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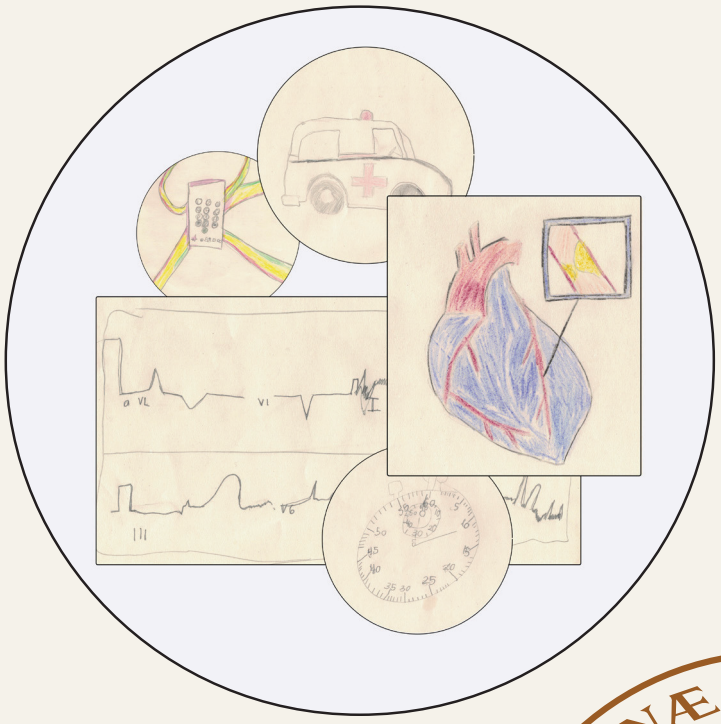

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Department of Clinical Physiology
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Title and subtitle Electrocardiographic detection of myocardial ischemia due to acute coronary occlusion

Background: A novel, graphical ECG decision support (Electrocardiographic Decision Support – Myocardial Ischemia, EDS-MI) as well as smartphone 12-lead ECG have the potential to be used in the early management of patients with suspected acute coronary occlusion. However, both methods lack clinical validation.

Other ECG findings, beyond ST elevation, may be used for differentiating ST-elevation myocardial infarction (STEMI) from other conditions with ST elevation.

With decreasing prevalence of STEMI at the emergency department (ED), the diagnostic yield of STEMI criteria in that setting may be low.

Methods: In study I, reference values for EDS-MI were established and tested by applying EDS-MI to ECGs from 360 control patients and 53 patients with acute coronary occlusion. The reference values were then tested in 135 patients with non-ischemic ST deviation and 117 patients with acute coronary occlusion (study II).

In study III, agreement between smartphone 12-lead ECG and conventional 12-lead ECG amplitudes was evaluated.

In study IV, the prevalences of reciprocal ST-segment changes, PR depression, ST-segment convexity, and terminal QRS distortion for patients diagnosed with acute coronary occlusion and for those patients with non-ischemic ST deviation were measured.

In study V, the diagnostic yield of STEMI amplitude criteria as well as extended STEMI criteria were evaluated in a large population of patients with chest pain at the ED.

Results: Study I: Reference values for the EDS-MI were defined, which showed improved sensitivity compared to STEMI criteria.

Study II: EDS-MI showed improved specificity compared to STEMI criteria.

Study III: In most patients, replacement of the Wilson central terminal by arm electrodes resulted in only small changes in chest-lead ST-J amplitudes. In patients with ST deviation in leads aVR or aVL, however, changes in precordial-lead ST-J amplitudes were substantial.

Study IV: Identification of true STEMI among patients with different ST-elevation etiology may be improved by considering reciprocal ST depression, ST depression in aVR and chest-lead PR depression.

Study V: The positive predictive value of both conventional and extended STEMI criteria in ED chest pain patients is low.

Implications: EDS-MI has been shown to have potential to serve as an automatic decision support for the assessment of patients with acute coronary syndrome. Further studies in unselected clinical chest pain populations are needed.

The difference between chest leads in smartphone 12-lead ECG and conventional chest leads must be taken into account if smartphone 12-lead ECG should be implemented in clinical practice.

STEMI ECG criteria have low diagnostic yield at the ED, and other information must be included in the assessment of patients with suspected STEMI in that setting.

Key words Electrocardiography; ST elevation myocardial infarction; decision support, smartphone ECG; diagnostic accuracy; acute coronary occlusion		
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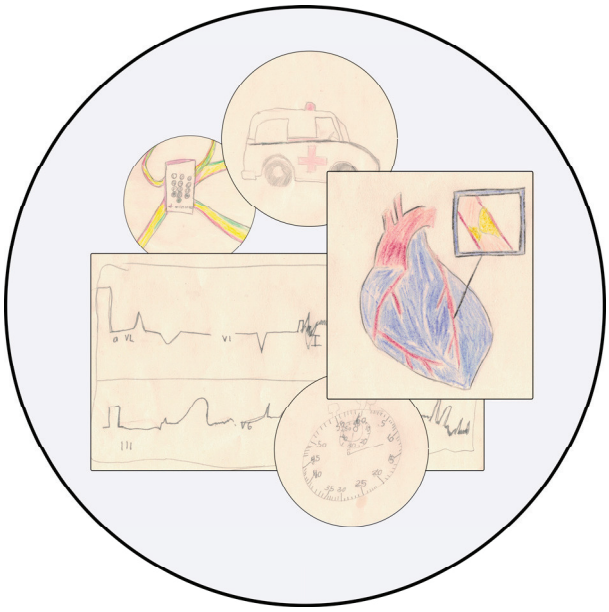

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To my family

It was true. Friday O'Leary had done all sorts of jobs in his time. He had been an inventor, a travelling musician, a sailor, another sailor, an American footballer, a fashion model, a Lego model, the King of Sweden, the Queen of Sweden, the first man never to have walked on the moon, a jet pilot, a detective, a mountaineer who explored mountains, a fountaineer who explored fountains, a ninja, a stunt-car racer, a film star, an earthworm-tamer, a famous French chef called Monsieur Canard, a TV presenter and a professional apple.
"But all those jobs were completely boring!" said Friday, jumping up so high he almost hit the sun with his face, narrowly missing it by only 149.599 million kilometres.
"What I've always wanted is to work in an office. That's the life for me!"

[From "Mr Gum and the Secret Hideout" by Andy Stanton]

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Populärvetenskaplig sammanfattning

I en värld med rasande snabb teknisk utveckling, bl.a. inom medicinsk teknik, spelar fortfarande en mer än 100 år gammal uppfinning en central roll i dagens sjukvård – EKG-apparaten. EKG registreras och tolkas på nästan alla nivåer inom sjukvården, från primärvård till högspecialiserad hjärtsjukvård. En särskilt framträdande roll har EKG för att upptäcka patienter med hjärtinfarkt. Hjärtinfarkt kan uppstå vid proppbildning i ett av hjärtats egna kärl (kranskärlen). Proppen i blodkärlet stoppar blodflödet och hjärtmuskeln drabbas av syrebrist. Ju längre tid som går från debut av symtom (ofta bröstsmärta) tills att kärlet kan öppnas, desto fler hjärtmuskelceller dör och risken att patienten dör ökar. Tillståndet kan behandlas genom att man exempelvis med hjälp av en långsmal ballong öppnar upp kärlet i samband med röntgen av kranskärlen (s.k. ”ballongsprängning”). Hjärtinfarkt kan diagnosticeras med hjälp av hjärtspecifika blodprover. Oftast behöver beslut om akut kranskärlsröntgen tas innan svaren på blodproverna finns tillgängliga. Beslutet om kranskärlsröntgen får då istället tas utifrån information från patienten och fynd på EKG. Korrekt tolkning av EKG är således av central betydelse för att patienten ska få rätt behandling.

Syrebristen i hjärtmuskeln som uppstår i samband med en hjärtinfarkt ger upphov till förändringar i EKG-kurvan. Särskilda kriterier för att ställa diagnosen finns, där förskjutning av den s.k. ST-sträckan på EKG intar en viktig roll (ST-höjningsinfarkt). EKG-diagnostik av hjärtinfarkt är associerat med flera utmaningar. Exempelvis beror de typiska EKG-förändringarna (ST-höjning) på var inom hjärtat syrebristen uppstår och de kan till och med helt saknas. Andra utmaningar är att kunskaperna inom EKG-tolkning bland sjukvårdspersonal är bristfälliga och presentationssättet av EKG onödigt komplicerat. Andra tillstånd än hjärtinfarkt kan också ge upphov till förändringar på EKG, som är snarlika de som ses vid hjärtinfarkt. Kranskärl kan också tillfälligt öppnas för att sedan stängas igen, vilket gör att EKG-fynden förändras.

I min avhandling, vilken består av fem arbeten, behandlas olika EKG-aspekter vid hjärtinfarkt.

Arbete I och II – Electrocardiographic Decision Support – Myocardial Ischemia (EDS-MI)

I arbete I och II studerades en automatisk metod tänkt att användas som stöd vid EKG-tolkning av akut hjärtinfarkt (Electrocardiographic Decision Support – Myocardial Ischemia, EDS-MI). I EDS-MI räknas informationen i EKG så att de delar av hjärtat som är utsatta för syrebrist kan markeras på en karta över hjärtat.

Tidigare studier har visat att metoden kan avgöra vilket av de tre kranskärlen som är stängt. Om metoden även skulle kunna användas för att upptäcka hjärtinfarkt – inte bara för att beskriva var hjärtinfarkten sitter när man vet att den finns – skulle metoden få större betydelse vid handläggningen av patienter med misstänkt hjärtinfarkt. Syftet med de två första arbetena var därför att utveckla EDS-MI så att metoden kan användas även för att upptäcka hjärtinfarkt. I arbete I togs kriterier för EDS-MI fram för att särskilja friska individer från patienter med akut hjärtinfarkt. I arbete II justerades metoden och testades på patienter med känd hjärtinfarkt och på patienter med EKG-förändringar av annan orsak än hjärtinfarkt. EDS-MI visade sig kunna särskilja hjärtinfarkt från andra diagnoser med högre tillförlitlighet än nuvarande EKG-kriterier, men metoden behöver studeras ytterligare i verkliga situationer.

Arbete III – EKG-registrering med hjälp av smartphone

I arbete III studerades en potentiell felkälla vid användning av smartphone för att registrera ett fullständigt EKG. En metod för att registrera ett fullständigt EKG med hjälp av smartphone har beskrivits av en annan forskargrupp. EKG-registrering med smartphone skulle kunna möjliggöra mycket tidig upptäckt av hjärtinfarkt och kunna fungera som ett substitut för EKG-apparater i områden där sådana saknas. Detta sätt att registrera EKG är dock begränsat av att inte ha tillgång till alla delar som finns i en riktig EKG-apparat. Skillnader jämfört med konventionellt EKG kan därför uppstå. Med kännedom om hur de olika delarna (avledningarna) av EKG skapas, kan man utifrån ett riktigt EKG beräkna hur EKG skulle ha sett ut om man istället hade registrerat det med smartphone-tekniken. Smartphone-EKG-utseendet beräknades för ett stort antal patienter med blandade diagnoser. För de flesta patienter var skillnaden mellan vanligt EKG och smartphone-EKG liten, men i fall där betydande EKG-förändringar fanns, exempelvis i fall av hjärtinfarkt, hade EKG-bilden påverkats betydligt om den hade registrerats enligt smartphone-metoden.

Arbete IV – andra EKG-förändringar än ST-höjning

I det fjärde arbetet studerades andra EKG-förändringar än höjning av ST-sträckan och huruvida dessa kan användas för att särskilja hjärtinfarkt från andra tillstånd som kan ge upphov till ST-höjning. Förekomsten av särskilda EKG-förändringar studerades hos patienter med känd hjärtinfarkt och hos patienter med antingen inflammation i hjärtsäcken/hjärtmuskeln, stressutlöst hjärtmuskelsjukdom (”takotsubo kardiomyopati”) eller s.k. tidig repolarisation. Några av tecknen som studerades talade starkt för hjärtinfarkt och några tecken talade istället för annan orsak till ST-höjning. EKG-tolkning vid misstänkt hjärtinfarkt bör därför omfatta mer än bara bedömning av ST-sträckan.

Arbete V – EKG-kriterier på akutmottagningen

Hur väl nuvarande EKG-kriterier fungerar för att upptäcka hjärtinfarkt på akutmottagningen är sparsamt beskrivet i litteraturen. Nuförtiden skickas de flesta patienter med stark misstanke om hjärtinfarkt direkt till kranskärlsröntgen och kommer därför sällan till akutmottagningen. Detta kan medföra att de patienter med hjärtinfarkt som väl hamnar på akutmottagningen har mindre typiska symptom och/eller mindre typiska EKG-förändringar. I arbete V studerades det diagnostiska värdet av nuvarande EKG-kriterier på just akutmottagningen i ett mycket stort patientmaterial. I små studier har en utvidgning av EKG-kriterierna visats sig kunna förbättra upptäckten av hjärtinfarkt. I arbete V studerade vi därför även om dessa utvidgade kriterier kunde förbättra diagnostiken. Vi fann att nuvarande EKG-kriterier har begränsad förmåga att förutsäga att en patient har hjärtinfarkt till följd av att ett kranskärl har stängt. Flera patienter med hjärtinfarkt och stängt kranskärl uppfyller inte dessa kriterier. De utvidgade kriterierna hittade visserligen fler patienter med hjärtinfarkt, men gav också fler utfall som felaktigt angav att hjärtinfarkt förelåg. Denna studie styrker ytterligare behovet av att andra EKG-fynd än ST-höjning tas med i bedömningen vid misstänkt hjärtinfarkt.

Sammanfattning

Automatiska beslutstöd kan ha en plats i diagnostiken av akut hjärtinfarkt, men EDS-MI behöver studeras ytterligare i verkliga situationer.

Registrering av EKG med smartphone kan medföra betydande skillnader mot vanligt EKG, vilket måste tas hänsyn till när sådana metoder tas i bruk.

Andra EKG-fynd än ST-höjning på EKG bör användas för att särskilja patienter med hjärtinfarkt från patienter med annan orsak till ST-höjning.

På akutmottagningen är nuvarande kriterier för ST-höjningsinfarkt undermåliga för att upptäcka patienter med hjärtinfarkt till följd av stängda kranskärl och behöver förbättras.

List of publications

I. The Olson method for detection of acute myocardial ischemia in patients with coronary occlusion. **Lindow T**, Olson CW, Swenne CA, Man S, Pahlm O. Journal of Electrocardiology. 2017 (50): 74 – 81.

II. Diagnostic accuracy of the Electrocardiographic Decision Support - Myocardial Ischaemia (EDS-MI) algorithm in detection of acute coronary occlusion. **Lindow T**, Pahlm O, Olson CW, Khoshnood A, Ekelund U, Carlsson M, Swenne CA, Man S, Engblom H. European Heart Journal Acute Cardiovascular Care 2018:2048872618768081.

III. Chest-lead ST-J amplitudes using arm electrodes as reference instead of the Wilson central terminal in smartphone ECG applications: Influence on ST-elevation myocardial infarction criteria fulfillment. **Lindow T**, Engblom H, Khoshnood A, Ekelund U, Carlsson M, Pahlm O. Annals of Noninvasive Electrocardiology 2018;23:e12549.

IV. Electrocardiographic changes in the differentiation of ischemic and non-ischemic ST elevation. **Lindow T**, Pahlm O, Khoshnood A, Nyman I, Manna D, Engblom H, Touborg Lassen A, Ekelund U. Scandinavian Cardiovascular Journal 2019;1-8.

V. Low diagnostic yield of ST-elevation myocardial infarction amplitude criteria in chest pain patients at the emergency department. **Lindow T**, Engblom H, Pahlm O, Carlsson M, Lassen AT, Brabrand M, Lundager Forberg J, Platonov PG, Ekelund U. (Submitted)

Summary

Background: A novel, graphical, computerized ECG algorithm (Electrocardiographic Decision Support – Myocardial Ischemia, EDS-MI) as well as smartphone 12-lead ECG have the potential to be used for early detection of patients with acute coronary occlusion. However, both methods lack clinical validation.

Several other ECG findings, beyond ST elevation, may be used for differentiating ST-elevation myocardial infarction (STEMI) from other conditions with ST elevation.

When patients with suspected STEMI are transferred directly to the coronary care unit, prevalence of STEMI at the emergency department (ED) decreases, which may affect the diagnostic yield of ECG criteria for STEMI.

Methods: In study I, reference values for EDS-MI were defined by applying EDS-MI to ECGs from 360 patients without acute ischemia and subsequently tested on 53 patients with acute coronary occlusion.

In study II, the reference values were then tested on ECGs from 135 patients with non-ischemic ST deviation and 117 patients with acute coronary occlusion.

In study III, agreement between smartphone 12-lead ECG and conventional 12-lead ECG amplitudes was evaluated.

In study IV, prevalences of reciprocal ST depression, PR depression, ST-segment convexity, and terminal QRS distortion for patients diagnosed with STEMI and for those with non-ischemic ST deviation were measured.

In study V, the diagnostic yield of STEMI amplitude criteria as well as extended STEMI criteria were studied in a large, unselected population of patients with chest pain at the ED.

Results: Study I: Reference values for the EDS-MI were defined. When these were used, EDS-MI showed improved sensitivity compared to STEMI criteria.

Study II: EDS-MI showed improved specificity compared to STEMI criteria.

Study III: In most patients, replacement of the Wilson central terminal by arm electrodes resulted in only small changes in chest lead ST-J amplitudes. In some patients with ST deviation in leads aVR or aVL, however, changes in precordial-lead ST-J amplitudes were substantial.

Study IV: Identification of true STEMI among patients with different ST-elevation etiology may be improved by considering reciprocal ST depression, ST depression in aVR and chest-lead PR depression.

Study V: The positive predictive value of both conventional and extended STEMI criteria in ED chest pain patients is low.

Implications: EDS-MI has been shown to have potential to serve as an automatic decision support for the assessment of patients with suspected acute coronary occlusion, but further studies in unselected clinical chest pain populations are needed.

The use of either the right or left arm as reference for the chest leads in smartphone 12-lead ECG may result in clinically important differences in chest lead amplitudes compared to conventional ECG recording. This must be taken into account if smartphone 12-lead ECG is implemented in clinical practice.

Other findings than ST elevation should be included in ECG interpretation of suspected STEMI cases.

STEMI ECG criteria have low diagnostic yield at the ED, and other information must be included in the assessment of patients with suspected STEMI in that setting. Improved ECG criteria or other diagnostic methods are needed to improve detection of patients with acute coronary occlusion.

Abbreviations

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
CMR	Cardiovascular magnetic resonance imaging
ECG	Electrocardiogram
ED	Emergency department
EDS-MI	Electrocardiographic Decision Support – Myocardial Ischemia
LAD	Left anterior descending coronary artery
LCx	Left circumflex coronary artery
LBBB	Left bundle branch block
LV	Left ventricle
LVH	Left ventricular hypertrophy
LR+/-	Positive/negative likelihood ratio
NPV	Negative predictive value
NSTEMI	Non-ST elevation myocardial infarction
MaR	Myocardium at risk
MPI	Myocardial perfusion imaging
PCI	Percutaneous coronary intervention
PPV	Positive predictive value
RCA	Right coronary artery
STEMI	ST-elevation myocardial infarction
mV, µV	millivolt, microvolt
WCT	Wilson central terminal

Thesis at a glance

Title	Primary aim	Main results	Conclusions
The Olson method (EDS-MI)* for detection of acute myocardial ischemia in patients with coronary occlusion	To determine the upper limit of normal of the ischemic scores using EDS-MI.	Reference values for EDS-MI were defined. EDS-MI showed improved sensitivity compared to STEMI criteria.	EDS-MI needs to be tested in patients with different etiology of ST deviation.
Diagnostic accuracy of the electrocardiographic decision support – myocardial ischemia (EDS-MI) algorithm detection of acute coronary occlusion	To optimize the diagnostic accuracy of EDS-MI in patients with acute coronary occlusion and patients with non-ischemic ST deviation.	EDS-MI showed improved diagnostic accuracy compared to STEMI criteria.	EDS-MI has a potential to be used as an automatic decision support in detection of acute coronary occlusion, but needs to be validated in a larger, unselected chest pain population.
Chest-lead ST-J amplitudes using arm electrodes as reference instead of the Wilson central terminal in smartphone ECG applications: Influence of ST-elevation myocardial infarction criteria fulfillment	To compare the chest-lead ST-J amplitudes using either the right or the left arm electrode as reference to those in the conventional 12-lead ECG.	In most cases, replacement of the Wilson central terminal with either the right or left arm results in only small changes in chest-lead amplitudes but significant changes occur in selected cases.	The difference between chest leads in smartphone 12-lead ECG and conventional chest leads must be taken into account if smartphone 12-lead ECG should be implemented in clinical practice.
Electrocardiographic changes in the differentiation of ischemic and non-ischemic ST elevation	To study whether reciprocal ST-segment changes, PR depression, ST-segment convexity or terminal QRS distortion can discriminate STEMI from non-ischemic conditions with ST elevation.	Identification of true STEMI among patients with different ST-elevation etiology may be improved by considering several other ECG findings in the diagnostic process.	It is important to consider reciprocal ST depression, ST depression in aVR and PR depression in the chest leads when differentiating STEMI from other conditions with ST elevation.
Low diagnostic yield of ST-elevation myocardial infarction amplitude criteria in chest pain patients at the emergency department	To evaluate the diagnostic accuracy of conventional and extended ECG criteria for STEMI in the detection of AMI with coronary occlusion.	A minority of patients with AMI and coronary occlusion met STEMI criteria. Most patients who met STEMI criteria did not have AMI nor coronary occlusion.	The diagnostic yield of conventional and extended STEMI criteria in chest pain patients at the emergency is low.

*In paper I, Electrocardiographic Decision Support – Myocardial Ischemia (EDS-MI) was referred to as "the Olson method".

Abbreviations: EDS-MI: Electrocardiographic Decision Support – Myocardial; ECG: electrocardiography; STEMI: ST-elevation myocardial infarction; AMI: acute myocardial infarction.

1. Introduction

In an era of rapid technology development and advanced diagnostic methods, a more than hundred-year-old invention maintains a pivotal role in the management of patients with cardiovascular disease, acute ischemic heart disease in particular – the electrocardiograph.

Cardiovascular disease is the most common cause of death worldwide, and approximately 10 million people die from ischemic heart disease each year [1]. In Europe, coronary heart disease accounts for approximately 20% of all-cause deaths among both men and women [2]. Although the differences between countries are large, there is an overall trend of decreasing mortality due to ischemic heart disease across Europe over the last decades [3]. One explanation is the introduction of percutaneous coronary intervention (PCI) as the primary treatment option in patients with ST-elevation myocardial infarction (STEMI), which is superior to thrombolysis regarding reperfusion rate, reinfarction and short-term mortality [4]. Another explanation is an increased use of preventive treatments and risk factor control [5]. In Sweden, the decline in short-term mortality in patients with myocardial infarction observed between 1995 and 2010 seems to have plateaued for all age groups, with a mean 30-day mortality at approximately 4% [6, 7]. In the US, the proportion of STEMI compared to non-ST elevation myocardial infarction (NSTEMI) has been reported to decline (40% in 2001 vs. 27% 2011) [8], whereas in Sweden, the proportions have been stable during the last decade (STEMI ~30%) [6, 7]. The mean age for patients with myocardial infarction is higher for women than for men [6, 9]. Women also have more comorbidities, longer door-to-balloon time than men, a longer time from symptom to first medical contact [9], and a higher incidence of silent or unrecognized myocardial infarction [10].

When a coronary artery becomes acutely occluded, it is important to restore blood flow as soon as possible in order to reduce mortality [11-13]. Detection of an acute coronary occlusion is dependent on correct interpretation of the electrocardiogram (ECG). This thesis addresses different electrocardiographic aspects on detection of

myocardial ischemia due to acute coronary artery occlusion: improved detection by the use of an automatic visual decision support, a potential pitfall in using smartphone-based 12-lead ECG, the use of different electrocardiographic findings when differentiating ST elevation due to acute coronary occlusion from non-ischemic conditions, and the diagnostic accuracy of conventional, as well as extended ECG criteria, for acute myocardial infarction (AMI) and coronary occlusion at the emergency department (ED).

1.1 Basics of electrocardiography

An electrical potential, a "membrane potential" is present across almost all cell membranes. At rest, cardiac myocytes have a negative membrane potential because of the distribution of ions across the cell membrane: the outside of the cell is positively "charged" relative to the inside of the cell [14]. The concentration of potassium ions (K^+) is higher inside the cell than outside, giving rise to a chemical gradient for diffusion of K^+ out of the cell. If K^+ follows this gradient, the membrane potential will become less negative, i.e. it will depolarize. Sodium (Na^+) and calcium ions (Ca^{2+}) however, have higher concentrations outside the cell and "want to" move into the cell. If these ions would move in and out of the cell freely, the membrane potential would eventually vanish. In order to maintain the resting membrane potential – to counteract the chemical gradients – ion pumps exchange ions over the cell membrane. For example, the Na^+/K^+-ATP pump moves 2 K^+ into the cell in exchange of 3 Na^+ out of the cell, resulting in a net loss of positively charged ions inside the cell [15]. Thanks to this pump, Na^+ that has followed its chemical gradient can be removed from the cell, and K^+ can be regained.

It is important to maintain the resting membrane potential unless the cell is deliberately excited. During ischemia the resting membrane potential is decreased, which affects the function of some of the important ion channels and pumps (*section 1.2.1*). A myocyte is excited when an action potential, i.e. a sudden and large change in membrane potential, occurs. Some myocytes are specialized in that they exhibit pacemaker activity, i.e. they depolarize spontaneously. When the membrane potential of such a cell reaches a certain threshold, an action potential is generated. The action potential of the pacemaker cell depolarizes neighboring cells, which starts a "wave of depolarization" through the conduction system, and eventually the myocytes. When a myocyte cell membrane is depolarized to a certain threshold, fast Na^+ channels and slow Ca^{2+} channels open while K^+ channels close. The rapid inflow of Na^+ (and the

ceased outflow of K^+) quickly results in a decreased membrane potential. The inside of the cell now becomes slightly positively charged relative to the outside of the cell. This is followed by a short repolarization when Na^+ channels close again and specific K^+ channels open. The depolarized state is maintained by continued inflow of Ca^{2+}. When the Ca^{2+} inflow eventually ceases, K^+ channels open and K^+ ions move out of the cell and the negative resting membrane potential is restored – the myocyte is repolarized (Fig. 1) [15].

Depolarization and repolarization of the myocytes cause potential differences between different parts of the heart. Since the human body is electrically conductive, electrical potentials can be measured on the surface of the skin. These potentials have both magnitude and direction, i.e. they can be represented by a vector that changes (in both magnitude and direction) during the cardiac cycle [16].

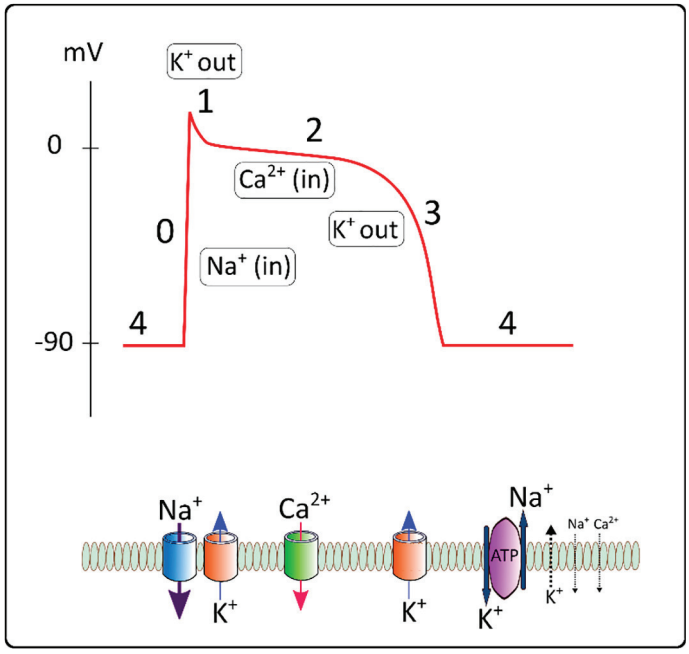

Figure 1. A simplified description of the action potential and the resting membrane potential in a cardiac myocyte.

Upper image: At rest, the membrane potential is approximately -90 mV. The opening of fast Na^+ channels is responsible for the rapid change of membrane potential (phase 0), which is followed by a short repolarization (phase 1). Slow Ca^{2+} channels maintain the depolarization (phase 2). When K^+ channels open, the membrane repolarizes (phase 3) and eventually reaches the resting membrane potential (phase 4).

Lower image: At rest, the ions aim to follow their chemical gradient, K^+ out of the cell, and Na^+ and Ca^{2+} into the cell. Energy (adenosine triphosphate (ATP)) is needed to restore and maintain the resting membrane potential.

1.1.1 Historical perspective

More than a century ago, Waller showed that voltage differences between two sites on the skin changed in pace with the heartbeats [17], but the tracings, however, were of poor quality [16]. When Willem Einthoven invented the string galvanometer in the beginning of the 20th century, the ECG waveforms could be recorded (voltage measurements as a function of time) [18-20]. In 1924, Einthoven was awarded the Nobel Prize in Physiology or Medicine for his invention [21]. By describing the electrical activation within the heart, Thomas Lewis moved Einthoven's invention into the clinical setting [22, 23].

With the use of electrodes on the arms and on the left leg, three leads could be recorded: lead I describing the potential difference between the left arm and the right arm, lead II describing the potential difference between the left leg and the right arm, and lead III describing the potential difference between the left leg and the left arm (Fig 2).

When the Wilson central terminal (WCT) was introduced – the mean potential at the right arm, left arm and left leg – three additional limb leads could be recorded (VR, VL and VF), as well as the precordial leads (V1 – V6) (Fig. 3). Leads VR, VL and VF were replaced later by their augmented counterparts aVR, aVL and aVF according to Goldberger [24, 25]. aVR describes the potential difference between the right arm and the mean potential at the left arm and left leg, aVL describes the potential difference between the left arm and the mean potential at the right arm and the left leg, and aVF describes the potential difference between the left leg and the mean potential at the right and left arm [26]. The potential at aVL can also be described as (I – III)/2, aVF as (II + III)/2, and aVR as – (I + II)/2. The chest leads describe the potential difference between a chest electrode (C1, C2…, or C6) and the WCT (Fig. 2). The combination of Einthoven's 3 original limb leads (I, II, III), the 3 augmented Goldberger leads (aVR, aVL, aVF) and the 6 precordial leads (V1 – V6) constitute the standard 12-lead ECG. In this lead system, only eight of them are truly unique leads. Six of these are the precordial leads. The 6 limb leads, however, are very closely related. If only 2 of them are recorded, the remaining 4 can be calculated. If leads I and II are recorded, lead III can be calculated as II – I, aVR as – (I + II)/2, aVL as I - II/2 and aVF as II – I/2 [26].

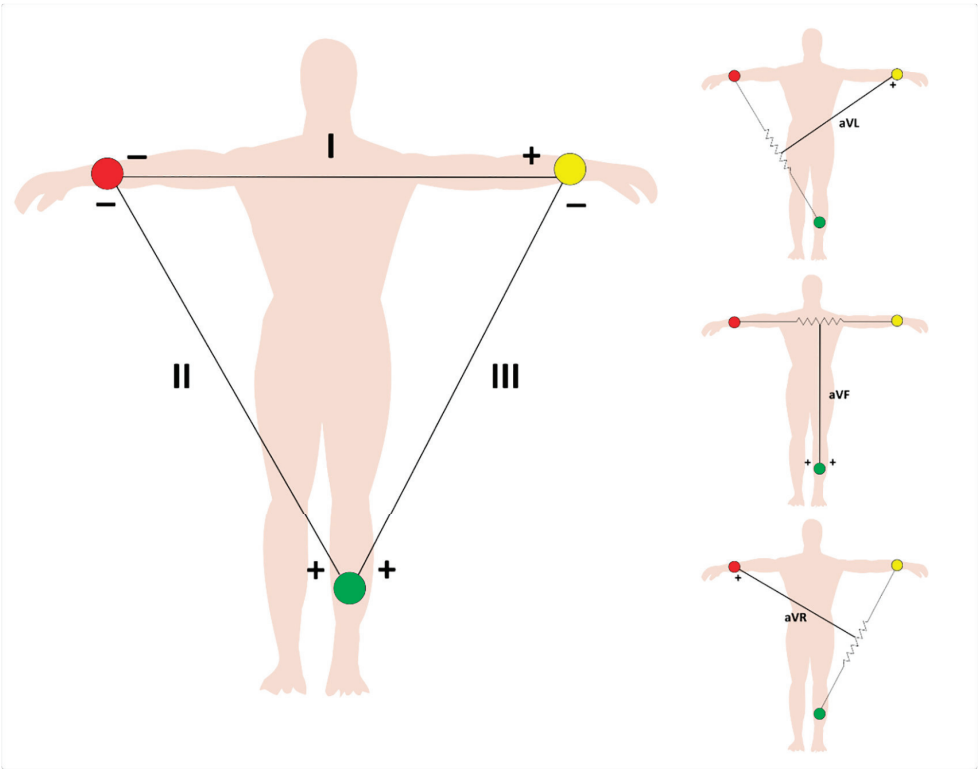

Figure 2. Generation of the six limb leads in a 12-lead ECG. When recording a 12-lead ECG, 9 electrodes (and one ground electrode) are used. Lead I describes the potential difference between the left and right arm electrodes, lead II describes the difference between the potentials at the left leg and the right arm electrodes and lead III between the potentials at the left leg and left arm electrodes. aVL describes the potential difference between the potentials at the left arm and the mean potential at the left leg and right arm electrodes, aVF describes the difference between the potential at the left leg electrode and the mean potential at the arm electrodes, and aVR describes the difference between the potential at the right arm electrode and a mean potential at the left-sided electrodes.

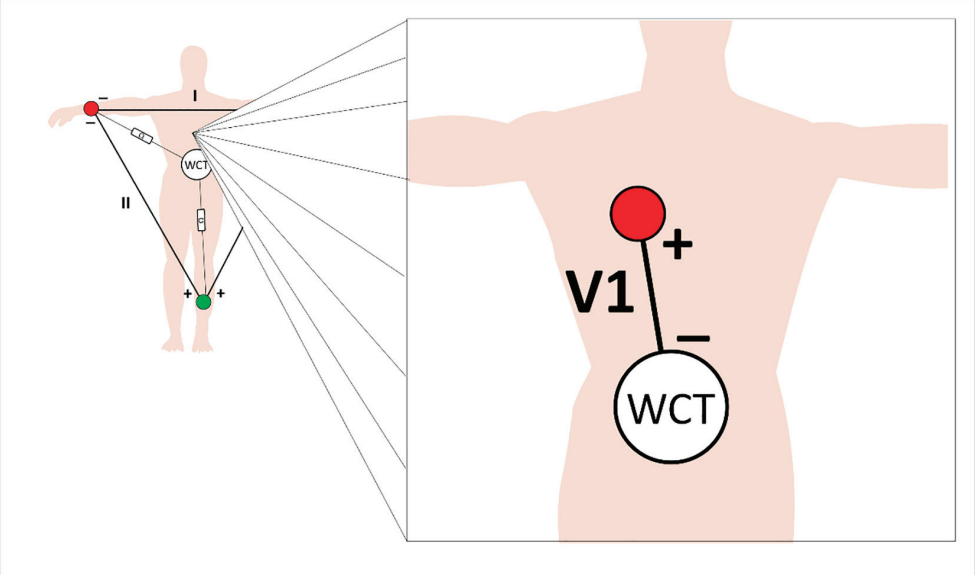

Figure 3. Generation of the chest leads in the 12-lead ECG. The six chest leads use a common reference electrode, the Wilson central terminal (WCT), which is the mean potential at the right arm, the left arm and the left leg electrodes. For example, V1 describes the difference between the potential at the first chest electrode and the WCT.

1.2 Pathophysiology and presentation of acute myocardial infarction

The most common cause of AMI is disruption of an atherosclerotic plaque [27, 28] (Fig. 4). Atherosclerotic disease is, for example, associated with age, male sex, smoking, hypertension, diabetes and genetics. Atherosclerotic lesions, contain lipid-rich material, inflammatory cells and proliferated smooth muscle cells within the intimal layer of an artery, which to varying degrees leads to narrowing of the lumen [27, 29]. These lesions predominantly appear at arterial bifurcations. Some plaques remain asymptomatic, but some, usually referred to as “vulnerable plaques”, either rupture or become eroded, which in turn may be complicated by intraluminal thrombosis and hemorrhage into the disrupted plaque. Although, the risk of complete arterial occlusion is higher for plaques that result in severe stenoses, the majority of AMI are caused by non-obstructive lesions [30].

The subsequent reduction of blood flow due to coronary occlusion results in myocardial ischemia. In the very early phases of myocardial ischemia (<15 min) glycogen levels diminish and myofibrils are relaxed. During prolonged ischemia glycogen levels are depleted, myofibrils are stretched/damaged, mitochondrial swelling occurs, the cell membranes are disrupted and myocardial cells are eventually irreversibly damaged [31]. Reimer and Jennings described, in the 1970-ies, the so-called "wavefront phenomenon" of ischemic necrosis in an experimental study of coronary artery occlusion in dogs. The myocardial injury occurred first at the subendocardial layers, and later subepicardially. Infarct size was increased with prolonged ischemia [32, 33]. In another experimental study, Maroko et al showed that reperfusion after coronary artery occlusion resulted in salvaged myocardium [34], and an incentive for developing methods for acute revascularization was established. A few years later, the first use of intracoronary thrombolytics was described [35], followed by larger trials which confirmed the benefits on mortality in patients with AMI [36]. Later on, thrombolytics were replaced by PCI as the primary treatment strategy for STEMI patients [4]. Despite the positive effect on mortality in STEMI patients since the introduction of PCI – first the bare metal stents and later the drug-eluting stents – mortality is still substantial. Mortality among STEMI patients in Sweden is approximately 10% during the first year after STEMI [6, 37], and remains elevated during long-term follow-up [38].

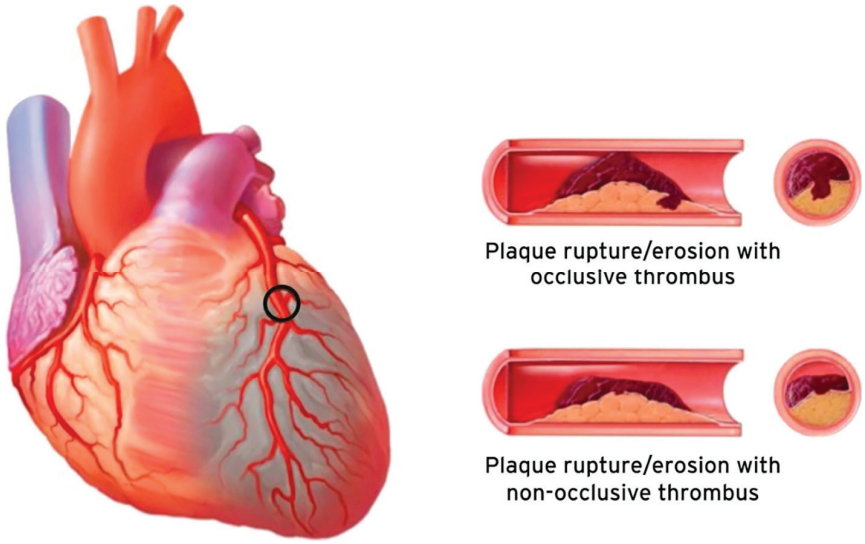

Figure 4. Acute myocardial infarction is most often caused by plaque rupture/erosion within a coronary artery, in this case, the left anterior descending artery (*left image*). The plaque rupture precipitates thrombotic formation, which may occlude the vessel (*upper right image*). Reprinted with permission from Thygesen et al [28].

Acute coronary syndrome (ACS) refers to signs and symptoms associated with either unstable angina or AMI (with or without ST elevation). In the acute setting, the physician needs to determine whether ACS is present, determine the risk for severe complications and decide on adequate treatment. Symptoms indicative of ACS include chest or epigastric pain or discomfort, sometimes radiating to the arms or jaws, dyspnea or fatigue [28]. The presentation may vary from atypical chest pain, or even no symptoms, and non-specific ECG changes to severe ST elevation and cardiogenic chock. The characteristics of the chest pain, however, have limited value in diagnosing ACS. In a systematic review of prospective studies on diagnostic test accuracy among patients admitted to the ED with symptoms suggestive of ACS, the positive likelihood ratio was statistically significant only for pain radiation, dynamic chest pain pattern during the last 24 hours and pain that was described to be similar to prior episodes of ischemia. The positive likelihood ratio for "typical" chest pain, for example, was not statistically significant and the effect or absence of effect of nitroglycerine could neither exclude nor diagnose ACS [39]. Several non-ischemic conditions, both benign and malignant, may present with similar symptoms, such as pericarditis, aortic dissection, pulmonary embolism, musculoskeletal pain, esophageal diseases or anxiety [40].

When determining the risk of the patient, several scoring systems have been developed [41-43]. Biomarkers, such as cardiac troponins, are used to establish the diagnosis of myocardial infarction [28]. Myocardial ischemia due to acute coronary occlusion should be detected as early as possible in order to restore blood flow [11, 44] and reduce morbidity and mortality [45]. Therefore, decision of immediate treatment strategies, such as acute revascularization, must often be made before cardiac biomarkers are available and is usually based on electrocardiographic findings [28, 46]. According to European guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, ECG recording should be performed within 10 minutes and a decision of reperfusion therapy should be made "*as soon as possible*" [46, 47]. The goal of recording an ECG within 10 minutes is however rarely accomplished. A prehospital ECG was obtained within 10 minutes after ambulance arrival, in 29% of men and 14% of women, in a retrospective study of 539 STEMI patients [48].

1.2.1 Electrophysiology in the ischemic myocyte

In 1879, Burdon-Sanderson and Paige noted that a mechanical injury to the surface of a frog´s heart resulted in positive charges in the injured compared to the non-injured sites [49]. Approximately 40 years later, ischemic ST-segment changes in the ECG were described by Pardee (Fig. 5), who described transient ST elevation during

the acute phase of myocardial infarction [50]. The mechanisms of ST-segment deviation during acute ischemia were explained many years later [49, 51].

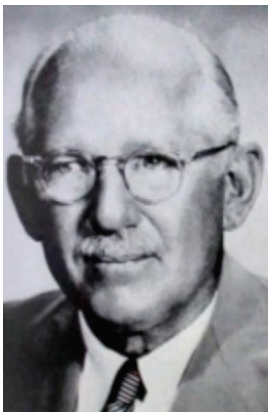

Figure 5. Harold Ensign Bennet Pardee (1886-1973) first described the ECG changes in myocardial infarction in humans in his paper "An electrocardiographic sign of coronary artery obstruction" published in Archives of Internal Medicine in 1920 [52]. Reprinted with permission from Kligfield et al [50].

Ischemia (inadequate blood supply) results in cellular metabolic dysfunction through ATP depletion and accumulation of lactic acid. Specific K^+ channels, which are normally inactivated by ATP, open. The Na^+/K^+-ATP pump also ceases to produce a net outflow of positively charged ions [53, 54]. The resting membrane potential in an ischemic myocyte is therefore relatively less negative than non-ischemic myocytes. During ischemia, the fast Na^+ channels are inactivated, and depolarization is dependent on the slow Ca^{2+} channels, and this affects the action potential amplitude and duration. The ischemic changes can be summarized as a less negative resting membrane potential, a slowed depolarization, a lower amplitude and shorter duration of the action potential [55]. The difference in resting potential and action potential between ischemic and non-ischemic cells results in electrical currents both during electrical diastole and systole.

Acute occlusion of a coronary artery causes serial ECG changes that affect not only the ST segment but also the QRS and T waves. The first ECG sign following an acute coronary occlusion may be "hyperacute" (tall, symmetrical and peaked) T waves [56], sometimes not absolutely, but relatively increased in amplitude [57]. These changes are soon followed by ST-segment elevation. The ST-segment changes during ischemia are not entirely understood but can be explained by the concept of "*diastolic and systolic injury currents*" (Fig. 6). The diastolic injury current relates to the flow of currents from the ischemic, partially depolarized myocardium towards the non-ischemic regions, resulting in a depressed TQ segment [58], which presents as an elevation of the ST segment due to compensation of a negative shift in the TQ

segment by the ECG recorder. The systolic injury current can be described by a negatively charged area within the ischemic myocardium compared to non-ischemic myocardium, resulting in an injury current directed towards the ischemic region [54]. With ongoing ischemia, changes to the terminal part of the QRS complex occur, for example loss of S wave or increased R-wave amplitude [59].

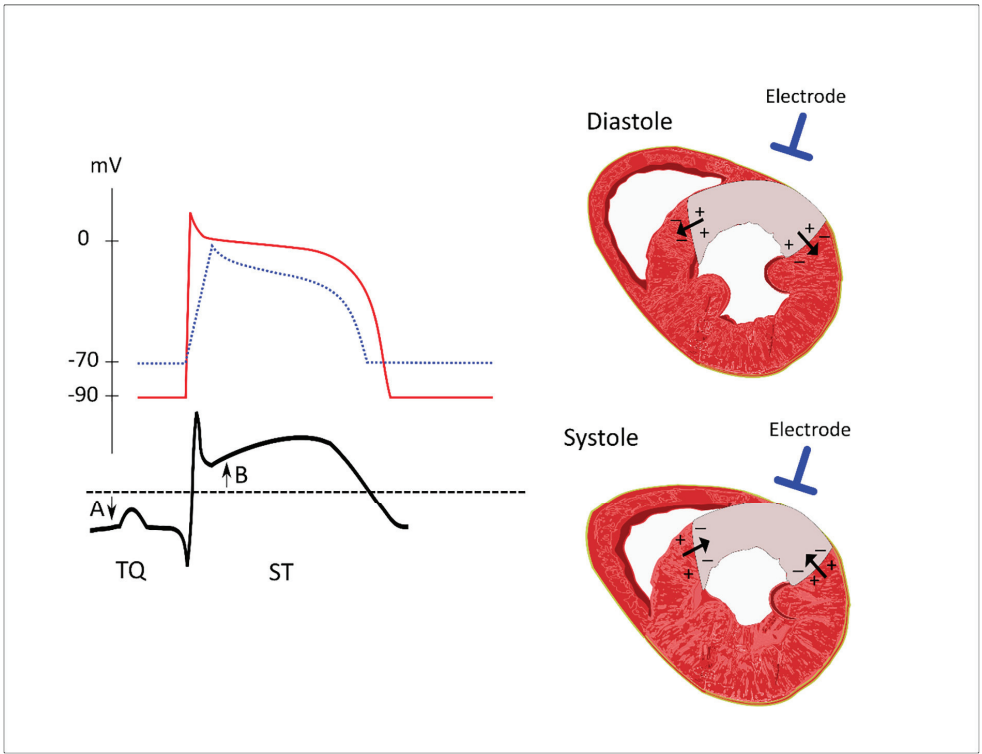

Figure 6. The theories of diastolic and systolic currents.
The resting membrane potential is more negative in a normal myocyte compared to an ischemic myocyte (*upper left image, red full line*: action potential in a normal myocyte; *blue dashed line*: action potential in an ischemic myocyte). In diastole, the relatively positively charged ischemic myocardium (*grey area*) results in a flow of currents from the ischemic to the normal myocardium and away from the recording electrode (*upper right image*). This results in depression of the TQ segment (*A, lower left image*), which will be displayed as elevation of the ST segment. The action potentials in ischemic myocytes have decreased amplitude and duration (*upper left image, blue dashed line*). In systole, the ischemic myocytes are "less" depolarized than the normal myocytes, which results in a flow of currents from the normal myocardium to the ischemic myocardium (*grey area*), and towards the recording electrode. This results in elevation of the ST segment (*B, lower left image*).

1.3. Electrocardiographic challenges in identification of acute coronary occlusion

There are several challenges in electrocardiographic detection of acute coronary occlusion, for example: absence of ST elevation on the ECG in case of transmural ischemia located distant from the ECG leads; low interpretation skills among physicians who meet these patients at the ED; several non-ischemic conditions also present with ST elevation; the display format is not optimized for STEMI identification; ECG changes as well as the patency of the vessel are dynamic; the prevalence of STEMI among patients at the ED is declining; treatment may be delayed due to delayed ECG recording and interpretation. Also, in patients with left or right bundle branch block or ventricular pacing pre-existing repolarization abnormalities are present, which make conventional ECG criteria for acute coronary occlusion difficult to apply.

First of all, the "STEMI concept" itself is troublesome [60]. In the early management of patients with acute coronary syndrome, we aim to identify those patients who may benefit from emergent revascularization, i.e. patients with acute occlusion, or near-/impending occlusion. In the large placebo-controlled trials on fibrinolytic therapy, which consistently showed increased survival when treating patients with suspected AMI with fibrinolysis [36], ECG criteria differed or were poorly defined. For example, the point of measurement along the ST segment was never mentioned [61-68], and some of the studies did not even have ECG changes as an inclusion criterion [61, 62, 66-68]. In a sub-group analysis of a meta-analysis of these studies, based on ECG findings, the mortality benefit was largest in patients with ST elevation [36]. Even without coronary angiography, significant ST elevation, in a sense, became an "equivalent" of acute coronary occlusion. As will be presented below, patients with acute coronary occlusion may however present without ST elevation [69]. The name "ST-elevation myocardial infarction" implies that the patients we are seeking to identify indeed have ST elevation on the ECG. However, this may not be the case. A patient without ST elevation on the ECG, but acute coronary occlusion, is therefore at risk of being denied an emergent coronary angiography, since he is not classified as a "STEMI patient" (Fig. 7). Also, it may be surmised that the ST segment is the only important ECG feature available for deciding whether an acute coronary occlusion is present or not, whereas other electrocardiographic changes besides ST elevation are actually important both for diagnostic and prognostic purposes.

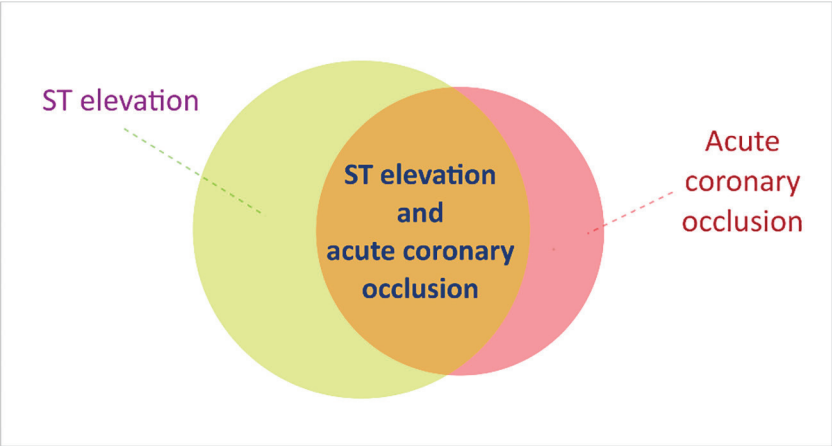

Figure 7. The ST-elevation myocardial infarction concept implies that patients who benefit from an immediate revascularization have ST elevation on the ECG. However, ST elevation is common in patients without coronary occlusion and acute coronary occlusion can occur without ST elevation on the ECG.

1.3.1. Absence of ST elevation ≠ absence of acute coronary occlusion

The ST-segment deviation will be displayed as ST elevation in the ECG if the overall ST vector - in the case of myocardial ischemia: the so called "ischemic vector" - is directed towards the positive pole of a certain lead. If the lead axis had been the opposite, ST depression would have been present [70]. Thus, the interpretation of ST elevation as a sign of myocardial ischemia due to acute coronary occlusion requires the understanding that an ischemic vector directed away from the exploring lead will be displayed as ST depression. In general, patients with persistent chest pain or chest discomfort and ST elevation in two contiguous leads in the 12-lead ECG are described as STEMI patients and treatment with acute PCI is recommended [46]. According to the European guidelines, in the absence of left ventricular hypertrophy or left bundle branch block, STEMI is considered to be present if STEMI criteria are fulfilled; ST elevation ≥0.1 mV in all leads except V2 – V3 where the following cut-offs are used instead: male ≥40 years old, 0.2 mV, <40 years old ≥0.25 mV, female ≥0.15 mV) (Table 1, Fig. 8) [28, 46]. However, these criteria have been shown to have low sensitivity. Two decades ago, during the thrombolytic era, a meta-analysis of ECG criteria for STEMI in pre-hospital detection of patients with AMI, showed fairly high sensitivity (68%) and excellent specificity (97%) [71]. A more recent study in a prehospital setting showed lower sensitivity as well as specificity for ST elevation in detecting AMI (36/91%)[72].

Table 1. ECG amplitude criteria* for ST-elevation myocardial infarction according to the fourth universal definition of myocardial infarction[28]

I, II, III, aVL, aVF V1, V4, V5, V6	All patients: ≥0.1 mV
V2, V3	Male patients ≥40 years: 0.2 mV Male patients <40 years old: ≥0.25 mV Female patients (any age): ≥0.15 mV
Lead pairs considered for significant ST elevation**	aVL/I, II/aVF, aVF/III V1/V2, V2/V3, V3/V4, V4/V5, V5/V6

*ST elevation should be measured at the J point

**Amplitude criteria must be met in two anatomically contiguous leads

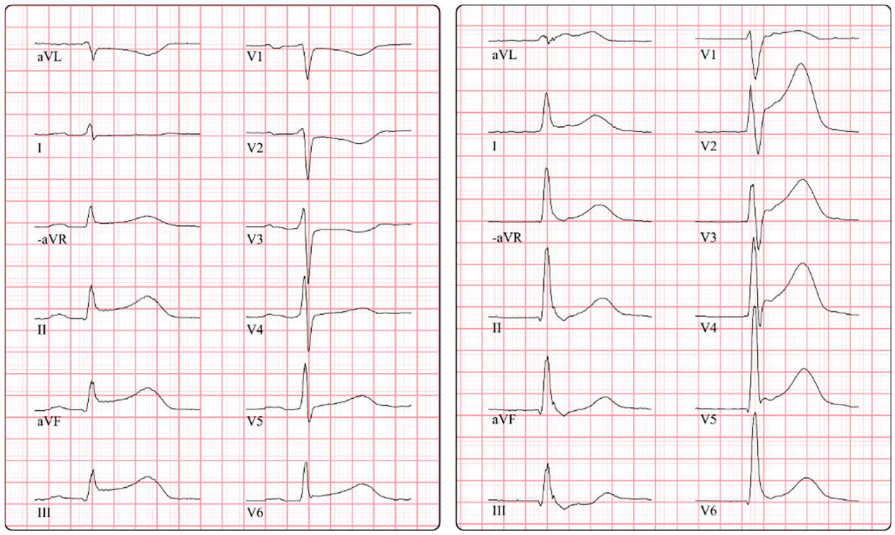

Figure 8. ECGs from two patients with ST-elevation myocardial infarction. The left ECG shows inferior ST elevation (II, III and aVF) ≥0.1 mV, i.e. significant ST elevation in at least two contiguous leads. The right ECG shows ST elevation in V2 – V6, and thus also meets STEMI criteria.

Despite an increasing prevalence of cardiovascular disease, incidence of STEMI among patients presenting at the ED has been described to be declining [73], while the total number of ED visits increases [74], resulting in a decreasing prevalence of STEMI at the ED. The positive and negative predictive values (PPV, NPV) of any test depend on the prevalence of disease. Among 2486 ED chest pain patients, Hillinger et al. observed both a low PPV (54%) for STEMI criteria in the diagnosis of STEMI, as adjudicated by two cardiologists [75].

When contrast-enhanced cardiovascular magnetic resonance imaging was used as gold standard for the diagnosis of acute myocardial infarction in 116 patients with acute chest pain, sensitivity of STEMI criteria was only 50% [76]. By extending the criteria to include ≥0.1 mV ST depression in two contiguous leads, or ≥0.1 mV ST depression in a lead anatomically contiguous to a lead with significant ST elevation (for example ST depression in aVL and ST elevation in lead III) sensitivity increased to 84%, with slightly lower specificity (97 vs. 93%). Interestingly, infarct size was similar between patients who met STEMI criteria and those who met the extended criteria [76]. Similar results were found by Perron et al., who studied ECGs recorded during coronary artery balloon occlusion in patients with stable angina. In that study, sensitivity could be increased, while maintaining high specificity, by adding 7 inverted leads (–V1, –V2, –V3, –aVL, –I, –aVR and –III) and classifying presence of significant ST elevation (≥0.1 mV, except for leads –V2, –V3 (≥0.05 mV)) in at least 2 contiguous leads (out of 19 leads), as STEMI or "STEMI equivalent". For detection of coronary occlusion, the greatest increase of sensitivity (from 61 to 75%) was due to the addition of leads –V1, –V2, –V3, which resulted in a loss of specificity from 96 to 93%. The further addition of the inverted limb leads (–aVL, –I, –aVR and –III) resulted in an additional increase of sensitivity to 78% without any further loss in specificity (Fig. 9) [77].

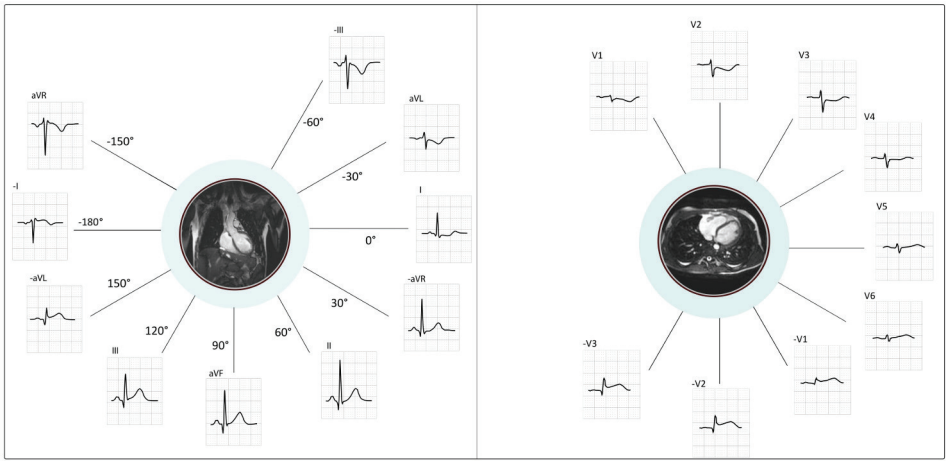

Figure 9. **Explanation and basis of the extended STEMI criteria.** Limb leads (to the left) and chest leads (to the right) are presented in anatomical context.
Left image: The inverted version of lead III (–III) is adjacent to aVL and the inverted version of aVL (–aVL) is adjacent to lead III. The inverse of aVR (–aVR) is between lead I and II, and the inverse of I (–I) is adjacent to aVR and –aVL. In this ECG, significant ST elevation is present in only one of the conventional leads (lead III), but in two contiguous leads when the extended STEMI criteria are applied (III and –aVL).
Right image: In the extended STEMI criteria, the inversion of leads V1, V2 and V3 (–V1, –V2, –V3) are also included in order to cover the lateral aspects of the left ventricle. ECG shows ST depression in V1 – V3, which is equivalent to ST elevation in –V1, –V2 and –V3.

Among patients with ACS and isolated ST depression in leads V1 – V4, approximately 25% have an occluded artery, most often the left circumflex artery (LCx) (Fig. 10). Often, revascularization is delayed, and clinical outcome is poor [78]. In a substudy of the therapeutic trial PARAGON-B, which compared lamifiban and placebo in NSTEMI patients, electrocardiographic findings, angiographic data and long-term outcome were studied. In these patients – none of them fulfilling STEMI criteria by definition - an occluded culprit artery was found in 27%, especially in the right or circumflex coronary artery. Despite similar pharmacological treatment, those with an occluded artery had larger infarcts and increased mortality compared to those with a non-occluded culprit artery [79].

European guidelines on management of STEMI states that isolated ST depression in V1 – V3 can be suggestive of acute myocardial ischemia and recommend the use of posterior leads (V7 – V9; ≥0.05 mV) for confirmation [46]. The electrodes for posterior leads should be placed at the level of V4 – V6, V7 in the posterior axillary line, V8 midscapulary and V9 paraspinally.

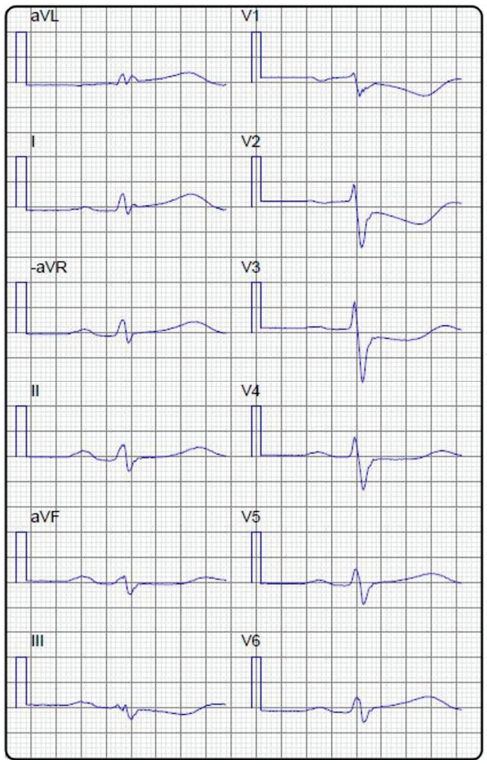

Figure 10. ECG from a patient with an acute coronary occlusion of the left circumflex coronary artery. ECG shows no significant ST elevation, but ST depression in V1 – V3.

ST elevation can be absent in the ECG for other reasons as well. For example, if the ECG is recorded very early in the process of an acute coronary occlusion, hyperacute T-wave changes may be present [80]. In rare cases, upsloping ST depression continuing into tall, symmetrical T waves ("de Winter pattern") represent an occlusion of the left anterior descending coronary artery (LAD) (Fig. 11A). This pattern is similar to hyperacute T waves, but were described to be "static", albeit recorded early after the start of symptoms [81, 82]. Upsloping ST depression is often seen during exercise or tachycardia. If present at lower heart rates, in combination with prominent T waves, a suspicion of acute myocardial ischemia should be raised [80]. Also, ECG changes are dynamic during ischemia, and the occurrence of ST elevation is highly dependent on the timing between ECG recording and the pathophysiologic processes, including the flow of the culprit artery. If an occluded vessel is reperfused, either spontaneously or as a result of the anti-thrombotic medication administered acutely, at the time of ECG recording, ST elevation can be absent. If an ECG is recorded after symptom resolution, deep negative T waves can

be present, representing a post-ischemic finding, most often due to a critical coronary stenosis or a complete occlusion with collateral circulation (Fig. 11B) [83]. If the vessel re-occludes, symptoms reoccur and the T waves may "pseudo-normalize" [80]. Also, since ECG changes represent a summation of the ischemic vectors, ischemia in opposing regions may attenuate ST-segment deviation [69, 84].

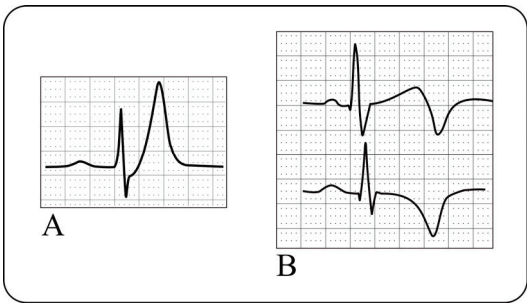

Figure 11. *Image A:* Upsloping ST depression in a precordial lead with a symmetrical, peaked T wave, often referred to as "de Winter pattern". If present at lower heart rates, in particular, ischemia should be suspected. *Image B:* Post-ischemic T wave changes. These T-wave changes may pseudo-normalize in case of reocclusion of the coronary artery.

NSTEMI patients are managed differently from STEMI patients in that coronary angiography is not recommended to be performed emergently [47]. Several studies have evaluated the effect of early invasive strategies in NSTEMI [85-88]. "The NSTEMI group" is however heterogenous, and patients with an acute coronary occlusion but no ST elevation – who at least theoretically would benefit from immediate revascularization – are in minority. A multi-center study, in which >3000 patients with NSTEMI or unstable angina were randomized to either early or delayed invasive strategy, failed to show any statistically significant benefit for death, new AMI or stroke using an early invasive strategy. However, median time to coronary angiography in the group of patients who underwent early coronary angiography was 14 hours (interquartile range 3 – 12), i.e. even "early angiographies" were in fact performed with delay if an acute coronary occlusion would have been present. Nonetheless, there was a relative reduction of the composite secondary outcome of death, myocardial infarction or refractory ischemia of approximately 30% in the group of patients who underwent early revascularization [88]. In a small randomized clinical trial, high-risk patients with NSTEMI were randomized to either an early (<6 hours) or a delayed invasive strategy. Adverse outcomes (death, AMI, urgent revascularization) were more prevalent in the group who underwent delayed coronary angiography (21% vs. 2%). In that study, data on coronary occlusion was not reported [87].

1.3.2. Limb leads are not presented adjacently

Electrocardiographic detection of STEMI is complicated – unnecessarily – by the non-contiguous limb lead display. In the international standard ECG display, the limb leads are presented as two groups of leads in a non-anatomical order: I, II, III; and aVR, aVL and aVF. This contrasts with the chest lead display, which follows a contiguous order: V1, V2, …, and V6. A contiguous limb lead display is used in Sweden since 1979, the so-called Cabrera display. In this presentation, the order of the limb leads is instead: aVL, I, –aVR, II, aVF, III (Fig. 12). In that presentation, aVR is replaced by its inverted version, –aVR, which assumes its logical place between lead I and II. A contiguous display compared to a non-contiguous display is advantageous in several ways. Since STEMI criteria are met when significant ST elevation is present in two contiguous leads, the identification of contiguous lead pairs is essential. In the standard display, only three lead pairs are present: aVL/I, aVF/II, aVF/III. They are not presented adjacently and must instead be identified by "memorizing" which leads are contiguous. In the Cabrera display, two additional lead pairs can be identified: I/–aVR and –aVR/II, and the contiguous leads are presented adjacently.

With its positive pole in the upper right quadrant of the thorax, positive amplitudes in aVR will be seen when amplitudes in leads I and II are negative and vice versa. If Q waves are present in lead I and II, an initial R wave will be present in aVR, and if ST elevation is present in leads I and II, ST depression will occur in aVR. This is a likely cause of the common "neglect" of aVR during ECG interpretation [89]. The importance of including aVR (or –aVR) in ECG interpretation in ACS cases has been highlighted in many papers [90-95]. When leads are presented in contiguous order, reciprocal limb lead changes are more intuitively appreciated [96]. Such ST-segment changes are important to take into consideration in the differential diagnosis of ST elevation [97], and may aid in culprit identification [98]. The advantage of using the Cabrera display instead of the standard display has been put forth in several papers and was recommended as an alternative in the 2007 AHA/ACC standards paper [96, 99-103]. Today, the Cabrera display is available in most commercial ECG recorders but is routinely used only in selected areas (Sweden, and parts of Finland, Italy and Japan).

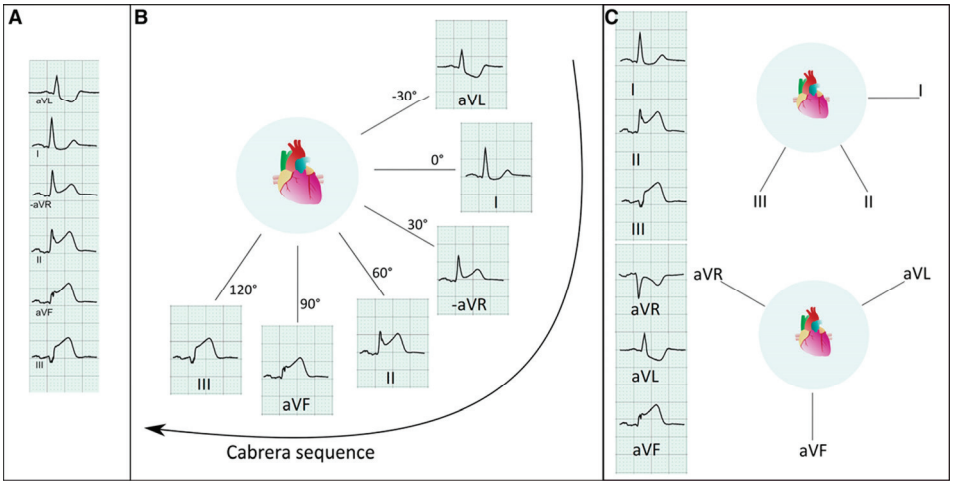

Figure 12. The Cabrera limb lead display. *Image A* shows the limb lead display used in Sweden, the Cabrera display. In this display, the leads are presented in contiguous, anatomical order (*Image B*). This differs from the standard limb lead display, in which leads are presented as two groups (I, II, III and aVR, aVL, aVF) (*Image C*), Reprinted with permission from Lindow et al [104].

1.3.3. Low interpretation skills

Another challenge in detecting patients with acute coronary occlusion is the reportedly low interpretation skills among physicians who often first meet such patients at the ED [105, 106]. In a study by Eslava et al, almost one fifth of first-year internal medicine residents misdiagnosed STEMI [106]. Trzeciak performed a questionnaire-based study including 31 internal medicine residents and 31 emergency medicine residents who received a set of clinically relevant ECGs presented with a brief history and information on patient risk factors. Interestingly, one of the ECGs showed ST depression in V1 – V3 with a corresponding history of a 50-year old male smoker with hypertension who experienced substernal chest pain. Only 26% of internal medicine residents correctly interpreted this ECG as acute myocardial infarction ("posterior MI"). Also, despite absence of a clinical history suggestive of ischemia, almost 50% of the study participants mis-interpreted an ECG with early repolarization as AMI [105].

Remote ECG interpretation by telemedicine, in an attempt to decrease the time to treatment, increases the need for accurate ECG interpretation even in the absence of access to full clinical information. Such a scenario was tested in 124 ED physicians, who were asked to determine whether 36 ECGs were consistent with a diagnosis of acute coronary occlusion, with the only clinical information that "a moderate risk of

ACS" was present. All 36 patients had undergone emergent angiography, and one third had TIMI 3 flow and no culprit lesion. Overall sensitivity to identify a true STEMI was 65% and specificity was 79%. Inter-rater agreement was poor (0.33). Diagnostic accuracy improved with increasing experience [107].

As previously mentioned, it is of great importance to reduce the duration of ischemic symptoms and time to reperfusion treatment, in order to reduce mortality. A longer duration from time from onset of symptoms to revascularization is associated with increased infarct size, and short- and longterm mortality [11-13]. Thus, all efforts need to be made to shorten time to treatment. An absolute pre-requisite to obtain this goal is that the ECG is correctly interpreted so that patients in need of acute revascularization can be identified. To overcome the low interpretation skills, either the ECG interpretation curriculum should be enhanced [108], or diagnostic aids could be used [109-111].

1.3.4. Non-ischemic ST deviation

The ST segment is most often isoelectric. Some ST elevation in precordial leads, especially in V2 and V3, is present in most healthy men [112], and is thus considered a normal male pattern [113]. This is reflected in the STEMI criteria, with different amplitude thresholds for leads V2 and V3 for men compared to women, and for young men compared to older men [28]. At the ED, the attending physician must make a rapid decision regarding reperfusion therapy [46]. This process is complicated by the fact that other, non-ischemic conditions also may present with ST elevation [114]. ST elevation and chest pain may occur in patients with peri-/myocarditis, takotsubo cardiomyopathy or aortic dissection. Furthermore, non-ischemic etiologies of ST elevation such as left ventricular hypertrophy (LVH) [115-117] and early repolarization [116, 118, 119] may be present in patients with non-cardiac chest pain, as well as in patients with cardiac chest pain not due to an acute coronary occlusion [84]. In a retrospective analysis of 1345 cases of catherization laboratory activation due to suspected STEMI, 187 (14%) were considered false positive, of whom 66% had negative biomarker results. Early repolarization pattern, peri-/myocarditis, takotsubo cardiomyopathy and LVH accounted for 45% of the 187 cases [120]. In a smaller study, during "the thrombolytic era", 11% of patients received such therapy without evolving acute myocardial infarction (negative biomarkers). 60% of them had ST elevation due to LVH or early repolarization [116]. Bosson et al conducted a retrospective study of the causes of ECG software misinterpretation compared to clinically identified STEMI by reviewing the results of the in-built interpretation software in almost 50 000 pre-hospital ECG recordings. Early repolarization pattern, probable peri-/myocarditis and LVH accounted for 37% of false positive software

interpretations. Presence of ECG artifacts was the most common cause of misinterpretation [121].

Inappropriate catherization laboratory activation have several different negative implications, such as procedural-related risks, unnecessary cost, patient anxiety, and potential community risks, e.g. traffic-related risks [122]. The risk of false activation of the catherization laboratory must however be weighed against the risk of delayed reperfusion in patients with acute coronary occlusion, and a "cath lab" activation can still be reasonable even though no PCI is performed [122]. The lack of an occluded culprit artery does not necessarily mean that the activation was inappropriate. Both the patency of the vessel and the ECG findings may change rapidly. For example, in a STEMI trial, one third of STEMI patients had an open vessel at the time of PCI (Thrombolysis in Myocardial Infarction (TIMI) flow >1) [123].

1.3.4.2. Perimyocarditis

Pericarditis is a common cause of ED admission, described to account for 5% of patients with chest pain [124]. The etiology of pericarditis is multi-factorial with both infectious (bacterial/viral) and non-infectious (systemic- and metabolic diseases, radiation, cardiac interventions, etc) causes [125]. Often, pericarditis is associated with some degree of myocarditis and the conditions share common etiologies, especially cardiotropic viruses [126]. According to European guidelines of management of pericardial disease, a predominant myocarditis with pericardial involvement should be labelled as "perimyocarditis", and pericarditis with minor concomitant myocardial involvement should be referred to as "myopericarditis" [124]. In this thesis, the term "perimyocarditis" is used interchangeably for all patients considered as having either pericarditis or myocarditis or both.

Classically, perimyocarditis presents with centrally located chest pain increased by inspiration and recumbent positions but may simulate that of typical ischemic chest pain, for example with radiating pain [127]. A pericardial rub during auscultation has been described as a specific finding of pericarditis [127] but may occur even in large transmural myocardial infarction [114]. Perimyocarditis is a difficult differential diagnosis of acute myocardial infarction [120, 121, 128] and, as previously mentioned, a common cause of initially false positive STEMI diagnosis [120, 121]. In 45 patients admitted to the intensive care unit due to suspected acute myocardial infarction, who had normal coronary angiograms, radionuclide imaging showed diffuse or focal myocarditis in 78% [128]. In pericarditis, in contrast to myocardial infarction, ST elevation is often widespread, entailing both precordial and limb leads beyond a typical "coronary territory". This diffuse ST elevation, and the diffuse PR depression often associated with pericarditis, has been attributed to the involvement of both the

ventricular and atrial epicardial layers [114]. Since the pericardium is electrically inert, ECG changes suggest at least epicardial involvement [124]. Cardiovascular magnetic resonance imaging (CMR) has high diagnostic accuracy for the diagnosis of perimyocarditis [129, 130].

1.3.4.2 Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) may alter repolarization resulting in secondary ST-segment and T-wave changes, which may result in a false positive diagnosis of acute myocardial infarction [116]. ST-segment changes due to LVH entail both ST elevation in V1 and V2, and down-sloping ST depression in leads V5, V6, I and aVL [131]. Among 413 patients with electrocardiographically defined LVH who presented with symptoms suggesting acute myocardial ischemia, only 26% had either unstable angina or myocardial infarction. Notably, even though ischemia diagnoses were rare, short-term mortality was substantial (8%), mainly due to congestive heart failure [132]. Similar results were found ten years later by Pope et al, who found both a 50% higher false-positive admission rate (for suspected ACS) and a higher short-term mortality in patients with LVH with secondary ST-T abnormalities compared to patients without such ECG changes [133]. In a retrospective analysis of 411 consecutive patients referred for primary PCI from an emergency department, LVH was independently associated with increased likelihood of false-positive activation, defined as lack of an angiographic culprit lesion and TIMI grade III flow (4.3) [117]. Armstrong et al showed that the false-positive activation rate could be decreased by applying an ST elevation to R-S wave amplitude ratio (≥0.25) for leads V1 – V3 [115].

1.3.4.3 Early repolarization

Early repolarization pattern is a non-ischemic ECG finding which, according to recent consensus definition, includes slurring or notching in two contiguous leads on the downslope of a prominent R wave (so-called J waves) and occurs with or without ST elevation (Fig. 13) [118]. The definition of early repolarization has varied and has for a long time been considered a benign normal variant, although epidemiological studies have shown an increased risk of sudden cardiac death in patients with inferior J-point elevation [134]. The mechanism behind J waves has been attributed to differences in the early phases of the action potential in the endocardium and the epicardium [135]. Based on the location of J-wave abnormalities, early repolarization can be divided into different types: type I (lateral; J waves in I, V4 – V6), type II (inferior; J waves in II, III and aVF) or type 3 (global J-wave abnormalities) [135].

In electrocardiographic assessment of ACS, early repolarization with ST elevation is a common cause of STEMI misinterpretation [121] and a cause for false activation of the coronary angiography laboratory [120]. In early repolarization, the ST segment is most often concave [113]. Concave morphology is often considered as a non-ischemic ST elevation pattern. However, in a retrospective analysis of ECGs from patients with LAD occlusion, concave morphology was present in 43% of patients, being increasingly common in patients with shorter symptom duration [136].

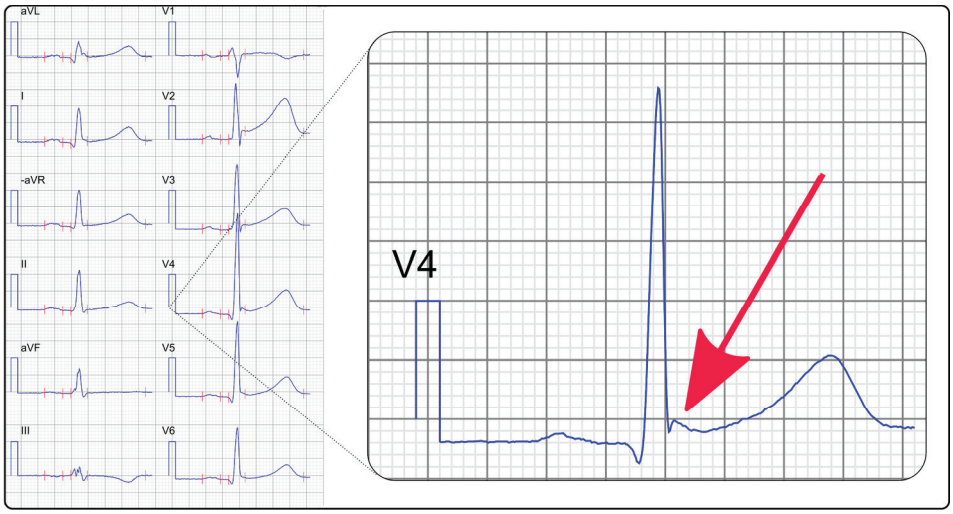

Figure 13. ECG with early repolarization pattern.
ECG shows ST elevation in V2 – V4. In V4, a distinct end-QRS notch is present, and in V5 a slowed inscription of the terminal portion of the QRS is present (slur). The nadir of the notch is ≥0.1 mV above the baseline (red arrow, right image). ST elevation is present in several precordial leads.

1.3.4.4. Takotsubo cardiomyopathy

Almost 30 years ago, Japanese researchers described a novel cardiac condition in female patients with chest pain, ST-segment elevation, non-obstructed coronary arteries and apical "ballooning" of the left ventricle [137]. The condition was given the name "takotsubo cardiomyopathy" after the resemblance between the left ventricular shape during ventricular angiography and a Japanese octopus trap (takotsubo) (Fig. 14). In most cases, a physical or emotional stress trigger can be identified [138] associated with increased catecholamine levels causing microvascular constriction [139]. Several names have been used in the literature (takotsubo cardiomyopathy, stress-induced cardiomyopathy, "apical ballooning", "broken heart syndrome", takotsubo syndrome). The term takotsubo cardiomyopathy is used throughout this thesis.

Since takotsubo cardiomyopathy is similar to acute myocardial infarction, both regarding symptoms, ECG changes and increased levels of biomarkers, it is considered mandatory to exclude coronary artery occlusion. The ischemic injury of takotsubo cardiomyopathy is not, however, caused by a diseased epicardial coronary artery, as in ACS. Despite this, in-hospital mortality is comparable to optimally treated ACS, and serious complications such as lethal arrythmia and cardiogenic shock occur [138, 140].

Diffuse T-wave inversion and QT prolongation are common electrocardiographic findings in takotsubo cardiomyopathy [139]. In many cases, ST elevation is absent. When present, however, the ST-elevation pattern may be similar to that in acute myocardial infarction [141]. ST elevation in takotsubo cardiomyopathy commonly occurs in the early phases of the condition and is most often present in the precordial leads. Frangieh et al compared 200 admission ECGs from patients with takotsubo cardiomyopathy to those from 200 patients with AMI and found that ST depression in aVR was more prevalent in patients with takotsubo cardiomyopathy (31%) than in patients with infarction (3%). Except for aVR, ST depression was more common in patients with infarction [141]. Kosuge et al. also showed that in patients with ST elevation in the precordial leads, ST depression in aVR was more common in patients with takotsubo cardiomyopathy than in patients with LAD occlusion [99]. Vervaat et al showed low sensitivity (26%) for takotsubo cardiomyopathy for the criterion of ST depression in aVR in combination with ≤0.1 mV ST elevation in V1, when comparing 37 female patients with takotsubo and 103 female patients with anterior STEMI. Of note, all patients fulfilled STEMI criteria. When the frontal plane ST vector (60°) was used as a criterion for differentiating the two conditions, sensitivity was improved (49%), while specificity was similar (96 vs. 93%). Patients with takotsubo cardiomyopathy more often had an ST vector pointing inferiorly than LAD patients. The number of patients with distal LAD occlusion, which can be expected to also have more inferiorly directed ST vector, was small (10 patients) [142]. Zorzi et al performed a retrospective study comparing clinical and electrocardiographic findings in postmenopausal women with either takotsubo cardiomyopathy (N=31) or apical-anterior AMI (N=30), who were admitted due to chest pain and significant ST elevation in at least two contiguous leads. ST- elevation magnitude was greater among patients with STEMI, and PR depression occurred more often in patients with takotsubo cardiomyopathy compared to STEMI patients. Interestingly, although peak troponin values were markedly higher among STEMI patients, troponin values at admission were similar [143].

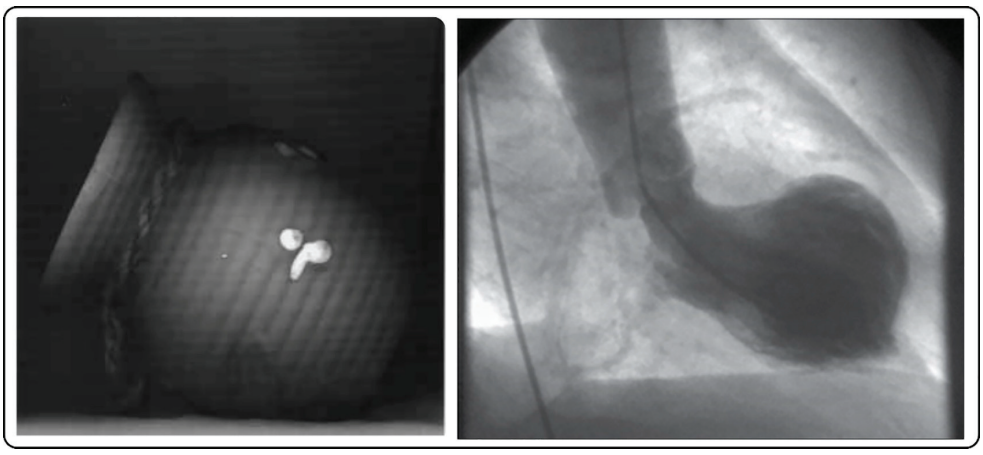

Figure 14. Takotsubo cardiomyopathy.
The octopus trap "takotsubo" (*left image*) resembles the shape of the left ventricle during ventriculography in a typical case of takotsubo cardiomyopathy (*right image*). Reprinted with permission from Kurisu et al [137] (*right image*) and Castillo Rivera et al [144] (*left image*).

1.3.4.5. Other conditions with pre-existing ST deviation

Other conditions – not associated with acute myocardial infarction - may also present with ST elevation, such as Brugada syndrome (coved ST elevation in V1 – V3), hyperkalemia, pulmonary embolism, hypothermia, left ventricular aneurysm and bundle branch block or ventricular pacing [113, 114]. Left bundle branch block (LBBB) assumes a special role in the diagnosis of ACS. Previously, new LBBB was considered as an equivalent to STEMI in the management of patients with suspected ACS [145]. However, few patients with chest pain and presumed new LBBB have an acute coronary occlusion [146, 147]. The anterior fascicle of the left bundle is supplied by septal branches from the LAD, which also supplies the right bundle, whereas the posterior fascicle of the left bundle is supplied by the right coronary artery (RCA) or by both RCA and LAD [148]. Hence, in the case of normal coronary anatomy, if acute coronary occlusion would be the primary cause of new LBBB, occlusion of both the RCA and the LAD would be required. Such a condition would result in catastrophic ischemia and severe hemodynamic instability.

As opposed to right bundle branch block and left anterior fascicular block, which can occur in proximal LAD occlusion [149], LBBB is rarely caused by acute coronary occlusion. However, even though LBBB in itself is not a sign of acute coronary occlusion, it is associated with several risk factors for ischemic heart disease (hypertension, chronic ischemic heart disease, valvular heart disease [150]) and detection of an acute coronary occlusion is, of course, important. Due to pre-existing

repolarization abnormalities, ECG interpretation is complicated in the presence of LBBB. In LBBB, the ST-segment is usually discordant to the QRS complex, i.e. in leads with predominantly positive QRS complex, the ST segment is negative and vice versa. In an acute coronary occlusion, the ST segment may instead become concordant to the QRS complex. The so-called Sgarbossa criteria, which take this into account, are specific for acute coronary occlusion in patients with LBBB, but lack in sensitivity [151]. A modification of these criteria was suggested by Smith et al, with improved sensitivity [152] (Fig. 15).

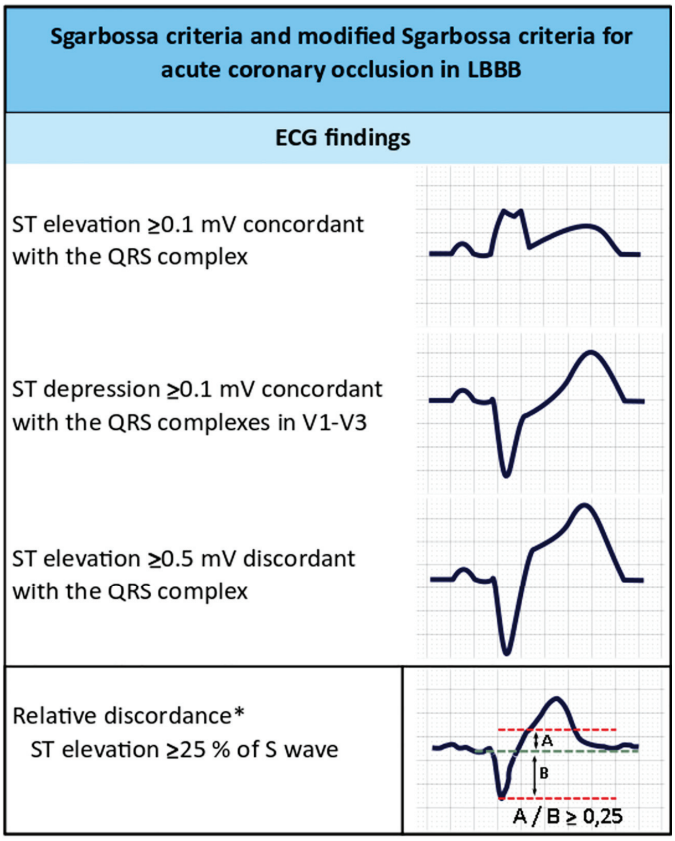

Figure 15. ECG criteria for diagnosing acute coronary occlusion in the setting of left bundle branch block. To meet the Sgarbossa criteria, either concordant ST deviation or excessively discordant ST elevation must be present. Smith et al suggested a modification of the third criterion by relating the ST elevation to the S-wave amplitude [152]. Re-printed with permission from Lindow et al [153].

Several of the above-mentioned challenges in the detection of patients with acute coronary occlusion are addressed in this thesis (Fig. 16).

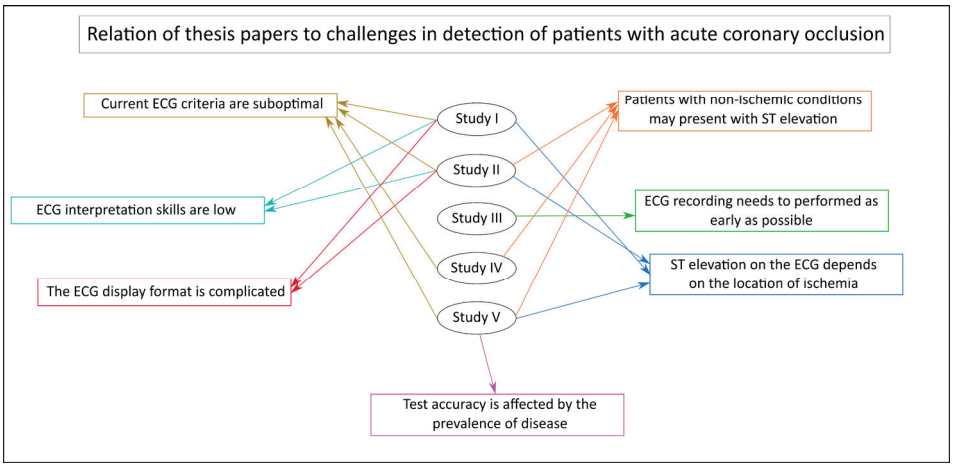

Figure 16. Schematic presentation on how the papers in this thesis are related to some of the challenges in detection of patients with acute coronary occlusion.

1.4. Electrocardiographic Decision Support – Myocardial Ischemia (EDS-MI)

Two of the studies in this thesis are related to the development and evaluation of an automatic ECG decision support, namely "Electrocardiographic Decision Support – Myocardial Ischemia" a.k.a. "the Olson method". Here follows a description of the basis for this method.

Cardiac electrical forces can be represented at any point in time by the 8 independent amplitudes in the 12-lead ECG or by a 3-dimensional vector. This vector has a specific direction and magnitude for each moment in the cardiac cycle. A lead system for recording a vectorcardiogram, which describes the evolution of the magnitude and direction of this vector along three orthogonal axes (X, Y, Z) was developed by Frank in the 1950-ies. This lead system was based on his torso model work, during which he measured the electrical potential at 200 surface positions on a model of a male torso with an electrical dipole at the position of the heart within the thorax [154, 155]. Orthogonal X, Y, Z leads can also be synthesized from the 12-lead ECG [156-158]. Such a process, would, at least in theory, rectify the problem that the

effect of the left ventricular walls on lead amplitudes is greater from certain parts of the heart than from others. For example, anteroseptal leads (V2 and V3) are farther away from the inferolateral wall than from the anteroseptal wall. Ischemia located in the anteroseptal wall would then result in greater ST deviation in V2 or V3 than would ischemia in the inferolateral wall. Although the model is imperfect, for example the human torso is not homogenous as Frank's model was, calculation of X, Y, Z leads from the 12-lead ECG is an attempt to take these differences into account [156].

The Olson method, a name that was later changed to Electrocardiographic Decision Support – Myocardial Ischemia (EDS-MI), is an automatic, visual, ECG-based decision support in the management of patients with acute coronary syndrome, developed by Charles William Olson (Huntington, NY, USA) and colleagues during the past decade, and initially aimed at localizing and describing the extent of ischemia caused by acute coronary occlusion [156, 159]. In EDS-MI, the information in the 12-lead ECG is transformed into a visual presentation of ischemia in three steps. First, the ST-J amplitudes are converted into a corrected ST vector at the electrical center of the heart. Second, the left ventricle (LV) is divided into 12 segments and a theoretical vector is established for each segment, as if that segment was uniformly ischemic. Third, the contribution of each myocardial segment to the ischemic vector is determined.

In the first step, the ST-J amplitudes in the 12 leads are used to calculate a vector in "3D space" with correction for lead strength, based on the information in Frank's surface diagrams (Fig. 16) [154, 159]. For each lead, the recorded ST-J amplitude, is multiplied by a set of three conversion values, calculated by Charles Olson based on the information in the image surface diagram described by Frank. This accomplishes a conversion of the ST deviation into a single vector at the heart's electrical center (Fig. 17). This ST vector is rotated to obtain a vertical position within the thorax, based on previous studies on the long axis of the LV [160]. By this rotation, the four left ventricular walls will be represented by 90-degree quadrants on a Mercator map, described below.

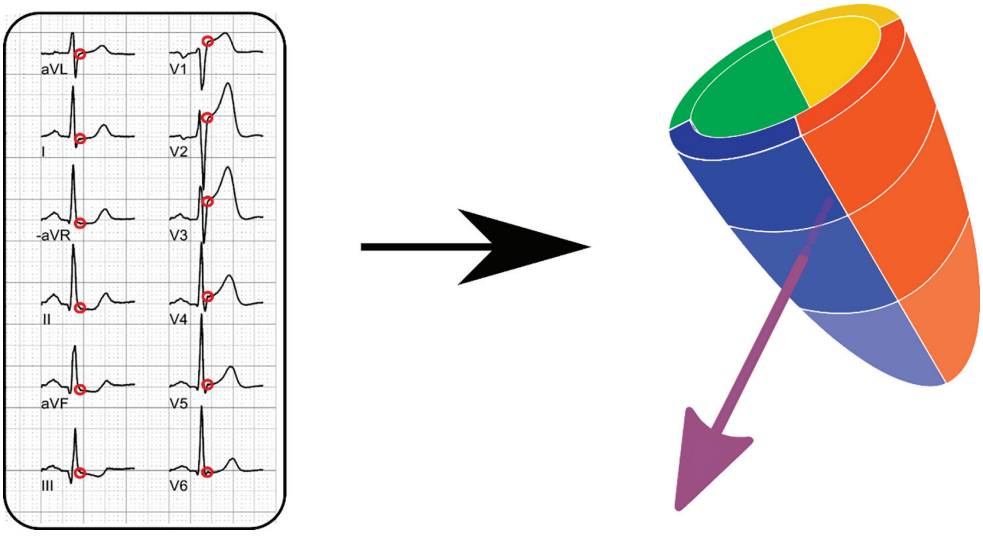

Figure 17. The ST-J amplitudes are converted into a three-dimensional vector originating at the electrical center of the heart.

In the second step, a "reference framework" is established by dividing the LV myocardium into 12 segments (Fig. 18). One or more of these segments are then identified as the likely generator of the ST vector. The 12-segment LV model was developed by Selvester in his studies of myocardial infarction size and location [161]. The LV model is a Mercator projection, which divides the LV into four walls: septal, anterior, lateral, and inferior. Each wall is divided into three regions from apex to base.

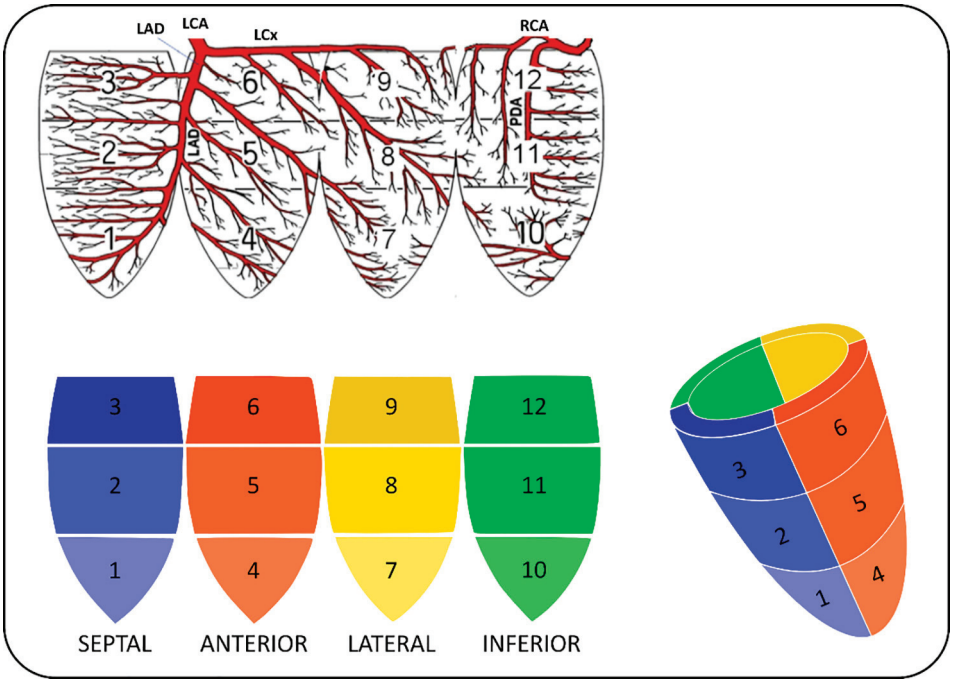

Figure 18. The 12-segment model of the left ventricle.

Upper left image: The Mercator model presented in EDS-MI. The left ventricle is divided into four walls (septal, anterior, lateral and inferior), and each wall into three segments from apex to base.
Lower left image: Color-coded version of the Mercator map used in subsequent explanatory images.
Lower right image: The walls lie at approximately 90° from each other.
Abbreviations: LAD: left anterior descending coronary artery; LCA: left coronary artery; LCx: left circumflex coronary artery; RCA: right coronary artery; PDA: posterior descending coronary artery.

In the third step, EDS-MI generates a hypothetical ischemic vector for each of the 12 LV segments in the model (Fig. 19). This vector represents the direction of an ischemic vector which would result if that segment were uniformly ischemic. The four walls are at approximately 90° from each other, and the three segments of each wall lie along a gentle arc from apex to base, with a total of approximately 20° of deviation along the arc. The result is a set of 12 vectors, each perpendicular to the center of its segment. This set of hypothetical vectors is the same for all subjects.

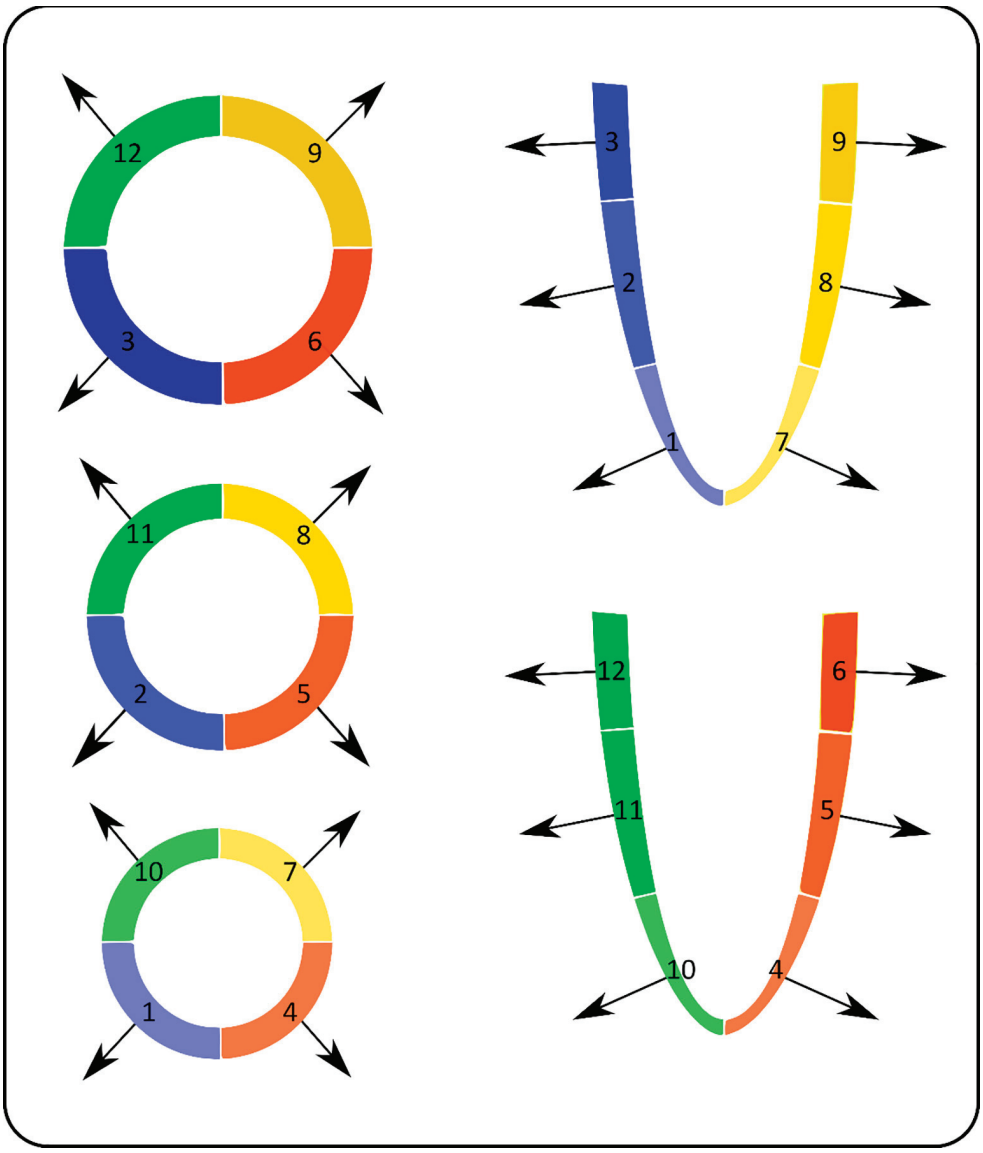

Figure 19. Illustration of the 12 segmental vectors, which are perpendicular to the center of each segment.

In the third step, the subject's ST vector is related to the direction of the hypothetical ischemic vectors for each of the 12 segments. The product of the two vectors is multiplied by the cosine of the angle between them (magnitude of hypothetical vector from a myocardial segment) × (magnitude of ST vector from each of the subject's ECG leads) × (cosine of angle between these vectors) [156, 159]. If the ST

vector has a direction that is close to a segmental vector, the magnitude of the ST vector will be large, indicating that the particular segment "contributes" to a large extent to the overall ST vector (Fig. 20). The location of the largest dot product (referred to as an ischemic score) indicates the center of the presumed ischemia. The location and extent of ischemia is depicted on a map of the left ventricle in the shape of an ellipse and its size is proportional to the ischemic scores (Fig. 21) [159].

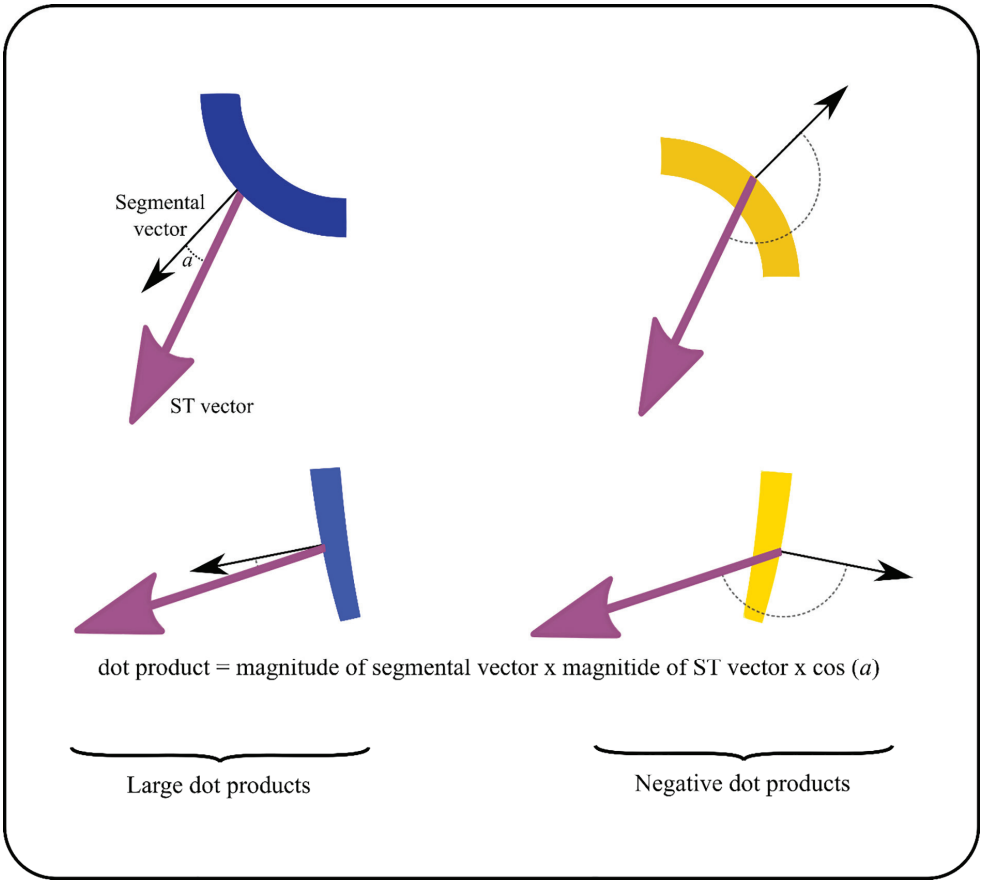

Figure 20. The product of the two vectors (ST vector and segmental vector) is multiplied by the cosine of the angle between them (*a*). If the ST vector (*purple arrows*) has a direction that is close to a segmental vector (*black arrows, blue segments*), the magnitude of the ST vector will be large, indicating that the particular segment "contributes" to a large extent to the overall ST vector. The segment that has largest dot product indicates the center of ischemia.

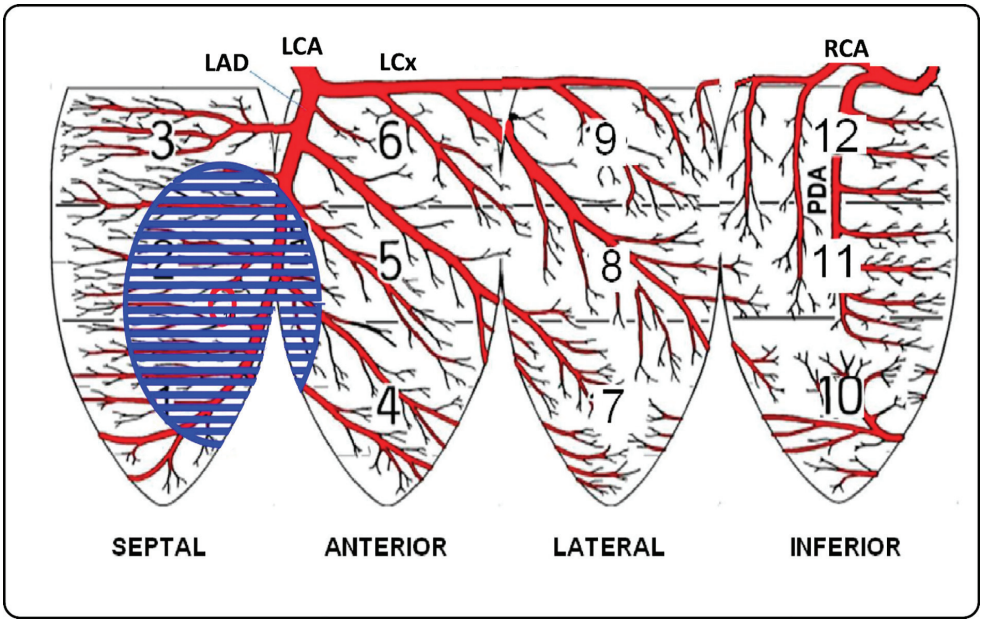

Figure 21. Presentation of location and extent of ischemia in EDS-MI. This patient had an LAD occlusion and EDS-MI shows a large ischemic area in the septal wall (*blue ellipse*).

In 2015, Kamphuis et al studied how EDS-MI performed in culprit artery identification, compared to expert cardiologists. ECGs from 53 patients with acute coronary occlusion were assessed both by EDS-MI and the expert cardiologists. EDS-MI identified the culprit artery in 89% of cases, and the expert cardiologists in 81%. The mis-classifications by EDS-MI were all LCx culprits classified as right coronary artery (RCA) [162]. Coronary artery anatomy varies between individuals, especially regarding the perfusion territory of RCA and LCx [163]. The ECG does not reflect the perfusing artery but the electrophysiological changes within an ischemic area of the myocardium. Neither the ischemic location nor the ischemic extent by EDS-MI had been compared to a reference standard such as CMR.

Before study I, EDS-MI had only been suggested to be used for ischemia localization and, based on that, identification of the culprit artery. If the method could be used also for detection of ischemia, the impact of the method would be greater. Detection of myocardial ischemia by EDS-MI is addressed in studies I and II.

1.5. The ECG for estimating the extent of myocardial ischemia

The ECG can be used for risk assessment based on the amount of ischemic myocardium. The magnitude of the ST deviation can be indicative of the extent of ischemia and holds prognostic information [164]. For example, a score can be calculated from the amount of ST elevation in several leads [59, 165]. A higher score indicates a larger amount of ischemic myocardium, or myocardium at risk (MaR) [59]. Thirty years ago, Aldrich et al developed a method to determine the risk area in the myocardium based on ST-J amplitudes. In that study, 148 patients with STEMI, but without previous myocardial infarction, who did not receive thrombolytic therapy were included. The sum of ST elevation in leads with ≥0.1 mV ST elevation as well as the number of leads with ST elevation with ≥0.1 mV were compared with final AMI size, according to a QRS scoring system (the Selvester QRS score, described below: *1.5.1*) applied on the pre-discharge ECG. The myocardial infarction was classified as either inferior or anterior based on the lead with maximal ST elevation. From multivariable regression analyses two formulas were defined to determine the AMI size [165]:

Anterior STEMI: $3\ x\ [(1.5\ x\ number\ of\ leads\ with\ ST\ elevation) - 0.4]$

Inferior STEMI: $3\ x\ [0.6\ x\ (\sum ST\ elevation\ in\ II, III, aVF) + 2.0]$.

In the first version of EDS-MI [159], a coefficient had been established based on correlations made with the Aldrich score, to calculate the extent of ischemia using the ischemic scores (Charles Olson, *personal communication*).

When the Aldrich algorithm was determined, the MaR was correlated to final infarct size according to ECG scoring, in patients who were not revascularized. Calculations of MaR based on ST-vector magnitudes have also been compared to, and shown to correlate with, the extent of ischemia as assessed by myocardial perfusion imaging (MPI) [166]. When using the ST amplitudes as a surrogate for the ischemic extent, one must take into account the location of the ischemic area in relation to the leads, since the electrical potential is inversely proportional to the distance between the myocardium and the recording lead [156]. In EDS-MI, an attempt to accomplish this is to correct the ST vector for lead strength, by using a model of the torso, as described by Frank [156, 159] (*see section 1.4*). This model does not consider the large differences in torso shape and size between patients. When the Aldrich algorithm was established, patients with previous myocardial infarction were

excluded. When assessing the MaR using imaging methods (either MPI or CMR imaging, discussed below: *1.7*), no differentiation between viable but ischemic myocardium and acutely infarcted/necrotic myocardium is made. With increasing time from onset of symptoms to reperfusion, the amount of viable myocardium decreases and thus the ST-segment deviation, which reflects the ischemic changes in viable myocardium, may decrease when the infarcted area increases. ST-segment changes will then be "replaced" by QRS changes. Hence, estimation of myocardium at risk when relying only on ST-segment deviation can, in many cases, be an underestimation [167-170]. When taking QRS changes, as a surrogate for infarcted myocardium, into account when estimating the ischemic extent, better correlation between ECG changes and MPI can be obtained [168, 169]. The performance of EDS-MI in estimating the extent of ischemia is addressed in study II.

1.5.1. Selvester QRS scoring

Q waves occur in the ECGs if the early depolarization vectors are directed away from the exploring lead, and can be present in the ECG even in healthy individuals [70]. If Q waves occur in leads which normally do not exhibit Q waves, or have increased amplitude or duration, they may indicate myocardial infarction. Necrotic myocardial cells are not depolarized, which changes the depolarization vector away from the infarcted area, resulting in a Q wave. This is, as with the ST deviation, dependent on the location of infarction. If the infarction is located in the lateral wall of the left ventricle, prominent R waves can occur in leads V1 – V2 instead [171]. Pathological Q waves have traditionally been attributed to chronic transmural infarction, but have lately been shown to rather correlate with the extent of injury, rather than the "transmurality" [172]. Also, Q waves may occur in patients during the acute phase of an ischemic event, without being attributed to irreversibly injured myocardium [84]. Nonetheless, presence of pathological Q waves is indicative of myocardial infarction. Based on computer simulations and anatomic measurements at autopsy, Selvester et al created a scoring system to estimate the amount infarcted myocardium [173]. This QRS scoring system has 50-criteria from which 31 points can be gathered. Each point is meant to represent 3% of left ventricle. The scoring system is based on Q-wave durations, R-wave amplitudes and durations, R/S or R/Q ratios and has been validated and slightly modified since the original description (Table 2) [174-176]. Selvester QRS scoring is included in study II in order to account for already infarcted myocardial regions in the electrocardiographic assessment of MaR.

Table 2. Selvester QRS scoring system

Lead	Criterion	QRS points
I	Q ≥30 ms	1
(2)	R/Q ≤ 1	1
	R ≤0.2 mV	1
II	Q ≥40 ms	2
(2)	Q ≥30 ms	1
aVL	Q ≥30 ms	1
(2)	R/Q ≤ 1	1
aVF	Q ≥50 ms	3
(5)	Q ≥40 ms	2
	Q ≥30 ms	1
	R/Q ≤ 1	2
	R/Q ≤ 2	1
V1	Any Q	1
(1)		
V1	R/S ≥1	1
(4)	R ≥50 ms	2
	R ≥1 mV	2
	R ≥40 ms	1
	R ≥0.6 mV	1
	Q & S ≤0.3 mV	1
V2	Any Q	1
(1)	R <R V1	1
	R ≤10 ms	1
	R ≤0.1 mV	1
V2	R/S ≥1.5	1
(4)	R ≥60 ms	2
	R ≥2 mV	2
	R ≥50 ms	1
	R ≥1 mV	1
	Q&S ≤0.4 mV	1
V3	Any Q	1
(1)	R ≤20 ms	1
	R ≤0.2 mV	1
V4	R/Q ≤1	1
(3)	R/Q ≤0.5	2
	R/S ≤0.5	2
	R/Q ≤1	1
	R/S ≤1	1
	R ≤0.7 mV	1
V5	Q ≥30 ms	1
(3)	R/Q ≤1	2
	R/S ≤1	2
	R/Q ≤2	1
	R/S ≤2	1
	R ≤0.7 mV	1
V6	Q ≥30 ms	1
(3)	R/Q ≤1	2
	R/S ≤1	2
	R/Q ≤3	1
	R/S ≤3	1
	R ≤0.6 mV	1

Only one criterion per cell is used. If several criteria within a cell are met, the one with the most points is used. The highest possible points that can be given for each lead is presented below the lead within brackets.

1.6. Other automated/visual decision supports

1.6.1. Computed electrocardiographic imaging

Computed electrocardiographic imaging (CEI) is a complicated automated method which converts the 12-lead ST-J amplitudes into a body-surface potential map, which in turn is translated into a 17-segment bullseye map of the left ventricle (Fig. 22). On this map the location of the maximal epicardial potential is depicted using different colors; red (maximum), yellow (intermediate) and green (minimal) [177]. This method was tested for a large set of ECGs with ST-segment deviation due to different etiologies (STEMI, pericarditis, early repolarization, LVH, pre-excitation). After a 1-hour tutorial on how to interpret CEI images, 3 physicians interpreted 276 CEI images and their results were compared to STEMI criteria. Sensitivity for STEMI criteria was 61% for all 3 major coronary vessels, but markedly higher for LAD occlusion (74%) compared to LCx occlusion (34%). Sensitivity using CEI ranged from 51 to 76% for the three observers. For LCx occlusion, the performance was higher for all three observers of CEI images (59, 71, and 71%) compared to STEMI criteria. Specificity ranged from 88 – 96%, compared to 78 % for STEMI criteria. Specificity was markedly higher for pericarditis (93 – 100% using CEI, compared to 8 % for STEMI criteria) [109].

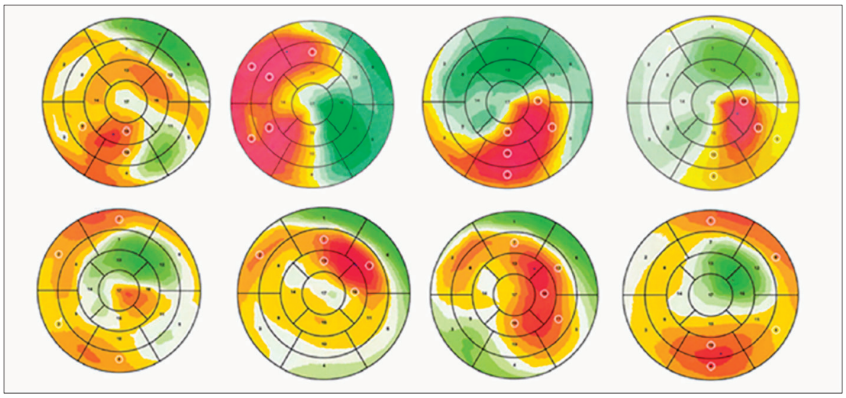

Figure 22. Bulls-eye plots of Computed Electrocardiographic Imaging (CEI).

The upper row displays images from patients undergoing balloon occlusion of a coronary artery, from left to right: prior to occlusion; balloon occlusion of LAD; RCA and LCx. *The lower row* displays images from patients with non-ischemic ST deviation, from left to right: pre-excitation; pericarditis; early repolarization syndrome; left ventricular hypertrophy.

1.6.2. Vessel-specific leads

Vessel-specific leads (VSL) were derived from body-surface potential mapping performed during coronary balloon inflation in patients undergoing PCI for stable angina. Each of 3 VSL was designed for optimal detection of acute occlusion of LAD, RCA or LCx. A transformation matrix was developed so that information in the 12-lead ECG could be translated into these 3 VSLs [178]. This method has been modified since its development, e.g. by including separate thresholds for patients with LVH, and has been shown to be superior to STEMI criteria regarding both sensitivity and specificity in detection of acute coronary occlusion [110, 111]. However, validation in a clinical setting has not been performed.

1.7. Cardiac magnetic resonance imaging in the assessment of acute myocardial ischemia

Ischemia due to acute coronary occlusion leads to depolarization and repolarization abnormalities, diastolic and systolic dysfunction, and myocardial edema and eventually myocardial necrosis. Depending on collateral circulation, pre-conditioning or individual demand, the "window of opportunity" to prevent complete irreversible myocardial injury varies [179]. Myocardium at risk (MaR) is defined as the amount of myocardium being hypoperfused during ischemia. The hypoperfused myocardium can either eventually be infarcted or else partially or fully salvaged due to either active or spontaneous reperfusion [32]. When determining the ability of electrocardiographic findings in estimating the extent of ischemia, the initial MaR, rather than the final infarct size, is the patophysiological equivalent. Previously, MaR was determined by MPI, which requires intravenous injection of a radioactive tracer before revascularization [180]. Later, CMR has proved to accurately depict the amount of ischemic myocardium and has the practical advantage that no injection is needed before revascularization. Also, the patient is not exposed to ionizing radiation. Myocardial ischemia causes interstitial edema by increasing cellular osmolarity and (eventually) membrane permeability due to plasma membrane rupture [181]. Estimation of MaR by CMR can be done by using T2-weighted short tau inversion recovery (T2-STIR), which highlights myocardial edema [182-184] (Fig. 23). Using this approach, imaging can be performed after the acute event. According to a validation study by Carlsson et al (2009), the amount of edema was similar within 1 week from revascularization [182]. MaR can also be

assessed by evaluating contrast-enhanced time-resolved balanced steady state free precession sequences (CE SSFP) [185, 186]. In study II, estimation of MaR as well as the location of ischemia using EDS-MI is validated using CMR as the reference standard.

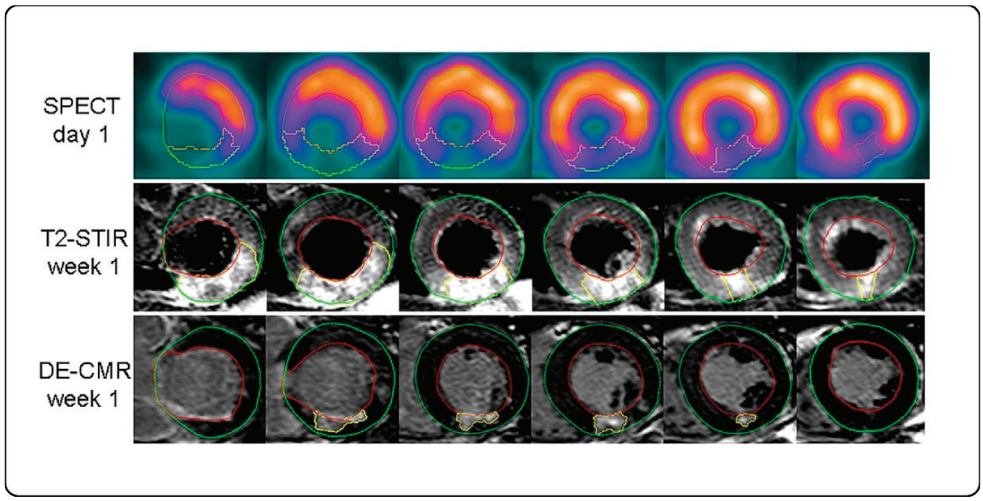

Figure 23. Myocardium at risk by single photon emission computed tomography (*upper panel*) and T2-STIR cardiovascular magnetic resonance (CMR) imaging (*middle panel*) and final infarct size by delayed-enhancement CMR images (*lower panel*) in a patient with acute STEMI who underwent percutaneous coronary intervention. The green line delineates the epicardium and the red line delineates the endocardium. In the middle panel, the myocardium at risk is delineated in yellow. The difference between the myocardium at risk and the final infarct size (delineated in yellow in the images in the lower panel) defines the salvaged myocardium after reperfusion. Myocardium at risk can also be shown as enhanced myocardium in steady-state free precession cine images after gadolinium contrast agent administration [185, 186]. Reprinted with permission from Carlsson et al [182].

1.8. Smartphone 12-lead ECG

The third study in this thesis addresses a potential pitfall when a smartphone is used to record a 12-lead ECG. In recent years smartphone cardiology technologies have been introduced. These technologies have mainly focused on arrhythmia and in general apply either one of the following two techniques: a) using the phone's camera and lamp as a photoplethysmographic sensor to detect one's pulse, or b) using external electrodes, ECG amplifier and a transmitting device that, for example, can be built into a phone case and connected to an application (app) in the smartphone

[187]. Using the latter technique, one-lead recording of ECG has been validated for the diagnosis of atrial fibrillation. By placing a finger from each hand onto each of the two electrodes, lead I can be recorded [188]. Accordingly, lead II and III could be recorded by placing one of the electrodes onto the left leg and a finger on either the right hand (lead II) or the left hand (lead III) on one electrode.

If a smartphone app could be used to record all 12 ECG leads, this would have the potential to replace the conventional 12-lead ECG in the very early detection of acute coronary occlusion, e.g. immediately upon symptom onset at the patient's home. Furthermore, such technologies could be an inexpensive substitute for ECG machines in healthcare settings where ambulance infrastructure is under-developed, or ECG machines are scarce.

In 2015, a pilot study describing the use of a smartphone device for recording a 12-lead ECG in the assessment of acute myocardial ischemia was performed [189]. The smartphone 12-lead ECG recording included some differences compared to the standard 12-lead ECG. For example, the leads were sequentially recorded, instead of simultaneously, as in the standard ECG recording. Also, the reference electrode for the chest leads was different compared to the standard ECG, in which chest leads are created by subtracting the potential at the Wilson central terminal (WCT) from the potential at each chest electrode. In the smartphone 12-lead ECG application, the right or the left arm was used as reference instead of the WCT [189, 190]. The use of the right or left arm instead of the WCT reference results in different ST-J amplitudes. How the diagnostic accuracy in STEMI detection is affected was not known. Since, any ECG waveform, as it would appear in the smartphone application, can be calculated from the standard chest leads (V leads) and the relevant augmented lead (aVR or aVL) in the conventional 12-lead ECG, smartphone ST-J amplitudes can be calculated from standard ECG amplitudes (Fig. 24).

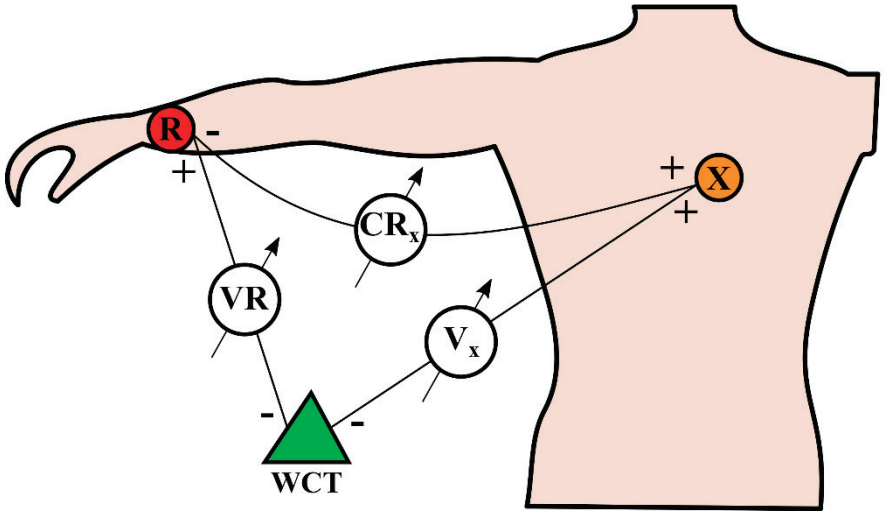

Figure 24. The lead CR_x describes the potential difference between chest lead electrode *x* and the right arm electrode (*R*). According to Kirchoff's voltage law, the sum of voltages in a closed circuit is zero, $VR + CRx + (-)Vx = 0$, $CRx = Vx - VR$. V_x is known from the chest lead amplitudes in the 12-lead ECG. *VR* can be calculated from *aVR* in the 12-lead ECG. $VR = R - WCT$, i.e. the potential difference between *R* and Wilson central terminal (*WCT*; $^1/_3$ (*R* + the potential at the left arm electrode (*L*) + the potential at the left leg electrode (*F*)). *aVR* is the potential difference between *R* and the "Goldberger terminal", in this case (*L* + *F*)/2.

$$aVR = R - \frac{(L+F)}{2}, \qquad L + F = 2(R - aVR)$$

$$VR = R - \frac{(R + L + F)}{3} = R - \frac{(R + 2(R - aVR)}{3} = \frac{2\,aVR}{3}$$

Thus, when the right arm electrode is used as reference instead of WCT, the chest lead amplitude CRx = Vx – $^2/_3\,aVR$. Similarly, when the left arm is used as reference: $CL_x = V_x - {}^2/_3\,aVL$.

Both the left arm and the right arm electrodes as reference for recording chest leads have been used in clinical practice, before WCT was included in the standard procedure [191-193]. Since physicians, nowadays, are familiar with the ECG appearance when conventional V leads are used, and diagnostic criteria are based on these ECG amplitudes, any difference in either pattern or amplitude introduced by recording the chest lead differently may have important clinical implications.

The differences between conventional chest lead amplitudes and CR/CL leads, as suggested for use in the smartphone 12-lead ECG, are evaluated in study III.

1.9. Other electrocardiographic changes during ischemia

STEMI amplitude criteria represent an oversimplification of ECG interpretation in the setting of suspected ischemia. Several other electrocardiographic changes occur during ischemia and have been suggested for improved prediction of outcome.

Reciprocal ST depression, i.e. ST-segment depression in leads spatially opposite to those who present with ST elevation, has been suggested to be used both for prognostic and diagnostic purposes. The most commonly appreciated reciprocal ST depression is that of ST depression in inferior leads in patients with anterior ST elevation. Otto et al evaluated various ECG changes among 428 patients with chest pain of presumed ischemic origin in a prehospital setting for the diagnosis of acute myocardial infarction. If ST elevation was present with concomitant reciprocal ST depression, the positive predictive value increased from 49 to more than 90% [194]. Not only does reciprocal ST depression predict an ischemic origin, it also holds prognostic information, since such an ST pattern is more common in patients with proximal LAD occlusion, than in patients with distal occlusion, and thus predicts a larger ischemic area [195]. Both takotsubo cardiomyopathy and LAD occlusion may present with anterior ST elevation. Reciprocal ST depression, is, however, more common in patients with anterior ST elevation due to LAD occlusion than due to takotsubo cardiomyopathy [141]. In patients with inferior ST elevation, reciprocal ST depression in aVL has been suggested to be used to differentiate STEMI from pericarditis. Bischof et al conducted a retrospective study in which they described the presence ST depression in aVL in patients with STEMI with acute occlusion of a culprit artery perfusing the inferior wall as well as in patients with a clinical diagnosis of pericarditis. Among patients with acute coronary occlusion, all patients (N=154) had ≥0.25 mV ST depression in aVL, but none of the 49 patients with pericarditis [97].

PR depression has been described as a sensitive marker for pericarditis. Porela et al showed that the PPV for pericarditis was high (97%) if it was present in both limb leads and precordial leads [196]. PR depression is also more prevalent in patients with takotsubo cardiomyopathy, than in STEMI [143]. However, PR depression may occur in patients with STEMI, for example due to atrial infarction [69, 197].

ST changes during ischemia reflect altered repolarization due to changes in the action potentials in the ischemic myocardium [55]. Changes during depolarization are also present [198], albeit often seldom used in clinical practice. During ischemia, QRS prolongation, diminished S-wave amplitudes or increased R-wave amplitudes have been described and attributed to slowed conduction in either the Purkinje fibers or

within the myocardium [199]. S-wave disappearance in leads with Rs configuration or J-point elevation above 50% of the R-wave amplitude in leads with qR configuration are referred to as terminal QRS distortion, and have been shown to predict a poor prognosis [200-202]. Absence of S waves, as a sign of severe ischemia (grade III) according to Birnbaum et al, was applied only to leads V1 and V3, since those leads normally have a terminal S wave [200]. In a recent paper by Lee et al, terminal QRS distortion was suggested to be used in the differential diagnosis of anterior STEMI and early repolarization. In that study, terminal QRS distortion, was considered present if both S wave and J wave in leads V2 and V3 were absent. None of the patients with anterior ST elevation due to early repolarization had terminal QRS distortion according to this definition.

Thus, previous studies have reported different strategies to differentiate STEMI from specific non-ischemic condition using reciprocal ST-segment changes, PR depression or terminal QRS distortion [97, 141, 143, 196, 203]. However, in clinical reality, the differential diagnosis is rarely restricted to two diagnoses. These electrocardiographic changes that may assist in the differential diagnosis between STEMI and non-ischemic ST elevation (early repolarization, perimyocarditis, takotsubo cardiomyopathy) are evaluated in study IV.

1.10 Diagnostic yield of STEMI criteria

The clinical performance of a diagnostic test can be measured in different ways (Fig. 25). Sensitivity and specificity are two frequently encountered measures. Sensitivity is the proportion of true positive test results among all patients who have the target disease, i.e. it describes the ability of the test to identify an individual with the disease. Specificity is the proportion of true negative tests among all patients who do not have the disease, i.e. the ability of the test to identify an individual without the disease. An ideal test would have both high sensitivity and specificity, but these measures are inversely related. Consider a test with a certain cut-off value for determining the presence of disease, e.g. values above this threshold indicates a positive test result. By decreasing the cut-off sensitivity increases, but specificity decreases [204]. Whether the values for sensitivity and specificity are acceptable or not depends on the clinical scenario. For example, the consequences of a false negative result may be far worse than the consequences a false positive diagnosis, and a higher sensitivity would then be preferred. In some screening situations, high specificity is preferred. If serial testing is used, false positive results from a test with

high sensitivity can be effectively excluded by a confirmatory test with high specificity. No information on disease severity is provided by sensitivity and specificity values. If the cut-off used in the test is related to disease severity, it is more likely that patient with severe disease are positive than patients with less severe disease.

Sensitivity and specificity are measures that result from studies of diagnostic accuracy in a setting where the diagnosis is already known, based on a reference standard for that diagnosis. The prevalence of disease in such a study rarely reflects the true prevalence in the population [205]. If the prevalence of the disease in the population in which the test will be applied is known, predictive values of the test can be determined. The positive predictive value (PPV) of a test, calculated as the proportion of patients with a true positive test among all patients with a positive test, gives us the probability that a patient with a positive test result indeed has the disease. The negative predictive value (NPV), calculated as the proportion of patients with a negative test among all patients with a negative test, instead gives us the probability that a patient with a negative test result is free from disease [204]. If the prevalence of disease is different than when the diagnostic accuracy of a test was determined, the predictive values will change (Fig. 26).

	Status of the patient according to reference standard		
Test result	Has the condition	Does not have the condition	
Positive	A (true positive)	B (false positive)	A/(A+B) **Positive predictive value**
Negative	C (false negative	D (true negative)	D/(C+D) **Negative predictive value**
	A/(A+C) **Sensitivity**	D/(B+D) **Specificity**	

Figure 25. Sensitivity, specificity and predictive values.
The boxes are color coded to indicate which calculation each box is included in. For example, box A is coded in yellow and red and includes the number of patients who both have the condition and a positive test result (*true positives*). The number in box A is used for calculating both sensitivity (*yellow*) and the positive predictive value (*red*). Similarly, box C is yellow and green, since the number of false negatives is included in both calculation of sensitivity (*yellow*) and negative predictive value (*green*).

Disease prevalence 50%

Test result	STEMI	No STEMI	
Positive	400	100	**PPV = 80%**
Negative	100	400	**NPV = 80%**
	Sensitivity = 80%	Specificity = 80%	

Disease prevalence 2%

Test result	STEMI	No STEMI	
Positive	16	196	**PPV = 5%**
Negative	4	784	**NPV = 99%**
	Sensitivity = 80%	Specificity = 80%	

Figure 26. Diagnostic accuracy for the same test in two populations with different prevalence of STEMI

The boxes are color coded as in figure 25: the boxes are color coded to indicate which calculation each box is included in. For example, the upper left box is coded in both yellow and red and includes the number of true STEMI patients. This number is used for calculating both sensitivity (*yellow; true positives / all STEMI patients*) and the positive predictive value (*red; true positives / all patients with a positive test*). Boxes with green color are included in the calculation of negative predictive value, and boxes with blue color in the calculation of specificity.

Sensitivity and specificity are the same in both examples, but the prevalence of STEMI is lower in example A than in B, which affects the predictive values.

Abbreviations: STEMI: ST-elevation myocardial infarction; PPV: positive predictive value; NPV: negative predictive value

The prevalence of AMI, or STEMI, in settings in which ECGs are recorded has changed over the years. ECG machines are available at any primary health care center, in ambulances and emergency departments. If people change their behavior of seeking medical assistance or if ECGs are applied in more patients in the ambulance than before, the predictive values of the test will be different than at the time it was tested. In the United States, a declining incidence of STEMI at the emergency department has been reported, by approximately 25% between 2006 and 2011 [73]. With increasing total ED visits, as well as for patients with chest pain, this leads to a decreased prevalence of STEMI at the ED [74]. One explanation is that an increased proportion of patients with typical STEMI symptoms and ECG changes are transferred directly from the ambulance to the cardiac care unit, i.e. bypassing the ED. A declining incidence may also be due to better treatment of risk factors for AMI, such as hypertension and diabetes, improved smoking habits etc., resulting in fewer complications of acute coronary events in patients with stable ischemic heart disease.

Few recent studies have analyzed the accuracy of STEMI criteria in this setting [75]. The diagnostic accuracy of STEMI criteria in chest pain patients at the ED is evaluated in study V. In that study, the use of extended STEMI criteria, described above *(see section 1.3.)* is also assessed, as well as the added value of reciprocal ST-segment changes.

2. Aims of the work

General aim: The general aim of this thesis was to assess different aspects on electrocardiographic detection of myocardial ischemia due to acute coronary occlusion: a) improved identification of patients with acute coronary occlusion by an automatic decision support (studies I and II), b) evaluation of smartphone 12-lead ECG to be used in early detection of acute coronary occlusion (study III), c) consideration of electrocardiographic changes other than ST-J amplitudes in STEMI differential diagnosis (study IV), d) the diagnostic yield of STEMI criteria at the ED (study V), and finally e) improved detection of acute coronary occlusion by extending the conventional STEMI amplitude criteria (study V).

Study I: The primary aim of this study was to determine the upper limit of normal of the ischemic scores in individuals without myocardial ischemia in order to create a basis for a clinically applicable algorithm for detection of acute coronary occlusion. A secondary aim was to apply these limits to ECGs from patients with acute coronary occlusion.

Study II: In study II, the primary aim was to optimize the diagnostic accuracy of EDS-MI in patients with verified acute coronary occlusion as well as patients with non-ischemic ST deviation and compare its performance with STEMI criteria. We also aimed to describe the agreement between ischemia localization and estimation of myocardium at risk between cardiovascular magnetic resonance and EDS-MI with or without Selvester QRS scoring.

Study III: We aimed to compare the chest-lead ST-J amplitudes, using either the right or left arm electrode as reference instead of the Wilson central terminal, to those in the conventional 12-lead ECG.

Study IV: In this study, we aimed to study whether reciprocal ST-segment changes, PR depression, ST-segment convexity or electrocardiographic findings of terminal QRS distortion can discriminate STEMI from non-ischemic conditions in a group of patients with different ST-elevation etiology.

Study V: We aimed to evaluate the diagnostic accuracy of conventional and extended ECG criteria for STEMI in the detection of AMI due to acute coronary occlusion, as well as the incremental value of reciprocal ST depression, in a large cohort of unselected emergency department chest pain patients.

3. Material and methods

3.1. Study populations

Two datasets of patients with verified acute myocardial ischemia were included in the thesis, here referred to as "the Leiden material" and "the SOCCER material". The Leiden material was included in study I and II, and the Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER) material in study II, III and IV. Two datasets of patients without myocardial ischemia were also included. One of them includes of 360 randomly selected patients without acute myocardial ischemia, and the other includes patients with non-ischemic conditions with ST deviation (early repolarization, left ventricular hypertrophy, perimyocarditis and takotsubo cardiomyopathy).

In addition, patients from the Swedish cohort of the Evaluation of Unknown Predictors of Electrocardiographic Changes – a Transnational study (EXPECT) database were included in the thesis. This dataset consists of all patients admitted to the ED at Skåne University Hospital in Lund and Helsingborg Hospital between Jan 2010 and Dec 2014 who had an ECG recorded upon admission. Patients from the EXPECT database are included in study V. Also, a subgroup of this dataset was included in study IV. The different study populations are summarized in Table 3.

3.1.1. The Leiden material

In study I and II, 53 patients with acute coronary occlusion from a previous study [162] were included. These patients were retrospectively retrieved from a database at Leiden University Hospital between 2008 and 2010. All patients had been triaged for primary PCI due to chest pain (<2 hours symptom duration) and showed evidence of single-vessel occlusion at coronary angiography, defined as TIMI flow grade 0 and restoration of blood flow after PCI [162, 206]. ECGs with poor signal quality, left or right bundle branch block were excluded. If multiple ECGs were

available, the ECG nearest in time to the PCI procedure was included. One of the patients was excluded due to misplaced electrodes. Nineteen patients had an LAD occlusion, 24 patients an RCA occlusion and 9 patients had an LCx occlusion.

3.1.2. The SOCCER material

In study II, 65 patients from the SOCCER study [207] were included. The SOCCER study was a randomized controlled trial conducted in Lund and Malmö, Sweden between Jan 2012 and Aug 2015, with the aim of evaluating the effect of supplemental oxygen in STEMI patients accepted for PCI. The database included 95 patients, by whom 46 had been treated with supplemental oxygen and 49 patients instead received "room air" in the ambulance. These patients underwent CMR 2 – 6 days after STEMI to determine the MaR and final infarct size. In study II, only patients with angiographic evidence of acute coronary occlusion (complete occlusion or near occlusion with evidence of thrombus according to the angiographic report) (65 out of 95 patients) were included.

In study III, all patients from the SOCCER study who met STEMI criteria (Table 1) were included (n=74), regardless of the angiographic result.

In study IV, all patients from the SOCCER study with ≥0.1 mV ST-J elevation in at least one lead were included (n=85).

3.1.3. Non-ischemic patients

In study I, ECGs were recorded before performing an exercise ECG stress test, a MPI test, a Holter monitoring or a pre-operative ECG evaluation (non-cardiac surgery). These patients thus had a very low likelihood of having acute transmural myocardial ischemia. Patient inclusion was performed consecutively from a set starting date (April 1st –2015) until the database included 30 patients for each sex, and each age decade (30–39, 40–49, 50–59, 60–69, 70–79, 80–89). ECGs with poor signal quality or other technical deficiencies, and ECGs with a QRS width exceeding 120 ms were not included. These patients were also included in study III.

In study II, 135 patients with non-ischemic ST deviation were included (perimyocarditis (n=72), takotsubo cardiomyopathy (n=23), LVH (n=26) and early repolarization (n=14). Of these 135 patients, 66 were included from a previous study [109]; perimyocarditis (n=26), LVH (n=26) and early repolarization pattern (n=14). These patients were identified by a search process in the digital ECG database at Skåne University Hospital in Lund. ECGs were re-interpreted by an expert ECG

reader and clinical diagnoses were confirmed through patient records. These patients were also included in study III. The remaining 69 of the 135 patients with non-ischemic ST deviation included in study II (perimyocarditis (n=46) and takotsubo cardiomyopathy (n=23)) were retrospectively identified among patients who had been referred for a diagnostic CMR. These patients were included if a final clinical diagnosis of acute peri-/myocarditis or takotsubo cardiomyopathy was made. All patients with takotsubo cardiomyopathy underwent acute coronary angiography without significant coronary artery stenosis and had imaging evidence of transient ventricular dysfunction and recovery at follow-up CMR or echocardiography. These patients were also included in study IV.

3.1.4. The EXPECT material

The Swedish part of the EXPECT database [208] consists of all patients who had an ECG recorded on arrival at the EDs of Skåne University Hospital in Lund or Helsingborg General Hospital between January 1, 2010 and December 31, 2014. In study IV, 35 patients with early repolarization from this database were included. These patients were identified by evaluating all ECGs in the database, recorded between Oct and Dec 2014, with ≥0.1 mV ST elevation in any lead (except aVR) for early repolarization pattern criteria fulfillment. Patients were not included if they had elevated troponins, or a cardiac diagnosis at discharge (ACS, perimyocarditis).

In study V, all patients ≥30 years in the Swedish part of the EXPECT database, with a chief complaint of chest pain, who had an ECG recorded within 4 hours of presentation to the ED were eligible for inclusion. Patients were excluded if the ECG were of inadequate quality, QRS duration ≥120 ms or if ECG findings of LVH were present. Data had been extracted from the Region Skåne patient records, the regional digital ECG and clinical chemistry databases, the Swedish Pharmacy Register [209], and the Swedish Population Register [210]. We further cross-linked the database with the Swedish Coronary Angiography and Angioplasty Register (SCAAR) [211]. SCAAR includes practically all patients who undergo coronary angiography or percutaneous coronary intervention (PCI) in Sweden and is a part of the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) register.

Table 3. Overview of datasets included in the thesis

Database	N (total)	Inclusion criteria	Exclusion criteria	Included in study
SOCCER material [207]	95	Clinical STEMI patients referred for primary PCI	Previous myocardial infarction, contraindications to MRI, QRS duration ≥120 ms	II (patients with acute coronary occlusion III, IV (patients with ST elevation)
Leiden material [162]	53	Patients triaged for primary PCI. Evidence of acute coronary occlusion	Previous myocardial infarction, QRS duration ≥120 ms	I, II
Patients without acute myocardial ischemia	360	ECG recorded before an exercise test, MPI, Holter monitoring, preoperative non-cardiac surgery evaluation	QRS duration ≥120 ms	I, III
Patients with non-ischemic ST deviation, dataset I [109]	66	Interpretative statement in the ECG records of either pericarditis, early repolarization or LVH	Inadequate ECG quality, atrial flutter, QRS duration ≥120 ms	II, III
Patients with non-ischemic ST deviation, dataset II	69	Perimyocarditis or takotsubo cardiomyopathy as clinical discharge diagnosis and appropriate findings at CMR	Inadequate ECG quality, coronary stenosis at coronary angiography (takotsubo) QRS duration ≥120 ms	II, IV
EXPECT [208]	19932	Age ≥30 years, chest pain as chief complaint, ECG recorded within 4 hours of arrival	Inadequate ECG quality, QRS duration ≥120 ms, ECG findings of LVH	IV (35 patients with early repolarization) V

3.2. Statistical analysis (general)

Continuous variables are presented as means and standard deviations if normally distributed, otherwise as medians and interquartile ranges (IQR). For assessment of correlation between variables, Pearson r correlation test or Spearman's rho were used. Student's t test was used for comparison of means between groups, and Mann Whitney U-test for comparison of medians. -2 test was performed to compare proportions between groups. Agreement between different methods or between different readers was assessed by Kappa statistics. When calculating odds ratios, logistic regression was used.

Sensitivity was calculated as true positives / number of patients with the condition tested for, specificity as true negatives / number of patients without the condition tested for, PPV as number of patients with a true positive test / number of patients with a positive test result, NPV as number of patients with a true negative test result / number of patients with a negative test result. Positive likelihood ratio (LR+) was calculated as sensitivity / (1 – specificity), and negative likelihood ratio (LR-) as (1 – sensitivity) / specificity. Sensitivity, specificity, positive and negative predictive values, and likelihood ratios were presented with 95% confidence intervals. Statistical analysis was performed using SPSS Statistics (Version 25; SPSS Inc., IBM Corporation, NY, USA). A p-value of <0.05 was considered statistically significant.

4. Design and analyses

4.1. Study I and II

Study I and II dealt with the development and validation of EDS-MI. In study I, the normal variation of EDS-MI was explored in order to establish reference values for the ischemic wall scores. These test limits were then applied to patients with verified acute coronary occlusion. In study II, the reference values for EDS-MI were tested in patients with acute coronary occlusion or with non-ischemic ST deviation (perimyocarditis, takotsubo cardiomyopathy, early repolarization).

As described above (*section 1.4.*), a score is generated for each 12 segments in the left ventricle, by conversion of ST-J amplitudes in the ECG into an ST vector. In study I, in which EDS-MI is referred to as "the Olson method", ischemic wall scores were calculated by adding the segmental scores for each wall (septal (segments 1 – 3), anterior (segments 4 – 6), lateral (segments 7 – 9) and inferior (segments 10 – 12)). Mean ischemic wall scores were calculated for each age decade (30 – 39, 40 – 49, … , 80 – 89) for each sex separately. When these reference values for the test had been established, they were compared to the ischemic wall scores for patients with acute coronary occlusion, and sensitivity and specificity were calculated. These reference values were used also in study II. In that study, the elevation angle of the ST vector (positive angles below the transverse plane and negative above) was also explored in an attempt to improve test accuracy.

In study II, Selvester QRS scoring was calculated for all patients with STEMI. Selvester QRS scoring is a scoring system for assessing infarcted myocardium based on Q-, R- and S-wave changes (*section 1.5.1*). This was included in the study to adjust for the effect of already infarcted myocardium when estimating the MaR based on ST-elevation parameters. For example, if two patients with coronary occlusion experience loss of myocardial perfusion to the same extent, but one of them already has large areas of necrosis, the ST elevation is expected to be lower than in the patient

without necrotic myocardium. MaR was therefore calculated according to EDS-MI both with and without QRS scoring. MaR and location of ischemia by EDS-MI was compared to that of CMR.

4.1.1. Ethics

For study I, the study protocol was approved by the local advisory board on medical ethics. The database did not include any sensitive personal information and no potential harm to the study participants could be identified. The patients with acute coronary occlusion had been included in a prior study of EDS-MI [119]. Study II was approved by the Regional Ethical Review Board in Lund (Dnr 2017/251).

4.1.2. Statistical analyses

Upper limits of normal for each wall score were calculated with 95% and 99% confidence using mean + 1.96 and 2.58 standard deviations, respectively. A Pearson r correlation test was used to describe the correlation between the ischemic scores and height, weight and body-mass index (BMI). Student's t test was used to compare mean ischemic wall scores between different groups.

Mann–Whitney U test was used for comparison of median elevation angles between groups. McNemar's test was used for comparison of sensitivity and specificity between EDS-MI and STEMI criteria. Difference in MaR is presented as a modified Bland–Altman plot. Cohen's kappa test was used to determine the level of agreement between the results for CMR and EDS-MI in localizing ischemia.

4.2. Study III

In Study III, the chest ST-J amplitudes as they would appear in the smartphone ECG, using either the right (CR leads) or the left arm (CL leads) as reference, were simulated by re-calculating the chest lead amplitude for 500 patients (74 patients with STEMI, 66 patients with non-ischemic ST deviation and 360 controls). The ST-J amplitude in a smartphone-ECG chest lead "x" was calculated as follows:

$$R\ as\ reference: CRx = Vx - \frac{2\ aVR}{3}$$
$$L\ as\ reference: CLx = Vx - \frac{2\ aVL}{3}$$

The simulated chest lead amplitudes were compared to those in the conventional 12-lead ECG (V leads).

4.2.1. Ethics

Ethical approvals by the ethical review board had been obtained for the studies from which the ECGs were included.

4.2.2. Statistical analyses

Student's t test was used for comparison of mean ST-J amplitudes between CR/CL leads and V leads. Pearson correlation test was used to assess correlation between ST-J amplitudes in CR/CL lead and V leads. When sensitivity and specificity was calculated, fulfillment of STEMI criteria in V leads was considered reference standard. For example, when STEMI criteria were met in both V leads and CR leads, the test result was considered true positive, and if they were met in CR leads but not in V leads, the result was considered false positive.

4.3. Study IV

In Study IV, other ECG findings than ST-elevation amplitudes were explored among patients with ischemic or non-ischemic ST elevation. The presence of PR depression, ST-segment convexity, J waves and terminal QRS distortion were assessed independently by three observers. Two observers, who were blinded to the study design as well as to clinical information, interpreted half of the ECGs each. TL interpreted all ECGs blinded to clinical information. The presence of these findings, as well as reciprocal ST depression were analyzed, regarding prevalence among patients with or without an ischemic condition as a cause of ST elevation.

J waves were defined as either QRS slurring or notching. QRS slurring was defined as a slowed inscription of the end of the QRS of a prominent R wave, initiated at least 0.1 mV above the baseline. QRS notching was defined as a positive deflection (entirely above the baseline) on the end of the downslope of a prominent R wave, at

least 0.1 mV to nadir from the baseline [118]. PR-segment depression was defined as depression of ≥0.05 mV compared to the TP segment, measured adjacent to QRS onset [143, 196]. For analysis of terminal QRS distortion, all QRS complexes were designated to either a qR morphology (including qRs, qRS, qR), Rs morphology (R-wave amplitude >S-wave amplitude, including Rs, Rsr, RsR, R), or other (QS and rS). All ECGs without pathological Q waves were then analyzed for fulfillment of terminal QRS distortion criteria. Terminal QRS distortion was considered present in leads with an initial R wave if the S wave and J wave were absent [203], and in leads with qR configuration if the J-point elevation exceeded 50% of the R-wave amplitude [200-202]. In this analysis, the inverted version of aVR (–aVR) was used instead of aVR.

Patients with anterior ST elevation (V2 – V4) were analyzed regarding presence of ST depression (≥0.025 mV and 0.05 mV respectively) in inferior leads (II, III and aVF) and of ST elevation and ST depression in aVR (≥0.025 mV and 0.05 mV). Patients with inferior ST elevation were analyzed regarding presence of ST depression in aVL and I, V2 and V3, and aVR (≥0.025 mV and 0.05 mV respectively). The cut-off of 0.025 mV has been used in previous studies on reciprocal ST-segment changes [97]. A cut-off of 0.05 mV was also studied, in order to explore whether this cut-off would change diagnostic accuracy by improving specificity.

4.3.1. Ethics

Ethical approvals by the regional ethical review board were obtained for the studies from which the ECGs were included.

4.3.2. Statistical analyses

χ-2 test was performed to compare proportions of prevalence of terminal QRS distortion, reciprocal ST-segment changes, PR depression and ST-segment convexity between groups. Odds ratios for the prediction of STEMI were calculated using a univariate binary logistic regression model. Variables with a p-value <0.05 at univariate analysis were entered into a multivariable model. Fleiss Kappa test was used to determine the level of inter-observer agreement.

4.4. Study V

In study V, the diagnostic yield of STEMI criteria among chest pain patients at two EDs were evaluated. Clinical outcomes were AMI and an occluded/near-occluded coronary artery at angiography, and AMI and occlusion/near-occlusion which was intervened upon (PCI or CABG). Besides conventional STEMI criteria (Table 1) [28]), extended STEMI criteria [76, 77] which include leads –V1 to –V3 and –aVL, –I, –aVR and –III (Fig. 9) were applied to all patients. Using the extended STEMI criteria, the following contiguous lead pairs were *also* considered for significant ST elevation: –III/aVL, I/–aVR, –aVR/II, III/–aVL, –aVL/–I, –I/aVR, –V1/–V2, –V2/–V3. For all leads, except –V2 and –V3, the ST-J amplitude criterion was set at $\geq$0.1 mV. For leads –V2/–V3 $\geq$0.05 mV was required.

We also analyzed the additive diagnostic value of reciprocal ST depression, i.e. ST depression (≥0.025 mV) in leads II, III or aVF in patients with anterior ST elevation (V2 – V4), or in aVL, I, V2 or V3 in patients with inferior ST elevation (II, aVF, III).

4.4.1. Ethics

The study was approved by the Regional Ethics Review Board in Lund (Dnr 2015/129 and 2018/705).

4.4.2. Statistical analyses

-2 test was used for comparison of frequencies between groups. Logistic regression was used to calculate the odds ratio for conventional and extended STEMI criteria in predicting patient outcomes.

5. Results and comments

5.1. EDS-MI for detection of acute coronary occlusion (Study I and II)

EDS-MI is described in detail above *(section 1.4.)*. In previous papers, EDS-MI has been shown to accurately predict the culprit artery in patients with acute coronary occlusion [159, 162]. Culprit artery prediction may be of use at the catherization laboratory, but before that patients with acute coronary occlusion must be accurately detected. Ischemia detection and localization is based on the calculation of ischemic scores. In a particular segment of the left ventricle, the score depends on the magnitude of the ST vector and the direction of this vector in relation to the left ventricular segment. If the magnitude of the vector is large and the vector has a direction that is perpendicular to a specific segment, the score will be high in that segment. The scores in each segment is then summed for each wall (septal, anterior, lateral and inferior). Hence, the method is completely based on the ST-J amplitudes but takes into account the spatial information, to a larger extent than does STEMI criteria. STEMI criteria, for example, does not consider the possible absence of ST elevation in patients with transmural ischemia of the lateral wall.

Ischemic wall scores were higher in men than in women, and higher in younger men than in older men. Therefore, the upper test limits were stratified by sex and by age in men, similar to STEMI criteria [28]. These limits were then applied to patients with acute coronary occlusion, of which all had ischemic wall scores above the 99% confidence limit. The upper test threshold could be increased further without any loss in sensitivity. Sensitivity was higher for EDS-MI than for STEMI criteria (100% (93 – 100) vs. 81% (68 – 89). Two examples of patient who were positive for ischemia using EDS-MI, but who did not meet STEMI criteria are presented in figure 27.

Thus, the results from study I indicated that the method also could be used for *detection* of ischemia. However, since very few patients without myocardial ischemia had significant ST elevation (only 3 patients met STEMI criteria), further studies on how the method would perform in patients with non-ischemic ST deviation was necessary. Likely, if ST deviation would have been present, even in the absence of ischemia, the scores could be high, and the specificity of the method would be inadequate. This issue was addressed in study II.

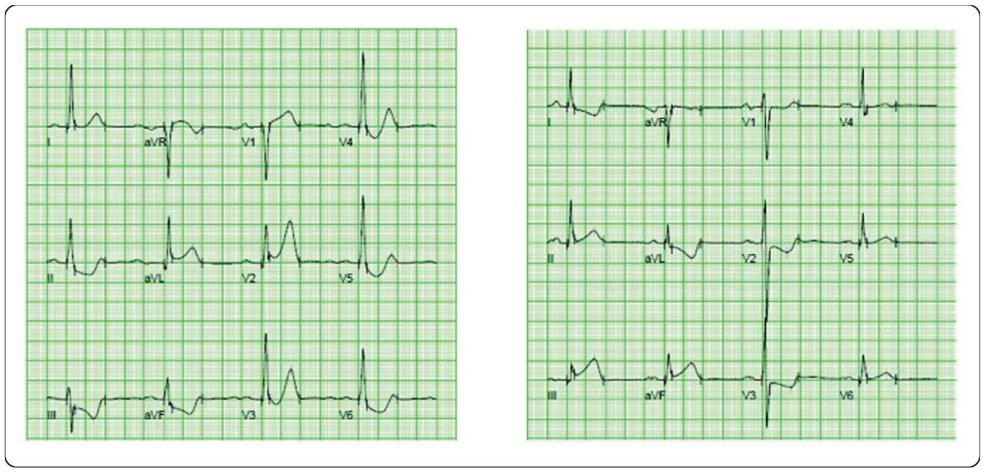

Figure 27.
Left image: ECG from a patient with acute LAD occlusion. ECG shows significant ST elevation in only one lead (aVL), non-significant ST elevation in V1 and V2, and ST depression in inferior leads, i.e. STEMI criteria are not met. Using EDS-MI, the ischemic wall score was highest for the anterior wall, well above the upper test limit, i.e. EDS-MI was positive for ischemia.

Right image: ECG from a patient with RCA occlusion. ECG shows ST depression in V2 – V3, significant ST elevation in lead III and sub-threshold ST elevation in aVF, i.e. STEMI criteria are not met. The highest ischemic wall score was located in the inferior wall and exceeded the suggested threshold for ischemia.

In study II, the thresholds established in study I were tested in patients with acute coronary occlusion as well as non-ischemic patients with ST deviation. When only the thresholds for the ischemic scores provided in study I were used, many non-ischemic patients were falsely classified as ischemic. This was somewhat expected, and we had therefore aimed to explore the additive value of including information on the ST vector in the cranio-caudal plane (the elevation angle). Could, for example, a patient with LAD occlusion with high ischemic scores in the anterior wall be differentiated from a patient with a non-ischemic condition who also presented with anterior ST elevation?

While maintaining a sensitivity of >90% (92%), specificity increased to 81% when criteria on the elevation angle of the ST vector were added to the test algorithm, based on the location of the largest ischemic score. In study I, detection of ischemia was based on calculation of the ischemic wall scores, which are the sum of scores of the basal, middle and apical wall segments. Due to the summation of scores in the basal, middle and apical segments, directional information regarding the elevation of the ST vector was lost; for example, superiorly and inferiorly directed ST vectors could yield the same ischemic wall score, even though the basal score is larger for a superiorly directed ST vector and the apical score is larger for a inferiorly directed ST vector. Patients with ischemia and those without ischemia could be differentiated by incorporating the elevation angle in the diagnostic algorithm. Since patients with perimyocarditis, for example, often present with ST elevation in both precordial and inferior limb leads [114], the ST vector will have a more inferior direction compared to patients with LAD occlusion, who often instead show reciprocal ST depression [195] (Fig. 28). A similar approach was used for patients with the maximal ischemic score in the inferior wall, but it was not needed for the septal or the lateral wall. Diagnostic accuracy was higher using EDS-MI compared to STEMI criteria (Table 4), but the selection of patients warrants further studies in non-selected chest pain populations.

Table 4. Sensitivity and specificity for EDS-MI and STEMI criteria

	EDS-MI	STEMI criteria	
Culprit artery	*Sensitivity*		p
All	92%	85%	0.035
LAD	90%	92%	1
RCA	94%	81%	0.016
LCx	93%	73%	0.25
Non-ischemic condition	*Specificity*		
All	81%	44%	<0.001
Perimyocarditis	76%	22%	<0.001
Takotsubo cardiomyopathy	70%	61%	0.75
Left ventricular hypertrophy	100%	96%	1
Early repolarization	93%	29%	0.004

Abbreviations: EDS-MI: Electrocardiographic Decision Support – Myocardial Ischemia; STEMI: ST segment elevation myocardial infarction; RCA: right coronary artery.
LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery.

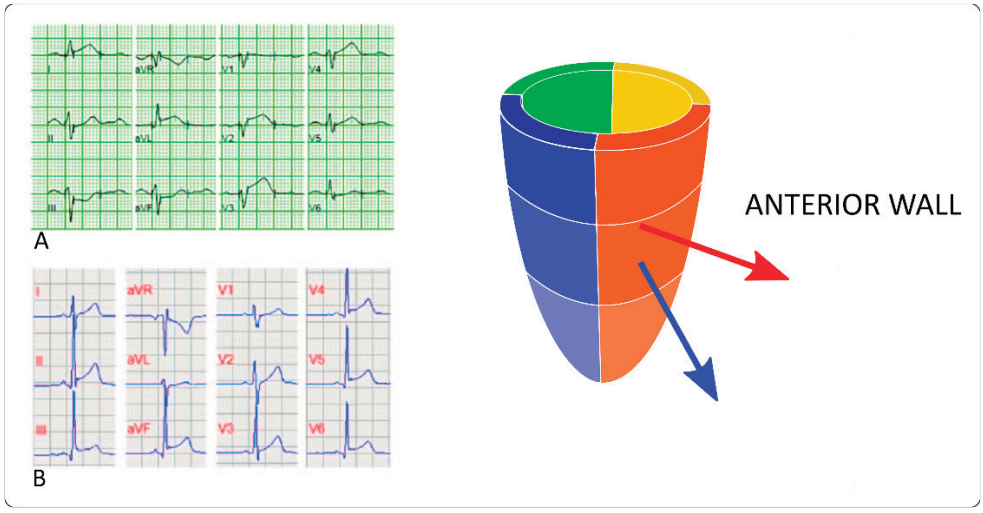

Figure 28. *Image A* shows an ECG from a patient with LAD occlusion. ECG shows anterior ST elevation and reciprocal ST depression in inferior leads. *Image B* shows an ECG from a patient with perimyocarditis, with both lateral and inferior ST elevation.

Both ECG met STEMI criteria and the ischemic wall scores exceeded the thresholds for the anterior wall. However, the ST vector has a more cranial direction in the patient with LAD occlusion (*red arrow, right image*) compared to the patient with perimyocarditis (*blue arrow*). When this information was included in the algorithm, only the patient with LAD occlusion was positive for ischemia.

5.2. EDS-MI for localizing and estimating the extent of myocardial ischemia (Study II)

In study II, both the ability of MaR estimation and ischemia localization by EDS-MI were assessed by comparing the results to that of CMR, which was performed in 63 STEMI patients. Mean MaR was 32% (±10) according to CMR, and 33% (± 10) according to EDS-MI when Selvester QRS scoring was included in the MaR estimation, and 17.5% (±10) without Selvester QRS scoring. Even though the bias was small, the variability was large (as shown in Fig. 29), clearly limiting the clinical value of the described extent of ischemia using EDS-MI. Although incorporating information on possibly infarcted areas (Selvester QRS scoring) is theoretically appealing, it is likely not entirely accurate. When Selvester QRS scoring was developed, it was intended to be used to assess chronic MI, not acute MI. Also, Q waves, which are an important part of the scoring, do occur in many STEMI patients, without necessarily representing irreversibly injured myocardium [84].

Further, the estimation of MaR using EDS-MI is based on a previous translation of the Aldrich scores into ischemic scores. However, in acutely revascularized patients, the correlation between the Aldrich score and myocardium at risk or final infarct size, is poor [212].

When location of ischemia was defined as the wall with the highest ischemic wall score for EDS-MI and for CMR as the wall with highest proportion of ischemic myocardium, EDS-MI correctly localized the ischemia in 71% of the cases (kappa value 0.59). If the septal and anterior walls were instead considered as the same location, representing a rough estimate of LAD territory, the proportion of observed agreements was 83% (kappa value 0.72). An example using EDS-MI for detection and localizing ischemia is depicted in Fig. 30.

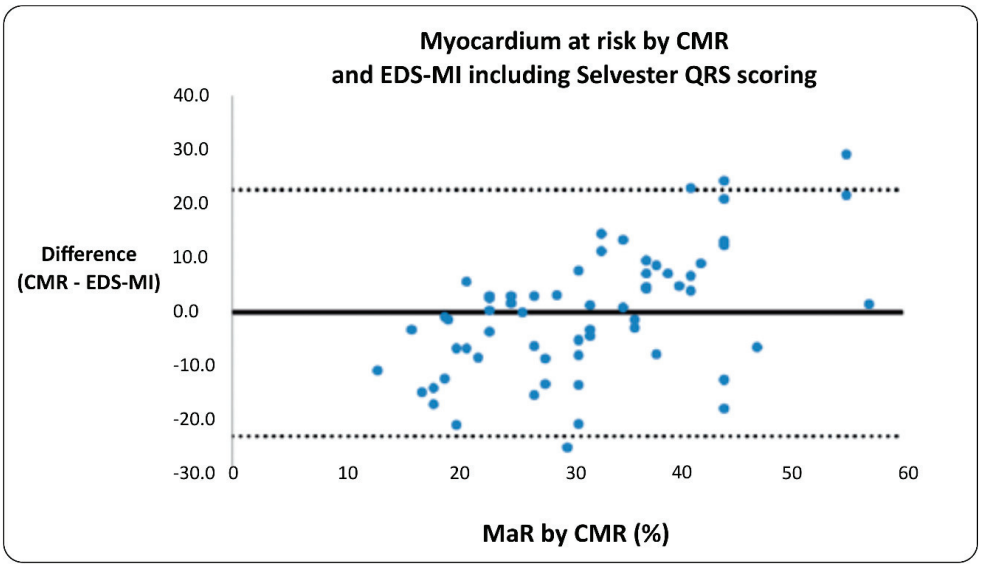

Figure 29. Modified Bland-Altman plot showing the difference in myocardium at risk between cardiovascular magnetic resonance and EDS-MI. The difference in myocardium at risk (CMR – EDS-MI) is depicted on the y axis and MaR according to reference standard (CMR) on the x axis. The mean bias between methods is small (*solid line,* ~1%), but the limits of agreement (*dotted lines,* 22.5%/-23.7%) are large. There is a tendency towards overestimation of MaR by EDS-MI in patients with smaller MaR by CMR, and underestimation by EDS-MI at higher MaR by CMR
Abbreviations: EDS-MI: Electrocardiographic Decision Support – Myocardial Ischemia; CMR: cardiovascular magnetic resonance imaging; MaR: myocardium at risk.

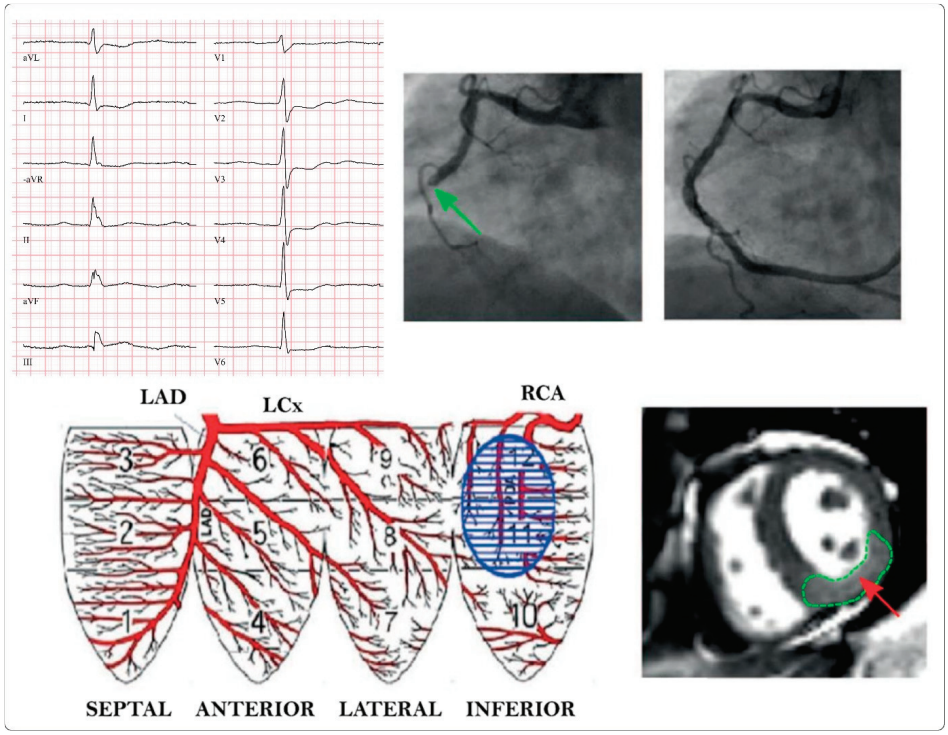

Figure 30. The image in the *upper left* shows an ECG with isolated ST elevation in III and precordial ST depression. The ECG does not meet STEMI criteria. The *upper middle and right* images show the result from the coronary angiography; a complete occlusion of the right coronary artery (*upper middle image, green arrow*), which is successfully treated with percutaneous coronary intervention (*upper right image*). The patient was positive for ischemia using EDS-MI, and ischemia was located in the basal and middle segments of the inferior wall (*lower left image*), concurrent with the location of ischemia at the CMR study on the *lower right image*, in which the ischemic area is delineated in green (*red arrow*). Abbreviations: EDS-MI: Electrocardiographic Decision Support – Myocardial Ischemia; CMR: cardiovascular magnetic resonance imaging.

5.3. Chest-lead ST-J amplitudes using arm electrodes as reference instead of the Wilson central terminal in smartphone ECG applications (study III)

In study III, chest-lead ST-J amplitudes, using either the right or left arm electrode as reference (CR or CL leads) were compared to those in the conventional 12-lead ECG (V leads). As expected, in patients with little or no ST deviation in either aVR or aVL, as in most non-ischemic patients, the difference in amplitude in CR or CL leads compared to those in V leads was small. In STEMI patients, when ST-J amplitudes in leads aVR and/or aVL were affected, changes of precordial-lead ST-J amplitudes were, in some cases, substantial (Fig. 31).

When fulfillment of STEMI criteria in the conventional 12-lead ECG was used as reference standard, sensitivity and specificity were 94% (87 – 98) and 95% (93 – 97) for CR leads; for CL leads sensitivity and specificity were 81% (71 – 88) and 97% (95 – 99). STEMI criteria were met in V leads in 51 STEMI patients using the conventional ECG. These patients had either significant ST elevation in two contiguous V leads only or in both V leads and in two contiguous limb leads. In 33 patients, STEMI criteria were met in V leads only. Among this latter group of patients, STEMI criteria were no longer met in 9% of these patients when CR or CL leads were used, i.e. these STEMI cases would have been missed if conventional STEMI criteria would have been applied to the smartphone 12-lead ECG. With conventional 12-lead ECG, STEMI criteria were fulfilled in V leads in 34 patients with non-ischemic ST deviation (pericarditis n=23, early repolarization pattern n=10, LVH n=1). Ninety-seven percent of these patients remained positive with CR leads and 71% with CL leads.

In patients with either ST elevation or ST depression in aVR or aVL, CR- or CL-lead ST amplitudes will be different compared to V-lead ST amplitudes. ST elevation in aVR or aVL may occur in proximal LAD occlusion [84, 90], resulting in diminished CR- or CL-lead amplitudes compared to V leads. If ST depression is present in aVR or aVL, which for example can occur in aVL in inferior STEMI, CR or CL leads could show a pattern of widespread ST elevation (ST elevation in both inferior and precordial leads). Such an ECG pattern may mimic a pericarditis pattern. In 9 of 23 of STEMI patients without significant ST elevation in the chest leads in the conventional ECG, ST elevation ≥ 0.1 mV appeared in the chest leads when CL leads were used and for two patients when CR leads were used. In patients with pericarditis, chest lead amplitudes were instead diminished when CL leads were used, which could obscure the typical pattern of widespread ST elevation [114].

Even though specificity was high for both CR and CL leads (95% vs. 97%), the use of CR leads increased the number of false positive STEMI from 3 to 15 patients in non-ischemic controls, i.e. a five-fold increase.

Several other pitfalls may occur when smartphone 12-lead ECG is used, such as the obvious risk of lead misplacement when applied by people without medical training. Also, unlike modern electrocardiographs in which the leads are recorded simultaneously, the leads are recorded sequentially by the smartphone, which can make J-point detection difficult. The timing of the J point, which affects diagnostic accuracy of ACS [213], may differ between conventional ECG and smartphone 12-lead ECG, since single-lead measurement has been shown to underestimate QRS duration [214].

Since ST-J amplitudes may differ significantly compared to conventional ECG recording this must be taken into account before implementing smartphone 12-lead ECG in clinical practice, either by changing interpretative criteria, or rather by attempting to develop a better substitute for the WCT, for example by estimating the temporal relation between the sequentially recorded limb leads. This would allow for calculation of aVL and aVR. In this way, the ST amplitudes in CL and CR leads can be transformed into ST amplitudes in the corresponding lead.

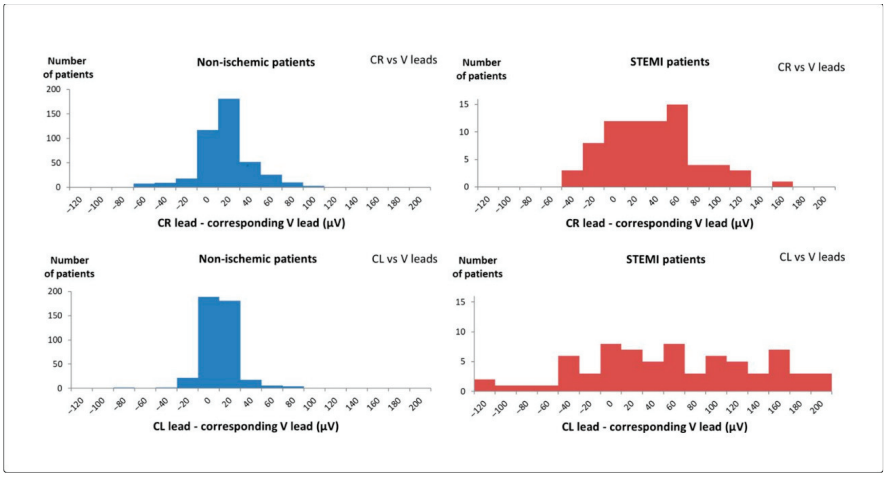

Figure 31. Differences between CR/CL amplitudes and the corresponding V amplitudes described with histograms for non-ischemic patients (*blue bars*) and STEMI patients (*red bars*). The bars represent number of patients with a difference in ST-J-amplitude between CL and V lead of < -120 µV, -100 – -120 µV, …, 180 – 200 µV, > 200 µV.
Upper panel: CR leads vs. V leads.
Left panel: Non-ischemic patients.
Right panel: STEMI patients.
In non-ischemic patients, the difference in ST-J amplitude compared to V leads was larger in CR leads than in CL leads, whereas the opposite was found in STEMI patients.

5.4. Electrocardiographic changes in the differentiation of ischemic and non-ischemic ST elevation (Study IV)

In previous papers, several ECG findings have been suggested to be used for differentiating STEMI from non-ischemic conditions which present with ST elevation. In study IV, the prevalence of PR depression, terminal QRS distortion, ST-segment convexity and reciprocal ST depression were described for patients with STEMI as well as for a heterogenous group of patients with chest pain and ST elevation but a non-ischemic underlying condition (perimyocarditis, early repolarization or takotsubo cardiomyopathy). Study IV confirms several previous observations on ECG findings that can be used to identify true STEMI. However, in contrast to previous studies which have compared findings in STEMI with those in ST elevation of a specific non-ischemic etiology, this study supports the use of selected criteria in situations with multiple non-ischemic differential diagnoses.

Compared to ECGs in non-ischemic patients, ECGs in STEMI patients showed a higher prevalence of convex ST-segments, terminal QRS distortion and reciprocal ST depression. PR depression in the chest leads, and ST depression in aVR were more frequently encountered among patients with ST elevation and a non-ischemic condition. In multivariable analysis, reciprocal ST depression remained as an independent predictor of an ischemic etiology, increasing the likelihood ten-fold (odds ratio 9.9 (3.5 – 28.1). The likelihood of having an ischemic etiology was instead decreased if PR depression in the chest leads or ST depression in aVR were present.

The usefulness of appreciating reciprocal changes in patients with STEMI is well established, and has been described to provide both prognostic information and to aid in culprit artery identification [195, 215, 216]. It has also been described to be useful when differentiating STEMI from non-ischemic conditions. In patients with inferior ST elevation, reciprocal ST depression in aVL has been described to discriminate between pericarditis and inferior STEMI [97]. In patients with anterior ST elevation, reciprocal ST depression has been suggested to be used for discrimination between anterior STEMI and takotsubo cardiomyopathy [141, 217]. This study supports the use of reciprocal ST depression when differentiating STEMI from non-ischemic ST elevation, as the presence of reciprocal ST depression, both in anterior ST elevation as well as in inferior ST elevation, strongly suggests an ischemic etiology (Fig. 28).

In the present study, PR depression was most common in takotsubo patients (62%). Besides in pericarditis and atrial infarction, PR-segment deviation can occur in sympathetic overstimulation, which theoretically may explain the high prevalence of PR depression in takotsubo patients [197]. As reported previously [143, 196, 197, 218], PR depression is commonly encountered in both pericarditis, takotsubo cardiomyopathy as well as in STEMI patients. However, chest-lead PR depression rarely occurred in STEMI patients, a result that is concurrent with the findings of Porela et al [196], who compared electrocardiographic features in STEMI and acute perimyocarditis, as well as with the findings of Zorzi et al (STEMI vs. takotsubo cardiomyopathy) [143]. It should be noted that PR depression may occur due to atrial infarction in patients with STEMI [197, 218]. For example, in a retrospective study of patients with inferior AMI, severe complications such as free-wall rupture was observed to be more common in patients with large PR depression (≥0.12 mV), compared to patients without. In those patients, PR depression was common even in the chest leads [218].

Terminal QRS distortion was more prevalent in STEMI patients than in non-ischemic patients (Fig. 28). Lee et al. showed that absence of both S and J wave in V2 – V3 can be a specific sign of LAD occlusion [203]. This ECG finding is easily applicable and therefore may be clinically very useful. In study IV, such a pattern in leads V2 or V3 was rare (8% of STEMI patients, 2% of non-ischemic ST elevation). We combined this criterion with the classical definition of terminal QRS distortion criteria, based on the morphology of the start of QRS. In leads with qR configuration, terminal QRS distortion was considered to be present when the ST elevation at the J point exceeded 50% of the R-wave amplitude, and in leads with an initial R wave (Rs or R configuration), i.e. not only V2 – V3, absence of S and J wave was considered to be positive for terminal QRS distortion. With this definition, terminal QRS distortion occurred in 40% of STEMI patients, but only 7% of patients with non-ischemic ST elevation (Fig. 30).

ST-segment convexity was more common in STEMI compared to non-ischemic conditions but occurred in less than ¼ of STEMI patients. Previously, it has been suggested that STEMI is less likely in patients with concave ST elevation [219]. This was dismissed by Smith et al., who reported that concave morphology was more common than convex morphology in patients with LAD occlusion [136], consistent with the findings in study IV. The diagnostic accuracy of the different electrocardiographic findings evaluated in study IV is presented in Tables 5 and 6.

Table 5. ECG findings to be used to detect patients with STEMI: Sensitivity, specificity and likelihood ratio for an ischemic etiology

	Sensitivity	Specificity	LR+/LR-
Any STEMI			
Convex ST elevation	22 (14 – 33)	91 (84 – 96)	2.6/0.9
Terminal QRS distortion	40 (28 – 53)	93 (85 – 97)	5.7/0.7
Anterior STEMI			
Convex ST elevation	14 (4 – 32)	93 (83 – 98)	1.9/0.9
ST depression in lead II*	40 (25 – 56)	100 (95 – 100)	**/0.6
Terminal QRS distortion	21 (8 – 41)	96 (87 – 99)	4.8/0.8
Inferior STEMI			
Convex ST elevation	26 (12 – 43)	90 (76 – 97)	2.5/0.8
ST depression in lead I*	83 (67 – 93)	100 (88 – 100)	**/0.2
Terminal QRS distortion	61 (42 – 78)	81 (61 – 93)	3/0.5

A true positive test is defined as presence of the ECG finding AND a STEMI diagnosis, a true negative result is defined as absence of the ECG finding AND a non-ischemic diagnosis.
Abbreviations: STEMI: ST-elevation myocardial infarction, LR+: positive likelihood ratio; LR-: negative likelihood ratio

* ≥0.025 mV

** LR+ cannot be calculated since specificity is 100%

Table 6. ECG findings to be used to detect non-ischemic patients: Sensitivity, specificity and likelihood ratio for a non-ischemic etiology

ECG finding	Sensitivity	Specificity	LR+/LR-
Non-ischemic etiology and any location of ST elevation			
Chest lead PR depression	38 (28 – 49)	88 (79 – 94)	3.2/0.7
ST depression in aVR*	80 (69 – 88)	70 (54 – 83)	2.6/0.3
Non-ischemic etiology and anterior ST elevation			
Chest lead PR depression	38 (27 – 50)	86 (72 – 95)	2.7/0.7
ST depression in aVR*	80 (69 – 88)	70 (54 – 83)	2.6/0.3
Non-ischemic etiology and inferior ST elevation			
Chest lead PR depression	46 (30 – 63)	83 (66 – 93)	2.7/0.7
ST depression in aVR*	77 (61 – 89)	66 (48 – 81)	2.2/0.4

A true positive test is defined as presence of the ECG finding AND a non-ischemic diagnosis, a true negative result is defined as absence of the ECG finding AND a STEMI diagnosis.
Abbreviations: LR+: positive likelihood ratio; LR-: negative likelihood ratio
*≥0.025 mV

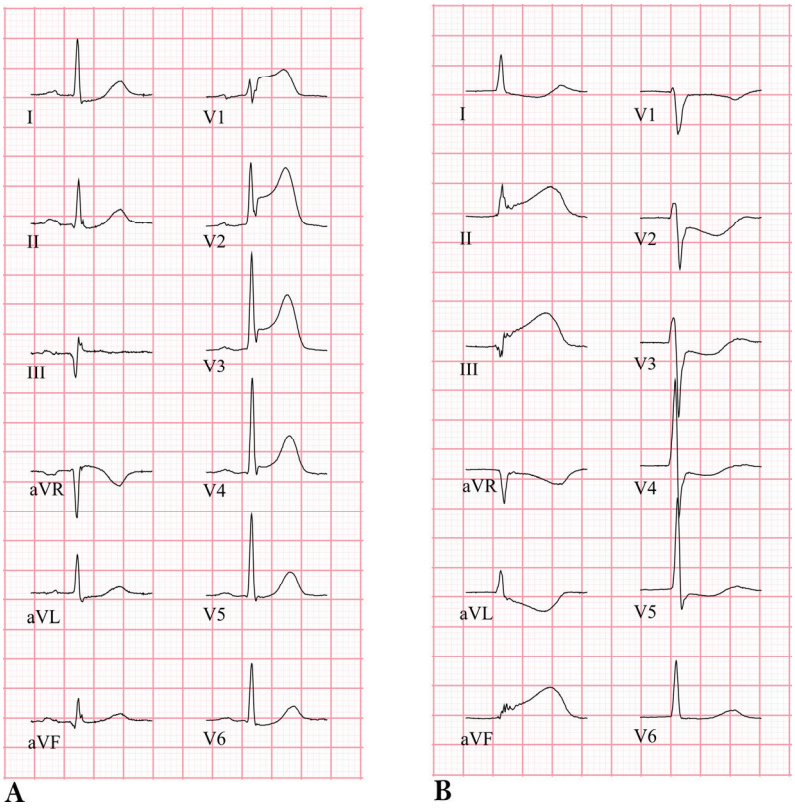

Figure 32. Terminal QRS distortion

Image A: A patient with LAD occlusion. ECG shows ST elevation in leads V1 – V4. In V2 and V3, which both have Rs morphology, the S wave is absent, and the patient is positive for terminal QRS distortion.

Image B: A patient with RCA occlusion. ECG shows ST elevation in leads II, III and aVF and ST depression in I, aVR, aVL and the precordial leads. In leads III and aVF, which have qR morphology, the ST-J amplitude markedly exceeds the R-wave amplitude and the patient is positive for terminal QRS distortion.

5.5. Diagnostic yield of STEMI amplitude criteria among chest pain patients at the emergency department (Study V)

In study V, the diagnostic yield of STEMI amplitude criteria in an ED setting was assessed in 19932 ED chest pain patients (≥30 years) who had an ECG recorded within 4 hours upon arrival at the ED. These criteria were shown to have a low positive predictive value (12%) in detection of AMI due to acute coronary occlusion/near-occlusion (Table 7). Among patients with AMI, an occluded or near-occluded coronary artery was identified at angiography in approximately 50% of patients meeting STEMI criteria.

The PPV for AMI and coronary occlusion/near-occlusion was increased when STEMI criteria were met and reciprocal ST depression was present. However, the number of false positives was still high, due to the low prevalence of disease. The NPV was high (99%), also due to the low prevalence, but 22% of patients with AMI who did not meet STEMI criteria had occluded/near-occluded coronary artery at coronary angiography, i.e. STEMI criteria alone were unreliable in ruling-out AMI with coronary occlusion. This is similar to the occlusion rate among NSTEMI patients in previous reports [78, 79].

Overall, sensitivity for AMI with coronary occlusion/near-occlusion was poor (17%), but specificity was high 99%, with similar values for patients who also underwent PCI or were recommended to undergo CABG. The low sensitivity and low PPV is in line with the results from a recent study by Hillinger et al [75], although both sensitivity (35%) and PPV (54%) were higher in their study. In that study, only patients with symptom onset or peak within 12 hours were included, whereas we included patients with any chest pain duration. In our material, 7% had AMI and 1.3% an occluded coronary artery at angiography compared to 18% and 5.5% in Hillinger's study.

As is described earlier in this thesis, small studies have shown increased sensitivity with maintained high specificity for AMI [76] or coronary occlusion [77] by extending the STEMI criteria to include several inverted leads (Fig. 9). In study V, the use of these extended STEMI criteria did increase sensitivity, but with a concomitant decrease in specificity and PPV.

There are probably multiple causes behind the low diagnostic yield of the ECG criteria for STEMI in ED patients. First of all, STEMI assessment typically includes

more than evaluating simple ST amplitude criteria, which are an over-simplification of ECG interpretation. In addition to reciprocal ST depression, the identification of PR depression [196], QRS changes [203] or STEMI-equivalent patterns [220, 221] are diagnostically helpful. Human interpretation also includes consideration of the likelihood of disease. In the study by Hillinger et al. [75], human ECG reading achieved a substantially higher sensitivity than computerized assessment. Second, absence of ST elevation is not equivalent to absence of severe ischemic heart disease. Coronary artery disease in need of acute reperfusion can occur without ST elevation, e.g. in left main stenosis or subtotal LAD occlusion [81, 222]. Culprit vessel patency may change rapidly [123] so that a patient with occlusion and spontaneous reperfusion may be classified as NSTEMI [221]. Third, partly because of ED bypass, there is a low prevalence of patients with acute coronary occlusion at the ED, and this affects the PPV negatively. Many patients instead have ST elevation from non-ischemic causes, e.g. pericarditis [121], left ventricular hypertrophy [117] and early repolarization pattern [114]. Also, many ED patients have intermittent chest pain, while the guidelines recommend that ECG criteria for STEMI should be applied to patients with persistent chest pain [46]. In clinical practice, however, a STEMI diagnosis is, likely, initially considered in each ED chest pain patient.

Table 7. Diagnostic accuracy of conventional and extended STEMI criteria

	STEMI criteria	STEMI criteria AND reciprocal STD*	Extended STEMI criteria	Extended STEMI criteria AND reciprocal STD*
AMI AND coronary occlusion (n = 198)				
Sensitivity	23.7 (18.0 – 30.3)	19.9 (14.0 – 25.4)	34.9 (28.2 – 41.9)	20.7 (15.3 – 27.0)
Specificity	97.7 (97.5 – 97.9)	99.2 (99.1 – 99.3)	93.4 (93.6 – 94.2)	99.1 (99.0 – 99.2)
PPV	9.4 (7.3 – 11.9)	19.6 (15.0 – 25.2)	5.5 (4.6 – 6.7)	18.8 (14.5 – 24.0)
NPV	99.2 (99.2 – 99.3)	99.1 (99.1 – 99.2)	99.3 (99.2 – 99.4)	99.2 (99.2 – 99.3)
AMI AND ≥ 90% coronary stenosis/occlusion (n = 351)				
Sensitivity	17.1 (13.3 – 21.4)	13.1 (9.8 – 17.1)	29.6 (24.9 – 34.7)	14.3 (10.8 – 18.5)
Specificity	97.8 (97.5 – 98.0)	99.2 (99.1 – 99.4)	94.2 (93.8 – 94.5)	99.0 (99.0 – 99.3)
PPV	12.0 (9.6 – 14.8)	23.7 (18.5 – 29.8)	8.4 (7.1 – 9.8)	22.9 (18.1 – 28.6)
NPV	98.5 (98.4 – 98.6)	98.5 (98.4 – 98.5)	98.7 (98.6 – 98.8)	98.5 (98.5 – 98.6)
AMI AND coronary occlusion/near-occlusion and PCI ad hoc (n=294) or CABG decision (n=46)				
Sensitivity	17.7 (13.8 – 22.2)	13.6 (10.1 – 17.7)	30.7 (25.8 – 35.9)	14.8 (11.2 – 19.0)
Specificity	97.7 (97.5 – 98.0)	99.2 (99.1 – 99.4)	94.2 (93.8 – 94.5)	99.1 (99.0 – 99.3)
PPV	12.0 (9.6 – 14.8)	23.7 (18.5 – 29.8)	8.3 (7.1 – 9.7)	22.9 (18.1 – 28.6)
NPV	98.6 (98.5 – 98.6)	98.5 (98.5 – 98.6)	98.7 (98.7 – 98.8)	98.5 (98.5 – 98.6)
AMI alone (n=1336)				
Sensitivity	9.4 (7.9 – 11.0)	6.0 (4.8 – 7.4)	17.4 (15.4 – 19.5)	6.5 (5.3 – 8.0)
Specificity	97.8 (97.8 – 98.2)	99.4 (99.3 – 99.5)	94.5 (94.2 – 94.9)	99.3 (99.2 – 99.4)
PPV	24.9 (21.4 – 28.7)	41.2 (34.7 – 48.2)	18.6 (16.7 – 20.6)	39.9 (33.8 – 46.4)
NPV	93.8 (93.7 – 93.9)	93.6 (93.6 – 93.7)	94.1 (94.0 – 94.2)	93.7 (93.6 – 93.8)

Sensitivity, specificity, positive and negative predictive values are described as %.
*Any ST depression (≥0.025 mV) in II, III or aVF in case of anterior ST elevation or any ST depression (≥0.025 mV) in either I, aVL, V2 or V3 in case of inferior ST elevation.
Abbreviations STEMI: ST elevation myocardial infarction; STD: ST depression; AMI: acute myocardial infarction; PPV: positive predictive value; NPV: negative predictive value

When a large proportion of STEMI patients are directed to the coronary care unit instead of the ED, it is likely that the patients who turn up at the ED have a more atypical presentation, for example atypical symptoms or atypical ECG changes. This is a likely explanation for the observed low sensitivity of STEMI criteria. Although sensitivity and specificity are not related to the prevalence of disease (as opposed to PPV and NPV), they can still be affected by a difference in attributes of the patients. When patients with acute coronary occlusion who present with obvious ST elevation are triaged for acute coronary angiography and bypass the ED, the proportion of patients with acute coronary occlusion but without obvious ST-segment changes likely becomes larger at the ED, compared to the whole population of patients with acute coronary occlusion. This negatively affects sensitivity of the STEMI criteria (Fig. 33).

Almost one fourth of patients with AMI who did not meet STEMI criteria had an occluded or near-occluded coronary artery, i.e. they would likely would have had benefit from early revascularization. This highlights the importance of finding other ECG criteria to detect patients with acute coronary occlusion as well as the needs for other potential diagnostic resources.

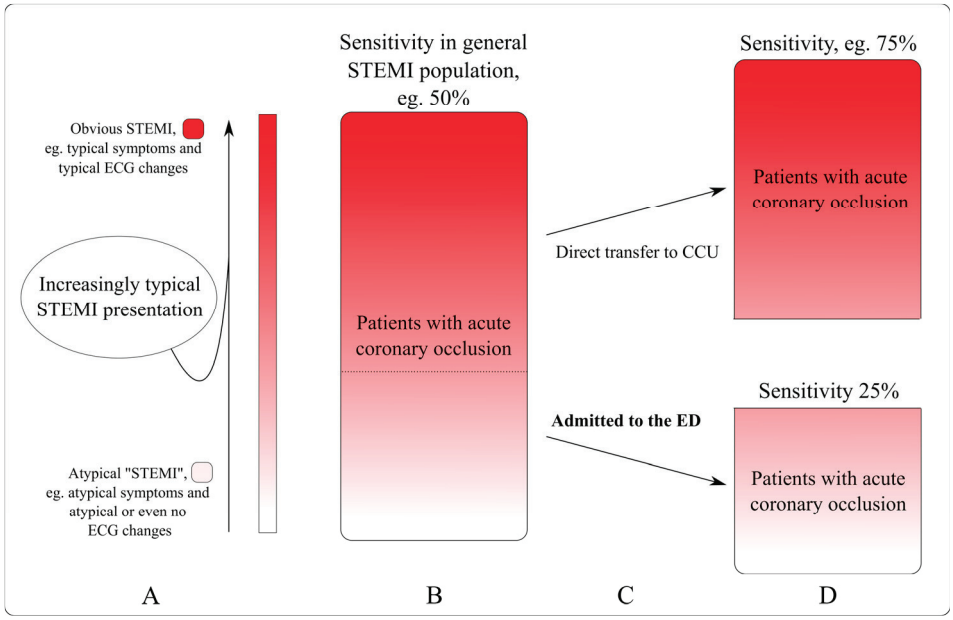

Figure 33. Schematic explanation of how sensitivity of STEMI criteria can be affected by an increased proportion of patients with suspected acute coronary occlusion being transferred directly to a coronary care unit (CCU).
A. The entire population of patients with acute coronary occlusion is heterogeneous and patients may present with either typical ECG changes and typical symptoms on one end of the spectrum, or with atypical symptoms and atypical ECG changes on the other. In this illustration, patients with typical presentation are represented by an intense red color and patients with atypical presentation represented by white/pink colors (A and B).
B: The rectangle represents the entire "STEMI" population. STEMI criteria have been assigned a hypothetical sensitivity, 50%.
C: Patients with typical symptoms and/or typical ECG changes (more red) are more likely to be directed to the coronary care unit than those at the lower end of the rectangle in B (pink/white), who instead are more likely to present at the emergency department (ED).
D: Since atypical ECG changes are more likely among those patients who present at the ED, STEMI criteria will not detect as many patients with acute coronary occlusion as in the population in B, i.e. sensitivity decreases.

6. Limitations

6.1. Study I

Study I aimed to describe the normal variation of the ischemic wall scores using EDS-MI. The patients used for establishing the reference values cannot be considered to represent a healthy, normal population, as they were recruited for the study when performing other tests at the department of clinical physiology, and hence many of these patients are likely to have ischemic heart disease. Nonetheless, these patients adequately represent patients that are to be considered true negatives for a test aiming at identifying acute transmural ischemia due to acute coronary occlusion. The likelihood for these patients of having such a condition, at the time of ECG recording, is negligible.

In the same study, the reference values were both tested and adjusted after applying them to patients with acute coronary occlusion. The number of patients included for this purpose was small, especially when subgrouping them into groups based on sex. This limits the validity of the suggested reference values, and further evaluation is necessary.

6.2. Study II

The major limitation of study II regards the selection of patients. First of all, the patients with acute coronary occlusion were included from two previous studies with different study design. One of these studies had a retrospective design where patients were included based on the finding of an acute coronary occlusion at angiography, and in the other study patients were prospectively included based on physicians' decisions to refer the patient for primary PCI. From these two databases, only

patients with acute coronary occlusion were included. The selection of patients with non-ischemic ST deviation was based on either previously performed ECG interpretations, or among patients referred for CMR with a suspected diagnosis of either perimyocarditis or takotsubo cardiomyopathy. In summary, the study is a pooled analysis of studies with diverging patient populations and different study settings. Thus, the study can be considered only as a *proof-of-concept* study, which needs to be validated in a clinical, unselected population.

Interpretation of the correlations between ECG changes and MaR by CMR, final infarct size and troponin levels are highly affected by temporal changes known to occur during an ischemic process, due to variations of vessel patency or variable amounts of already infarcted myocardium.

6.3. Study III

Study III included patients from several previous studies with different inclusion criteria. However, it was not the clinical outcome that was considered in the purpose of the study, but the difference between chest lead amplitudes, which potentially may affect the clinical outcome.

It is not known in which context the 12-lead smartphone ECG is intended to be used. Our study highlights the importance of studying the performance of smartphone 12-lead ECG in a relevant population, since it is shown, in our results, that clinically important changes may occur.

Our study was based entirely on re-calculating the ST-J amplitudes to what they had been if either the right or left arm were used as reference instead of the WCT. This may not represent the actual ST-J amplitudes if they would have been recorded with the smartphone in real-life However, it is unlikely that the difference would have been smaller than described in this study.

ECG amplitudes in this study are either manually determined or automatically determined by the software. This does not, however, affect the differences between chest lead amplitudes in the conventional ECG and the smartphone ECG, as this difference is mathematically derived.

6.4. Study IV

A limitation to study IV is that patients were included from different studies and not consecutively from the same setting. For example, STEMI patients were triaged for primary PCI whereas most of the non-ischemic patients were not. Nonetheless, all patients had acute chest pain and at least 0.1 mV ST elevation, which makes STEMI a relevant differential diagnosis in all these patients.

There are different types of early repolarization patterns. The inclusion of patients with early repolarization was based on a random sample among patients admitted to an emergency department. All patients had their maximal ST elevation in anterior leads and the results may not be applicable to early repolarization with other ST-elevation patterns. Nine patients with early repolarization had > 0.1 mV ST elevation in V4, V5 or V6, and 2 patients > 0.1 mV ST elevation in inferior leads. The classification of different early repolarization patterns is not based on the location of maximal ST elevation, but the location of early repolarization ECG changes, i.e. the J waves and (often) associated ST elevation [135]. Even though an ECG may be classified as either anterolateral or inferior early repolarization, with J-point abnormalities in V4 – V6 or II/III/aVF respectively, the maximal ST elevation may still be present in V2. Since this study focused on differentiating ischemic and non-ischemic ST elevation, we did not include any sub-grouping of early repolarization patterns. Nonetheless, the results from study III may not be applicable to early repolarization with other ST elevation patterns.

Blinded interpretation of ECG variables was made regarding terminal QRS distortion, PR depression and ST-segment convexity, but not for ST-J amplitudes. Also, although the first author (TL) was blinded to the clinical diagnosis during interpretation, he was not unfamiliar with the ECGs from previous studies [224] and he identified the patients with early repolarization in the EXPECT database. However, the other two ECG interpreters were blinded to both study design and final diagnoses, and in most cases inter-rater agreement was strong, suggesting that the impact on the results was minor.

Ideally, the ECG signs shown to be useful in this study should have been tested in a different group of patients with chest pain and ST elevation for validation of the findings. This was not done, and further studies are therefore needed to validate the findings.

Reciprocal ST-segment changes were studied using two different cut-offs, 0.025 mV and 005 mV. The choice of including these two cut-offs was based on previous

studies (0.025 mV [97]), or based on a hypothesis that accuracy could be improved if a larger cut-off was used (0.05 mV). It is not certain that a cut-off of 0.025 is a practical cut-off in clinical practice. A difference between 0.015 and 0.025 mV, for example, cannot be expected to be possible to distinguish by eyeballing.

6.5. Study V

Only a minority of the patients underwent coronary angiography, and verification bias may have affected the results. Likely, this would not lead to an underestimation of the described low sensitivity. Also, vessel patency may vary during an ischemic process [123]. In order to overcome this limitation, we analyzed both occluded and nearly occluded (≥90% stenosis) arteries as outcomes. Nonetheless, we cannot know the actual state of vessel patency at the time of ECG recording. Also, only single ECGs from the ED were analyzed, while in routine care repeated ECGs are often recorded, which may improve the diagnostic yield. Also, all types of chest pain were included, i.e. there was no differentiation of typical, atypical or non-anginal pain. It is clear from our study, that management decisions must include more information than STEMI criteria fulfillment and chest pain as a cause of admission.

Since PPV and NPV are highly dependent on the prevalence of disease, the results from study V are not generalizable to ED settings with different proportions of ED bypass of STEMI patients. According to SCAAR register data, during the study period 1806 patients were sent to the coronary catherization laboratory due to suspected STEMI directly from the local ambulances, from the EDs or from the wards at the two hospitals. Since coronary angiography was performed in approximately 150 patients at the ED who met STEMI criteria, this indicates a high rate of ED bypass.

Patients with an increased QRS duration were excluded from this study since conventional amplitude criteria are not applicable, at least not fully, to patients with left or right bundle branch block, ventricular pacing or LVH. However, it is possible that exclusion based on QRS duration may have erroneously excluded some cases where STEMI criteria would have been applicable, i.e. patients with prolonged QRS duration not due to bundle branch block, LVH or ventricular pacing.

The validity of AMI as an outcome in the context of STEMI is questionable, since AMI includes NSTEMI diagnoses. However, AMI as an outcome is less affected by verification bias since it does not require angiographical data. Instead, it is to some

extent affected by incorporation bias [225] – the ECG changes are likely included when physicians are making the AMI diagnosis. Since the main problem of incorporation bias is *overestimation* of diagnostic accuracy, the impact on the conclusions in this case is very small.

Computerized ECG measurements were used in the analysis. We thereby limited the variability of the measurements and avoided human error but may have, in some cases, introduced errors. Computer-based measurements are dependent on the quality of the recording, as are, of course, manual measurements. The use of computerized measurements may differ from manually defined ST-J amplitudes. Eskola et al. found good agreement between human and computerized amplitude in defining whether ST elevation is present or not, but with a bias towards slightly larger amplitudes with the former [226]. This may have led to an underestimation of sensitivity and overestimation of specificity compared to using human measurements.

7. Conclusions

Study I

Study I showed the variation of the ischemic scores for EDS-MI (the Olson method) in patients without acute myocardial ischemia. When applied to a group of patients with acute coronary occlusion, the test reference limits yielded a very high sensitivity and specificity. Future studies were needed for instance to explore specificity in patients with non-ischemic ST-elevation conditions (*Study II*).

Study II

EDS-MI showed potential of serving as an automatic decision support for the assessment of patients presenting with ST changes and suspected acute coronary syndrome in detection and localization of ischemia, but not for estimation of the extent of ischemia. Further studies in unselected clinical chest pain populations are needed.

Study III

For most patients, replacement of the Wilson Central Terminal by arm electrodes as reference for the chest leads results in only small changes in ST-J amplitude. However, in patients with STEMI or other diagnoses which affected ST-J amplitudes in leads aVR and/or aVL, changes of precordial-lead ST-J amplitudes are in some cases substantial.

Study IV

Identification of true STEMI among patients with different ST-elevation etiologies may be improved by considering several ECG changes in addition to ST elevation; primarily reciprocal ST depression, ST depression in aVR and PR depression in the chest leads.

Study V

The diagnostic yield of ECG amplitude criteria for STEMI in chest pain patients at the ED is low. Most patients meeting STEMI criteria had neither coronary occlusion nor AMI. Future studies to improve the ECG detection of ED patients with AMI due to acute coronary occlusion are warranted.

8. Clinical implications and future perspective

This thesis addresses different electrocardiographic aspects of detection of acute coronary occlusion; improved detection by the use of an automated, visual diagnostic aid, early detection by the use of smartphone 12-lead ECG, improved detection by including other electrocardiographic findings in the ECG than ST-elevation amplitudes, and the diagnostic accuracy of current STEMI amplitude criteria in an ED setting.

The first two studies dealt with the automatic decision support EDS-MI, which is based on the ST-J amplitudes in the 12-lead ECG and takes into account the spatial information provided by these. EDS-MI showed potential in improving the diagnostic accuracy compared to STEMI criteria. However, it is likely that even though additional information is added to this method, compared to conventional amplitude criteria, it may be too simplistic to account for the complexity of ECG changes in acute coronary syndrome. Also, as is shown in study V, the comparison of EDS-MI to STEMI criteria may not be the optimal choice, since STEMI criteria have poor diagnostic performance. Also, the direct visual presentation of the findings on a map of the left ventricle provides no information to the interpreter in potentially understanding pitfalls or detecting artifacts, unless the interpreter is well acquainted with the algorithm. These aspects limit the usefulness of the method in clinical practice. With high pace, diagnostic algorithms based on artificial intelligence are emerging, often taking much more information into account than simply the ST-J amplitudes. Such methods are likely to be superior to a simple method such as EDS-MI, despite its theoretical attractiveness. Nevertheless, by showing that EDS-MI can improve detection of ischemia, as in studies I and II, knowledge that the spatial information in the ECG needs to be taken into account during ECG interpretation is confirmed.

The third study addressed a possible pitfall in performing 12-lead ECG recording without the Wilson Central Terminal, as was suggested by developers of a smartphone-based 12-lead ECG apparatus. It was clearly shown that the ECG pattern may differ significantly compared to conventional ECG recording, and that this must be considered before implementation into clinical practice, either by changing interpretative criteria, or rather by attempting to develop a better substitute for the Wilson Central Terminal. With rapid technology developments, it is important for the research community to stay alert in order to address potential pitfalls in new technologies.

In the fourth study, other electrocardiographic findings in patients with ST elevation were evaluated. Some of these findings were shown to be predictive of either STEMI or non-ischemic conditions with ST elevation. This highlights the importance of using a holistic approach when interpreting the ECG in patients with suspected acute coronary occlusion. However, it is important that the possible adverse implications of denying a patient an acute coronary angiography, when coronary occlusion is a potential differential diagnosis, is considered.

The fifth study described that the diagnostic accuracy of STEMI amplitude criteria at the emergency department is remarkably low. This is to a large extent caused by a very low prevalence of STEMI patients at the emergency department. Nonetheless, this study shows that using STEMI criteria to identify patients with acute coronary occlusion is a too simple approach in this situation and many other factors are needed to be taken into consideration.

Identification of patients in need of acute revascularization is a complex diagnostic process, where rapid and correct decisions can improve the outcome of the patient. The STEMI/NSTEMI concept may not be ideal in differentiating these patients. In studies evaluating the effect of early versus delayed intervention by PCI in NSTEMI patients, mortality benefit has not been shown for an early invasive strategy [85-87]. However, these studies fail to recognize that the NSTEMI group of patients is heterogeneous and that a minority of those patients have acute coronary occlusion. Patients with NSTEMI and acute coronary occlusion are, at least in theory, likely to benefit from acute revascularization, but since the patients without acute coronary occlusion are in majority, the results may be clouded. Studies are needed to confirm the hypothesis that patients without ST elevation but with an acutely occluded coronary artery benefit from early revascularization. Such a study needs to move beyond the STEMI/NSTEMI concept. In general, there is a continuing need for education in ECG interpretation, improved diagnostic methods and future research in this area to better identify patients with acute coronary occlusion.

9. References

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Publications not included in the thesis

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Appendix

A. Practical tips for ECG interpretation of suspected acute coronary occlusion.

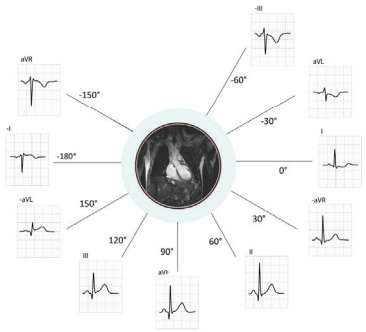
Practical tips for ECG interpretation of suspected acute coronary occlusion

STEMI amplitude criteria

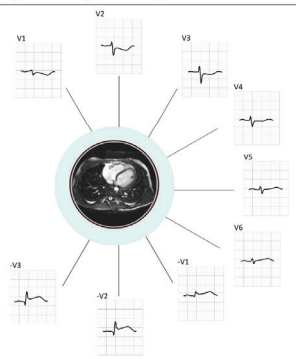
measured at ST-J

signficant ST elevation requires fulfilled criteria in 2 contiguous leads

aVL, I, -aVR, II, aVF, III V1, V4, V5, V6	All patients: > 0.1 mV
V2, V3	Male patients ≥ 40 years: ≥ 0.2 mV Male patients < 40 years: ≥ 0.25 mV Female patients (any age): ≥ 0.15 mV
Lead pairs	aVL/I, I/-aVR, -aVR/II, II/aVF, aVF/III V1/V2, V2/V3, V3/V4, V4/V5, V5/V6



STEMI criteria can be extended. For example, the inverted version of aVL (-aVL) is contiguous to III and -III to aVL. -aVR is contiguous to I and II.



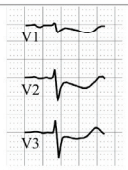
Ischemia in the lateral wall can result in ST depression in V1 to V3, which is equivalent to ST elevation in -V1 to -V3.

Reciprocal ST depression suggests ischemia

Anterior ST elevation - ST depression in II, aVF, III
Inferior ST elevation - ST depression in aVL, I, V2, V3

ST depression in V1 - V3
- LCx occlusion?

Consider using posterior leads



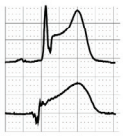
Concave ST elevation does not exclude STEMI

PR depression in the chest leads
(≥0.05 mV at QRS onset, in reference to TP segment)
- uncommon in STEMI patients

Terminal QRS distortion is suggestive of ischemic ST elevation and is associated with severe ischemia if present in 2 contiguous leads

Lead with initial R

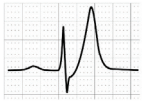
Lead with initial q



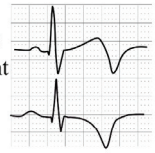
Absent S and J wave

STJ / R ≥ 0.5

Upsloping ST depression in precordial leads and tall symmetrical T waves (without tachycardia)
- LAD occlusion?



Biphasic or inverted T waves in precordial leads in a patient with recent chest pain
- critical LAD stenosis?



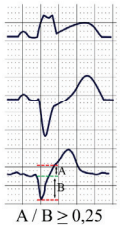
ECG changes are dynamic - record serial ECGs

Acute coronary occlusion in the presence of left bundle branch block

ST elevation ≥ 0.1 mV concordant with the QRS complex

ST depression ≥ 0.1 mV concordant with the QRS complexes in V1-V3

Relative discordance
ST elevation ≥ 25 % of S wave



A / B ≥ 0,25

Study I

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The Olson method for detection of acute myocardial ischemia in patients with coronary occlusion

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Abstract An automated ECG-based method may provide diagnostic support in the management of patients with acute coronary syndrome. The Olson method has previously proved to accurately identify the culprit artery in patients with acute coronary occlusion.

Methods: The Olson method was applied to 360 patients without acute myocardial ischemia and 52 patients with acute coronary occlusion.

Results: This study establishes the normal variation of the Olson wall scores in patients without acute myocardial ischemia, which provides the basis for implementation of the Olson method for triage of patients with acute coronary syndrome. All patients with acute occlusion had Olson wall scores above the upper limit of normal.

Conclusion: The Olson method can be used for ischemia detection with very high sensitivity. Future studies are needed to explore specificity in patients with non-ischemic ST elevation.

Keywords: Olson method; Acute ischemia detection; Acute coronary occlusion; Automated decision support

Introduction

Ischemic heart disease is one of the leading causes of death worldwide [1]. Acute myocardial infarction due to decreased myocardial blood supply is in most cases caused by thrombosis on a ruptured coronary atherosclerotic plaque [2]. In the era of myocardial reperfusion, the primary clinical challenge is to determine if an occlusion of one of the three major coronary vessels is present in a patient suspected of acute coronary syndrome (ACS). Correct interpretation of the ECG is an essential component in this decision process. However, even with the use of computer-based interpretation and expert physician interpretation, the standard 12-lead ECG has limitations. ST-elevation acute coronary syndrome is considered present when there is significant ST-segment elevation in two contiguous leads [3,4]. ST-segment deviation that is not directed toward the positive poles of at least two of the standard 12 ECG leads will not meet this criterion, even when an acute occlusion is present. For example, acute ST elevation in lead III (but not in aVF) combined with ST depression in lead aVL may indicate presence of transmural ischemia in the myocardial regions that are normally perfused by the right coronary artery [5]. Isolated ST depression in V1–V3 may be present in acute occlusion of the left circumflex artery [6–8]. Neither of these would thus be detected by means of ST elevation in two contiguous leads. The anatomic relationship between the myocardial regions and the anatomic regions reflected by the standard 12-lead ECG makes the sensitivity of the STEMI criteria unnecessarily low. Another unnecessary limitation is that in the international ECG display format only the six chest leads are presented in their orderly sequence, whereas the limb leads are presented in two separate sequences: leads I, II, and III as one sequence and the anatomically interspersed three augmented leads as another. This limb lead display makes it difficult for a human observer to realize which leads are contiguous [9].

Finally, ECG interpretation can be difficult, especially for non-experienced physicians who often first meet the patient with suspected ACS at the emergency department [10,11]. An automated method using all available cardiac spatial information displayed in an intuitive manner may overcome

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0022-0736/

these obstacles, and provide diagnostic support for the clinical diagnosis of acute coronary occlusion [12–14].

Using a vectorcardiographic approach, the Olson method processes ST-J measurements in all 12 ECG leads and determines the location of the acutely ischemic myocardium in patients with acute coronary occlusion. ST-J-amplitudes are entered into a computer, and an algorithm produces a prediction of the involved left ventricular wall. This prediction is based on calculating so-called Olson scores for 12 myocardial segments [15]. The method has been validated for locating the culprit artery with an accuracy at least at the level of a rule-based algorithm applied by experts [16]. The results are intuitively presented on a 12-segment projection of the left ventricle (Fig. 1). This information can be useful when performing PCI [17], but if it could be used also for detection of acute coronary occlusion, the impact of this automated method would be enhanced. Since the application of the Olson method in individuals without acute myocardial ischemia has not been studied, there is as yet no established threshold above which Olson scores should rise before ischemia should be suspected.

The aim of this study is to determine the upper limit of normal of the Olson scores in individuals without myocardial ischemia, in order to create a basis for a clinically applicable algorithm for detection of transmural ischemia. A secondary aim is to compare these values with values from patients with verified acute coronary occlusion for studying sensitivity.

Ethical considerations

The database of patients without acute coronary occlusion

No potential harm to research individuals was identified and the database did not include any sensitive personal information. The study protocol was approved by the local advisory board on medical ethics.

The database of patients with acute coronary occlusion

This database was included in an earlier study of the Olson method [16].

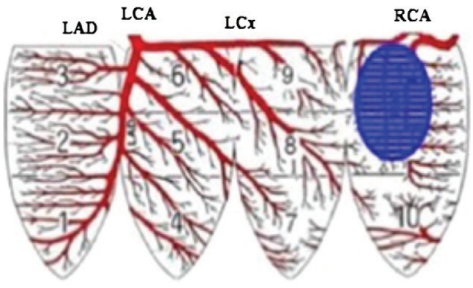

Fig. 1. The location of the area of transmural ischemia in the Mercator view of the 12-segment model used in the Olson method. This case represents an occlusion of the right coronary artery [15].

Materials and methods

Study population

Two study populations were included in this study.

1) 30 ECGs for both genders and each age decade (30–39, 40–49, 50–59, 60–69, 70–79, 80–89), recorded and stored at the Clinical Physiology Department in Växjö Central Hospital from April 2015 were collected, in total 360 ECGs. ECG collection was performed consecutively from the set starting date until each gender/age group was completed. All ECGs included had been recorded either before a planned exercise test or myocardial perfusion imaging test, before a Holter monitoring or as a screening ECG before non-cardiac surgery. The study thus included only patients with a very low likelihood of having ongoing transmural ischemia. ECGs with poor signal quality or other technical deficiencies, and ECGs with a QRS width exceeding 120 ms were not included. Patient height and weight were recorded when available (prior to exercise test and myocardial perfusion imaging), and BMI was calculated (Table 1).
2) ECGs from, initially, 53 patients with acute coronary syndrome were previously included in a study of the Olson method [16]. One of the ECGs was excluded due to misplaced electrodes. These patients were triaged for primary PCI and underwent emergent coronary angiography at the Leiden Medical University Center. The angiogram showed complete single-vessel occlusion among the three major coronary arteries (TIMI flow grade equal to zero and restoration of flow following PCI). In 19 cases the LAD was the culprit site, in 9 cases the LCx and in 24 cases the RCA.

Electrocardiography

All 12-lead ECGs in patients without acute myocardial ischemia were recorded using computerized electrocardiographs, at the Clinical Physiology Department in Växjö Central Hospital using an EC Sense digital ECG recorder (Cardiolex, Solna, Sweden). Automated measurements were made of ST-J amplitudes, relative to the level of the PR segment immediately before QRS onset for all 12 leads. For the ischemic patients, ST-J amplitudes were measured using the measurement program LEADS as described in the study by Kamphuis et al. [16]. In the group of patients with acute coronary occlusion, all patients had at least one ECG recorded within two hours before catheterization and the ECG nearest to PCI was selected. Patients with technical deficiencies or complete left bundle branch block were excluded from both study populations. In the group of patients without acute ischemia, patients with complete right bundle branch block were excluded. In the group of patients with acute ischemia, patients with documented previous myocardial infarctions were excluded. Among the 52 patients with acute ischemia, 42 patients had significant ST elevation (STEMI) in two contiguous leads using the

Table 1
Baseline characteristics of patients without acute myocardial ischemia.

	Women (n = 98*)	Men (n = 113[a])
Height (m), mean (SD)	1.66 (0.07)	1.78 (0.08)
Weight (kg), mean (SD)	72 (14)	85 (17)
BMI (kg/m^2), mean (SD)	26 (5)	27 (4)

[a] Data available for 98 women and 113 men.

computerized ST-J-amplitude measurements, which means that 10 patients (19%) would not have been recognized by means of significant ST elevation in two contiguous leads.

The Olson method

In the Olson method, the left ventricle is divided into four walls according to the Selvester model [18], i.e. the septal, anterior, lateral and inferior wall, and each wall is divided into three segments from base to apex (Fig. 1). A hypothetical ischemia vector has been calculated for each segment, as if that segment was uniformly ischemic (Fig. 2a). These 12 vectors constitute a patient-independent reference frame. An ST-deviation vector representing an assumed "ischemic current" is calculated from ST-J amplitudes in all 12 leads in the 12-lead ECG. For each lead, the measured ST amplitude is multiplied by three conversion coefficients based on Frank's surface diagrams with correction for lead strength and lead direction, resulting in a single vector, the "ST deviation vector" in the X, Y and Z direction (three orthogonal axes at the electrical center of the heart) (Fig. 2b) [15]. The contribution of each of the 12 segments to the ST-deviation vector is determined by relating the ST-deviation vector to the hypothetical segmental vector. This is done by multiplying the magnitudes of these two vectors and the cosine of the angle between them, producing a scalar product of the two vectors [15]. Positive scalar products for each of the 12 leads are then added for each myocardial segment, creating an "Olson score". In this study, we added these scores for those three segments that correspond to a specific wall. The result is "the Olson wall score". Scores for segments 1 to 3 are added to provide the Olson wall score for the septal wall, segments 4 to 6 for the anterior wall, segments 7 to 9 for the lateral wall and segments 10 to 12 for the inferior wall.

The procedure of determining the presence of acute transmural ischemia with the Olson method is performed by first identifying the wall with the largest Olson wall score (i.e. either the septal, anterior, lateral or inferior wall). This score is then compared to the gender- and age-based threshold (i.e. the upper limit of normal) for that wall. If the Olson wall score of the wall with the maximal score exceeds the threshold,

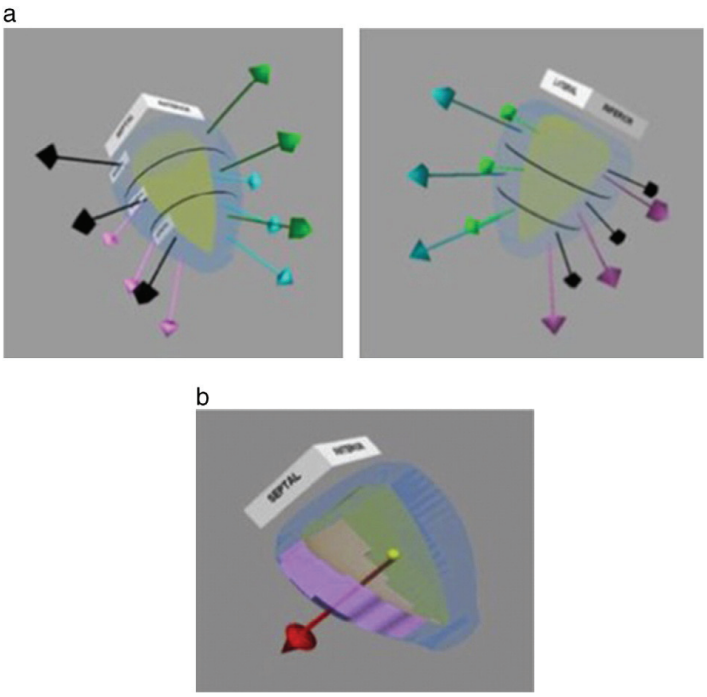

Fig. 2. **a.** The directions of the ST vectors that would be generated by a transmural "current of ischemia" in each of the 12 myocardial segments are represented by arrows: septal (black), anterior (green), lateral (blue) and inferior (purple). The left image presents the septal/anterior view, and the right image presents the lateral/inferior view [15].**b.** ST vector originating at the electrical center of the heart from a study subject with transmural ischemia confined to the inferior left ventricular wall [15].

Table 2A
Olson wall scores[a] in female patients without acute myocardial ischemia.

Age group	Septal	Anterior	Lateral	Inferior
30–39 (n = 30)	275 (226–323)	248 (211–286)	86 (76–97)	47 (29–66)
40–49 (n = 30)	279 (210–347)	232 (188–276)	86 (72–100)	62 (37–86)
50–59 (n = 30)	328 (252–404)	294 (237–350)	94 (81–106)	49 (32–65)
60–69 (n = 30)	250 (177–324)	251 (198–303)	98 (83–113)	52 (26–77
70–79 (n = 30)	203 (154–252)	193 (168–217)	100 (79–120)	89 (54–124)
80–89 (n = 30)	230 (164–297)	233 (178–289)	92 (78–106)	71 (44–98)

[a] Mean (95% confidence interval).

the test is indicative of transmural ischemia. If the score does not exceed the threshold, the test is negative. If the test is positive, the wall with the highest Olson wall score identifies the likely location of the ischemia.

Statistical methods

The Olson wall scores are described using means and standard deviations. Upper limits of normal for each wall score were calculated with 95% and 99% confidence using mean + 1.96 and 2.58 standard deviations, respectively. A Pearson r correlation test was used to describe the correlation between the Olson scores and height, weight and BMI. T-test for independent samples was used to compare mean Olson wall scores between different groups. Sensitivity and specificity are presented with 95% confidence intervals.

Results

Mean Olson wall scores in different age groups among patients without acute myocardial ischemia are presented in Table 2A and B for men and women, respectively. Mean Olson wall scores were higher in the septal and anterior walls in men aged 30–39 years compared to men ≥40 years ($p < 0.001$, Table 2B). There was no difference between different age groups in female patients. The normal variation of the Olson wall scores is presented in Tables 3 and 4, for men and women respectively, with separate upper limits of normal for the septal and anterior walls for male patients <40 years and ≥40 years (Table 4).

The mean Olson wall scores were lower in women than in men for the septal, anterior and lateral walls (all p-values <0.001) There was no statistically significant difference between the mean Olson wall scores for the inferior wall between men and women ($p = 0.46$). Olson wall scores were weakly correlated with weight and height as well as BMI, with the highest r-value for height vs. the anterior wall (0.32, $p = 0.001$) (Table 5). There was no statistically significant difference in mean Olson wall scores between obese (BMI ≥30) and non-obese patients (p-values were 0.75, 0.63, 0.24 and 0.34 for the septal, anterior, lateral and inferior walls, respectively).

Mean Olson wall scores were higher in patients with acute myocardial ischemia than in patients without acute ischemia for both men and women ($p < 0.001$). The distribution of Olson wall scores in patients without acute ischemia and those with acute transmural ischemia is presented in Fig. 3a and b. All patients with acute occlusion had maximal Olson wall scores above the upper limit of normal for the corresponding wall (calculated as the 99% prediction interval), i.e. a sensitivity of 100% (93–100). For both genders, this upper limit resulted in 7% (n = 25) of patients without acute myocardial ischemia being falsely classified as ischemic, i.e. the average specificity was 93% (90–95) (Table 6). Thresholds were modified to decrease the numbers of false positive findings (Tables 3 and 4). With these thresholds, maximal sensitivity was maintained (100% of the ischemic patients were recognized), while none of the female patients and 1% of the male patients (n = 2) without acute ischemia were classified as ischemic.

When applying strict STEMI criteria [19] to the patients without acute myocardial ischemia, 3 patients would be falsely classified as ischemic (specificity 99% (98–100)).

Discussion

The Olson method has been proven to accurately identify the culprit artery in patients with acute coronary occlusion [16]. This study establishes the normal variation of the Olson wall scores in patients without acute myocardial ischemia, which provides the basis for implementation of the Olson method also for ischemia *detection*. When using the upper limit of normal calculated as the 99% prediction interval, sensitivity was 100% with an acceptably low number of false

Table 2B
Olson wall scores[a] in male patients without acute myocardial ischemia.

Age group	Septal	Anterior	Lateral	Inferior
30–39 (n = 30)	760 (635–885)	624 (534–714)	132 (114–151)	27 (18–36)
40–49 (n = 30)	378 (286–470)	371 (285–456)	106 (90–121)	42 (24–60)
50–59 (n = 30)	477 (368–587)	423 (340–506)	109 (91–126)	44 (26–62)
60–69 (n = 30)	446 (321–572)	389 (307–471)	106 (89–22)	49 (25–72)
70–79 (n = 30)	361 (271–450)	305 (240–370)	91 (78–105)	54 (28–81)
80–89 (n = 30)	349 (235–463)	252 (184–319)	112 (86–137)	120 (80–161)

[a] Mean (95% confidence interval).

Table 3
Olson wall scores in female patients without acute myocardial ischemia (n = 180).

Wall	Mean	SD	Upper limit 95% confidence[a]	Upper limit 99% confidence[a]	Modified tresholds
Septal	261 (235–287)	175.2	604	713	849–1439[b]
Anterior	242 (223–260)	126.5	490	568	738–927[b]
Lateral	93 (87–98)	39.3	169	194	266–1629[b]
Inferior	62 (52–72)	68.6	196	239	363–1027[b]

[a] The upper limit of normal with 95% and 99% confidence defined as mean + 1.96 and 2.58 standard deviations, respectively.
[b] The same sensitivity and specificity would be maintained within this range.

positives (9% and 5% respectively for women and men). With this material, thresholds could be modified further to decrease the number of false positives (none of the female controls and only 1% of the male controls).

Normal limits of the ST amplitude are lower in women than in men [20]. Mean Olson scores were lower in non-ischemic women than in men for 3 out of 4 walls, and thresholds were therefore stratified for gender. Conventional STEMI criteria are adjusted for age in male patients in leads V2 and V3 [19]. In the group of patients without acute ischemia, Olson wall scores were higher in both the septal and anterior wall in younger men and separate thresholds were therefore established for men aged <40 years and ≥40 years.

In the Olson method, the ST-segment information is converted into vectors in three orthogonal leads, based on the assumptions in Frank's torso model. In those studies, very few variations of torso size and shape were included [21,22]. In this study, weight, height as well as BMI did not significantly affect the Olson wall scores.

Correct ECG interpretation is essential for the management of patients with acute coronary syndrome and it is important to determine if an acute coronary occlusion is present, since it can be treated with revascularization [3,4]. Detection rate for acute coronary occlusion using STEMI criteria is low [23]. An automatic and graphical aid could be of great help to physicians in the emergency care room in the clinical diagnosis of acute coronary occlusion [12,13]. The Olson method uses all available cardiac spatial information in the 12-lead ECG and displays the likely ischemic area in an intuitive manner (Fig. 1). This has the potential of overcoming some of the obstacles in ischemia detection, such as the previously mentioned difficulties in covering the entire myocardium, the non-contiguity in lead display and perhaps also the general interpretative difficulties. As with any diagnostic test, test results must be interpreted in the clinical context and in association with other available information. One of the strengths of the ECG is that it is available in the very early stages of management of patients with suspected ACS, for example in the pre-hospital environment, before other diagnostic modalities as well as results of cardiac biomarkers are available. Since the method is automated and uses readily available information in the 12-lead ECG, it could have a potential in providing early diagnostic support to the inexperienced interpreter in particular. The results of this study indicate that this can be done with excellent sensitivity and a very low number of false positives. 19% of the patients with acute coronary occlusion would not have been recognized by means of significant ST elevation in two contiguous leads (sensitivity 81% (68%–89%). ECG examples of patients that did not fulfill this criterion are presented in Figs. 4–6. Compared to this, the Olson method performs better regarding sensitivity, since all patients with acute coronary occlusion were recognized (sensitivity 100%). Future studies are needed to explore sensitivity and specificity in patients with chest pain with and without acute transmural myocardial ischemia. Future studies of the clinical impact of the Olson method on management of patients with ACS are also needed.

In previous studies of the Olson method, it has been tested for accuracy in culprit detection in acute coronary occlusion, while assuming normal coronary anatomy. The ECG, however, reflects the ischemic area and not the perfusing artery. Since coronary anatomy can vary between individuals, the Olson method needs further validation of its performance as regard locating myocardial ischemia by comparing the method to a gold standard for ischemia localization such as myocardial perfusion imaging or cardiac MRI, rather than coronary angiography.

Table 5
Correlation between Olson wall scores and height, weight, and body mass index.

Wall	Height	Weight	Body mass index
Septal	r = 0.16 (p = 0.02)	r = −0.01 (p = 0.87)	r = −0.11 (p = 0.12)
Anterior	r = 0.23 (p = 0.001)	r = 0.02 (p = 0.75)	r = −0.11 (p = 0.11)
Lateral	r = 0.11 (p = 0.12)	r = −0.05 (p = 0.48)	r = −0.11 (p = 0.11)
Inferior	r = −0.11 (p = 0.1)	r = −0.12 (p = 0.083)	r = −0.09 (p = 0.19)

Data were available for 98 women and 113 men.

Table 4
Olson wall scores in male patients without acute myocardial ischemia (n = 180).

Wall[a]	Mean	SD	Upper limit 95% confidence[b]	Upper limit 99% confidence[b]	Modified thresholds
Septal <40	760 (635–885)	336.3	1419	1627	1627–1695[c]
Septal ≥40	402 (356–449)	286.8	964	1142	1158–1337[c]
Anterior <40	624 (534–714)	220	1055	1192	1192
Anterior ≥40	348 (314–382)	212.7	765	897	1163–1209[c]
Lateral	109 (102–116)	49.6	206	237	237–1068[c]
Inferior	56 (46–67)	71.7	197	2241	382–992[c]

[a] The septal and anterior walls have separate thresholds for patients <40 and ≥40 years.
[b] The upper limit of normal with 95% and 99% confidence defined as mean + 1.96 and 2.58 standard deviations, respectively.
[c] The same sensitivity and specificity would be maintained within this range.

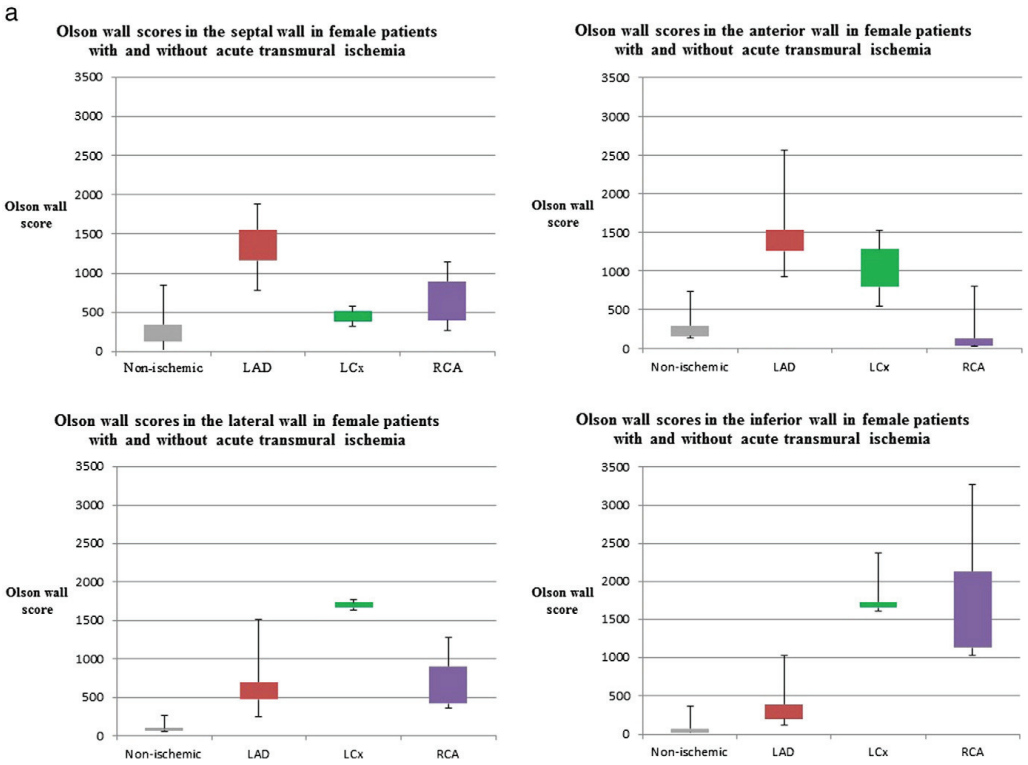

Fig. 3. **a.** Box-plots showing the distribution of Olson wall scores of the four different walls (septal (upper left), anterior (upper right), lateral (lower left), inferior wall (lower right)) in women without acute myocardial ischemia (gray boxes, n = 180) and female patients with acute occlusion of the three main coronary arteries (LAD red boxes (n = 6), LCx green boxes (n = 2) and RCA purple boxes (n = 5)).**b.** Box-plots showing the distribution of Olson wall scores of the four different walls (septal (upper left), anterior (upper right), lateral (lower left), inferior (lower right)) in male patients without acute myocardial ischemia (gray boxes, n = 180) and male patients with acute occlusion of one of the three main coronary arteries (LAD red boxes, (n = 13), LCx green boxes (n = 7), RCA purple boxes (n = 19)).

Limitations

This study does not address the performance of the Olson method in patients with some electrocardiographic signs of acute coronary occlusion, or its equivalence, such as de Winter sign, Wellen's syndrome and global circumferential ischemia (e.g. caused by left main stem occlusion). Also, it is not known how the method performs in patients with non-ischemic ST elevation, such as pericarditis or early repolarization syndrome.

A limitation to this study is that the computer-based measurements of the J-point amplitudes were not performed with the same ECG software in the two different study groups. This however reflects clinical reality, where different software is used at different institutions. Another limitation is that the number of patients with coronary artery occlusion is small, especially when subgrouping this material into gender-based groups. The main aim of this study, though, is to describe the normal variation of the Olson method in non-ischemic patients, and the sensitivity and specificity still need further evaluation with larger samples and different groups of patients.

Table 6
Sensitivity/specificity[a] with different thresholds.

	Sensitivity	Specificity
Upper limit 95% confidence	100% (93–100)	87% (85–91)
Upper limit 99% confidence	100% (93–100)	93% (90–95)
Modified thresholds	100% (93–100)	99% (98–100)
STEMI criteria	81% (68–89)	99% (98–100)

[a] Presented with 95% confidence intervals.

Conclusion

This study shows the variation of the Olson wall scores in patients without acute myocardial ischemia. When applied to a group of patients with acute coronary occlusion, these upper limits of normal yielded a very high sensitivity and a low number of false positives. Future studies are needed for instance to explore specificity in patients with non-ischemic ST-elevation conditions.

b

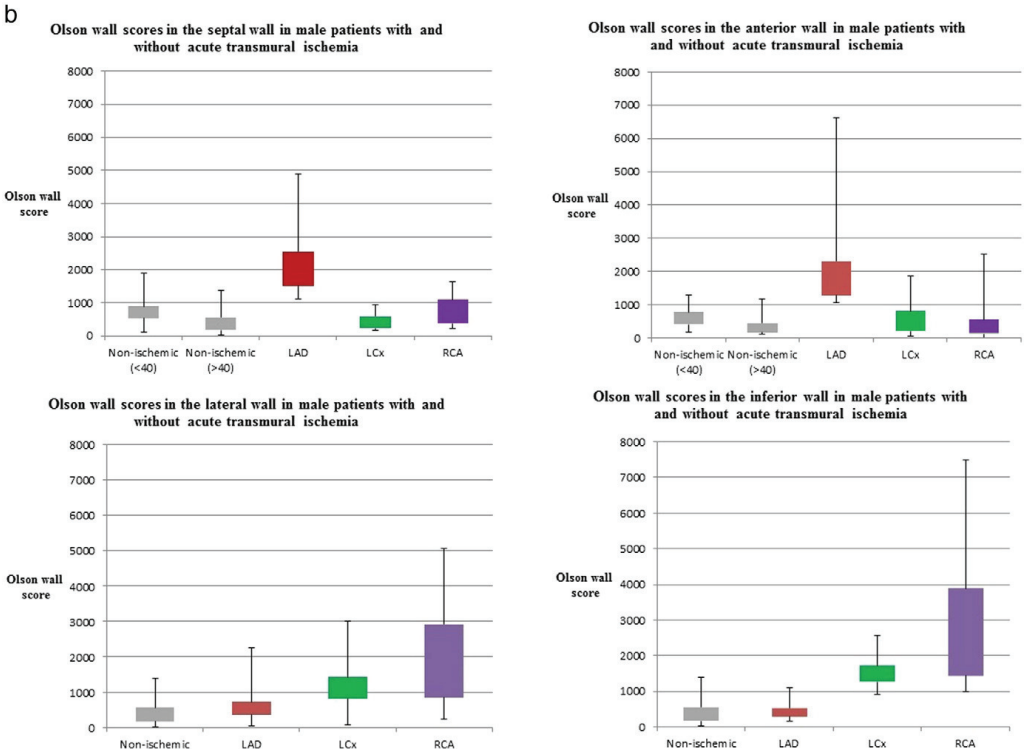

Fig. 3. (*continued*).

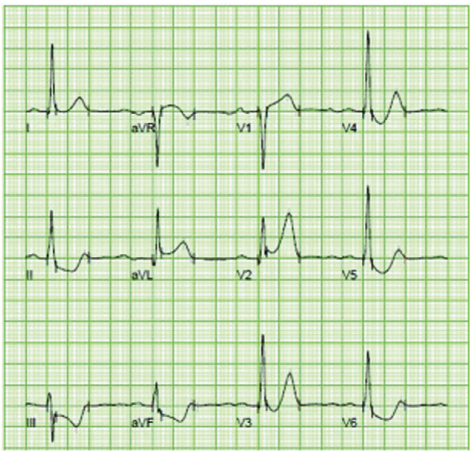

Fig. 4. ECG from a patient with acute occlusion of the right coronary artery showing significant ST elevation in lead aVL and ST depression in lead III, thereby not fulfilling strict STEMI criteria of ST elevation in two contiguous leads. Maximal Olson wall score was in the inferior wall, positive for ischemia.

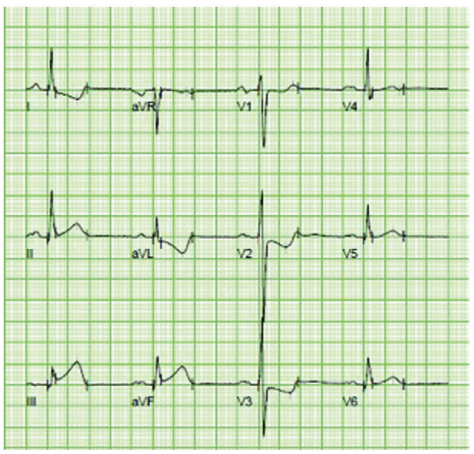

Fig. 5. ECG from a patient with acute occlusion of the right coronary artery showing significant ST depression in leads V2 and V3, significant ST elevation in lead III and sub-threshold ST elevation in lead aVF, thereby not fulfilling strict STEMI-criteria of ST elevation in two contiguous leads. Maximal Olson wall score was in the inferior wall, positive for ischemia.

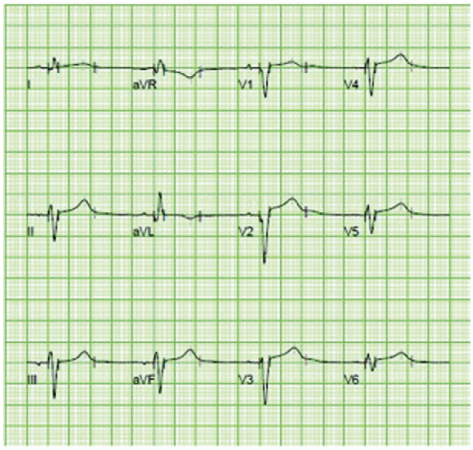

Fig. 6. ECG from a patient with acute occlusion of the left anterior descending coronary artery showing slight ST elevation in several leads, not fulfilling strict STEMI criteria of significant ST elevation in two contiguous leads. Maximal Olson wall score was in the anterior wall, positive for ischemia.

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Study II

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Diagnostic Accuracy Of The Electrocardiographic Decision Support – Myocardial Ischaemia (EDS-MI) Algorithm In Detection Of Acute Coronary Occlusion

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Abstract

Electrocardiographic Decision Support – Myocardial Ischaemia (EDS-MI) is a graphical decision support for detection and localization of acute transmural ischaemia. A recent study indicated that EDS-MI performs well for detection of acute transmural ischaemia. However, its performance has not been tested in patients with non-ischaemic ST-deviation. We aimed to optimize the diagnostic accuracy of EDS-MI in patients with verified acute coronary occlusion as well as patients with non-ischaemic ST deviation and compare its performance with STEMI criteria. We studied 135 patients with non-ischaemic ST deviation (perimyocarditis, left ventricular hypertrophy, takotsubo cardiomyopathy and early repolarization) and 117 patients with acute coronary occlusion. In 63 ischaemic patients, the extent and location of the ischaemic area (myocardium at risk) was assessed by both cardiovascular magnetic resonance imaging and EDS-MI. Sensitivity and specificity of ST elevation myocardial infarction criteria were 85% (95% confidence interval (CI) 77, 90) and 44% (95% CI 36, 53) respectively. Using EDS-MI, sensitivity and specificity increased to 92% (95% CI 85, 95) and 81% (95% CI 74, 87) respectively ($p=0.035$ and $p<0.001$). Agreement was strong (83%) between cardiovascular magnetic resonance imaging and EDS-MI in localization of ischaemia. Mean myocardium at risk was 32% (± 10) by cardiovascular magnetic resonance imaging and 33% (± 11) by EDS-MI when the estimated infarcted area according to Selvester QRS scoring was included in myocardium at risk estimation. In conclusion, EDS-MI increases diagnostic accuracy and may serve as an automatic decision support in the early management of patients with suspected acute coronary syndrome. The added clinical benefit in a non-selected clinical chest pain population needs to be assessed.

Keywords

Acute coronary occlusion, automatic ECG interpretation, decision support, non-ischaemic ST deviation

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Introduction

In patients with acute coronary occlusion rapid revascularization is imperative.[1,2] By the use of automatic and graphical aids, diagnostic accuracy may be improved.[3,4] Signs of acute coronary occlusion are considered present when ST elevation myocardial infarction (STEMI) criteria are fulfilled.[5] Electrocardiographic Decision Support – Myocardial Ischaemia (EDS-MI), previously referred to as 'the Olson method', is a graphical decision support for detection and localization of acute transmural ischaemia.[6] EDS-MI has previously

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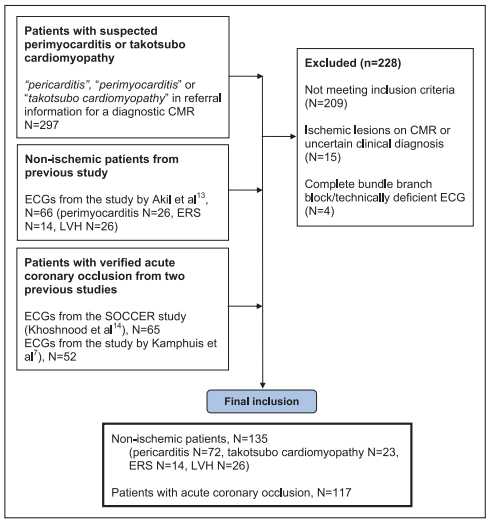

Figure 1. Diagrammatic presentation of inclusion and exclusion of patients with acute coronary occlusion and non-ischaemic conditions.
CMR: cardiovascular magnetic resonance; ECG: electrocardiogram; ERS: early repolarization syndrome; LVH: left ventricular hypertrophy.

proved to accurately identify the culprit artery in patients with acute coronary occlusion.[7] A recent study indicated that EDS-MI has higher sensitivity than STEMI criteria.[8]

There are several non-ischaemic conditions that can mimic STEMI, such as acute perimyocarditis, early repolarization syndrome (ERS) and takotsubo cardiomyopathy.[9–11] Furthermore, ST deviation can be present in patients with left ventricular hypertrophy (LVH). We aimed to optimize the diagnostic accuracy of EDS-MI in patients with verified acute coronary occlusion as well as patients with non-ischaemic ST deviation and compare its performance with STEMI criteria. We also aimed to describe the concordance between ischaemia localization and estimation of myocardium at risk (MaR) between cardiovascular magnetic resonance (CMR) and EDS-MI with and without Selvester QRS scoring.[12]

Ethical considerations

The Regional Ethical Review Board in Lund approved the study. Anonymized data from previous studies[7,13,14] were included in this study. Necessary ethical approval for these studies was obtained by the regional ethical boards.

Material and methods

In this study, 135 patients with non-ischaemic ST deviation and 117 patients with acute coronary occlusion on coronary angiography were retrospectively included (Figure 1; Table 1).

Inclusion and exclusion criteria were as follows: inclusion criteria (ischaemic patients): patients referred to primary percutaneous coronary intervention (PCI) with evidence of acute coronary occlusion during coronary angiography; inclusion criteria (non-ischaemic patients): patients with non-ischaemic ST deviation due to peri-/myocarditis, LVH, ERS or takotsubo cardiomyopathy; exclusion criteria (all): complete bundle branch block, technically deficient electrocardiogram (ECG); exclusion criteria (non-ischaemic patients): evidence of ischaemic heart disease on CMR imaging, uncertain clinical diagnosis.

Patients with acute coronary occlusion

From two previous studies,[7,14] 117 patients referred to acute primary PCI and with verified acute coronary occlusion were included in this study (Table 2). ECGs were recorded within 3 h from PCI (98% within 2 h). If several ECGs had been obtained, the ECG nearest in time to PCI was included.

Non-ischaemic patients with ST deviation

In total, 135 patients with non-ischaemic ST deviation were included: peri/-myocarditis (n=72), takotsubo cardiomyopathy (n=23), LVH (n=26) and ERS (n=14).

Of these 135 patients, 66 were included from a previous study:[13] pericarditis (n=26), LVH (n=26) and ERS (n=14). The remaining 69 of the 135 non-ischaemic patients (perimyocarditis (n=46) and takotsubo cardiomyopathy (n=23)) were retrospectively retrieved among patients who had been referred for a diagnostic CMR and were included if a final clinical diagnosis of acute peri-/myocarditis or takotsubo cardiomyopathy was made.

All patients with takotsubo cardiomyopathy underwent acute coronary angiography without significant coronary artery stenosis and had imaging evidence of transient ventricular dysfunction and recovery at follow-up CMR or echocardiography.

If available, automated measurements of J-point amplitudes[15] and QRS measurements[16] for all 12 leads were used (n=69). If no automated measurements were available, ST-J and QRS measurements were manually determined using computerized callipers (n=183). The ST-J amplitude was defined as the amplitude of the J point, relative to the level of the PR segment immediately before QRS onset in all 12 leads. Selvester QRS scores were calculated for the ischaemic patients who performed CMR (n=63).[12]

STEMI criteria (significant ST elevation (≥0.1 mV in all leads except V2 and V3 (≥0.15 mV for women, ≥0.2 mV men ≥40 years, 0.25 mV men < 40 years)) in at least two contiguous leads) were applied to all patients.

Table 1. The study populations.

	Original paper study design	Inclusion criteria,[a] original study	Inclusion criteria, present study	Exclusion criteria,[a] original study	CMR	ECG
Acute coronary occlusion, population #1	Khoshnood et al.[14] Prospective	Clinical STEMI diagnosis Referred for primary PCI *N*=95	Acute occlusion at coronary angiography according to patient records *N*=65	Previous myocardial infarction	*N*=63 (Two exams of low quality excluded from analysis)	If several ECGs, ECG nearest to PCI included
Acute coronary occlusion, population #2	Kamphuis et al.[7] Retrospective	Suspected ACS Referred for primary PCI Acute coronary occlusion at coronary angiography (TIMI 0) *N*=53	Acute occlusion at coronary angiography (TIMI 0) *N*=52 (One patient excluded due to misplaced electrodes)	Previous myocardial infarction	None	If several ECGs, ECG nearest to PCI included
Takotsubo cardiomyopathy	Present study Retrospective	N/A	Clinical diagnosis of takotsubo cardiomyopathy Negative coronary angiography *N*=23		All patients referred for CMR Four not performed/ incomplete	If several ECGs recorded during hospital stay, the ECG with the largest ST deviation was included.
Pericarditis, population #1	Present study Retrospective	N/A	Clinical diagnosis of peri-/ myocarditis *N*=46		All patients referred for CMR	If several ECGs recorded during hospital stay, the ECG with the largest ST deviation was included
Pericarditis, population #2 ERS LVH	Akil et al.[13] Retrospective	Interpretative statement of 'pericarditis' in the ECG database confirmed by patient records	Clinical diagnosis of peri-/ myocarditis (*N*=26), ERS (*N*=14) and LVH (*N*=26)		None	Single ECG identified in search process.

[a]Inclusion and exclusion criteria relevant for this study are presented. General exclusion criteria for this study can be found in the Methods section and in Figure 1.
CMR: cardiovascular magnetic resonance; ECG: electrocardiogram; ERS: early repolarization syndrome; LVH: left ventricular hypertrophy; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction.

EDS-MI

A detailed description of EDS-MI can be found in previous papers.[6,8] EDS-MI is an automatic and graphical electrocardiographic decision support algorithm based on the Selvester model of the left ventricle[17] and the transformation of the ST-J amplitudes into an ST vector in 3D space (Figure 2). Cardiac electrical forces can be represented, at any time point, by the 12 leads in the ECG, or by a three-dimensional vector. Such a vector can be synthesized from the 12-lead ECG amplitudes. In EDS-MI, according to the image surface of Frank[18,19] with correction for lead strength,[6] an ST vector is calculated, from which so-called ischaemic wall scores and a suggestion of the location of transmural ischaemia are generated (Figure 2).[8,20,21] In the previous study of EDS-MI, presence of ischaemia was determined by first identifying the wall with the highest ischaemic wall score (i.e. either the septal, anterior, lateral or inferior wall). If the highest ischaemic wall score exceeded a wall-specific gender- and age-based threshold, the test was considered positive for ischaemia (Table 3).[8] In the present study, the elevation angle (positive angles below the transverse plane and negative above) was explored with the aim of improving test accuracy and the additive value of including such information in the test algorithm was studied.

Table 2. Baseline characteristics.

	Ischaemia (*N*=117)	No ischaemia (*N*=135)
Age, years: mean (SD)	63 (14)	49 (19)
Male gender	83 (71%)	91 (67%)
Smoker	44 (38%)	–
Diabetes	13 (11%)	–
Hypertension	37 (32%)	–
Previous medication		
ACE-inhibitor/angiotensin II receptor blocker	20 (17%)	–
Anticoagulants	1 (1%)	–
Aspirin/other antiplatelet drug	6 (5%)	–
β-blocker	11 (9%)	
Calcium channel blockers	8 (7%)	–
Diuretics	14 (12%)	–
Oral antidiabetics/insulin	9 (8%)	–
Nitrates	2 (2%)	–
Statins	9 (8%)	–
Symptom to PCI, min: median (IQR))	138 (114)	–
Time from ECG to PCI <2 h	98%	–
Peak troponin levels, ng/L: (median (IQR))	3862 (5702)	–
Myocardium at risk by CMR, %LV: mean (SD)	57 (32)	
Final infarct size by CMR, %LV: mean (SD)	17 (10)	
Culprit lesion		
LAD	49 (42%)	–
RCA	53 (45%)	–
LCx	15 (13%)	–
Non-ischaemic condition		
Perimyocarditis	–	72 (53%)
ERS	–	14 (10%)
LVH	–	26 (19%)
Takotsubo cardiomyopathy	–	23 (17%)

ACE: angiotensin-converting enzyme; CMR: cardiovascular magnetic resonance; ECG: electrocardiogram; ERS: early repolarization syndrome; IQR: interquartile range; LAD: left anterior descending artery; LCx: left circumflex artery; LV: left ventricle; LVH: left ventricular hypertrophy; PCI: percutaneous coronary intervention; RCA: right coronary artery.

For both STEMI criteria and EDS-MI, a true positive test was defined as a positive test result *and* presence of an acute coronary occlusion at the coronary angiography and a true negative test result as a negative test result *and* a non-ischaemic diagnosis.

In EDS-MI, the location of ischaemia is depicted on the map of the left ventricle in the shape of an ellipse with its centre located in the myocardial segment with the highest ischaemic score. The size of the ellipse is meant to represent the myocardium at risk (MaR).[6]

MaR was calculated for 63 of the ischaemic patients. In those patients, CMR was performed 2–6 days after the primary PCI on a Philips 1.5T Achieva at Skåne University Hospital, Lund or on a Siemens 1.5T Avanto at Skåne University Hospital, Malmö. T2-weighted images (T2-weighted triple inversion recovery imaging (Lund) or T2-prepared steady-state free precession (Malmö)) to depict the MaR[22] were acquired in short-axis view, from base to apex of the left ventricle. For assessment of final infarct size, late gadolinium images covering the entire left ventricle were acquired approximately 15 min after injection of the gadolinium-based contrast agent. Analysis of MaR and infarct size[23] was performed using the post-processing software Segment (v. 1.9 R3084).[24] The location of the ischaemic region was translated into one or more of 12 left ventricular segments (Figure 2). Ischaemic location was designated to the wall with the greatest proportion of MaR.

Statistical methods

Continuous variables are presented as means and standard deviations if normally distributed, otherwise as medians and interquartile ranges (IQR). Student's *t*-test was used for comparison of mean ischaemic wall scores between ischaemic and non-ischaemic patients. Mann–Whitney *U* test was used for comparisons of median elevation angles between groups. Receiver operating characteristic analysis was used for evaluation of additional test parameters (elevation angles).

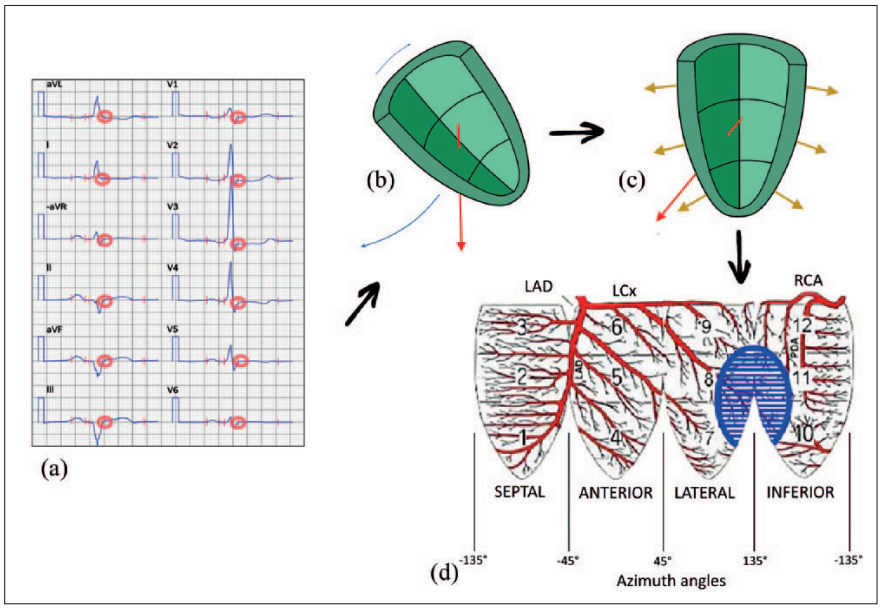

Figure 2. The ischaemic wall score and the suggested location of transmural ischaemia are generated from the ST-J amplitudes in the 12-lead electrocardiogram (ECG; (a), Cabrera format), from which an ST vector in 3D space is calculated (red arrow, (b)). By the use of information on the anatomical long axis of the left ventricle from cardiovascular magnetic resonance studies[20,21] the left ventricle (and the ST vector) is rotated in the transversal and frontal plane to obtain an approximate vertical position (c). By this rotation, the four left ventricular walls will be represented by the azimuth angles (90° quadrant for each wall) on the Mercator model of the left ventricle (d). For each segment, the magnitude of the ST vector (red arrow (c)) is multiplied with the cosine of the angle between the ST vector and a segmental vector (a hypothetical representation of transmural ischaemia in that segment (yellow arrows (c)). The resulting scalar products are added for segments within the same wall (septal, anterior, lateral or inferior) to create an 'ischaemic wall score' which is used for determination of presence of ischaemia.[6,8] The location of the highest score is depicted on the map of the left ventricle (d). This patient had an acute occlusion of a large circumflex artery (with shared dominance). In the ECG, no significant ST elevation was present, but ST depression in anteroseptal leads. Electrocardiographic Decision Support – Myocardial Ischaemia was positive for ischaemia located in the middle and apical lateral and inferior wall in excellent accordance with the angiographic finding.
LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery.

Sensitivity and specificity are described with 95% confidence intervals (CIs). McNemar's test was used for comparisons of sensitivity and specificity between EDS-MI and STEMI criteria. Difference in calculated MaR is presented as a modified Bland–Altman plot. Pearson's correlation test was used to determine correlation between normally distributed variables, and Spearman's rank correlation test between non-normally distributed variables. Cohen's kappa test was used to determine the level of accordance between the results between CMR and EDS-MI in localizing ischaemia. A p-value of < 0.05 was considered statistically significant.

Results

Detection of acute coronary occlusion

Sensitivity and specificity of STEMI criteria were 85% (95% CI 77, 90) and 44% (95% CI 36, 53) respectively. STEMI criteria were positive in 39% of takotsubo patients, in 76% of patients with perimyocarditis, in 71% of ERS patients and in 4% of LVH patients. Using EDS-MI sensitivity and specificity were 92% (95% CI 86, 96) and 81% (95% CI 74, 87), respectively (p=0.0035 and p<0.001) (Table 4). Sensitivity for each of the three coronary arteries and specificity for different non-ischaemic conditions using both EDS-MI and STEMI criteria are presented in Table 4.

Mean ischaemic wall scores were higher in patients with acute coronary occlusion compared with patients with non-ischaemic conditions (p<0.0001). The majority of patients with left anterior descending artery (LAD) occlusion (100%), perimyocarditis (86%) and ERS (100%) had their largest ischaemic wall scores in either the septal or anterior wall. In contrast, most patients with right coronary artery (RCA) occlusion (87%) and all patients with LVH had their largest scores in the inferior wall. Sixty per cent of patients with left circumflex artery (LCx) occlusion had

Table 3. Ischaemic wall score thresholds according to Lindow et al.[8]

Wall	Upper limit 99% confidence
	Female patients
Septal	713
Anterior	568
Lateral	194[a]
Inferior	239[a]
	Male patients[b]
Septal <40	1627
Septal ≥40	1142
Anterior <40	1192
Anterior ≥40	897
Lateral	237[a]
Inferior	241[a]

[a]In the paper by Lindow et al. the thresholds could be increased up to 1620 and 1068 for the lateral wall for female and male patients respectively and up to 1027 and 992 for the inferior wall without any loss in sensitivity.[8]
[b]The septal and anterior walls have separate thresholds for male patients < 40 and ≥40 years.

Table 4. Sensitivity and specificity (EDS-MI and STEMI criteria).

	EDS-MI	STEMI criteria	*p*-value
Culprit artery	Sensitivity		
All[a]	92%	85%	0.035
LAD	90%	92%	1
RCA	94%	81%	0.016
LCx	93%	73%	0.25
Non-ischaemic condition	Specificity		
All[a]	81%	44%	<0.001
Perimyocarditis	76%	22%	<0.001
Takotsubo	70%	61%	0.75
LVH	100%	96%	1
ERS	93%	29%	0.004

[a]Net Reclassification Index 0.44 (95% confidence interval 0.38, 0.50).
EDS-MI: Electrocardiographic Decision Support – Myocardial Ischaemia; ERS: early repolarization syndrome; LAD: left anterior descending artery; LCx: left circumflex artery; LVH: left ventricular hypertrophy; RCA: right coronary artery; STEMI: ST segment elevation myocardial infarction; RCA: right coronary artery.

their largest scores in the lateral wall. Most patients with takotsubo cardiomyopathy had largest scores in the anterior wall (65%).

In patients with the largest ischaemic wall score in the inferior wall, the ST vector was more inferiorly directed in patients with coronary occlusion compared with patients without ischaemia (median elevation 63° (IQR 46, 73) and –11° (IQR –21, 7) respectively (p<0.05). In patients with the largest ischaemic score in the anterior wall, the ST vector was more superiorly directed in patients with coronary occlusion compared with patients without ischaemia (median elevation –2° (IQR –20, 4) and 20° (IQR 11, 28) respectively (p<0.05).

Using only the thresholds for the ischaemic scores in Table 2, a large number of patients were falsely classified as ischaemic. While maintaining a sensitivity of > 90% (92% (95% CI 86, 96), specificity increased to 81% (95% CI 74, 87) if criteria on the elevation angle of the ST vector were added to the test algorithm, depending on the location of the largest ischaemic score. A diagnostic flow chart is presented in Figure 3 and exemplified in Figure 4.

Localization and estimation of extent of myocardial ischaemia

Mean MaR was 32% (± 10) according to CMR. Mean MaR was 33% (± 11) according to EDS-MI when the estimated infarcted area according to Selvester QRS scoring was included in MaR estimation and 19% (± 7) without QRS scoring (Figure 5). Mean final infarct size was 17.5% (± 10) by CMR, and median infarct size according to Selvester QRS scoring was 12% (IQR 9). Correlation of EDS-MI and CMR parameters, troponin levels and Selvester QRS scoring are presented in Table 5. When QRS scoring was included, MaR by EDS-MI was weakly correlated with MaR by CMR (r=0.33 (95% CI 0.09, 0.53)), but moderately correlated with final infarct size (r=0.46 (95% CI 0.24, 0.68)) and troponin levels (r=0.39 (95% CI 0.16, 0.58)). Selvester QRS scoring was weakly to moderately correlated with both final infarct size and troponin levels (r=0.34 (95% CI 0.1, 0.54) and r=0.38 (95% CI 0.15, 0.57) respectively).

When location of ischaemia was defined as the wall with the highest ischaemic wall score for EDS-MI and for CMR as the wall with highest proportion of MaR, EDS-MI was correct in 71% of the observations (kappa value 0.59, p<0.005) (Table 6). If the septal and anterior walls were considered as the same location, representing a rough estimate of LAD territory, the proportion of observed agreements was 83% (kappa value 0.72, p<0.005).

Discussion

This study has shown increased diagnostic accuracy in detection of acute coronary occlusion when using an automated ECG method (EDS-MI) compared with STEMI criteria. Our results suggest that EDS-MI has the potential to be used as decision support in the early management of patients with suspected acute coronary occlusion, decreasing the number of unnecessary coronary angiographies.

In a previous paper on EDS-MI, the normal variation of the ischaemic wall scores was established.[8] The scores were lower in the lateral and inferior walls compared with the septal and anterior wall in patients without ischaemia

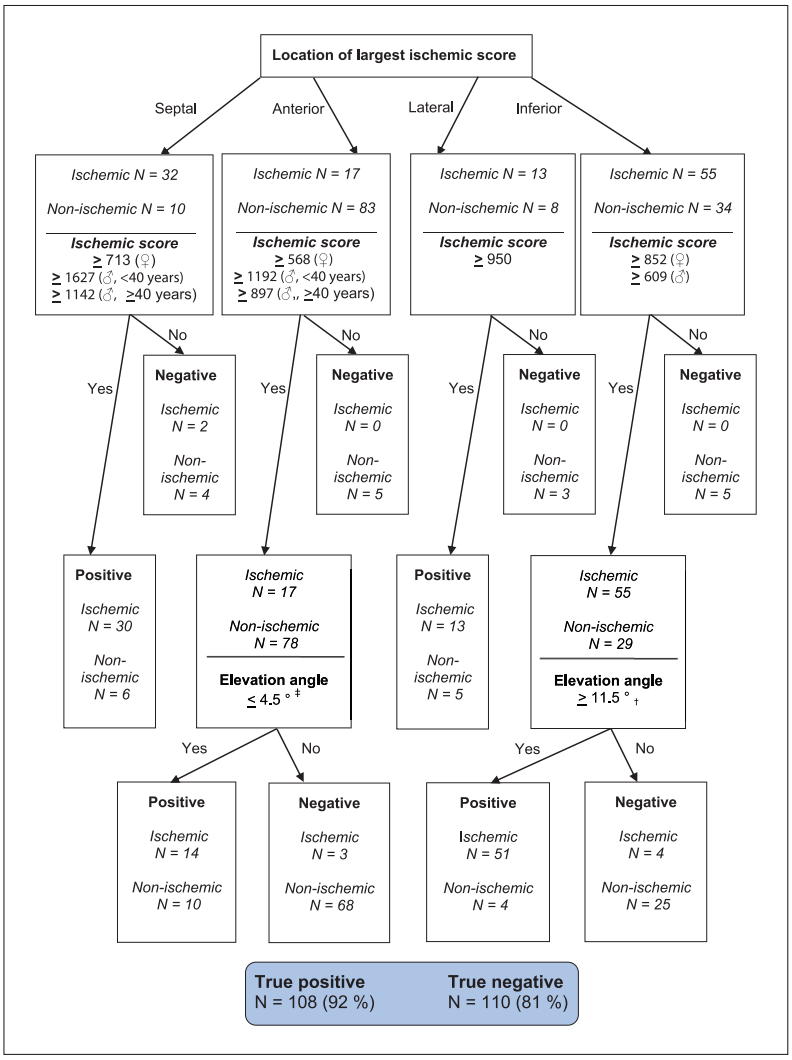

Figure 3. Diagnostic flow chart of the algorithm applied in this study. First, the wall with the largest ischemic score is located. Second, a wall-specific gender- and age-based threshold for the ischemic score is applied. If the largest score is located in the septal or lateral wall, the test is positive for ischemia if this threshold is exceeded. If the largest score is located in the anterior or inferior wall, the test is positive for ischemia if both the threshold is exceeded and the criterion of a certain ST vector elevation angle is fulfilled. Ischaemic patients, *n*=117; non-ischaemic patients, *n*=135.
‡Area under the curve (AUC) 0.87 (0.76, 0.98).
†AUC 0.94 (0.89, 0.99).

(Table 3). Since ischaemic patients had substantially higher ischaemic wall scores than non-ischaemic patients, threshold values in the lateral and inferior wall could be increased without any loss in sensitivity, and the range of this modification was described.[8] In the present study, an increase of the threshold values for these walls within this range contributed to the increased specificity of EDS-MI.

Neither specificity nor sensitivity of STEMI criteria is optimal in detection of acute coronary occlusion.[25–27] Among 1957 patients with non ST-elevation acute coronary syndrome, Wang et al. found an occluded culprit artery in 27% of the cases, more than half of them supplying the inferolateral left ventricle.[25] In transmural ischaemia, the vector of the ST displacement is directed towards the ischaemic

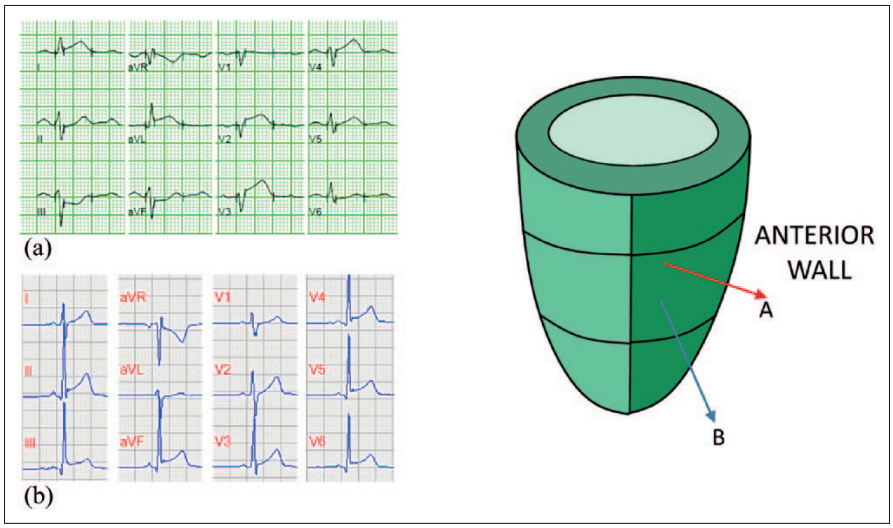

Figure 4. Electrocardiograms (ECGs) from two patients with the largest ischaemic score in the anterior wall. Upper left (a): a patient with left anterior descending artery occlusion. The ECG shows ST elevation in V2, V3, I and aVL and ST depression in III and aVF. Lower left (b): a patient with acute perimyocarditis. The ECG shows ST elevation in precordial leads and ST elevation in inferior limb leads shifting the ST vector in an inferior direction compared with the ECG above. To the right is a schematic presentation of the difference in elevation angle between the two patients. Red arrow A: negative elevation (slightly directed upward); blue arrow B: positive elevation (directed downward). Both ECGs fulfilled STEMI criteria. In EDS-MI, both patients fulfilled the threshold criteria but only the patient with coronary occlusion (a) fulfilled the criterion of an ST vector elevation angle (≤ 4.5°) and was therefore positive for ischemia, whereas the patient with perimyocarditis (b) was negative.
CMR: cardiovascular magnetic resonance; EDS-MI: Electrocardiographic Decision Support – Myocardial Ischaemia; MaR: myocardium at risk.

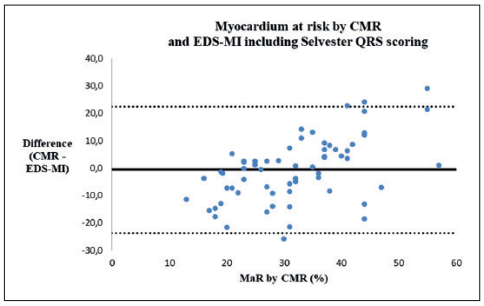

Figure 5. Difference between the estimation of MaR by CMR and EDS-MI with QRS scoring. Mean bias (–1%) indicated by solid line. Upper (22.5%) and lower limits (–23.7%) of agreement (calculated as ± 1.96 standard deviations) are indicated by dotted lines.
CMR: cardiovascular magnetic resonance; EDS-MI: Electrocardiographic Decision Support – Myocardial Ischaemia; MaR: myocardium at risk.

myocardium.[28] An injury current directed away from the exploring lead will be displayed as ST depression. For example, transmural ischaemia of the lateral wall may present as ST depression in V1–V3, hence not fulfilling STEMI criteria. This problem is avoided in EDS-MI by converting the ST amplitudes into an ST vector in 3D space. In this study, sensitivity was slightly increased, mainly due to an increased detection of RCA and LCx occlusion (Figure 6, Table 4).

In the previous study of EDS-MI in detection of ischaemia, the ischaemic wall score was calculated as the sum of scores of the basal, middle and apical wall segments (the dot products of the ST vectors and the segmental 'ischaemic' vectors).[8] Due to this summation, directional information regarding the elevation of the ST vector is lost; for example, superiorly and inferiorly directed ST vectors would yield the same ischaemic wall score, while the basal score is larger for the superiorly directed ST vector and the apical score is larger for the inferiorly directed ST vector. In the present study, the elevation angle of the ST vector was therefore explored with the aim of improving test accuracy. Patients with perimyocarditis or LAD occlusion could be differentiated by incorporation of the elevation angle in the diagnostic algorithm. Patients with pericarditis often present with widespread ST elevation,[29] both in precordial leads and inferior limb leads, thus shifting the ST vector in an inferior direction, whereas, in particular, patients with proximal LAD occlusion present with ST depression in inferior leads[30] (Figure 4). In LAD occlusion, absence of ST depression in lead III is strongly associated with an occlusion distal to the first diagonal branch,[30] which may be a potential pitfall in EDS-MI, since the absence of ST depression, or even

Table 5. Correlation of EDS-MI and CMR parameters, troponin levels and Selvester QRS scoring.

	MaR CMR	Final infarct size CMR	Troponin
EDS-MI MaR w. QRS scoring	0.33**	0.46**	0.39**
EDS-MI MaR w/o QRS scoring	0.25	0.36*	0.24
EDS-MI ischaemic score	0.27*	0.39**	0.26**
Selvester QRS scoring	0.24	0.34**	0.38**
Troponin	0.46**	0.67**	–
LAD occlusion			
EDS-MI MaR w. QRS scoring	0.53**	0.67**	0.7**
Selvester QRS scoring	0.29	0.49**	0.51**
RCA occlusion			
EDS-MI MaR w. QRS scoring	0.23	0.38	0.25
Selvester QRS scoring	0.15	0.09	0.12
LCx occlusion			
EDS-MI MaR w. QRS scoring	0.64	0.17	0.49
Selvester QRS scoring	0.6	0.54	0.43

*$p<0.05$.
**$p<0.01$.
EDS-MI: Electrocardiographic Decision Support – Myocardial Ischaemia; CMR: cardiovascular magnetic resonance; LAD: left anterior descending artery; LCx: left circumflex artery; MaR: myocardium at risk; RCA: right coronary artery; w.: with; w/o: without.

Table 6. Agreement of location of ischaemia.

		CMR			
		Septal	Anterior	Lateral	Inferior
EDS-MI	Septal	17	1	0	2
	Anterior	6	2	0	0
	Lateral	0	0	5	4
	Inferior	0	0	5	21

EDS-MI: Electrocardiographic Decision Support – Myocardial Ischaemia; CMR: cardiovascular magnetic resonance.

presence of ST elevation, in inferior leads would result in a more inferiorly directed ST vector. In this material, 14 patients with LAD occlusion had no ST depression in lead III. STEMI criteria were fulfilled in 12 (86%) of these patients and EDS-MI was positive in only 10 patients (71%). Two of these four false negative patients had their largest score in the anterior wall and negative results due to an inferiorly directed ST vector. One way to deal with these patients could be to exclude the criterion of a specific elevation angle for the ST vector if the ischaemic score reaches a certain high value and/or to lower the threshold for the ischaemic scores, at the cost of a lower specificity. Using EDS-MI, specificity was improved for all non-ischaemic groups, except takotsubo cardiomyopathy patients (Table 4). Based on ST deviation information only, differentiation between patients with LAD occlusion and patients with takotsubo cardiomyopathy is difficult.[31]

Culprit artery identification can be performed with high accuracy using EDS-MI.[7] However, the ECG reflects only the ischaemic area and not the perfusing artery, and coronary anatomy varies between individuals. Given that the applied techniques are validated for the scanners used, T2-weighted imaging[22,32] or contrast-enhanced steady state free precession[33,34] CMR provides accurate information on the location of the ischaemic myocardium and can serve as reference standard in this context.[35] During early management of suspected acute coronary syndrome, the task is to detect presence of ischaemia and – if present – to estimate the extent of ischaemia, which can be described as the MaR. The size of the final infarct depends both on the size of MaR and the time to treatment (revascularization) et cetera.[2,22] Therefore, in theory, it is MaR, and not the final infarct size, that is the pathophysiological equivalent of the ST deviation

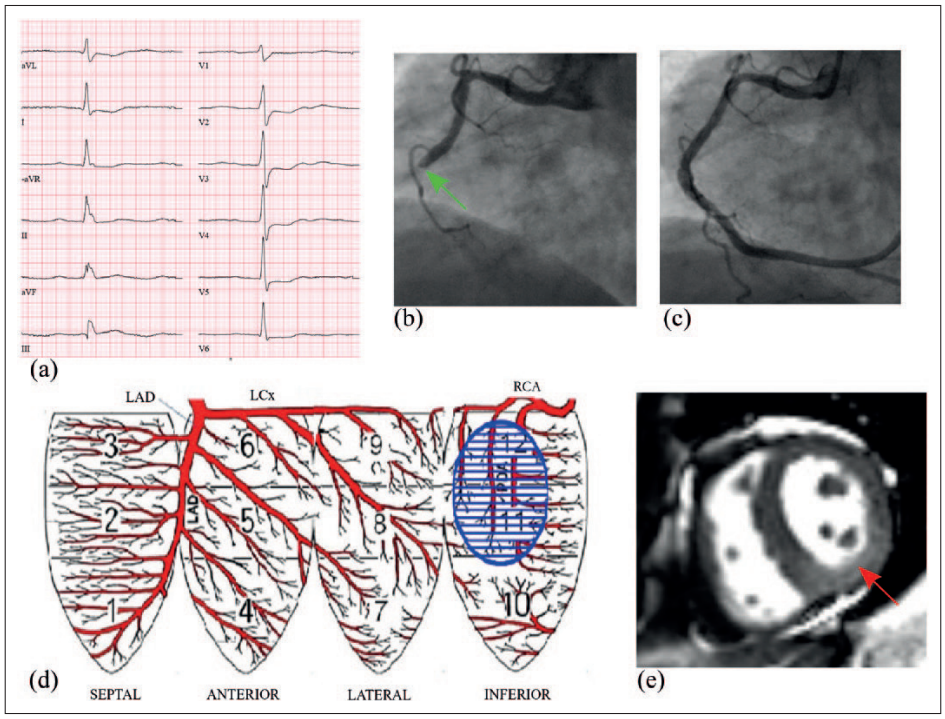

Figure 6. ECG shows slight ST elevation in III, ST depression in I, aVL and V2–V6, not fulfilling STEMI criteria ((a) Cabrera format, 50 mm/s). This patient had an acute occlusion of the right coronary artery (b) with restoration of flow after percutaneous coronary intervention (c). Electrocardiographic Decision Support – Myocardial Ischaemia was positive for ischaemia in the inferior wall (d). Cardiovascular magnetic resonance shows ischaemic injury in the inferior wall (T2-prepared steady-state free precession images) (e)).
LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery.

of the ECG in the acute setting. Electrocardiographic estimation of MaR based on ST information only has been shown to underestimate MaR,[36,37] since ST deviation is replaced by QRS changes during the process from ischaemia to infarction. Agreement in mean estimates of MaR between CMR and EDS-MI was improved when Selvester QRS scoring was included. However, even though the bias was small, the variability was large, clearly limiting the clinical value of the described extent of ischaemia using EDS-MI. Some discrepancy between MaR by ECG parameters and MaR by CMR would be expected, since MaR size is fixed during the ischaemic process, whereas ECG changes are dynamic. Our results showed slightly higher correlation between EDS-MI and infarct size compared with MaR, in part explained by including Selvester scoring in MaR estimation.

Agreement between EDS-MI and CMR regarding the location of ischaemia within the typical territories of the three large coronary vessels was strong. In a recent study by Nordlund et al., the perfusion territories of the three main coronary arteries using CMR were described.[35] While LAD perfuses the anterior wall and most of the septal wall, there is great overlap between RCA and LCx in the basal and mid-wall segments of the inferior and lateral wall. Therefore, in culprit identification, the most relevant distinction that it is possible to make would be whether the likely culprit is within LAD territory or not. Even though division of the left ventricle into the four walls in the Mercator plot used in EDS-MI is an overly simplistic presentation, disagreement between CMR and EDS-MI regarding ischaemia within the LAD territory was rare (Table 5).

Other ECG decision supports, 'vessel-specific leads' (VSL)[38] and 'computed electrocardiographic imaging' (CEI)[13] also presented improved specificity in patients with perimyocarditis compared with STEMI criteria.[38] Sixty-six of the patients included in this study were the same ones as used in the study by Wang et al. (VSL) and in the study by

Table 7. Specificity of three decision aids in different non-ischaemic conditions (same patients).

	N	EDS-MI	CEI	VSL
Perimyocarditis	26	78% (58, 89)	77%[a]	88% (76, 100)[b]
LVH	26	100% (87, 100)	100%[a]	96% (89, 100)[b]
ERS	14	100% (78, 100)	100%[a]	100% (100, 100)[b]

[a]CEI is a graphical decision support, but requires human interpretation. Median specificity for three reviewers. No confidence interval available.
[b]Confidence intervals presented in the paper by Wang et al. (Wang et al. 2016).
CEI: computed electrocardiographic imaging; EDS-MI: Electrocardiographic Decision Support – Myocardial Ischaemia; ERS: early repolarization syndrome; LVH: left ventricular hypertrophy; VSL: vessel specific leads.

Akil et al. (CEI). Specificity was similar between EDS-MI, VSL and CEI when the same patients with perimyocarditis, ERS and LVH were studied (Table 7).

The strength of the ECG in acute coronary syndrome management is that it is available before other diagnostic modalities, as well as before cardiac biomarkers. EDS-MI uses readily available information in the 12-lead ECG (ST-J amplitudes) and therefore its results will be presented automatically and instantly once the 12-lead ECG has been recorded, and provided that the algorithm is integrated in the ECG recorder. EDS-MI could be used as a diagnostic decision support in prehospital management, for non-experienced interpreters in particular. It is possible that human interpretation, which has the possibility of including other factors such as symptoms and history, PR segment depression, concavity/convexity of the ST segment and T-wave morphology might be superior to this method. However, in clinical practice, missed coronary occlusions are common, indicating that human interpretation is not sufficient. The intention is for EDS-MI to be used as a decision support and not to replace human interpretation. It is not known how EDS-MI would perform in patients with isolated right ventricular infarction, distal LAD occlusion and left main stenosis.

Limitations

The selection process of patients with acute coronary occlusion was different from that of the patients without ischaemia. Patients with acute coronary occlusion were included after the decision to perform an acute coronary angiography had been made, whereas this was not the case in most of the patients with non-ischaemic ST deviation. Also, this study design does not represent the true prevalence of the diagnoses included in patients admitted to the emergency department due to chest pain.

Troponin was not systematically collected until troponin values declined, which makes the correlation between troponin and MaR/infarct size by CMR and ECG findings difficult to interpret.

The number of patients included in this study is small, especially when subgrouping the material into analyses of different ischaemic locations, different culprit arteries and non-ischaemic diagnoses. Also, the SOCCER study was not primarily performed as an electrocardiographic study and although all ECGs included were recorded before coronary angiography, both the grade of occlusion and ECG changes can be dynamic during an ischaemic process. As this mainly affects sensitivity, this aspect also needs to be addressed in a larger independent sample. This study population can be regarded as a training set and sensitivity and specificity is then only valid for this population. These aspects limit the validity of the results of this study and validation of EDS-MI requires testing in a larger independent sample, preferably unselected chest pain patients with acute coronary syndrome as one of the possible diagnoses.

Conclusion

EDS-MI has the potential of serving as an automatic decision support for the assessment of patients presenting with ST changes and suspected acute coronary syndrome in detection and localization of ischaemia, but not in estimation of the extent of ischaemia. Further studies in unselected clinical chest pain populations are needed.

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Conflict of interest

The authors TL, OP, UE, AK, MC, CAS, SM and HE have no conflicts of interest. CWO has a registered patent on EDS-MI.

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Study III

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ORIGINAL ARTICLE

WILEY

Chest-lead ST-J amplitudes using arm electrodes as reference instead of the Wilson central terminal in smartphone ECG applications: Influence on ST-elevation myocardial infarction criteria fulfillment

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Background: "Smartphone 12-lead ECG" for the assessment of acute myocardial ischemia has recently been introduced. In the smartphone 12-lead ECG either the right or the left arm can be used as reference for the chest electrodes instead of the Wilson central terminal. These leads are labeled "CR leads" or "CL leads." We aimed to compare chest-lead ST-J amplitudes, using either CR or CL leads, to those present in the conventional 12-lead ECG, and to determine sensitivity and specificity for the diagnosis of STEMI for CR and CL leads.

Methods: Five hundred patients (74 patients with ST elevation myocardial infarction (STEMI), 66 patients with nonischemic ST deviation and 360 controls) were included. Smartphone 12-lead ECG chest-lead ST-J amplitudes were calculated for both CR and CL leads.

Results: ST-J amplitudes were 9.1 ± 29 μV larger for CR leads and 7.7 ± 42 μV larger for CL leads than for conventional chest leads (V leads). Sensitivity and specificity were 94% and 95% for CR leads and 81% and 97% for CL leads when fulfillment of STEMI criteria in V leads was used as reference. In ischemic patients who met STEMI criteria in V leads, but not in limb leads, STEMI criteria were met with CR or CL leads in 91%.

Conclusion: By the use of CR or CL leads, smartphone 12-lead ECG results in slightly lower sensitivity in STEMI detection. Therefore, the adjustment of STEMI criteria may be needed before application in clinical practice.

KEYWORDS
CL leads, CR leads, smartphone 12-lead ECG, ST-elevation myocardial infarction criteria, Wilson central terminal

1 | BACKGROUND

Smartphone technology in cardiology is developing fast and has great potential because of its widespread availability (Martínez-Pérez, de la Torre-Díez, López-Coronado, & Herreros-González, 2013). For example, smartphone-based one-lead recording of electrocardiograms (ECG) has been validated for the diagnosis of atrial fibrillation (Lau et al., 2013). If smartphone ECG with recording capability for all 12

leads would become a reliable substitute for the conventional 12-lead ECG, there is a potential for very early detection of ST-elevation myocardial infarction (STEMI) upon symptom onset, even at the patient's home. Also, the smartphone could substitute for an ECG machine in healthcare settings where ambulance infrastructure is underdeveloped or ECG machines are scarce.

Smartphone technology for assessment of acute myocardial ischemia by the generation of "smartphone 12-lead ECG" has recently been introduced (Muhlestein et al., 2015). In that application the three limb leads, I, II, and III, are recorded by placing adhesive electrode tabs on the left arm (L), right arm (R), and on the left leg (F), similar to the procedure for recording the conventional 12-lead ECG. One difference, however, is that the leads are recorded sequentially, not simultaneously. Another difference is the reference electrode for the chest leads. When recording the conventional 12-lead ECG, the chest leads are created by subtracting the potential at the so-called Wilson central terminal (WCT) from the potential at each chest electrode (C1, ..., C6). The WCT is the average potential of the three limb potentials, R, L, and F (Gargiulo, 2015; Kligfield et al., 2007). In the smartphone 12-lead ECG application, the right or the left arm is used as reference instead of the WCT (Baquero, Banchs, Ahmed, Naccarelli, & Luck, 2015; Muhlestein et al., 2015). The resulting PQRST waveforms of CR and CL leads are not identical to those of the corresponding leads recorded with the WCT reference. It is not known how this affects the accuracy of diagnosis of STEMI. In the ongoing ST LEUIS trial, smartphone 12-lead ECG is compared to conventional 12-lead ECG by sequentially performing simultaneous recordings of a conventional chest lead (V lead) and the corresponding CR or CL lead (Barbagelata et al., 2017). However, the comparison of ST-J amplitudes in V leads to those in CR or CL leads does not require such a recording procedure. The ECG waveforms and thus the ST-J amplitudes, as they would appear in the smartphone application, can be calculated from the V leads and the relevant augmented lead (aVR or aVL) in the conventional 12-lead ECG (Figure 1).

The purpose of this study was to compare the chest-lead ST-J amplitudes, using either the right or left arm electrode as reference, to those in the conventional 12-lead ECG. Also, we aimed to determine sensitivity and specificity for the diagnosis of STEMI for smartphone 12-lead ECG based on these reference electrodes, and to compare them to those obtained with the conventional 12-lead ECG.

2 | METHODS

A total of 500 ECGs from patients from three different study populations were included in this study. Seventy-four patients with STEMI (37 with a culprit lesion in the left anterior descending artery (LAD), 32 in the right coronary artery (RCA) and 5 in the left circumflex artery (LCx)) were recruited from the SOCCER study (Khoshnood et al., 2016). The SOCCER study included 95 patients referred for primary percutaneous coronary intervention (PCI) who had been randomized to either standard oxygen therapy or no supplemental oxygen. Patients with an ECG without significant ST

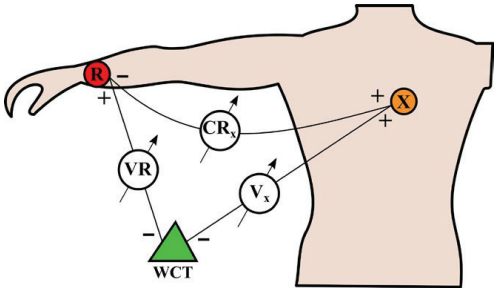

FIGURE 1 Electrode arrangement for recording leads Vx and CRx. R denotes the right arm electrode, and x denotes one of the six chest electrodes (1–6). WCT denotes the Wilson Central Terminal. The potentials indicated in the voltmeter symbols (Vx, CRx, and VR) obey Kirchoff's second law, that is, $CRx = Vx - VR = Vx - \left(\frac{2}{3}\right)aVR$. The same principles apply to all chest leads (V1–V6, CR1–CR6). If the left arm is used as reference, VL and aVL will replace VR and aVR in the formula

elevation in two contiguous leads (n = 19) or a technically deficient ECG (n = 2), were excluded from this study. Fifty-one patients had significant ST elevation in two contiguous chest leads and thus met STEMI criteria in V leads (LAD n = 37, RCA n = 10, LCx n = 4). Among these patients, 33 patients met STEMI criteria in V leads, but not in limb leads. Twenty-three patients had significant ST elevation in two contiguous limb leads, but did not meet STEMI criteria in V leads.

Sixty-six patients with nonischemic ST deviation due to pericarditis, (n = 26), early repolarization syndrome (ERS) (n = 14) or left ventricular hypertrophy (LVH) (n = 26) were included from another study (Akil et al., 2013). These ECGs were retrieved from a clinical ECG database and identified by a search in the interpretive statements. Confirmation of the clinical diagnosis was performed by reviewing patient records. In addition, 360 patients without ongoing myocardial ischemia (Lindow, Olson, Swenne, Man, & Pahlm, 2017) were included and served as controls. This dataset consisted of 30 ECGs for each gender and each age decade (30–39, 40–49,..., 80–89). All ECGs had been recorded either before a planned exercise test or myocardial perfusion imaging, before Holter monitoring or as a screening ECG before noncardiac surgery. Only patients with a very low likelihood of ongoing transmural ischemia were thus included. ST-J amplitudes in all 12 leads were measured at the J-point, that is, the end of QRS/beginning of ST segment, and the same point in time was used for all 12 leads. The amplitude level immediately before the beginning of QRS was designated as the zero level for each lead (Rautaharju, Surawicz, & Gettes, 2009).

ST-J amplitudes for smartphone chest leads were calculated when either the right arm (R) or the left arm (L) electrode potential was used as reference. The ST-J amplitude in a smartphone-ECG chest lead "x" was calculated as follows:

$$\text{R as reference: } CRx = Vx - \frac{2 \times aVR}{3}$$

$$\text{L as reference: } CLx = Vx - \frac{2 \times aVL}{3}$$

TABLE 1 Mean ST-J amplitudes (μV) in V leads, CR leads, and CL leads

	V1	CR1	CL1	V2	CR2	CL2
All patients	25 (57)	34 (49)	32 (63)	64 (146)	18 (149)	72 (126)
Controls	26 (26)	31 (28)*	25 (29)	58 (52)	63 (337)*	57 (291)*
STEMI	15 (123)	40 (102)*	67 (117)*	76 (349)	101 (337)	128 (291)*
Nonischemic ST deviation	29 (66)	42 (48)	33 (93)	86 (105)	21 (111)	91 (91)
	V3	**CR3**	**CL3**	**V4**	**CR4**	**CL4**
All patients	58 (144)	68 (154)	66 (132)	32 (112)	41 (129)	40 (107)
Controls	43 (51)	48 (61)*	42 (49)	20 (43)	25 (54)*	19 (41)
STEMI	125 (325)	150 (319)*	178 (282)*	102 (208)	127 (212)*	154 (184)*
Nonischemic ST deviation	66 (142)	79 (192)	71 (120)	21 (177)	35 (229)	26 (154)
	V5	**CR5**	**CL5**	**V6**	**CR6**	**CL6**
All patients	12 (82)	21 (107)	20 (86)	7 (61)	18 (88)	20 (86)
Controls	4 (30)	9 (43)*	3 (29)	3 (23)	9 (36)*	3 (29)
STEMI	62 (114)	87 (141)	114 (132)	36 (93)	61 (129)*	114 (132)*
Nonischemic ST deviation	1 (171)	14 (222)	5 (86)	7 (61)	20 (88)	5 (86)

*p-value <.05. The p-value refers to the comparison of mean ST-J amplitudes in the CR or CL lead and the corresponding V lead.

STEMI criteria (ST-J elevation ≥0.1 mV in all leads except V2 and V3 (≥0.15 mV for women, ≥0.2 mV men ≥40 years, 0.25 mV men <40 years) (Thygesen et al., 2012) were applied on V leads as well as CR and CL leads in all patients.

Necessary ethical approvals by the ethical review board were obtained for the studies from which the ECGs were included. Written informed consent was either obtained (Khoshnood et al., 2016) or waived by the ethical boards (Akil et al., 2013; Lindow et al., 2017).

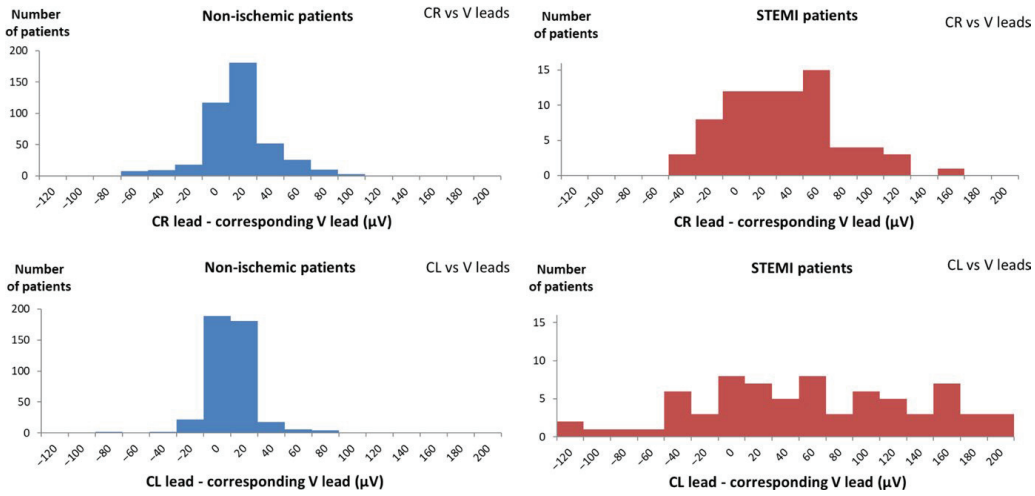

FIGURE 2 Differences between CR/CL amplitudes and the corresponding V amplitudes described with histograms for nonischemic patients (n = 426, blue bars) and STEMI patients (n = 74, red bars). The bars represent number of patients with a difference in ST-J-amplitude between CR/CL and V lead of <−120 μV, −100 to −120 μV, …, 180–200 μV, >200 μV. Upper panel: CR leads vs. V leads. Lower panel: CL leads vs. V leads. In nonischemic patients, the difference in ST-J amplitude compared to V leads is larger in CR leads than in CL leads, whereas the opposite is found in STEMI patients

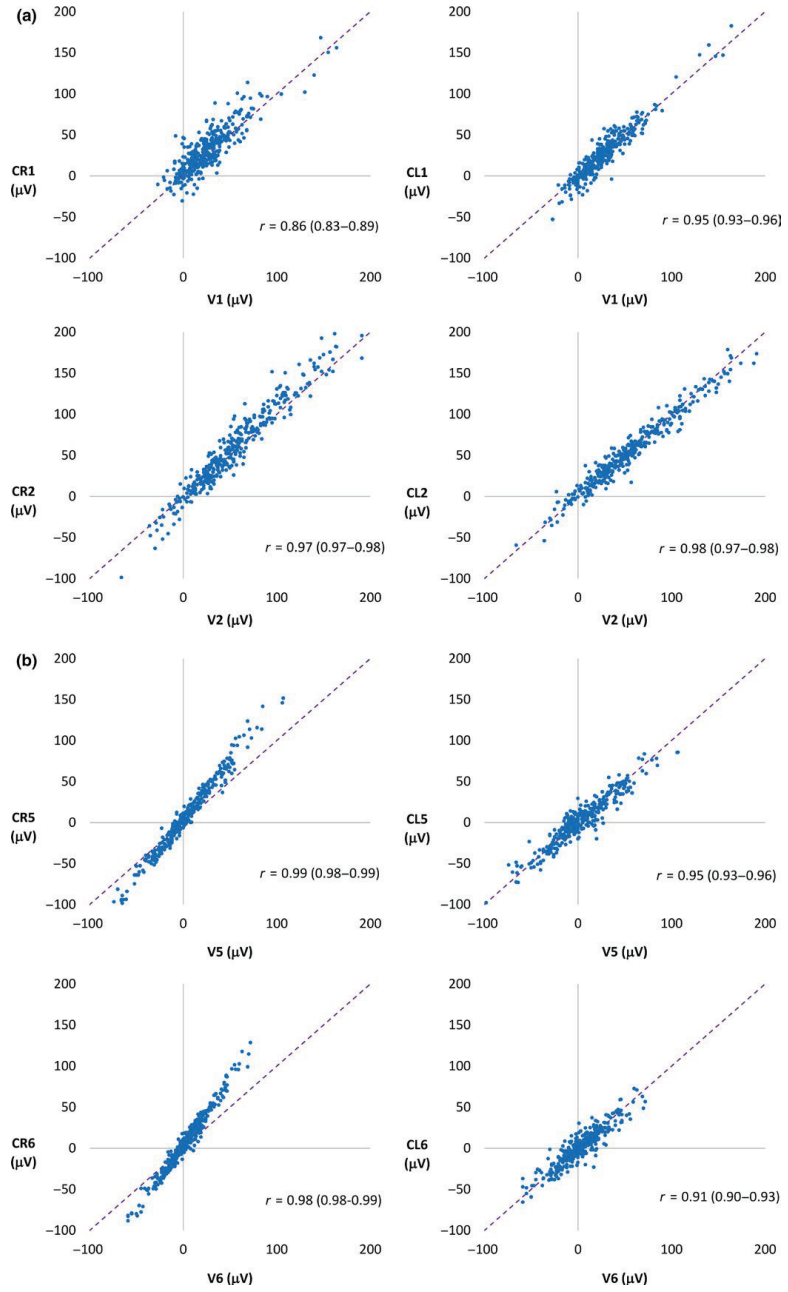

FIGURE 3 Nonischemic controls. Scatter plots of ST-J amplitudes (μV) with ST-J amplitudes in V leads on the *x* axis and in CR (left panel) and CL (right panel) leads on the *y* axis The purple dashed line represents the identity line. *R*-values are presented with 95% confidence intervals. (a) Electrode positions C1 and C2 on the chest. (b) Electrode positions C5 and C6 on the chest. CR lead amplitudes deviate from the identity line, to a greater extent, in lateral than in septal leads

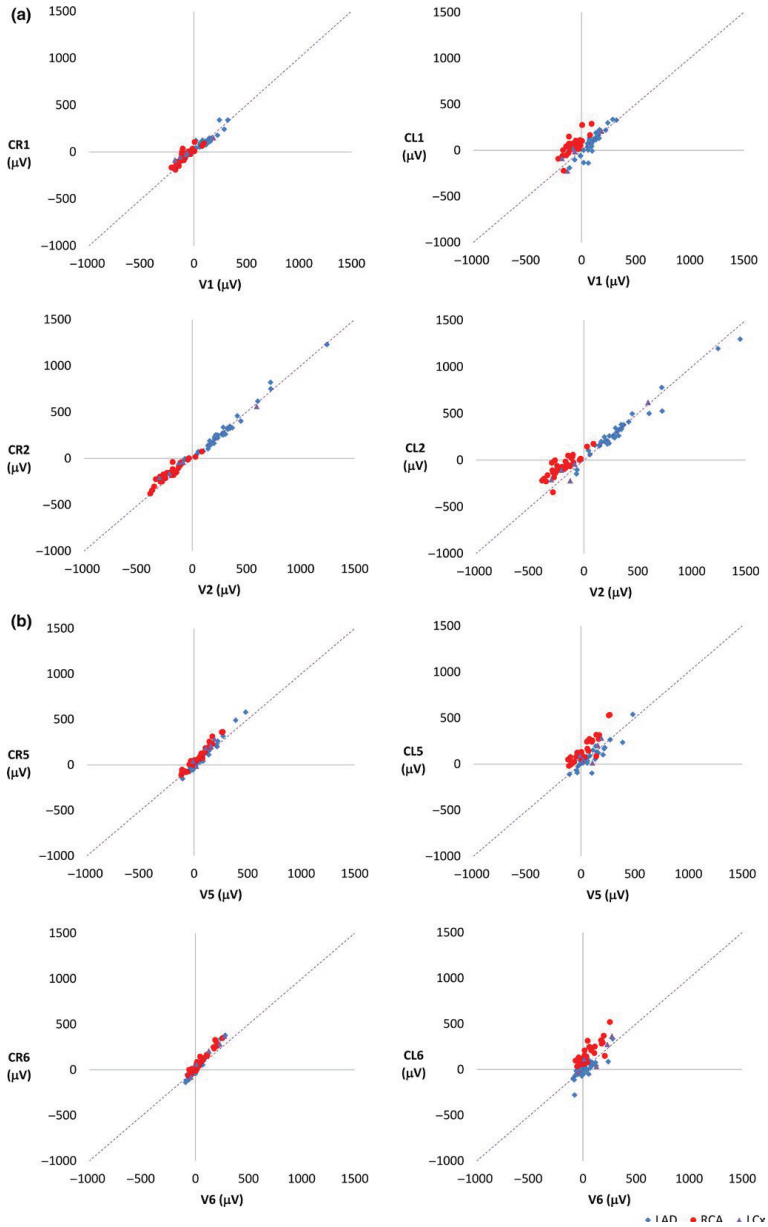

FIGURE 4 Patients with STEMI. Scatter plots of ST-J amplitudes (μV) with ST-J amplitudes in V leads on the *x* axis and in CR and CL leads on the *y* axis, CR leads in the left panel and CL leads in the right panel. The purple dashed line represents the identity line. LAD patients are represented as blue diamonds, RCA patients as red circles and LCx patients as green triangles. (a) Electrode positions C1 and C2 on the chest. (b) Electrode positions C5 and C6 on the chest. To a greater extent than for CR leads, CL lead amplitudes deviate from the identity line

2.1 | Statistical analysis

Descriptive statistics are presented as mean ± standard deviation. Student's *t* test was used for comparison of mean ST-J amplitudes between CR/CL leads and conventional 12-lead ECG leads (V leads). Pearson correlation test was used to assess correlation between ST-J amplitudes in conventional and smartphone ECG. When calculating sensitivity and specificity, fulfillment of STEMI criteria in V leads was considered reference standard. For example, when STEMI-criteria were fulfilled in both V leads and CR leads, the test result was considered true positive, and if they were met in CR leads but not in V leads, the result was considered false positive. Sensitivity and specificity are described with 95% confidence intervals. A *p*-value of <.05 was considered statistically significant.

3 | RESULTS

ST-J amplitudes for the entire study population (n = 500) were 9.1 ± 29 μV larger (p < .001) using the right arm as reference (CR leads) instead of the WCT and 7.7 ± 42 μV larger (p < .001) using the left arm as reference (CL leads). Mean ST-J amplitudes for all leads are presented in Table 1. In STEMI patients, ST-J amplitudes were 25.0 ± 41.8 μV larger for CR leads compared to V leads and 52 ± 90.5 μV larger for CL leads. The difference in ST-J amplitudes between CR/CL leads and V leads are described in Figure 2. In nonischemic patients, the difference in ST-J amplitude compared to V leads was found to be slightly larger in CR leads than in CL leads, whereas the opposite was found in STEMI patients.

In controls, correlation with lead V1 was higher for CL1 than for CR1 (Figure 3a), whereas the reverse was observed for the lateral leads (CR5, CR6, CL5, CL6) (Figure 3b). For leads V2–V4, correlations were similar for CL and CR leads. CR lead amplitudes deviated from the identity line in chest leads 2–6 to a larger extent than for CL lead amplitudes (Figure 3). In STEMI patients, the opposite was found, with greater deviation from the identity line in CL leads (Figure 4).

For all patients, sensitivity and specificity were 94% (87–98) and 95% (93–97) for CR leads when fulfillment of STEMI criteria in the conventional 12-lead ECG was used as reference standard; for CL leads sensitivity and specificity were 81% (71–88) and 97% (95–99). STEMI criteria were met in V leads in 51 STEMI patients. In 33 patients, STEMI criteria were met in V leads, but not in limb leads. Among these patients, STEMI criteria were met in 30 patients (91%) in both CR and CL leads. STEMI patients without significant ST elevation in two contiguous chest leads, that is, where STEMI criteria were not met in V leads, (22 patients with RCA culprit, 1 LCx), two patients had significant ST elevation in two contiguous chest leads using CR leads (9%) and nine using CL leads (39%).

In nonischemic patients, that is, controls and patients with nonischemic ST deviation, STEMI criteria in V leads on the conventional 12-lead ECG were not met in 399 patients. Ninety-five percent and 99% of these patients remained negative using CR leads and CL leads, respectively. In nonischemic controls, STEMI criteria were fulfilled in three patients using conventional 12-lead ECG and in CR and CL leads in 15 and 2 patients, respectively.

With conventional 12-lead ECG, STEMI criteria were falsely positive in V leads in 33 patients with nonischemic ST deviation (pericarditis n = 23, ERS n = 10, LVH n = 1). Ninety-seven percent of these patients remained positive with CR leads and 71% with CL leads. Detailed information on sensitivity and specificity is presented in Table 2.

4 | DISCUSSION

This study shows that replacement of the WCT by arm electrodes, in most patients, results in only small changes in ST-J amplitudes. However, in patients with STEMI or other diagnoses which affect ST-J amplitudes in leads aVR and/or aVL, changes in precordial-lead ST-J amplitudes may be substantial. This resulted in the changes in STEMI criteria fulfillment in some patients.

TABLE 2 Sensitivity and specificity regarding STEMI criteria fulfillment in chest leads using the conventional 12-lead ECG as reference standard

All patients (n = 500)			
	True positive	False negative	Sensitivity (%)
CR	83	5	94
CL	71	17	81
	True negative	False positive	Specificity (%)
CR	392	20	95
CL	401	11	97
STEMI patients (n = 74)			
	True positive	False negative	Sensitivity (%)
CR	47	4	92
CL	46	5	90
	True negative	False positive	Specificity (%)
CR	21	2	91
CL	14	9	61
No STEMI (controls and nonischemic ST deviation, n = 426)			
	True positive	False negative	Sensitivity (%)
CR	36	1	97
CL	25	12	68
	True negative	False positive	Specificity (%)
CR	371	18	95
CL	387	2	99
Patients with nonischemic ST deviation (n = 66)			
	True positive	False negative	Sensitivity (%)
CR	33	1	97
CL	24	10	71
	True negative	False positive	Specificity (%)
CR	26	6	81
CL	31	0	100

Before WCT became standard, both the left arm and the right arm electrodes were explored for use as reference for recording chest leads (Edwards & Vander Veer, 1938; Kossmann, 1985; Wolferth & Wood, 1932). In Scandinavia, CR leads were used until the 1970s, especially at departments where exercise ECG was performed, since ECG-waveform morphologies in CR leads differ very

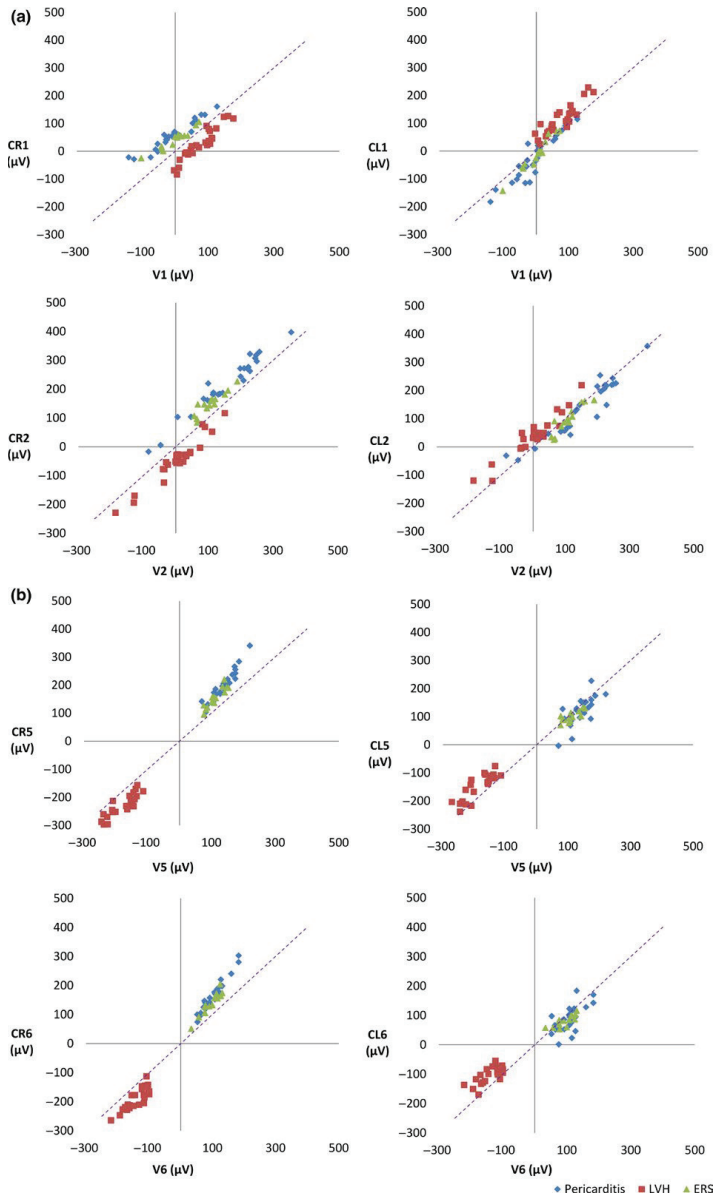

FIGURE 5 Patients with nonischemic ST deviation. Scatter plots of ST-J amplitudes (μV) with ST-J amplitudes in V leads on the *x*-axis and in CR and CL leads on the *y*-axis, CR leads in the left panel and CL leads in the right panel. The purple dashed line represents the identity line. Patients with pericarditis are represented as blue diamonds, LVH patients as red squares and ERS patients as green triangles. (a) Electrode positions C1 and C2 on the chest. (b) Electrode positions C5 and C6 on the chest

little from those in chest-head (CH) leads, which were used in exercise testing (Åstrand et al., 1967; Holmgren & Strandell, 1961; Jorfeldt, 1975). Since physicians are familiar with V leads, and diagnostic criteria have been developed for them, any difference in ECG patterns or amplitudes introduced by recording CR or CL leads may have important clinical implications. Åstrand et al. (1967) compared V leads to CR leads, and found higher amplitudes in lateral CR leads than in V leads and recommended a change in the ST-elevation criteria for lateral chest leads. This is in agreement with the findings in our study, with larger difference in amplitudes between CR leads and V leads in lateral leads compared to septal leads (Figure 3).

There are situations where ST-deviation patterns differ significantly between CR/CL leads and V leads. For example, in patients with ST elevation in aVR or aVL, CR- or CL-lead ST amplitudes will be diminished compared to V-lead ST amplitudes. In patients with proximal LAD occlusion, ST elevation in aVR or aVL may be present (Atar & Birnbaum, 2005; George, Arumugham, & Figueredo, 2010) and CR- or CL-lead amplitudes will be diminished. On the other hand, if ST depression is present in aVR or aVL in patients with inferior STEMI, CR or CL leads could show a pattern of widespread ST elevation, and may emulate a pericarditis pattern. In the present study, this was the case for 9 of 23 of STEMI patients without significant ST elevation in the chest leads in the conventional ECG, when CL leads were used and for two patients when CR leads were used. STEMI patients with ST elevation in lead III often have ST depression in aVL (Perron, Lim, Pahlm-Webb, Wagner, & Pahlm, 2007). In patients with pericarditis, chest lead amplitudes were instead diminished when CL leads were used (Figure 5), which could obscure the typical diagnostic pattern of widespread ST elevation in pericarditis (Wang, Asinger, & Marriott, 2003). It should be noted that even though specificity was high for both CR and CL leads (95% vs. 97%), the use of CR leads increased the number of false positive STEMI from 3 to 15 patients in nonischemic controls. In a population of patients with suspected acute coronary syndrome this increase appears acceptable. If, on the other hand, a 12-lead smartphone ECG is used as a screening tool in patients with low likelihood of having acute coronary syndrome an increased number of false positive STEMI will have to be considered.

Several technical issues regarding 12-lead ECG recording with a smartphone remain to be addressed. In conventional 12-lead ECG, in modern electrocardiographs, simultaneous recording allows for simultaneous measurement of amplitudes in all leads (Paul Kligfield et al., 2007). In the smartphone-ECG recording, the leads are sequentially recorded, which can make J point detection difficult. Since single-lead measurements have been shown to underestimate, for example, QRS durations (Kligfield et al., 2007), the timing of the J point may differ from what would have been measured by simultaneous recording. Furthermore, conventional 12-lead ECG recording is performed by medical staff with the patient in supine position. It is plausible that smartphone-ECG recordings will be performed in an upright or semirecumbent position, in prehospital settings, for instance, at the patient's home. ECG changes due to an altered body position have been reported in ST-monitoring (Adams & Drew, 1997). In 12-lead ECG recording performed in supine and upright position, only small changes have been reported (Baevsky, Haber, Blank, & Smithline, 2007; Madias, 2006). Neither of these studies, however, were performed in STEMI patients.

In conventional 12-lead ECG recording, lead misplacement is common (Rudiger, Hellermann, Mukherjee, Follath, & Turina, 2007), and ischemic patterns can be both missed and falsely introduced (Bond et al., 2012; Schijvenaars, Kors, van Herpen, Kornreich, & van Bemmel, 1997). Chest electrodes are often misplaced even when ECGs are recorded by experienced ECG technicians (Wenger & Kligfield, 1996). The risk of misplacement would most likely be increased when a new method is applied, especially in the hands of people without medical training. Although this matter is not covered in this article, we would recommend choosing either the right arm *or* the left arm as reference for the entire recording procedure—that is, not using different reference for different chest leads—as this would likely increase the risk of lead placement errors.

5 | CONCLUSIONS

By the use of CR or CL leads, smartphone 12-lead ECG results in slightly lower sensitivity in STEMI detection. Therefore, adjustment of STEMI criteria may be needed before application in clinical practice.

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CONFLICTS OF INTEREST

None (all authors).

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Electrocardiographic changes in the differentiation of ischemic and non-ischemic ST elevation

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ABSTRACT

Objectives. Pericarditis, takotsubo cardiomyopathy and early repolarization syndrome (ERS) are well-known to mimic ST elevation myocardial infarction (STEMI). We aimed to study whether ECG findings of reciprocal ST depression, PR depression, ST-segment convexity or terminal QRS distortion can discriminate between ST elevation due to ischemia and non-ischemic conditions. *Design.* Eighty-five patients with STEMI and 94 patients with non-ischemic ST elevation were included. All patients had acute chest pain and at least 0.1 mV ST elevation. Presence of PR depression, ST-segment convexity, terminal QRS distortion or reciprocal ST depression was assessed in each ECG. *Results.* In anterior ST elevation, ST depression in lead II ($\geq$0.025 mV) occurred in 40% of patients with STEMI but in none of the non-ischemic cases. In inferior ST elevation, ST depression in lead I ($\geq$0.025 mV) was present in 83% of patients with STEMI but in none of the non-ischemic cases. Chest-lead PR depression was uncommon in STEMI (12%) compared to non-ischemic cases (38%; $p < .001$). Convex ST elevation occurred in 22% of STEMI cases and in 9% of non-ischemic cases ($p = .01$). Terminal QRS distortion was more prevalent in STEMI (40%) than in non-ischemic ST elevation (7%). In multivariable analysis, reciprocal ST depression was associated with an ischemic diagnosis, whereas ST depression in aVR and chest-lead PR depression were associated with a non-ischemic diagnosis. *Conclusions.* Identification of true STEMI among patients with different ST-elevation etiology may be improved by considering reciprocal ST depression, ST depression in aVR and chest-lead PR depression.

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Introduction

In patients with acute chest pain, it is important to rapidly identify ST elevation myocardial infarction (STEMI) cases in order to restore the coronary circulation [1,2]. In general, this is done by determining whether the ECG fulfills STEMI criteria [1–3]. However, these criteria have limited diagnostic accuracy, with low sensitivity for acute coronary occlusion [4,5]. "STEMI mimics" such as pericarditis, takotsubo cardiomyopathy, and early repolarization syndrome (ERS) are common diagnoses in cases of erroneous catheterization laboratory activation [6–9].

Previous studies have reported different strategies to differentiate STEMI from single specific non-ischemic conditions [8,10–14]. However, in clinical reality, the differential diagnosis is not often restricted to two diagnoses.

We aimed to study whether reciprocal ST-segment changes, PR depression, ST-segment convexity or electrocardiographic findings of terminal QRS distortion can discriminate STEMI from non-ischemic conditions in a group of patients with different ST-elevation etiology.

Methods

This is a retrospective study in which patients were included from previously published studies [15–17]. In this study, patients with chest pain, ST elevation $\geq$0.1 mV in at least one lead and QRS width <120 ms were included.

Ninety-five STEMI patients referred to acute primary percutaneous coronary intervention (PCI) were recruited from a study on pre-hospital oxygen treatment in STEMI patients [16], of whom 85 patients met inclusion criteria (above). ECGs were recorded within 3 h from PCI (98% within 2 h). In case several ECGs were obtained, the ECG closest in time to PCI was included. Cardiovascular magnetic resonance imaging (CMR) was performed 2–6 d after the primary PCI on a Philips 1.5T Achieva or a Siemens 1.5T Avanto. T2-weighted images (triple inversion recovery imaging or T2-prepared steady-state free precession) were acquired in short-axis view, from base to apex of the left ventricle, to depict the myocardium at risk (MaR) [18]. Analysis of MaR was performed using the freely available post-processing software Segment version 1.9 R3084 (http://segment.heiberg.se) [19].

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We recruited 95 patients with non-ischemic ST elevation and final diagnoses of perimyocarditis ($n = 38$), takotsubo cardiomyopathy ($n = 22$) or ERS ($n = 35$), of whom 94 patients met the inclusion criteria. The patients with perimyocarditis or takotsubo cardiomyopathy were recruited from a study where patients with these diagnoses had undergone diagnostic CMR. All patients with takotsubo cardiomyopathy also underwent acute coronary angiography without significant coronary stenoses and had imaging evidence of transient ventricular dysfunction with recovery at follow-up CMR or echocardiography [15].

The 35 patients with ERS were included from the Evaluation of Unknown Predictors of Electrocardiographic Changes – a Transnational study (EXPECT) database [17]. These patients were identified by evaluating all ECGs for ERS criteria in the database between October and December 2014 with at least 0.1 mV of ST elevation in any lead (except aVR), a negative troponin test, and no cardiac diagnosis at discharge (myocardial infarction, unstable angina, perimyocarditis). The ERS criteria used were QRS duration <120 ms and an end-QRS slur or notch on the downslope of a prominent R wave, at least 0.1 mV from baseline to nadir of the notch or slur in two contiguous leads [20].

The ST-J amplitude was defined as the amplitude at the J point, relative to the PR junction in all 12 leads. Pathological Q waves were defined as a) any Q wave in leads V2–V3 ≥ 0.02 s, or b) QS complex in leads V2–V3, c) Q waves ≥0.03 s and 0.1 mV deep, or QS complex in any two anatomically contiguous leads of I, II, III, aVL, aVF or V4–V6, or d) an R wave ≥0.04 s in V1–V2 and R/S ≥ 1 with a concordant positive T wave in absence of a conduction defect [3]. The presence of an S wave was defined as any deflection, following an R wave, below the PR junction.

J waves were defined as either QRS slurring or notching. QRS slurring was defined as a slowed inscription of the end of the QRS of a prominent R wave, initiated at least 0.1 mV above the baseline. QRS notching was defined as a positive deflection (entirely above the baseline) on the end of the downslope of a prominent R wave, at least 0.1 mV to nadir from the baseline [20].

PR-segment depression was defined as depression of ≥0.05 mV compared to the TP segment, measured adjacent to QRS onset [12,13].

For analysis of terminal QRS distortion, all QRS complexes were designated to either a qR morphology (including qRs and qRS), Rs morphology (R-wave amplitude > S-wave amplitude, including Rs, Rsr, RsR and R), or other (QS and rS). All ECGs without pathological Q waves were then analyzed for fulfillment of terminal QRS distortion criteria. Terminal QRS distortion was considered present in leads with an initial R wave if the S wave and J wave were absent [11], and in leads with qR configuration if the J-point elevation exceeded 50% of the R-wave amplitude [21–23]. In this analysis, the inverted version of aVR (−aVR) was used instead of aVR.

Reciprocal ST depression was studied at two different cut-offs (0.025 and 0.05 mV). The cut-off of 0.025 mV has been used in previous studies on reciprocal ST-segment changes [10]. A cut-off of 0.05 mV was also studied, in order to explore whether this cut-off would change diagnostic accuracy, for example by improving specificity. Patients with inferior ST elevation were analyzed regarding presence of reciprocal ST depression in aVL and I, V2 and V3. Patients with anterior ST elevation (V2–V4) were analyzed regarding presence of reciprocal ST depression in inferior leads (II, III and aVF). Further, patients with anterior ST elevation were analyzed regarding ST-segment changes in aVR, at the same two different cut-offs as above (0.025 and 0.05 mV), regarding both ST elevation and ST depression.

In this study, we included anonymized data from previous studies [15–17] approved by the regional ethical review board. No additional personal data was registered for this study.

Besides ST-J amplitudes, which were retrieved from the previous studies, ECG interpretation regarding PR depression, ST-segment convexity, J waves and terminal QRS distortion was performed independently by three observers (TL, DM and IN) who were blinded to the clinical diagnosis. DM and IN were also blinded to the study design, and interpreted half of the ECGs each. In case of disagreement between TL and DM/IN, a decision was reached by consensus.

Continuous variables are presented as mean ± standard deviation or median and inter-quartile range as appropriate. The Shapiro–Wilk test was used to test for normality. Student's t-test or Mann–Whitney U test was used for comparisons of means or medians between groups for normally or non-normally distributed variables, respectively. χ^2 test was performed to compare proportions of prevalence of terminal QRS distortion, reciprocal ST-segment changes, PR depression and ST-segment convexity between groups. Odds ratios for the prediction of STEMI were calculated using a univariate binary logistic regression model. Variables with a p value <.05 at univariate analysis were entered into a multivariable model. Fleiss Kappa test was used to determine the level of inter-observer agreement. Sensitivity was calculated as true positives/number of patients with the condition tested for, specificity as true negatives/number of patients without the condition tested for, positive likelihood ratio (LR+) as sensitivity/(1 – specificity) and negative likelihood ratio (LR-) as 1 – sensitivity/specificity. Statistical analysis was performed using SPSS Statistics version 25 (SPSS Inc., IBM Corporation, Somers, NY). A p value of <.05 was considered statistically significant.

Results

Baseline characteristics of patients and general ECG variables are presented in Table 1. The prevalence of the various ECG findings in patients with STEMI and non-ischemic ST elevation are presented in Tables 2 and 3. Diagnostic accuracy (sensitivity, specificity and likelihood ratios) is summarized in Tables 4 and 5. A convex ST-segment was present in only 22% of STEMI patients but was still more common than in non-ischemic patients (9%; $p = .01$). PR depression occurred in 45% of non-ischemic cases (55% of pericarditis,

Table 1. Baseline characteristics.

	STEMI patients ($n = 85$)	Non-ischemic patients ($n = 94$)	Pericarditis ($n = 38$)	Takotsubo ($n = 21$)	ERS ($n = 35$)
Age, years, mean (SD)	65 (13)	46 (18)	38 (16)	68 (10)	42 (14)
Sex, % women	34	33	18	100	9
MaR, mean % (SD)	31 (11)	–	–	–	–
ECG variables					
HR, bpm (median (IQR))	71 (60–87)	73 (64–85)	80 (67–90)	76 (69–96)	65 (58–73)
Pathological Q waves, *n* (%)	22 (26)	8 (9)	1 (3)	4 (19)	3 (9)
Max STE (mV), mean (SD)	0.33 (0.22)	0.18 (0.08)	0.20 (0.09)	0.17 (0.07)	0.17 (0.08)
STE in V2–V4, *n* (%)	43 (51)	74 (79)	22 (58)	17 (81)	35 (100)
Max STE typical lead (%)	III (39)	V2 (39)	V2 (24) V3 (24)	V3 (33)	V2 (66)
STE in II/aVF/III, *n* (%)	40 (47)	28 (30)	23 (61)	3 (14)	2 (6)

ERS: early repolarization syndrome; SD: standard deviation; MaR: myocardium at risk; bpm: beats per minute; IQR: inter-quartile range; HR: heart rate; STE: ST elevation.

Table 2. Prevalence of ECG findings in patients with different ST-elevation etiology.

ECG finding	STEMI patients	Non-ischemic patients	*p* Value
All patients	$N = 85$	$N = 94$	
Convex STE, n (%)	19 (22)	8 (9)	.01
J waves, *n* (%)	23 (27)	59 (63)	<.001
J waves in leads with STE, *n* (%)	22 (26)	53 (56)	<.001
PR depression any lead, *n* (%)	26 (31)	42 (45)	.06
PR depression limb leads, *n* (%)	25 (29)	40 (43)	.09
PR depression chest leads, *n* (%)	10 (12)	36 (38)	<.001
Patients without pathological Q waves	$N = 63$	$N = 86$	–
Absent S and J in V2/V3, *n* (%)	5 (8)	2 (2)	.13
TQRSD, *n* (%)	25 (40)	6 (7)	<.001

STE: ST elevation; TQRSD: terminal QRS distortion.

Table 3. Reciprocal ST-segment changes in patients with anterior or inferior ST elevation.

	STEMI patients	Non-ischemic patients	*p* Value
Anterior STE; STE V2–V4	$N = 43$	$N = 74$	
STD in aVR			
≥0.025 mV, *n* (%)	13 (30)	59 (80)	<.001
≥0.05 mV, *n* (%)	5 (12)	36 (49)	<.001
STE in aVR			
≥0.025 mV, *n* (%)	11 (26)	0 (0)	<.001
≥0.05 mV, *n* (%)	7 (16)	0 (0)	<.001
STD in II			
≥0.25 mV, *n* (%)	17 (40)	0 (0)	<.001
≥0.05 mV, *n* (%)	9 (21)	0 (0)	<.001
STD in aVF			
≥0.25 mV, *n* (%)	15 (35)	6 (8)	<.001
≥0.05 mV, *n* (%)	11 (26)	0 (0)	<.001
STD in III			
≥0.25 mV, *n* (%)	20 (47)	12 (16)	.001
≥0.05 mV, *n* (%)	9 (21)	4 (5)	.01
Inferior STE; STE in II, aVF, III	$n = 40$	($n = 28$)	–
STD in aVL			
≥0.25 mV, *n* (%)	40 (100)	6 (21)	<.001
≥0.05 mV, *n* (%)	40 (100)	3 (11)	<.001
STD in I			
≥0.25 mV, *n* (%)	33 (83)	0 (0)	<.001
≥0.05 mV, *n* (%)	30 (75)	0 (0)	<.001
STD in V2			
≥0.25 mV, *n* (%)	34 (85)	2 (7)	<.001
≥0.05 mV, *n* (%)	32 (80)	1 (4)	<.001
STD in V3			
≥0.25 mV, *n* (%)	25 (63)	0 (0)	<.001
≥0.05 mV, *n* (%)	23 (58)	0 (0)	<.001

Max: maximal; STE: ST elevation; STD: ST depression.

62% of Takotsubo cardiomyopathy and 23% of ERS patients) and in 31% of STEMI cases ($p = .06$). PR depression in the chest leads was more common in non-ischemic conditions (58%) than in STEMI (12%; $p < .001$). J waves occurred in 63% of non-ischemic conditions (47% of pericarditis, 29% of Takotsubo and 100% of ERS patients) compared to 27% of STEMI cases ($p < .001$).

In patients without pathological Q waves, both the S and J waves were absent in either V2 or V3 in only five patients with STEMI and two patients with non-ischemic ST elevation ($p = .13$). Terminal QRS distortion was more common in STEMI than non-ischemic conditions (40% vs. 7%, $p < .001$). There was no difference in MaR in STEMI patients positive (MaR 29% of the left ventricle (LV)) versus negative (32% of the LV) for terminal QRS distortion ($p = .23$).

Table 4. ECG findings to be used to detect patients with STEMI: Sensitivity, specificity and likelihood ratio for an ischemic etiology.

	Sensitivity	Specificity	LR+/LR−
Any STEMI			
Convex STE	22 (14–33)	91 (84–96)	2.6/0.9
TQRSD	40 (28–53)	93 (85–97)	5.7/0.7
Anterior STEMI			
Convex STE	14 (4–32)	93 (83–98)	1.9/0.9
STD in lead II[a]	40 (25–56)	100 (95–100)	b/0.6
TQRSD	21 (8–41)	96 (87–99)	4.8/0.8
Inferior STEMI			
Convex STE	26 (12–43)	90 (76–97)	2.5/0.8
STD in lead I[a]	83 (67–93)	100 (88–100)	b/0.2
TQRSD	61 (42–78)	81 (61–93)	3/0.5

A true positive test is defined as presence of the ECG finding AND a STEMI diagnosis, a true negative result is defined as absence of the ECG finding AND a non-ischemic diagnosis.

STE: ST elevation; TQRSD: terminal QRS distortion; STD: ST depression; LR+: positive likelihood ratio; LR−: negative likelihood ratio.

[a] ≥0.025 mV.

[b] LR + cannot be calculated since specificity is 100 %.

Table 5. ECG findings to be used to detect non-ischemic patients: Sensitivity, specificity and likelihood ratio for a non-ischemic etiology.

ECG finding	Sensitivity	Specificity	LR+/LR−
Non-ischemic etiology and any STE pattern			
Chest lead PR depression	38 (28–49)	88 (79–94)	3.2/0.7
STD in aVR[a]	80 (69–88)	70 (54–83)	2.6/0.3
Non-ischemic etiology and anterior STE			
Chest lead PR depression	38 (27–50)	86 (72–95)	2.7/0.7
STD in aVR[a]	80 (69–88)	70 (54–83)	2.6/0.3
Non-ischemic etiology and inferior STE			
Chest lead PR depression	46 (30–63)	83 (66–93)	2.7/0.7
STD in aVR[a]	77 (61–89)	66 (48–81)	2.2/0.4

A true positive test is defined as presence of the ECG finding AND a non-ischemic diagnosis, a true negative result is defined as absence of the ECG finding AND a STEMI diagnosis.

STE: ST elevation; TQRSD: terminal QRS distortion; STD: ST depression; LR+: positive likelihood ratio; LR−: negative likelihood ratio.

[a] ≥0.025 mV.

Reciprocal ST depression was more common in patients with STEMI compared to patients with non-ischemic ST elevation (Table 3). In patients with anterior ST elevation, ST depression ≥0.025 mV in lead II occurred in 40% of STEMI patients, but in none of the non-ischemic cases ($p < .001$). In patients with inferior ST elevation, ST depression ≥0.025 mV in lead I occurred in 83% of STEMI patients, but in none of the non-ischemic cases ($p < .001$). For the majority of the leads studied, when a cut-off of 0.05 mV was used, reciprocal ST depression was less frequent in STEMI patients than when 0.025 mV was used (Table 3), and this resulted in a decreased sensitivity with only minor differences in specificity. For example, reciprocal ST depression in lead II (anterior ST elevation) occurred in 21% of STEMI patients when a cut-off of 0.05 mV used, but in 40% when 0.025 mV was used. Reciprocal ST depression in lead II was absent in all non-ischemic patients using either 0.025 or 0.05 mV as cut-off (Table 3).

In patients with anterior ST elevation, ST depression ≥0.025 mV in aVR was present in 80% of non-ischemic and in 30% of STEMI patients ($p < .001$). ST elevation in aVR, on the other hand, was present in 18% of STEMI patients (regardless of the location of ST-elevation), but in none of the non-ischemic patients ($p < .001$).

Results of the univariate and multivariable analysis of predictors of STEMI (*vs.* non-ischemic ST-elevation etiology) are presented in Table 6. At multivariable analysis adjusting for age and sex, reciprocal ST depression was the strongest independent predictor of ischemic ST elevation etiology (OR 9.9 (3.5–28.1), whereas chest-lead PR depression (OR 0.2 (0.05–0.5)) and ST depression in aVR (OR 0.2 (0.06–0.5)) were associated with a non-ischemic etiology.

Interobserver agreement was highest for the evaluation of absent S and J waves in leads with Rs (or R) configuration, with a κ of 0.96 (0.821.0). For the combined assessment of terminal QRS distortion, κ was 0.75 (0.59–0.90). The κ for PR depression was 0.80 (0.66–0.95), for J waves 0.78 (0.63–0.94) and for J-wave type (notch or slur) 0.73 (0.48–0.97). Interobserver agreement was lowest for ST-segment convexity (κ 0.68 (0.54–0.83)).

Discussion

In this study, we analyzed ECG findings other than ST-elevation amplitudes for differentiating STEMI from non-ischemic ST-elevation etiology (Figures 1 and 2), even in a heterogenous group of non-ischemic etiology. Reciprocal ST depression was more common in patients with STEMI than non-ischemic ST elevation and independently predicted an ischemic etiology. PR depression occurred in both STEMI and non-ischemic ST elevation, but PR depression in the chest leads was uncommon in patients with STEMI. Terminal QRS distortion and convex ST elevation were more common in STEMI than non-ischemic ST elevation, but convex ST elevation occurred only in a minority of STEMI patients.

Correct ECG interpretation is essential for the management of patients with acute coronary syndrome, since treatment delay is associated with increased mortality [24]. At the same time, it is important to avoid unnecessary coronary angiographies. False activation of the catherization laboratory is not uncommon and the non-ischemic diagnoses included in this study are common in these situations [9,25]. Of note, acute coronary angiography is often included in the evaluation of patients with takotsubo cardiomyopathy because of elevated cardiac biomarkers and its STEMI-like ECG appearance [26,27]. Besides ECG artifacts, perimyocarditis and ERS were the most common causes of false-positive software interpretations of STEMI in a prehospital study with >40.000 patients [28].

In this study, ST depression in both aVL and I was more common in inferior STEMI than in inferior non-ischemic ST elevation. Similarly, ST depression in lead II was more common in anterior STEMI than in anterior non-ischemic ST elevation. Reciprocal ST depression was the strongest independent predictor of STEMI (Figure 2).

In patients with suspected acute myocardial infarction, reciprocal changes in the ECG are important both for localizing the occlusion site and for assessment of infarct size and prognosis [29–31], and also for differentiating STEMI from non-ischemic conditions. For example, it has been suggested that reciprocal ST depression in aVL in patients with inferior ST elevation can be used to discriminate between pericarditis and inferior STEMI [10]; and to discriminate STEMI from takotsubo cardiomyopathy [8].

Furthermore, in this study, ST depression in aVR was common in patients with non-ischemic ST elevation, but uncommon in patients with anterior STEMI. ST deviation in aVR has been suggested as an important discriminator between Takotsubo cardiomyopathy and anterior STEMI [8,32]. Although ST depression in aVR is more common in patients with Takotsubo cardiomyopathy than in STEMI

Table 6. Univariate and multivariable predictors of ischemic STE.

	Model 1 Unadjusted OR (CI 95)	*p* Value	Model 2 PR depression in chest leads, reciprocal STD, convex STE, TQRSD, STD in aVR	Model 3 PR depression in chest leads, reciprocal STD, convex STE, TQRSD, STD, in aVR, age, sex
PR depression limb leads	0.6 (0.3–1.0)	.069	–	–
PR depression chest leads	0.2 (0.1–0.5)	<.001	0.2 (0.1–0.4)	0.2 (0.05–0.5)
Reciprocal STD[a]	12.5 (6.2–25.6)	<.001	8.7 (3.8–19.9)	9.9 (3.5–28.1)
Convex STE	3.0 (1.2–7.3)	.017	2.8 (0.9–8.6)	2.2 (0.5–9.2)
TQRSD	6.7 (2.6–17.3)	<.001	4.6 (1.4–15.5)	3.9 (0.9–17.0)
STD in aVR[b]	0.2 (0.09–0.04)	<.001	0.2 (0.08–0.5)	0.2 (0.06–0.5)

[a]Reciprocal STD is defined as presence of either STD ≥ 0.025 mV in lead II in patients with anterior STE or STD ≥ 0.025 mV in lead I in patients with inferior STE.TQRSD, Terminal QRS distortion.
[b]≥0.025 mV.

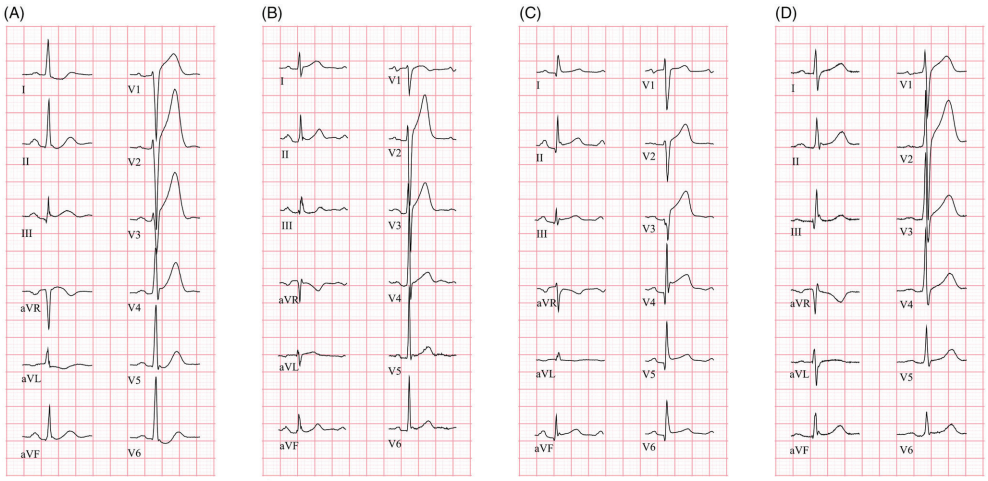

Figure 1. ECGs (25 mm/s) from four patients with different ST elevation etiologies. (A) Patient with STEMI. ECG shows PR depression ≥0.05 mV in the limb leads, but not in the chest leads, and slight ST elevation in aVR. (B–D) Non-ischemic patients with ST elevation (B: perimyocarditis; C: takotsubo cardiomyopathy; D: ERS). Both (B) and (C) show PR depression in both limb leads and chest leads, in (D) minor PR depression is present in the limb leads, and PR depression ≥0.05 mV in lateral chest leads. All non-ischemic patients show some degree of ST depression in aVR.

patients, concerns have been raised that such ECG findings are not accurate enough to safely exclude STEMI [33,34].

In this study, PR depression in limb leads occurred in both non-ischemic ST elevation and STEMI but PR depression in chest leads was uncommon in STEMI (Table 2; Figure 1). In previous papers, PR depression has been described to occur in both pericarditis and Takotsubo cardiomyopathy [12,13]. In this study, PR depression was most common in Takotsubo patients (62%). Porela et al. [13] compared electrocardiographic features in STEMI and acute perimyocarditis and also found chest-lead PR depression to be rare in STEMI patients (9%). In their study, PR depression in any lead in perimyocarditis was more prevalent (88%) than in our study (55%), even though the same electrocardiographic definition was used, perhaps due to (unknown) differences in disease duration. The PR depression is dynamic during the disease process and has been described to occur both earlier than ST elevation and have a shorter duration [35]. Of note, PR depression in STEMI patients can be a sign of atrial infarction, most often seen in patients with occlusion of the right or the left circumflex coronary artery and is associated with an increased risk of supraventricular arrhythmias [36]. Prominent PR depression (≥0.12 mV) in inferior leads in patients with acute inferior STEMI has been described to be associated with an increased risk of cardiac free-wall rupture and increased in-hospital mortality [37].

Terminal QRS distortion was more prevalent in STEMI patients than in non-ischemic patients (Figure 2) in this study. ST changes during ischemia reflect altered repolarization due to changes in the action potentials in the ischemic myocardium [38]. Depolarization changes are also present [39], albeit often less evident and seldom used in in the routine diagnostic process. Terminal QRS distortion has been

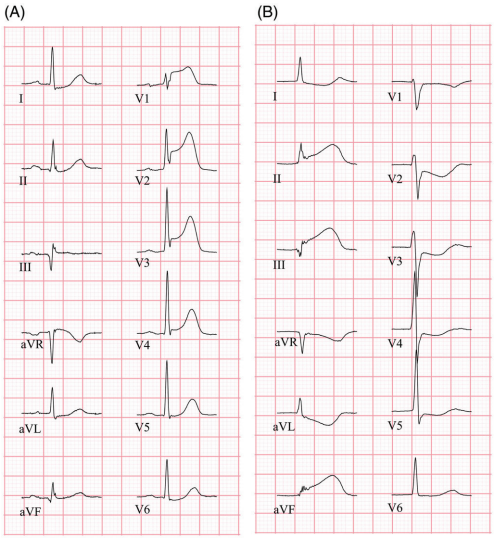

Figure 2. ECGs (25 mm/s) from two STEMI patients. (A) ECG shows concave ST elevation in V1 – V4 and ST depression in aVL, I and II. ST elevation is present in aVR. PR depression is absent in both limb leads and chest leads. Terminal QRS distortion is present in leads V2 and V3 (absent S and J wave in leads with ST elevation (Rs configuration)). (B) ECG shows concave ST elevation in inferior leads (II, aVF, III) with reciprocal ST depression in leads aVL and I, as well as precordial leads. PR depression is absent in both limb leads and chest leads. Terminal QRS distortion is present in aVF and III (ST elevation ≥50% of R-wave amplitude).

shown to predict poor prognosis [21–23]. Absence of S waves in leads V1–V3, which normally have a terminal S wave, indicates severe ischemia [21]. However, S waves can

be absent in these leads also in ERS. Lee et al. [11] showed that absence of both S and J wave in V2–V3 was highly specific for LAD occlusion when compared to patients with ERS. To determine the presence of an S wave requires very little effort and might thus be a clinically useful sign of ischemia. However, such findings in leads V2 or V3 were rare in our material (8% of STEMI patients, 2% of non-ischemic ST elevation). In this study, we combined "the Lee criterion" with the classical definition of terminal QRS distortion criteria in leads with qR configuration, but applied it to any lead with an initial R wave, not only V2–V3.

Although more prevalent in STEMI than in non-ischemic ST elevation (40 *vs.* 7%), terminal QRS distortion was not a statistically significant predictor at multivariable analysis (OR 2.7 (0.7–11.1)), Table 6), perhaps due to the limited number of patients.

Although ST-segment convexity was more common in STEMI compared to non-ischemic conditions, it occurred in less than ¼ of STEMI patients. Previously, it has been suggested that STEMI is less likely in patients with concave ST elevation [40]. This was dismissed by Smith et al., who reported that upwardly concave morphology was more common than convex morphology in patients with LAD occlusion [41], which our study confirms.

This study confirms several previous observations on ECG findings that can be used to identify true STEMI. However, in contrast to previous studies which have compared findings in STEMI with those with ST elevation of a specific non-ischemic etiology, this study supports the use of selected criteria in situations with multiple non-ischemic differential diagnoses. In patients with ST elevation of unknown etiology, reciprocal ST depression increases the likelihood of an ischemic etiology, whereas presence of chest-lead PR depression and ST depression in aVR instead suggests a non-ischemic etiology. Although inferior ST depression seems to be specific for anterior STEMI, it lacks in sensitivity, and hence a STEMI diagnosis cannot be ruled out. In inferior ST elevation, on the other hand, ST depression in lead I, is highly sensitive and specific for STEMI, also expressed as a lower negative likelihood ratio than for reciprocal ST depression in anterior ST elevation. (0.2 *vs.* 0.6, Table 5). Similarly, chest-lead PR depression seems to be specific for a non-ischemic diagnosis but lacks in sensitivity, whereas ST depression in aVR is highly sensitive for a non-ischemic diagnosis in anterior ST elevation but lacks in specificity. Thus, accurately differentiating STEMI from ST elevation of non-ischemic etiology requires a holistic ECG approach. Also, it should be taken into consideration when applying these ECG criteria that the consequences of delaying revascularization of a true STEMI may be far worse than performing an unnecessary coronary angiography.

A limitation to this study was that patients were included from different studies and not consecutively from the same setting. For example, STEMI patients were triaged for primary PCI whereas most of the non-ischemic patients were not. Nonetheless, all patients had acute chest pain and at least 0.1 mV ST elevation, which makes STEMI a relevant differential diagnosis in all these patients. Electrocardiographic changes during an ischemic process are dynamic. Comparisons of electrocardiographic changes, such as terminal QRS distortion, and CMR to assess myocardium at risk are therefore difficult. For example, in case of a spontaneous opening of a previously occluded artery, electrocardiographic changes will subside whereas MaR by CMR will remain the same.

Different ERS patterns exist, for example with lateral or inferior J waves and ST elevation [42]. Even though ERS patients were randomly selected from an ED population, all ERS patients had ST elevation in V2–V4 and the typical lead for maximal ST elevation was V2 (66%). The results in this study regarding ERS may, therefore, not be applicable to patients with other ST elevation patterns.

Several other ECG criteria have been suggested to be included in the differential diagnosis of ST elevation, such as the QT interval and QRS amplitudes [43], but these were not assessed in this paper.

Blinded interpretation of ECG parameters was made only regarding terminal QRS distortion, PR depression and ST-segment convexity, not regarding ST-J amplitudes. Also, although TL was blinded to the clinical diagnosis during interpretation, he was not unfamiliar with the ECGs from previous studies [15], and he identified the ERS patients in the EXPECT database. However, the other two ECG interpreters were blinded to both study design and final diagnoses, and in most cases inter-rater agreement was strong, suggesting that the impact on the results was minor. Reciprocal ST depression was based on ST-J amplitudes from the previous studies, most of them from automated measurements.

In this study, a validation group for the ECG signs found to be useful in the differentiation of ischemic and non-ischemic ST-elevation was lacking, and the findings, therefore, need to be confirmed in larger studies.

Conclusion

Identification of true STEMI among patients with different ST-elevation etiologies may be improved by considering different ECG changes in addition to the ST elevation; primarily reciprocal ST depression, ST depression in aVR and PR depression in the chest leads.

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