokinase and tissue-type plasminogen activator (TPA) for occluded coronary arteries were studied [35]. In a more recent study by Yan et al., ST-segment shifts predicted a higher risk of death or death or myocardial infarction in a 30-month median follow-up [75]. A study investigating the sensitivity of the 12-lead ECG system performed continuous ECG monitoring to 185 patients during and after surgery for 48-72 h and found out that 20.5 % of the study group had transient ischemic events.[34] Lastly a study article investigating silent ischemia emphasizes that ischemia monitoring offers considerable diagnostic and prognostic importance if used in properly selected patient group. [8] Still, hospital surveys show that only approximately 50 % of the hospitals use continuous ST-monitoring as a standard of practice. [62]

3.3.1 Optimal Lead Selection of Ischemia Monitoring

Specific leads have higher sensitivity for detecting ischemia/infarction. Additionally there has been unconventional bipolar lead configurations suggested, in addition to the standard 12-lead, that can be used during ambulatory ECG measurements,

i.e. Holter measurements. Examples of the leads used in these configurations are the bipolar chest leads and the Nehb leads, from which the Nehb leads have been shown to have good sensitivity in ischemia detection [50, 36]. The Nehb leads are a combination of three bipolar leads where three electrodes are attached to the thorax. However these leads are not commonly used.[40, p. 388]

A study focusing on the standard 12-lead ECG by London et al. demonstrated that leads II and V_5 alone yielded the highest sensitivity (80%) when detecting ischemia/infarction, as well as generally the superiority of precordial leads in the task. Adding lead V_4 increased the sensitivity to 96 %. [39] This is in concordance with AACN's (American Association of Critical-Care Nurses) guidelines on ST-segment monitoring. They recommend that if possible 12-lead ECG should be used, but in the case of fewer leads, leads V_3 and lead III are prioritized first. In patients undergoing a noncardiac surgery, lead V_5 is recommended to be the best lead for ischemia detection instead. [49]

Different amount of leads used to detect ischemic events have also been studied by Klootwijk et. al in patients with unstable angina. They concluded that 12-lead ECG is significantly more sensitive and detected 65 % more ischemic events in 15 % more patients than a 3-lead systems consisting of leads III, V_2 and V_5. Lead aVR was excluded from the 12-lead analysis. Additionally the first ischemic event was detected earlier by the 12-lead ECG. The study also identified the precordial leads to be independently more frequently involved in the ischemic episodes than the limb leads, namely the standard and augmented limb leads. For single lead sensitivity, V_2 was detecting most of the ischemic events in the 3-lead system, while V_2,V_3 and V_4 were equally sensitive in the 12-lead system. [30] These findings were in contrast to studies in which optimal leads were studied in exercise electrocardiography. The mentioned studies found V_5 to be the most sensitive one. [66, 54] Another study by Martinez et al. [44] showed also that the precordial leads V_2-V_4 were the most sensitive superseding V_5. It seems that lead II and precordial leads V_4 and V_5 are believed to be the most sensitive leads for ischemic detection.

The data used in this thesis have been collected using the standard 12-lead configuration, so that a valid comparison can be done with the diagnostic conventional ECG. Specifications about the collected data are explained in more detail in section 4) of this thesis.

3.3.2 Continuous Wireless Patient Monitoring

The trend in patient monitoring has been steadily shifting towards wireless patient monitoring. Although single simple parameters have been monitored for several years, a comprehensive and reliable patient monitoring system is something not yet available. An obvious reason for this is the great challenges in wireless patient monitoring. Unlike other applications benefitting from wireless technologies, the health-monitoring of humans in a clinical environment is something that must be done with special care since the consequences are more severe compared to most fields. The simplified system idea of a wireless patient monitoring system starts with biosensors measuring the desired physiological parameters. These measurements are then transferred using wireless or wired transfer to a central node from which the data is transmitted further for viewing or storing. Two of the key challenges in wireless patient monitoring are the telecommunication system and how that is implemented reliably and the challenge to achieve good quality signal in an ambulatory setting and developing algorithms that consider this. The latter includes also the important matter of clinical effectiveness, i.e. is the wirelessly acquired signal as good as one would acquire through traditional clinical methods. [68]

Wireless patient monitoring also include non-technology related issues making it more prone for errors. Such issues are for example movement and changes in posture that are known to affect the measurement of several vital signs.

Effect of Postural Changes, Noise and Electrode Placement

Continuous ST-segment monitoring has been shown to offer prognostic value as well as early warning in myocardial ischemia and infarction [51, 31]. Postoperatively, according to recommendations, a patient should be monitored a relatively long time, which with the conventional 12-lead diagnostic ECG would mean restricting the patient to a small area within the patient room. It would be most likely uncomfortable and complicate physical therapy. Due to these reasons a continuous wireless monitoring with as few leads as possible would be beneficial. Challenges occur when the patient can move and thus be in different postures when monitored, which differs from the traditional situation where the patient is assumed to monitored in a supine position. Studies considering this problem have been carried out to see whether there is significant differences in ECG in postures other than supine. The main area of interest in the ECG-waveform has been the QRS-complex and ST-segment. While some of these studies show, that postures including half-inclined, standing and sitting do not inflict significant changes on the ST-segment [42, 6] and can even be

considered equivalent to supine position, some demonstrate that in certain postures and patients the changes can reach a significant level which will cause ST-segment deviation not related to heart pathology. [1, 25].

Both studies reporting significant changes, namely in 15 % and 19 % of the measurements, identified the left lateral decubital position (lying on left side) as a posture causing clinically significant changes that resemble ischemic ST-segment shifts. The second most sensitive posture for ST-segment shifts was the right lateral decubital position, i.e. lying on the right side. According to the studies, ST-segment deviation of more than 1 mm can be caused by posture change, and these changes were exclusively seen in the precordial leads in the studies. Positional changes in the QRS-complex were also studied and a significant part of the population had some changes in their QRS-complexes. However, in the current ischemia monitoring setting these changes have only minor implications. This leads to a conclusion that although most of the ST-segment changes caused by postural changes are small, some are significant and thus must be taken into account when analysing ECG for MI or when doing automated ST-monitoring. A simple explanation for the different deviations in ECG, caused by the postural changes, could be the movement of the heart and other internal organs relative to the sensing elements. For example the left ventricle have been observed moving closer to the lateral chest wall when on left lateral decubital position. [53]

An important factor in separating the positional ECG changes from the actual ischemic ECG changes, is the well known fact that ischemic changes develop gradually over time unlike changes caused by a position change. More specifically the maximum ST-level changes develop in 15-20 minutes as opposed to a change occurring within seconds as is the case in change of posture. Based on this assumption there has also been suggestions of adaptive algorithms detecting this gradual change. [64]

Other factors worth noticing in a wireless monitoring environment are measurement noise and electrode placement as they are more common during movement and they have effects on accurate ST-segment analysis during ischemia monitoring. The spectral overlap of artifacts and the ECG prevents the usage of linear filters effectively. Noise and artifacts are usually easily spotted by a human from the signal, but in the case of computer-assisted monitoring, including automatic alarms, they can cause false alarms. The most frequent source of noise is poor electrode contact or movement causing motion in the skin-electrode interface. Likewise, the inconsistency of electrode placement in removal and reattachment situation can cause possible ST-segment deviation no related to heart perfusion and in the case of ischemia monitoring the accuracy and consistency of the electrode placement is of

high importance. [53, 52] It is obvious that recording ECG during movement affects the signal quality. However the question remains how much the movement affects overall and what is the risk associated because of the degradation of the signal.

3.3.3 Secondary Repolarization Abnormalities as a Source of False Alarms

If monitoring ischemia is based on measuring the absolute ST-deviation, it should expected that this kind of alarm logic will produce significant amount of false alarms caused by secondary repolarization abnormalities (see 3.2). To be able to reduce the amount of false alarms, filtering out the alarms caused by secondary repolarization abnormalities is highly beneficial. For example in case of automatic detection of RBBB the leads affected could be (V_1-V_4) made irrelevant or less sensitive. However the importance of preoperative ECG is crucial in order to decide whether the RBBB is new or chronical. Still the prognosis of patients with RBBB has been demonstrated to be independent of the onset [14].

4. MATERIALS AND METHODS

The data used in this thesis were collected in a hospital study done in collaboration with the Helsinki University Central Hospital (HUCH). The purpose of the study was to gather more information on PMI prevalence and whether the onset of the ischemic episodes possibly evolving to PMI's should be monitored continuously, what is the sensitivity of the conventional leads to ischemia and how well continuous ECG monitoring detects PMI events compared to snapshot ECG's done in the mornings. In addition to these questions, this thesis discusses general development of ischemia monitoring as well as wireless patient monitoring. With these objectives in mind an MI data utilization tool was developed alongside with measures aimed for easier utilization of the data and studying the detection sensitivity of real ischemia events in the setting of cardiac comorbidity and wireless monitoring.

4.1 Study Population

The measurement population consisted of 56 (33 men and 24 women) over 65-year (74.6 ± 6.5) old patients who had undergone a noncardiac vascular surgery. The selection criteria for the study population aimed in a high-risk population most likely to suffer from PMI events. The demographic information and other relevant ECG findings apart from ischemic are presented in table 4.1

Demographics	All Patients (n = 51)	Patients without MI (n = 32)	Patients with ischemia (n = 19)	Patients with MI (n = 5)
Age	74.6 ± 6.5	74.1 ± 6.7	75.5 ± 6.0	77.2 ± 2.7
Gender(Male)	29 (56 %)	19 (59.4 %)	10 (52.6 %)	1 (20.0 %)
Cardiac abnormalities				
LVH	7 (13.7 %)	2 (6.3 %)	5 (26.3 %)	1 (20 %
RBBB	6 (11.7 %)	4 (12.5 %)	2 (10.5 %)	0 (0 %)

Table 4.1 *Patient information*

Five patients were excluded from the analysis afterwards, making the total study population 51 patients. The patient ID's still go to number 56. The reasons for the

Excluded Patients	
Patient ID	Exclusion Reason
PMI10	RBBB + LPHB + QRS duration 200 ms
PMI19	Pacemaker rhythm
PMI21	Digitalis medication
PMI25	LBBB
PMI54	Holter not analyzable

Table 4.2 *Excluded patients and exclusion reasons why the ECG was not analyzable for ischemia; LPHB = Left Posteriot Hemiblock*

exclusions are listed in table 4.2. Of the total analyzed 51 patients, 7 had LVH and 6 had RBBB. From the RBBB patients, leads V_1-V_4 were excluded from the analysis. Monitoring was continued for 72 h or more or until the patient was sent home or refused to continue participating in the study. Ischemia was defined as described in section 3.2.4 for postoperative settings.

4.2 Data Collection and Processing

The data were collected during four months period in the non-cardiac surgery ward in HUCH. The continuous 12-lead ECG recordings were done using a SEER 12 digital holter ECG-device (manufacturer Getemed, Teltow, Germany and distributor GE Healthcare, Freiburg, Germany) for each patient after they undergone a noncardiac vascular surgery. The Holter device setup was attached to the patient after the surgery in the recovery room. A Mason-Likar modification of the standard 12-lead system was used on each patient. The measuring device itself was put into a pouch that the patient carried.

The SEER 12 device uses a sampling frequency of 1024 Hz with a digital sample resolution of 12 bits for all of the 12 channels and an analog bandwidth of 0.5 Hz to 120 Hz. It is able to measure ECG continuously over 72 h. In addition, separate diagnostic snapshot ECG's and high sensitive troponin T (hs-TnT) measurements were done once preoperatively and once per day postoperatively. The Holter ECG was removed during the snapshot ECG's. A daily enquiry for symptoms of ischemia was done for each patient as well. The measurement setup also included a Faros 360° eMotion (Mega Electronics Ltd, Kuopio, Finland) cardiac monitoring device with an integrated accelerometer. This device was attached to the patients sternum with a custom-made electrode by the device manufacturer. The objective was to record the patients orientation and movement in synchronization with the ECG signal.

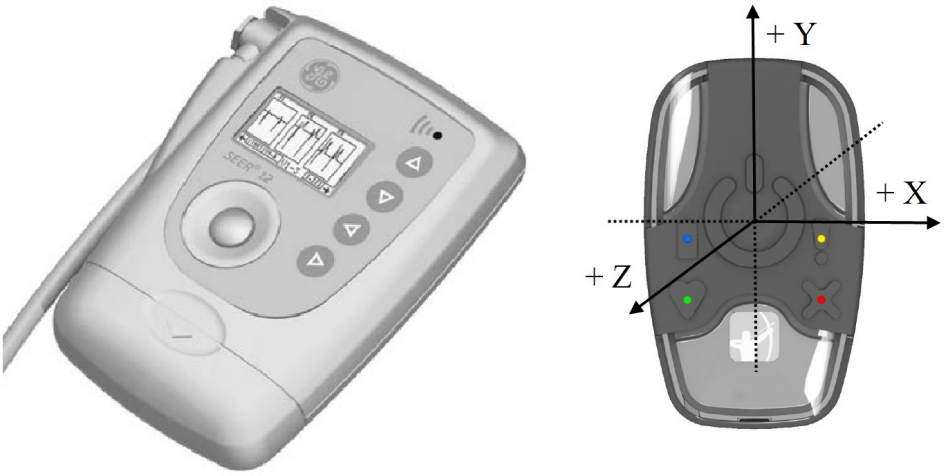

Figure 4.1 *SEER 12 (left) and Faros* 360° *eMotion (right). Not in scale.*

The Faros 360° is able to measure acceleration along 3 axis as well as 1-channel or 3-channel ECG. The device was set to measure acceleration with a sampling frequency of 50 Hz and 1-channel ECG with a sampling frequency of 250 Hz, although this data was not used in the scope of this thesis. The Faros' accelerometer was set to a resolution of ± 4 g. Due to insufficient battery life of the Faros device, 2-4 separate measurements were done per patient. A new fully charged device was changed for each patient on the first postoperative day after the snapshot ECG and on later postoperative days if needed. The device is illustrated in figure 4.1.

Due to the separate devices recording ECG and the orientation, a manual time synchronization of the the two measured (ECG and acceleration) signals were done. The nurses conducting the measurements were instructed to do a marker on both of the recordings simultaneously in the beginning of the measurement and at every reattachment of the equipment after a snapshot ECG. Using these markers, the ECG and accelerometer signals were manually time synchronized. Additionally the orientation of the Faros on the patient's chest was illustrated on a paper form, as the optimal upright position of the device was not always possible due to skin irritation or anatomical reasons. This was done so that the measurement axis and the device orientation on the patient chest could be corrected before posture classification.

In order to make use of a raw ECG-signal, fairly large amount of preprocessing needs to be done, so that more advanced signal processing can be carried out. In this thesis the initial processing of the ECG-signal was done by GE's EK-Pro version 14 [67]. The algorithm does high frequency filtering, detects the QRS complexes of

the ECG-signal and classifies every beat. For any ECG analysis this is essential. The details of the QRS-detection are not given here.

The algorithm produces several output files that contain the heartrate (HR), signal quality (SQI) and ST-value trend of the ECG-signal with a resolution of 1 value per second. Additionally the algorithm provides chronological information about the current average beat and its features.

Several steps had to be taken, in order for the data to be uniform and analyzable with relative ease. The 12-lead ECG signal was initially in a file format specified by the manufacturer. Due to complexity of this data format, a data format conversion to MIT(Massachusetts Institute of Technology)-format was done. The MIT-format is a format standard specified by Physionet and is used to store ECG signals in binary form. [55] The collected accelerometer data was in European Data Format (EDF) which is a public standard format for multichannel biological and physical signals. [27]

The two different signals were synchronized and individual accelerometer recordings were merged into a single recording simultaneously using the previously mentioned markers on both of the signals. As the total length of the accelerometer signal was always shorter than the ECG, the accelerometer signal was simply padded with data invalid values to achieve proper signal length as well as synchronization. Finally the sampling frequency of the ECG signal was downsampled to 500 Hz, due to Ek-Pro.

At this point the ECG signal was run through EK-Pro to get information on HR, SQI and most importantly the measured ST-values. The analysis of the accelerometer data was outside the scope of this thesis.

4.3 Data utilization and analysis

Used Tools

The flow of data consisted of three distinguishable steps. First the data was analyzed by the ECG algorithm. This data was given to a custom data analysis and viewing tool called simply as ECG tool. ECG tool is presented in the result part of this thesis. After preprocessing the data could be outputted from the ECG tool for further analysis. This data of the ischemic episodes, consisting of information such as timing of the episode, HR values, signal quality, patient position and ST-values during the episode, was passed to MATLAB 2015a, which was used for the statistical analyses.

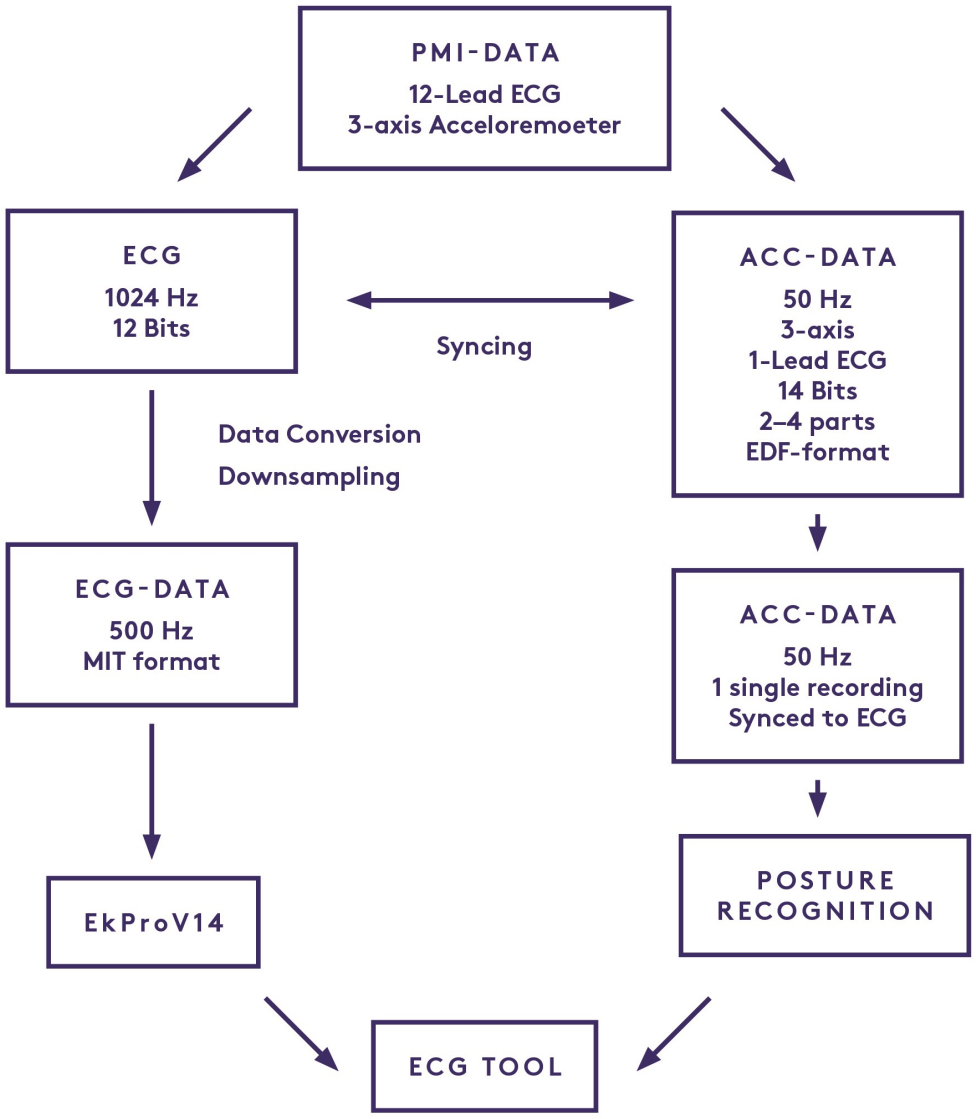

***Figure** 4.2 Preprocessing phases for the measured ECG and accelerometer data*

12-Lead Sensitivity to Ischemia

Statistical analyses were done concerning the sensitivity of each lead and several different analytical approaches were used. It is best to point out here, that no ST-elevation ischemia was diagnosed in the study and thus from here on only ST-depression is considered. Thus the average depth of ST-depression during each ischemic episode for each lead was calculated. The total duration of each ischemic episode was determined based on the single lead which fulfilled the established criteria during the whole episode. These different episodes were additionally combined to form a so called 'Combined episodes', to get a general view of the more realistic number of episodes regardless of the criteria not fulfilling continuously during this

episode. In other words if after a significant episode another episode began within 15 minutes, it was considered to be the same episode. Additionally calculated characteristics describing the ischemia within the study population were the ischemic time and the ischemic burden.

The following characteristics were used to assess lead sensitivity:

1. The incidence of ischemic leads from each of the combined ischemic episodes were calculated, if the lead was ischemic during the first 15 minutes of the episode.
2. The incidence of ischemic leads from each patients first ischemic episode were calculated, if the lead was ischemic during the first 5 minutes of the first episode.
3. In how many patients a lead was seen ischemic, regardless of the timing or duration of the episode.
4. For each lead the ischemic burden was calculated as the product of the ischemic time and the corresponding depth of the ST-depression during that time.

Finally the sensitivity of different lead systems have been compared to examine the optimal lead combination for detecting ischemia during continuous wireless monitoring.

Performance of the Continuous Realtime Monitoring

The performance of the continuous wireless monitoring was assessed based on the overall data quality of the collected data as well as how well and how soon it detected ischemic episodes in relation to the diagnostic snapshot ECG's. The detection of the first ischemic episode is of special interest, since it has the most impact on the timing of the treatment. The correlation between quality indicating alarms and the cumulative ischemia time and burden was studied in 12-hour periods.

Alarms used to assess the quality were related to how well the algorithm was able to analyze the ECG-signal. For example if the signal quality, for some reason, was so poor that no QRS-complexes could be detected, the corresponding time was considered lost, meaning that during this time no alarms could be given. This in its part will indicate a weakness in the wireless monitoring.

In the analysis all data-invalid sections were identified and counted to determine when the ECG leads have been off. Additionally all continuous half an hour periods of invalid data were calculated. This half an hour was considered to be a period of time that the patient might not be checked up on, in which case a missed alarm could lead to an injury or even fatality. Additionally the amount of excessively noisy data was calculated, which indicates heavily corrupted data where no QRS-complexes are detected. Such data is similarly considered lost and not analyzable.

5. RESULTS

5.1 Data Utilization With Custom Tool

ECG Tool Overview

For more convenient utilization of the data, a software tool was developed for visualization and analysis of the collected and preprocessed data. The tool was simply named as the ECG Tool. The tool was developed using C Sharp (C#)-programming language which uses the .NET software framework developed by Microsoft. The tool is confirmed to run in its develop environment Windows 7 operating system with .NET 4.0 installed. C# programming language was chosen mainly due to its large variety of predeveloped components, supporting features such as automatic garbage collection and expection handling and thus relative ease to develop versatile applications. [45]

Software Architecture

The software is designed to be a combination of three separate functional parts divided into separate modules. These functional parts are user controls, data preprocessing and data viewing. Probably the most complex part of the program is the preprocessing, which is unnoticed by the user. The visible part controlling the data reading and preprocessing is the user controls. The user controls determine what operations are done to the data regarding the preprocessing, and which case data is read into the program memory. For example selecting the "Use ST-references" tickbox will cause the data to be filtered based on the reference ST-levels predetermined from the patient nonischemic ECG. Another example could be selecting the "J-point" tickbox, which sets the ST-value to be taken from the J-point. On top of the user controls determining preprocessing the program has a hard coded logic for determining the significant ST-deviation episodes. The user controls are also cabable of other functionalities such as creating reference files from the data, navigating through the data and setting the parameters for viewing the data.

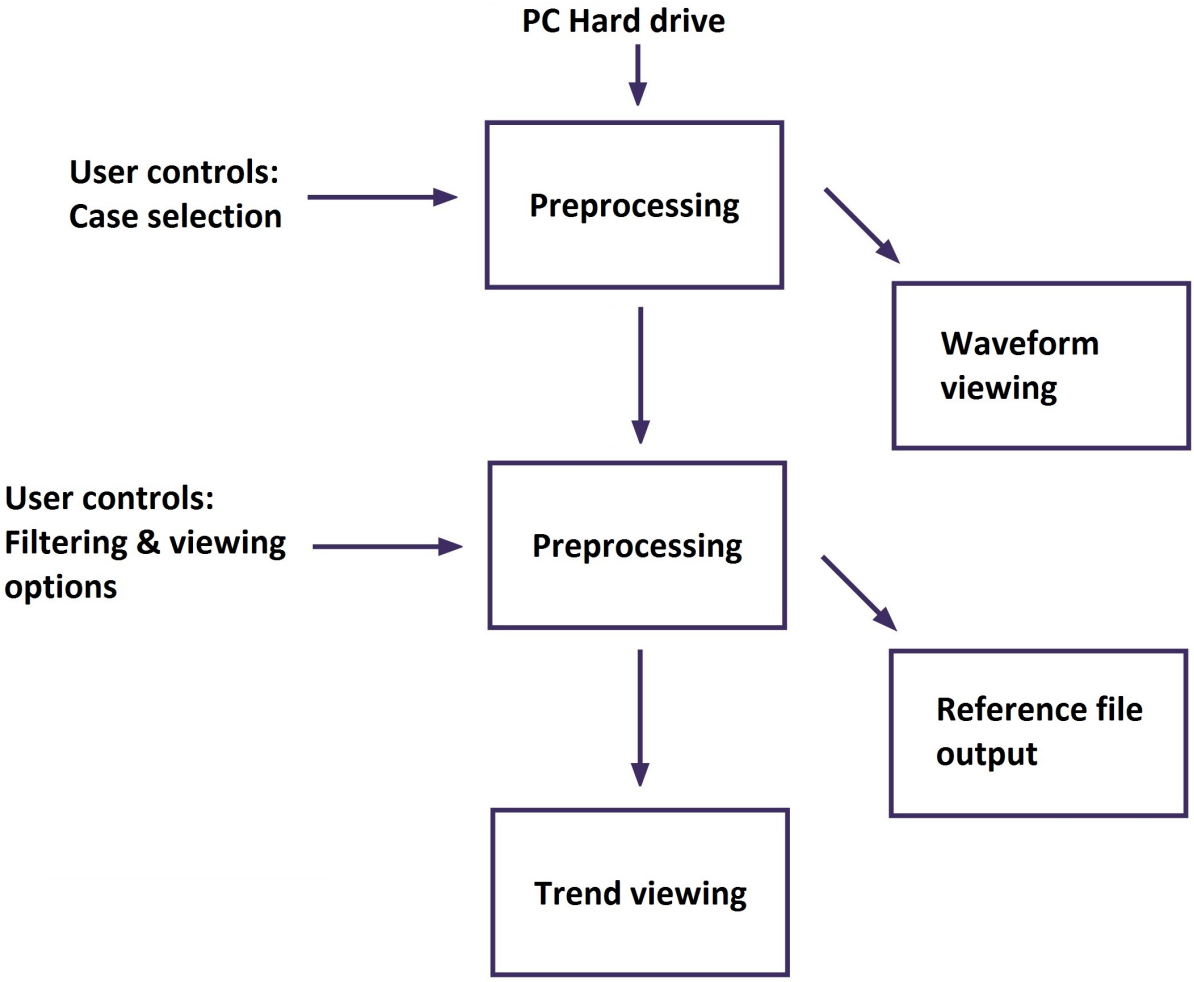

Figure 5.1 *A simplified cycle of data flow within ECG Tool, showing basic dependancies inside the program*

The data viewing parts of the program is where the user can evaluate the data visually using a lead by lead ST-trend view, a trend view of secondary parameters, such as HR, and a lead by lead view of the average QRS-complexes visualized at certain time point. Visualizing the ST-trend data involves scaling and filtering the data points to correctly show the data as a function of time for each separate lead. Combined with this logic is the secondary trend data visualization. A separate visualization module was created for the average QRS-complex viewing. Finally a completely separate module with its own program window is the ECG waveform view, where the user can inspect the actual ECG recording from specific points. This waveform view is implemented so that it is properly scaled so the ST-levels are clinically interpretable.

Software Features and Use of ECG Tool in Thesis

The ECG tool is operated using a graphical user interface (GUI) to enhance the usability of the tool. As explained in the previous section, several sources of information regarding ischemia monitoring have been embedded in the basic view of the tool. The tool loads in the data, including ECG waveforms, ST-values, HR values and more, in parts during runtime. The user can select different cases using the list menu on the right side of the user interface window. The basic view includes the following components that are illustrated in figure 5.2.

1. **ST-heatmap:** The ST-heatmap view presents 9 leads of the 12-lead ECG system one below another, by default excluding aVR. By contrast to a trend view of the ST-values as function of time, the heatmap paints all significant ST-depressions blue and elevation red. The criteria for this can be adjusted using the checkboxes on the right side of the view. The time scale is by default 120 min but can be set to 12 hour or 30, 45, 60 and 90 minutes.

2. **QRS-complexes:** The current average QRS-complex is shown on the right side of the corresponding leads heatmap. The longitudinal line cursor indicates the current time point.

3. **HR, SQI and Acceleration:** In the bottom of the basic view trends for HR, SQI and three accelerometer axis sum are shown. Blue denotes HR, red SQI and turquoise the accelerometer axis sum.

4. **Classified posture:** In the right bottom corner the posture classification result from the current time point is shown.

5. **QRS- and T-axis:** In the right top corner the current time point progression of QRS-axis in blue and T-axis in red are shown. These parameters are used to assess the conduction of the heart and are not used in this thesis.

6. **Checkboxes:** The checkboxes on the right side of the user interface are designed to control different parameters for the viewing as well as parameters for making the reference file. In some cases checking one checkbox inchecks another one, if the controls contradict with each other.

To inspect the actual ECG more closely the user can open the following view using control 'Show ECG'. The view opened by clicking this button is illustrated in figure 5.3.

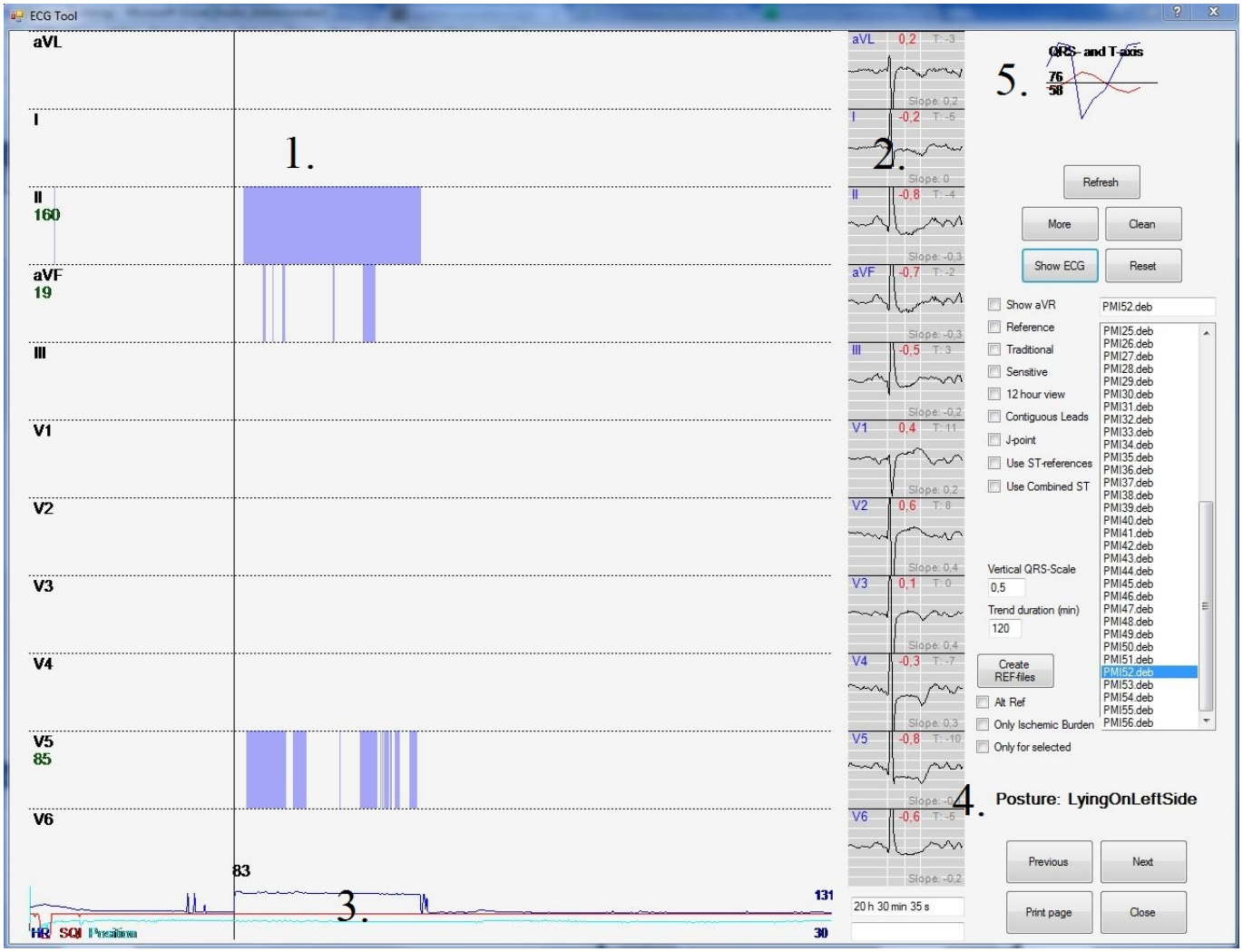

Figure 5.2 *Basic view of the ECG Tool: 1. ST-heatmap, 2. QRS-complexes, 3. HR,SQI,Acceleration trends, 4. Classified posture, 5. QRS- and T-axis*

In this view all of the ECG leads can be browsed. By default the view shows limb leads with paper speed of 50 mm/s. The view can show precordial leads as well and paper speed of 25 mm/s can be used by using the checkboxes on the left side of the view under the waveform. The aiding lines in the view are scaled to be as a millimeter grid for proper evaluation.

Both views presented in figures 5.2 and 5.3 can be printed using the "Print page" button. Notable is, that the ECG waveform is set to be printed in the correct scale, and a clinical evaluation can be done from the printed paper as well.

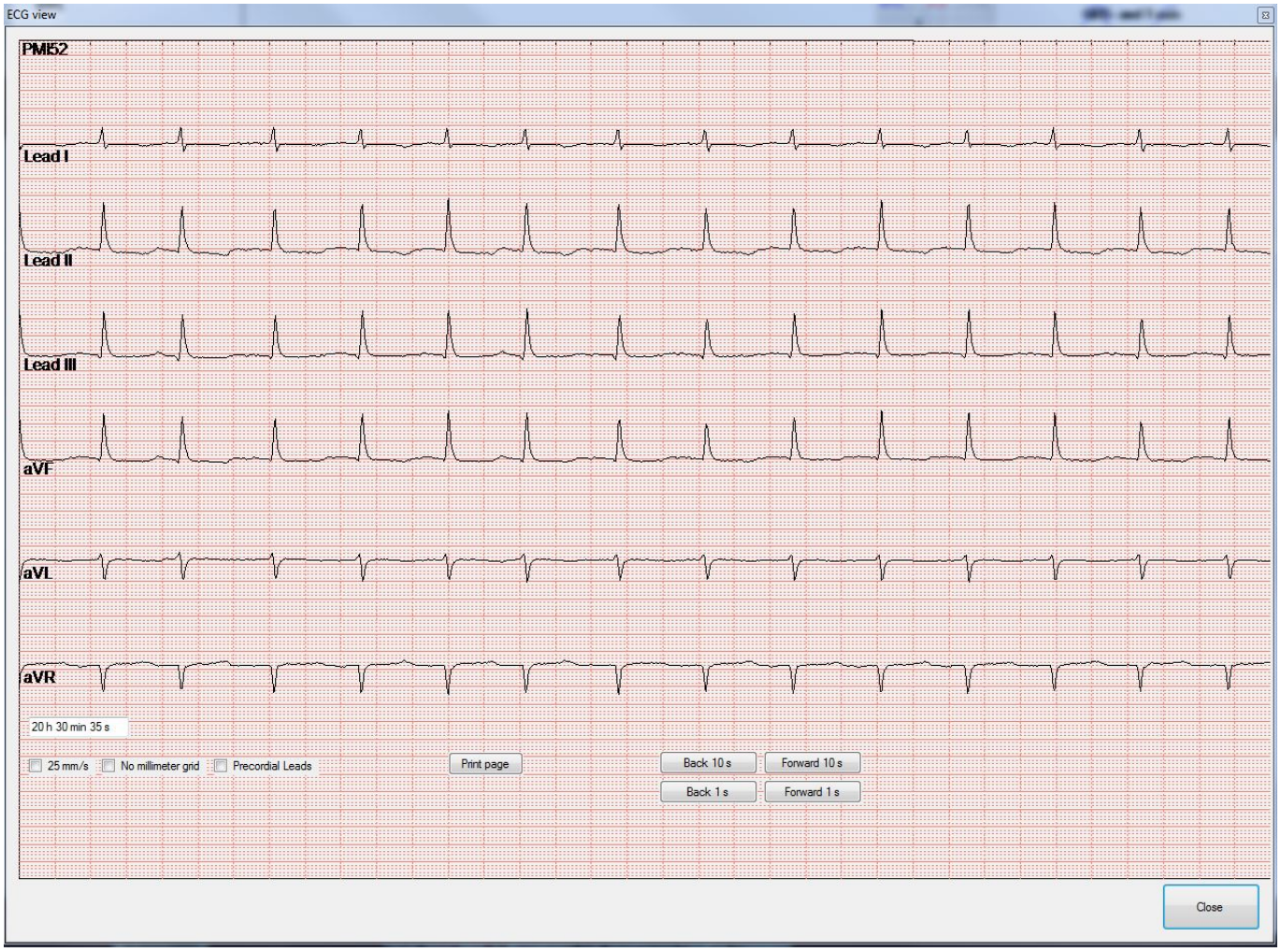

Figure 5.3 *View of the actual ECG waveform from selected time point*

Options For Ischemic Events Criteria

As described in section 3.2.4, the criteria for ischemic events depend whether the setting is non-operative (AMI) or operative (PMI). This thesis focuses on the post-operative setting, although the tool is applicable for other data as well. By default the tool colors ischemic events using criteria of $\geq$1 minute, ST-deviation of $\geq$0.1 mV (1 mm), excluding V_1-V_3 which have ST-deviation criteria of $\geq$0.2 mV (2 mm) measured from J_{80}. This criteria can be modified and the ST-level can be measured using only J-point or both J-point and J_{80}. The voltage limit can be set to a more sensitive level of $\geq$0.05 mV (0.5 mm) as well. Additionally the tool can take into account the criteria of anatomically contiguous leads (refer to AMI criteria in section 3.2.4). Lastly the criteria can be set to take into account the patients reference ST-values measured from a preoperative ECG by a cardiologist.

Ischemic Event Annotations

An important feature of the tool is to be able to create files containing references of the ischemic events. These reference-files are created based on the PMI criteria. A shortcoming of the criteria embedded in the tool was that the criteria do not take into account cardiac comorbidities that affect diagnosing ischemia. An example of a comorbidity is RBBB which in practice renders precordial leads V_1 to V_4 useless and thus all ischemic events occuring in these leads should be discarded. Poor signal quality on the other hand can make the ST-measurement unreliable. These ECG sections were manually inspected to ensure that a reliable measurement is possible. Based on the annotations of a cardiologist, the ischemic events contained in the reference files were annotated as true or false.

5.2 Ischemic Episodes In Study

5.2.1 Study Overview

A clinical investigation in Helsinki University Central Hospital, Finland was made where wireless, continuous ECG recordings for 56 patients over 65 years old undergoing noncardiac surgery were made. Standard 12-lead snapshot ECG's were also performed alongside with serum troponin T measurements for complete a diagnosis of PMI events. All of the detected ischemic events were annotated by an independent cardiologist. An analysis of the detected ischemic events using continuous ECG measurements compared to the snapshot ECG measurements was performed. In addition the most sensitive ECG leads were determined and an assessment of the performance of the wireless measurements was performed. According to our results continuous ST-monitoring shows clear benefits in detecting PMI-related events with only minor issues relating to the wireless nature of the recording.

5.2.2 Diagnosed Episodes

The defined criteria for a postoperative ischemic episode is described in section 3.2.4. Based on the criteria a cardiologist reviewed the snapshot ECG's as well as the ischemic episodes in the continuous recordings. Based on TnT elevation accompanied with an ischemic symptom and/or ischemic ECG (snapshot ECG), the cardiologist diagnosed 5 myocardial infarctions during the postoperative period. During 3262 hours of monitoring (average 64.0 hours $\pm$20.2 per patient) 19 patients out of the 51

analyzed (35 %) had 610 ischemic alarms corresponding to 2193 minutes of ischemia and ischemic burden of 466.8 $\frac{min}{\mu V}$. The number of combined ischemic episodes was 129. All of the ischemic episodes were denoted by ST-depression. Summary of the patients who had ischemia is shown in table 5.1.

	All Patients (n = 51)	Patients with ischemia or MI (n = 19)	Patients with MI (n = 5)
Ischemia seen in Continuous ECG	19 (37 %)	19 (100 %)	5 (100 %)
Ischemia/MI seen in snapshot ECG	3 (6 %)	3 (17 %)	3 (60 %)
Ischemic symptom	7 (14 %)	6 (33 %)	3 (60 %)
Significant TnT-elevation	24 (47 %)	13 (72 %)	5 (100 %)
T-wave inv.	1 (2 %)	1 (6 %)	1 (20 %)
RBBB	6 (12 %)	2 (11 %)	0 (0 %)

Table 5.1 *Ischemia within the patient population*

5.2.3 Performance of the Continuous Wireless Monitoring

Table 5.2 shows the times when PMI was diagnosed using the snapshot ECG's and the TnT-measurements. The day or days, when the PMI was diagnosed to have occured, are denoted as the first day being the day of the surgery. The times for the first ischemic episode seen in the continuous ECG are denoted as the absolute times starting from the recovery room.

In all PMI cases the first ischemic episode was detected prior or during the day to which it was diagnosed with continuous monitoring. Cases 29 and 34 had a diagnosed infarction outside the continuous recordings and thus detection of ischemic episodes from that time was not possible. Figure 5.4 shows the cumulative ischemic time of the PMI cases as well as case 52. Case 52 had significant ischemia present during the recording and is thus included in the figure as a comparison.

In the PMI cases only two showed ST-depression in the snapshot ECG's on the third day. Additionally ST-depression was diagnosed in three other cases with no PMI from the snapshot ECG's. From the continuous ECG recordings, ST-depression were seen and ischemia diagnosed in all 19 ischemic patients including all of the PMI cases. If the third day of the PMI cases and the whole ischemic time of the additional 3 ischemic cases, in which ST-depression was seen in the snapshot ECG, is summed, a total of 806 minutes (36.8 %) is achieved. Essentially this means that the snapshot ECG missed a total of 1386 (63.2 %) minutes of ischemic time. For example cases 29 and 39 were ischemic already on the first 24 hours. Case 39 had the most ischemic time in the time frame of 12-24 hours and case 29 in 36-60 hours.

Patient ID	Day which PMI diagnosed	First ischemic episode in continuous ECG
PMI 17	1.	3 h 50 min
PMI 18	2.	5 h 17 min
PMI 29	3. and 6.	6 h 45 min
PMI 34	1. and 4.	84 h 20 min
PMI 39	3.	6 h 30 min

Table 5.2 *Times when PMI was diagnosed from the snapshot ECG and the continuous monitored ECG.*

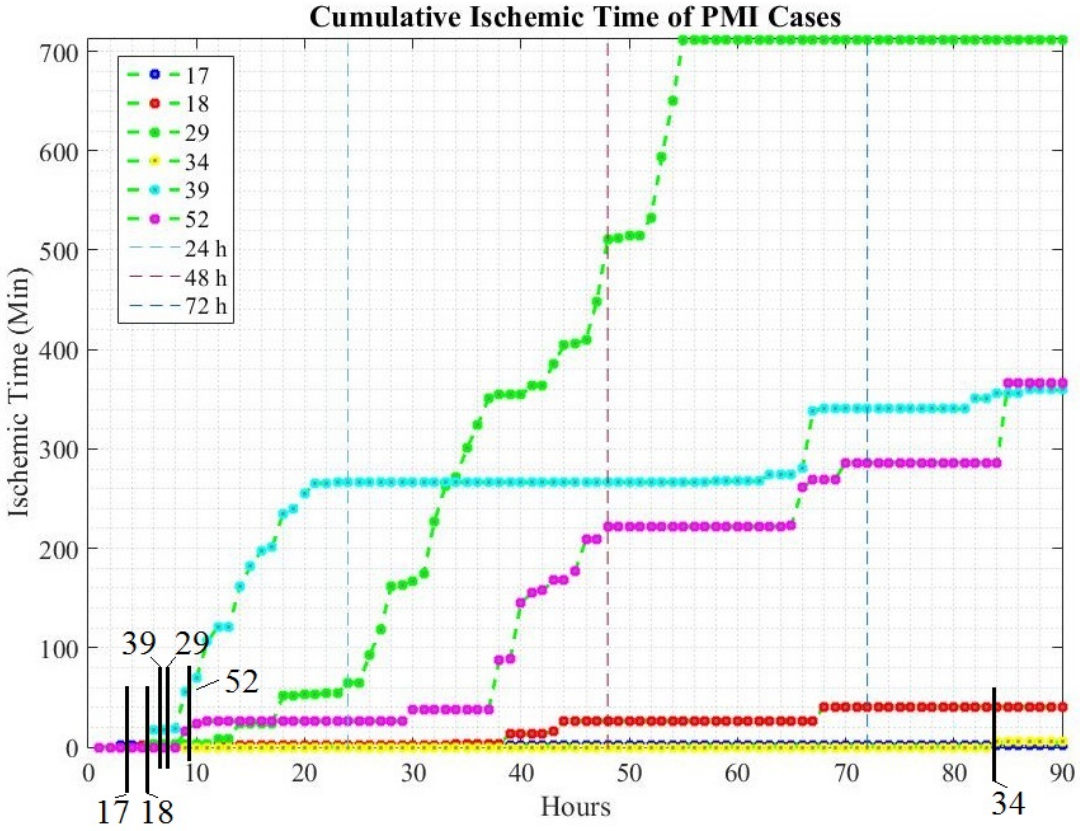

Figure 5.4 *Figure of the cumulative ischemic time of the PMI cases and in addition case 52. The first ischemic episode is marked in the graph with a short black vertical line. A decent amount of variation can be seen in the ischemic time between different cases.*

Still the significant ST-depression was not seen in the snapshot ECG until the third postoperative day.

The total monitoring time characterizes how much ischemic time has been detected relative to the amount of continuous monitoring time. Figure 5.5 shows how the detection of ischemic time develops as a function of monitoring time in the whole

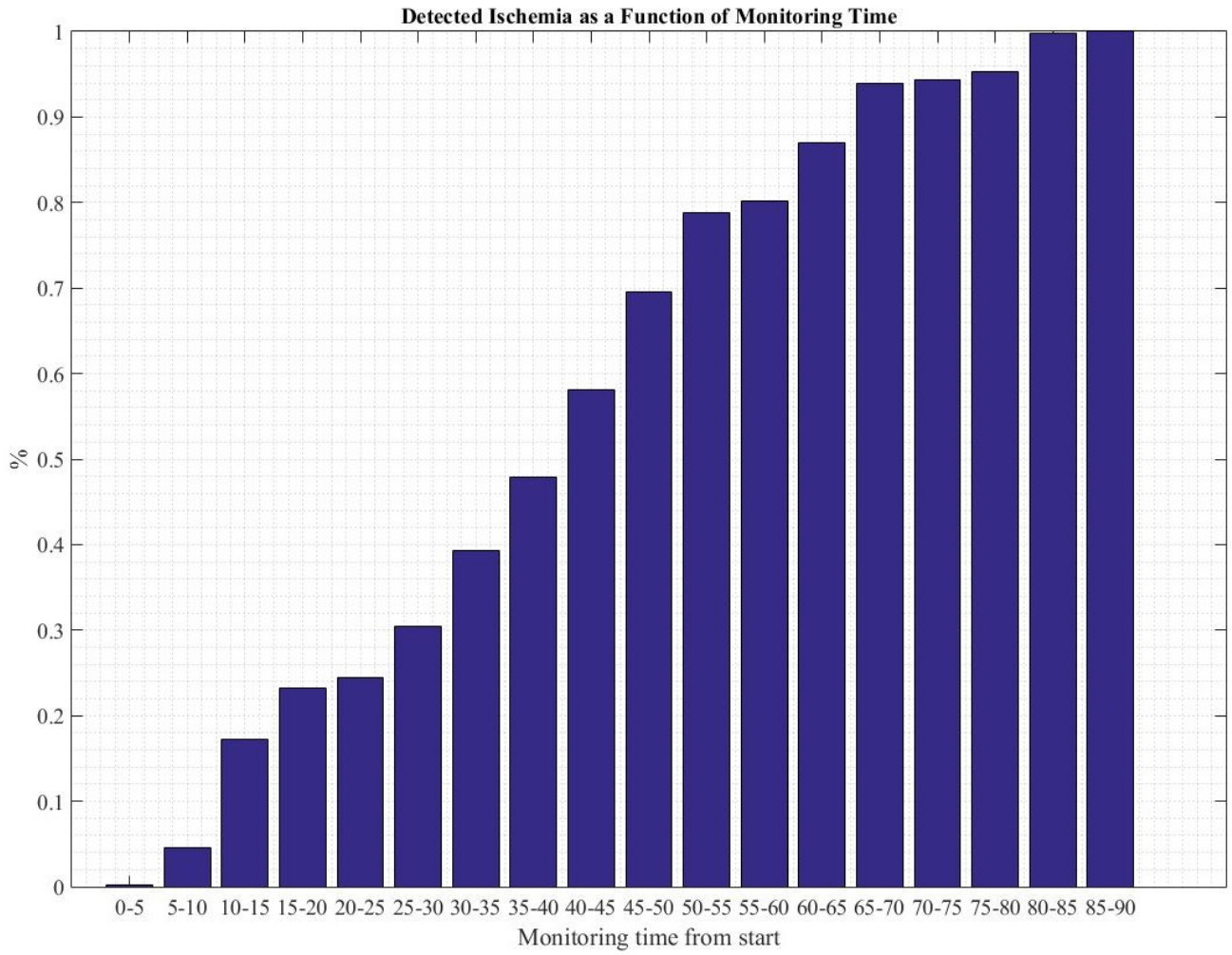

Figure 5.5 *Figure of the cumulative ischemic time as a function of monitoring time. The time bins are 5 hours up to 90 hours, during which all the detected ischemia is included.*

ischemic group of 19 patients. A clear ascending trend can be seen when the monitoring time is increased.

In total 225 hours of data were lost due to detachment of the lead wires, which equals to 7 % of the total recorded data and 4.4 (±6.8) hours per recording. As the standard deviation suggests, the lost data was distributed unevenly. In total 15 patients did not have any lost data and 13 patients had less than 1 hour of lost data. The time the continuous monitoring was off during the snapshot ECG's has been taken into account. Several times the patient had been delirious and taken the leads off on purpose. Overall 10 hours of the data were corrupted by artefacts or similar kind of causes, which equals 0.3 % of the total recorded data.

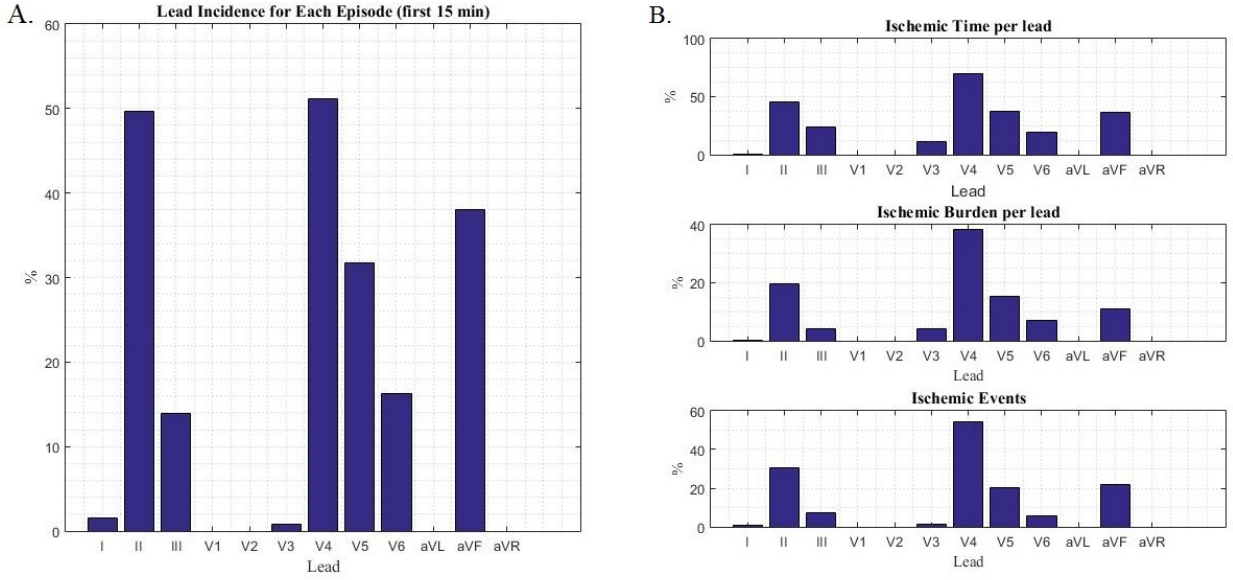

Figure 5.6 **A.** *Histogram of ECG leads fulfilling the ischemic criteria in the first 15 minutes of each combined episode in the study group* **B.** *Histograms of ischemic time, ischemic burden and ischemic alarm count of ECG leads in the study group*

5.3 12-lead Sensitivity

5.3.1 Individual Leads

The sensitivity of the leads is shown in figures 5.6 to 5.8 for the different calculated characteristics. From the total of 19 ischemic patients, leads V_4 (51.2 %) and II (49.6 %) are the most frequent leads where the ST-depression was seen first in the combined episodes. Following these leads were leads aVF (38.0 %) and V_5 (31.8 %). Throughout the whole population leads aVR, aVL, V_1 and V_2 did not have any real incidence of ischemia in any characteristic used.

When the RBBB cases, in which V_1-V_4 are ignored, are excluded, the sensitivity of V_4 (55 %) increases even more, The sensitivity of lead II (48.3 %) and lead V_5 (28.3 %) in turn decrease slightly.

Relative to the total ischemic time and burden in the population, the ischemic time and burden for each lead show that lead V_4 (burden 38.5 %, time 70.1 %) is on average the most frequent lead detecting ischemia as a function of time and burden. Leads II (burden 19.5 %, time 45.9 %), V_5 (burden 11.0 %, time 36.6 %) and aVF (burden 7.2 %, time 19.3 %) are the next most frequent leads in terms of ischemic time as well as burden. When reflected on the total alarm count (610) V_4 (54.6 %) were the most frequent, followed by leads II (30.5 %), aVF (21.6 %) and V_5 (20.5

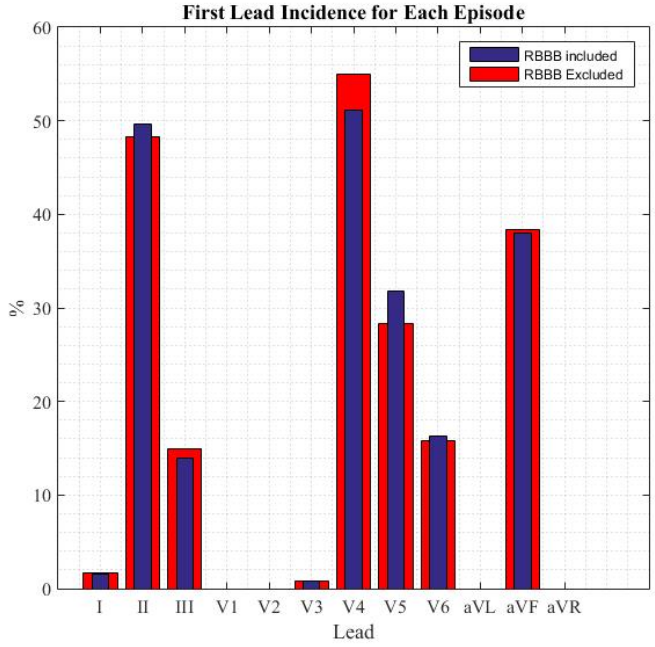

Figure 5.7 *Histogram of comparing the lead sensitivities with RBBB cases excluded or included (leads V_1-V_4 are ignored). The sensitivity of leads V_4, II and V_5 changes slightly.*

%). A notable contribution of 46 % relative to the overall detection of lead V_4 is however due to one single patient.

When considering the ischemic subgroup (n = 19) and the first ischemic episode of each recording, lead II is the most frequent lead contributing to the first alarm (47 %). Ischemia was also the most probable to be detected in lead II at least once per ischemic recording (79 %). The next best lead detecting the first episode was V_5 (37 %) followed by V_4 (26 %) and III (21 %) and aVF (21 %). Having at least one ischemic episode in the whole recording following lead II, were leads aVF (74 %), V_5 (58 %), V_6 (53 %) and V_4 (47 %).

Although the specificity of leads is not analyzed in this thesis, it is mentionable that most of the false alarms (97 %) were recorded from patients having RBBB, where leads V_1-V_4 generated significant amount of false ischemia detections due to the aforementioned condition. This was mostly due to two RBBB patients who were diagnosed not to have ischemia. The rest of the false alarms were due to medication (digitalis), noisy signal and other cardiac conditions affecting ST-levels.

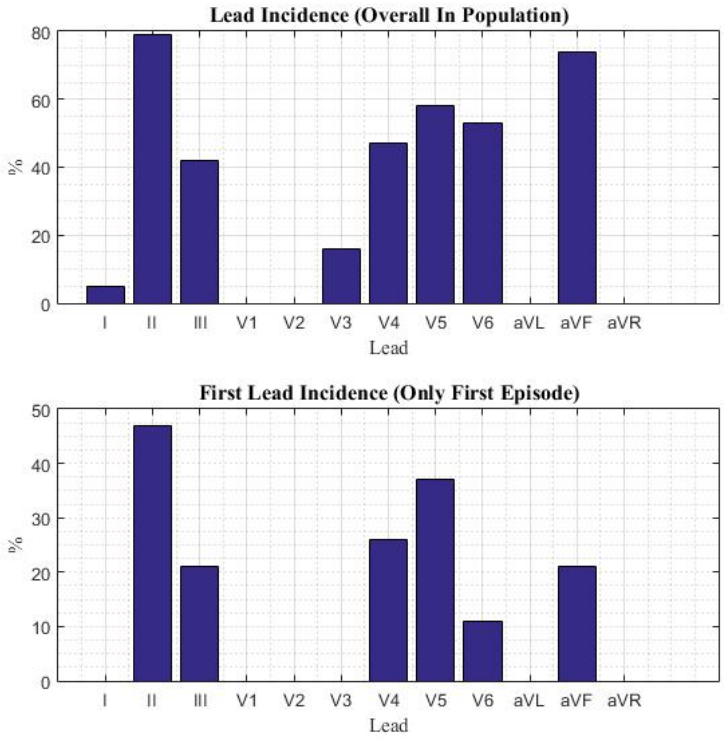

Figure 5.8 *Histograms of incidence of leads in all recordings and incidence of leads in the first ischemic episode in all recordings.*

5.3.2 Reduced Lead System Sensitivity

The sensitivities of different lead systems are shown in figure 5.9. A sensitivity of 100 % is achieved with the used 12-lead ECG system. The sensitivity of the standard limb leads yield a sensitivity of 59.7 % from the total combined episodes, mostly due to the contribution of leads II and aVF. Adding one of the following precordial leads, V_4, V_5, V_6, increases the detection sensitivity to 90.7 %, 68.2 % and 64.3 % respectively. When rationalizing the use of the single precordial lead in patients with RBBB by using V_5 on these patients instead of V_4, the 5-lead system sensitivity increases to 93.0 %. Here 5-lead system denote a 5-electrode system (3 limb electrodes + ground electrode + precordial electrode) which consists of limb leads and one precordial lead. Thus a 6-lead system would mean a 6-electrode system with limb leads and two precordial leads. With the two most sensitive precordial leads in a 6-lead system, namely V_4 and V_5, the sensitivity again increases to 96.1 %. A slight improvement up to a sensitivity of 97.8 % can be achieved using the 6-lead system and the same rationale with RBBB patients and lead V_4 as above and using a combination of V_5 and V_6 instead of V_4 and V_6 in RBBB patients.

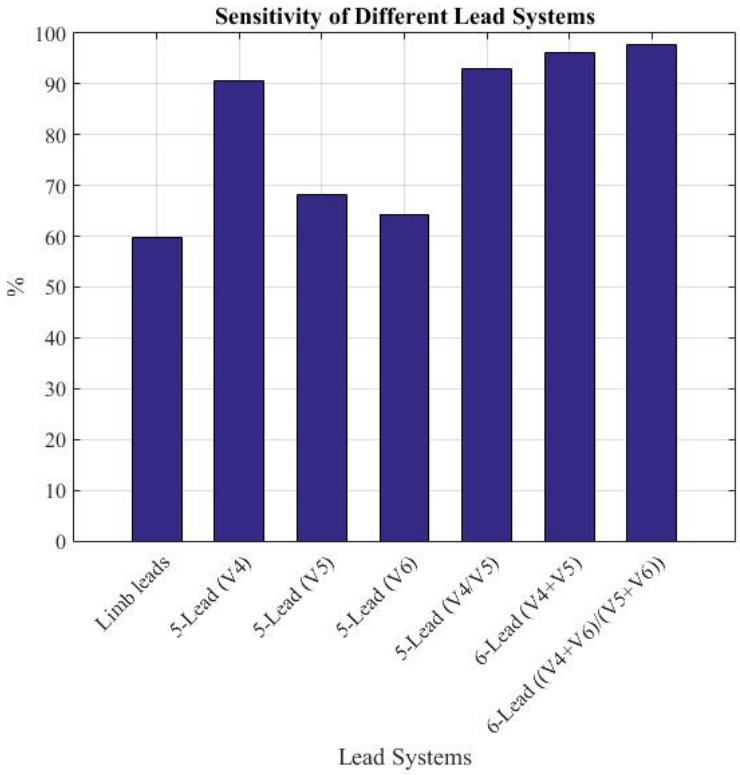

Figure 5.9 *Histogram comparing different ECG lead systems with different combinations of precordial leads. Denotations 'V4/V5' and '(V4 + V6)/(V5 + V6)' imply using different leads, in case of a RBBB patient where V4 should not be used so V5 is used instead.*

6. DISCUSSION

6.1 MI After a Non-cardiac Surgery

The findings regarding the incidence of PMI in a selected patient group retell the ones seen in literature. In addition the incidence of ischemia detected using continuous 12-lead ECG is similar to studies using the same methods. There was no incidence of ST-elevation in our study was which sets this study apart from several other studies such as London et. al's[39] but is inline with a study by Landesberg et al. [34] who had similar study setup as was used in our study. This suggests that the methods used have an impact on the results as well as the criteria used. An interesting result in our study was also that no significant ST-elevation was observed in the study group.

Apart from the previous studies a examination of the movement of the patients was also done in our study. However the results found regarding the findings are presented elsewhere.

6.2 12-Lead Sensitivity In ST-depression

The lead sensitivity findings derived using multiple analysis methods are similar to the ones seen in similar studies investigating lead sensitivities. The results of this thesis are enhancing the status of the left precordial leads (V_4 to V_6) to be the correct ones for ischemia monitoring. If continuous ST-monitoring is adopted, it is usually done with reduced number of leads compared to 12-lead ECG. The significance in selecting the correct precordial lead or leads is thus important, since it has been shown that a single precordial lead is capable of detecting over 90 % of ischemic episodes when used alongside with the limb leads.

It was of great interest to identify the leads that are the most sensitive to the first signs of ischemic changes as in a monitoring environment these leads would be the most beneficial ones guiding the early interventions. The first ischemic episode should be a cue to switch to 12-lead ECG for best detection of ischemic episodes.

In the study 6-lead combination when considering RBBB offered a very good sensitivity of 97.8 %. Thus, it seems that almost all ischemic events are detectable using two left side precordial leads, namely V_4 and V_6 or V_5 and V_6, in combination with the limb leads. Current AACN guidelines (see section 3.3.1), among several studies, recommend using leads II and V_5 after a non-cardiac surgery. This study points out that the sensitivity of V_4 exceeds the sensitivity of V_5 and could be considered more appropriate. However as pointed out in the results a single patient contributed greatly to the overall detection time of lead V_4 which might lead to a biased result. A 6-lead ECG should be used with two precordial leads, chosen from leads $V_4 - V_6$, for best sensitivity.

6.3 ECG tool in utilizing the data

The data utilization tool, made for data analysis purposes, was used heavily during this process. It was build to be specific to EkPro's output which meant that it could be used on other datasets as well for analysis. For the study as a whole, ECG tools role was significant. It allowed quick and broad view of each patients ECG, ST-levels and other essential parameters as a function of time. This was beneficial considering the amount of data at hand. Partly of this reason the ECG tool was also utilized in annotating the data with a cardiologist.

Using the tool to refine the data for further analysis in MATLAB turned out to be beneficial. However this was only because of the effort put in to the software which allowed outputting essential information with relative ease. Conducting the whole data visualization and analysis chain in MATLAB would have been obviously possible, but it is arguable if as usable, fast and flexible tool would have been created.

The tools development and functioning also posed weaknesses and obstacles. For example a lot of time was spent on issues not related to ECG analysis, but in the softwares functionality. Also, simple data manipulation operations might have taken more effort than if they would have been carriet out in MATLAB environment which for example has a better readiness for arithmetic manipulation of the data. Furthermore a great deal of future development of the tool is needed to make it more robust and versatile, although the program functioned quite reliably in the end of this thesis.

ECG tool also demonstrated how powerful it is to use a custom tool to inspect and visualize the data quickly for future algorithm development purposes as well as communication purposes with clinical experts.

6.4 Data Issues

A clear weakness of the study is the small size of the study population. Essentially this prevents one from doing significant conclusions based on the results. However it seems a clear result that a significant amount of ischemia remains undetected using the current standard of practice. Although the loss of data had a relatively small impact, many hours of data was still lost most likely alongside with ischemic episodes. This might have caused missed diagnosis of a ischemic patients due to bad timing of the cable being detached.

There is a lack of definitive criteria for postoperative ischemia when using Holter measurements as a method of continuous monitoring. Using different criteria shows different results and thus more standardizing should be done to improve this matter. While exploring the data with the ECG Tool, it became clear that slight changes in the criteria can greatly affect patient cardiac outcome. This is one reason why the creation of a data utilization tool was seen helpful for future development of ischemia monitoring. As an example

The protocol of changing the electrodes each day might have caused variations in the electrode positions. Since the precordial leads are located very near to each other, a slight misplacement can cause bias to the lead sensitivity.

Some bias was introduced to the the data because of large representation of lead V_4 in a single patient when considering the sensitivity of the leads. The relative amount of ischemic burden shown by lead V_4 in this single patient was notably large and thus had a biasing effect.

7. CONCLUSION

7.1 On Optimal Continuous Monitoring of Ischemia and Infarction

The goal of this thesis was to show the benefits of continuous ischemia monitoring compared to the current standard practice as well as ensuring the optimal amount of leads to do the monitoring and which leads to use.

Continuous ST-monitoring is currently poorly adopted and the results presented in this thesis show, that major part of the ischemic time remains undetected. Many hospitals, including HUCH, has a common practice of only measuring snapshot ECG's from non-cardiac postoperative patients. The dynamic nature of postoperative myocardial ischemia demand continuous monitoring, and a low sensitivity is achieved when only snapshot ECG's are used. Based on the data analysis it seems clear that the detected ischemic time increases as a function of monitoring time. Because of the restrictions set by wired measurements, continuous monitoring should be done using wireless measurements. Challenges regarding data loss, movement artifacts and more were tentatively assessed in this thesis. Although a notable degradation of the recordings was seen, the difference to normal wired measurements is likely small. In addition notifications of detachment of leads, poor signal quality or even current context of patient would most likely decrease the amount of lost data.

The importance of a preoperative ECG is significant. This allows using ST-monitoring on patients while knowing of any secondary ST-segment abnormalities. For example a preoperative ECG showing RBBB would guide the ST-monitoring to be using more preferably the left precordial leads, namely V_5 and V_6. Preoperative ECG allows also setting a baseline for the patients normal ST-level to which the change can be referenced to, for example in case of LVH.

The performance of the wireless measurements performed during this study turned out to be reasonable. Although a fair amount of data was lost because of situations where the leads were off, major part of the study group did not result in significant data losses. One of the reasons for data loss was intentional detachments of

the leads, which quite frankly is a hard problem to solve even in the conventional monitoring environment. The amount of artefact alarms was also low and most likely had minimum impact on the ischemia detection rate. However ischemia and the progression to infarction is a relatively slowly developing state, which would require continuous degradation of the signal to be completely missed. More relatively brief heart conditions such as many arrhytmias might suffer more from the movement artefacts as the artefact could mask the whole event much more easily. All in all it still must be noted that the study population at hand was relatively old and immobile because of the recent surgery on top of several other reasons. This leads to a question how the wireless measurement perform with a more active study population.

7.2 Future Deveploment Ideas and Suggestions

The detection specificity of the continuous measurements is a matter yet to be considered more deeply in the future. An obvious challenge for straightforward ST-monitoring is patients with RBBB or other conduction abnormality initially not known. If a prior diagnosis of the RBBB is available, setting up correct lead combination or configure the system correctly could be done manually so it does not take into account leads from V_1 to V_3. It would be beneficial if in situations where the RBBB is not prior knowledge, an algorithm would detect the RBBB and rather alarm because of the the RBBB, not because of possible ischemia. In patients who have for instance LBBB, ST-monitoring is rather questionable in the first place and more sophisticated methods to detect ischemia from the ECG for these patients should be considered. An important first step in developing the current ST-monitoring would be to classify the root cause of the repolarization abnormality and after that begin the ST-analysis. This approach would greatly reduce the amount of false ischemic alarms as well as reveal other repolarization abnormalities.

Ischemic ST-depression is usually concurrent with a HR-elevation. Thus, a more comprehensive multi-parameter index could be developed which considers also the changes in the HR-trend. The HR-trend could provide a continuous parameter supporting the decision making in the ST-analysis. Additionally a important part of the ST-analysis would be to have a pre-ECG available to set the baseline for the ST-values so the ST-deviation would be measured from this point.

Although the common practice of ischemia monitoring relies on ST-monitoring, it should be kept in mind, that the effect of ischemia to the ECG is much more comprehensive. This would mean expanding the analysis to other segments of the ECG from which the most promising area would be the QRS-complex. ECG is currently

rendered useless when a secondary ST-segment abnormality masks the ST-segment so that true ischemic changes cannot be seen.

Finally the use of accelerometer should be examined for possible benefits regarding also other information than posture information. For instance the current position and context of the patient would most likely benefit the care-givers to determine the current status of a ambulatory patient using wireless patient monitoring.

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