Acute coronary syndromes

The prognostic importance of hypertension, diabetes and vectorcardiographic markers

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To my family for constant reminders of life outside the bubble of medical science, clinical work and management.

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Abstract

Research questions:

1 Is hypertension and diabetes associated with the future risk of death, and recurrent manifestations of cardiovascular disease in acute coronary syndromes (ACS)?
2 How does myocardial ischemia affect depolarization and repolarization of the heart during the early phase of an acute myocardial infarction?
3 What is the prognostic value of accepted vectorcardiographic markers in relation to future risk of sudden cardiac death after ACS?

Methodology: Papers I, III and IV studied patients with ACS prospectively and consecutively included at the coronary care unit of Sahlgrenska University Hospital. Paper I deals with 2,329 patients who were followed for a median of 8 years. Paper III included 57 patients who were diagnosed with an anterior ST-elevation myocardial infarction with vectorcardiographic (VCG) registration starting within 4 hours from onset of chest pain and showing dynamic ST-vector magnitude. Paper IV investigated 643 patients who were subject to cardiac ultrasound and VCG registration during hospital stay and followed for 30 months. Clinical data and data on complications and pharmacological treatment were collected from hospital records and interviews. The Swedish National Population Register, the Swedish Cause of Death Register and the Swedish Hospital Discharge Register completed end-point data in paper I, II and IV. Paper II included 44,268 patients in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) during 2006 through 2008 with the whole spectrum of coronary artery disease. They were followed for an average 1.9 years. The SCAAR was also merged with the Swedish prescribed drug Register. All prognostic results were adjusted for background data.
Results: Paper I reports that diabetes was a predictor of death (HR 1.79; 95% CI 1.52-2.10) with an additive effect of hypertension (HR 2.10, 95% CI 1.71–2.57). In paper II hypertension increased the risk of myocardial infarction, stroke and congestive heart failure with a strong additive adverse effect of diabetes while hypertension alone was not a marker of the risk of death. The 10% increase in the risk of myocardial infarction during follow-up by hypertension was quadrupled by diabetes. In paper III the overall ventricular repolarization dispersion (Tarea) almost tripled (118 vs. 41µVs; p<.0001) and the heterogeneity of the action potential morphology (ventricular gradient) was 2.6 times higher (127 vs 49 µVs; p<.0001) at maximum than at minimum ischemia as judged from the degree of ST-elevation. In paper IV a wide angle between the main direction of depolarization and repolarization (QRS-T area angle) increased the risk of sudden cardiac death by 63% after adjusting for the left ventricular ejection fraction.
Conclusions: Diabetes is strongly associated with the risk of death after an ACS with a small additive effect of hypertension. Hypertension alone is associated with myocardial infarction, stroke and congestive heart failure during follow-up but diabetes is a more important risk factor. Myocardial ischemia initially and transiently increases the heterogeneity of repolarization which might explain why the risk of ventricular fibrillation is also transient and lacks prognostic value. A wide QRS-T area angle measured early after an acute coronary syndrome predicts sudden cardiac death regardless of left ventricular dysfunction.

Key words: Acute coronary syndromes; hypertension; diabetes; percutaneous coronary intervention; prognosis; myocardial ischemia; coronary artery disease; electrocardiography; vectorcardiography; arrhythmia; sudden cardiac death; electrophysiology; prognosis

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Summary in Swedish

Bakgrund

Dödligheten i kardiovaskulär sjukdom i samhället minskar, men fortsätter att orsaka flest dödsfall i västvärlden. Ett sätt att minska dödligheten i kardiovaskulär sjukdom är att förebygga dessa sjukdomstillstånd och deras komplikationer. Diabetes och hypertoni är kända riskfaktorer för kardiovaskulär sjuklighet med hög förekomst i samhället, men deras betydelse för prognosen efter ett akut koronart syndrom är inte fullständigt känd.
Bland personer som avlider i kardiovaskulär sjukdom dör en betydande andel plötsligt och oväntat. För denna grupp spelar prevention en viktig roll då händelseförloppet ofta är väldigt snabbt. Plötslig hjärtdöd orsakas ofta av arytmi. Våra möjligheter att förutspå arytmidöd är begränsade och baseras idag huvudsakligen på vänsterkammarfunktionen.

Frågeställningar

1. Ökar diabetes och hypertoni risken för död och andra kända kardiovaskulär komplikationer efter akuta koronara syndrom?
2. Hur påverkar myokardischemi i hjärtats framvägg depolarisation och repolarisation i det tidiga skedet av en akut hjärtinfarkt?
3. Vilket är det prognostiska värdet av accepterade vektorkardiografiska markörer vad gäller risk för plötslig hjärtdöd efter akuta koronara syndrom?

Studiepopulationer

I arbete I, III och IV studerades patienter ur en kohort patienter med akuta koronara syndrom som inkluderats prospektivt och konsekutivt vid Hjärtkliniken på Sahlgrenska Universitetssjukhuset i Göteborg. I arbete I studerades 2329 av dessa patienter under vårdtiden och följdes under en mediantid av 8 år med hjälp av Folkbokföringen, Dödsorsaksregistret och Slutenvårdsregistret. I arbete III studerades 57 patienter med anterior ST-höjningsinfarkt som monitoreras med vektorkardiografi med start inom 4 timmar från smärtdebut i det akuta infarktskedet och som uppvisade dynamik i ST-vektormagnituden. I arbete IV följdes 643 av patienterna som genomgått ekokardiografi och vektorkardiografisk monitorering under vårdtiden i 30 månader med hjälp av Folkbokföringen och journalgranskning. Arbete II omfattade alla patienter i Svenska coronarangiografi- och angioplastikregistret (SCAAR) som genomgick perkutan koronar intervention under 2006 och två får framåt. Totalt inkluderades 44268 patienter som följdes i snitt 1,9 år. Data sammaställdes från SCAAR, Läkemedelsregistret, Slutenvårdsregistret, Dödsorsaksregistret och Folkbokföringen.

Resultat
I arbete I var diabetes en riskfaktor för död under uppföljningstiden (hazard ratio 1.79; 95% CI 1.52-2.10) och hypertoni försämrade prognosen något ytterligare efter korrigering för bakgrundsvariabler. I arbete II ökade hypertoni risken för hjärtinfarkt, stroke och hjärtsvikt. Detsamma gällde diabetes. Diabetes, men inte hypertoni, var en riskfaktor för död efter korrigering för bakgrundsvariabler. Riskökningen för hjärtinfarkt som orsakades av hypertoni fyrdubblades av samtidig diabetes. I arbete III ökade dispersionen av kamrarnas repolarisation manifesterat som en tredubbling av T area (118 jfrt 41µVs; p<.0001) vid ST-vektormagnitudens maximum samtidigt som aktionspotentialernas heterogenicitet, mätt som ventricular gradient, ökade med 2,6 gånger (127 jfrt. 49 µVs; p<.0001) mellan tidpunkterna för lägsta och högsta ST-vektormagnituderna. I arbete IV var en vinkel större än 112° mellan depolarisationens och repolarisationens dominerande riktningar (QRS-T areavinkel) associerad med plötslig hjärtdöd (hazard ratio 1.91; 95% CI 1.24-2.94).

Slutsatser
Diabetes ökar risken för död efter akuta koronara syndrom och risken ökar ytterligare något vid samtidig hypertoni trots behandling. Hypertoni enbart var associerat med hjärtinfarkt, stroke och hjärtsvikt under åren som följde det akuta koronara syndromet, men i förhållande till diabetes var riskökningen liten. En vid QRST areavinkel var associerad med plötslig hjärtdöd och kan därför användas som ett komplement vid riskstratifiering efter akuta koronara syndrom om resultatet kan upprepas i framtida studier. Slutligen kunde vi konstatera att akut myokardischemi påverkar repolarisationen övergående i akutskedet, vilket kan förklara varför risken för kammarflimmer är förhöjd under motsvarande period och varför kammarflimmer i akutskedet i sig inte utgör någon riskfaktor hos patienter som överlever den akuta fasen av ett akut koronart syndrom.

List of original papers

This thesis is based on the following papers, which will be referred to in the text by their roman numerals.

I Acute coronary syndromes - the prognostic impact of hypertension, diabetes and its combination on long-term outcome.
Lingman M, Herlitz J, Bergfeldt L, Karlsson T, Caidahl K, Hartford M. Int J Cardiol. 2009;137:29-36.

II The impact of hypertension and diabetes on outcome in patients undergoing percutaneous coronary intervention.
Lingman M, Albertsson P, Herlitz J, Bergfeldt L, Lagerqvist B. Am J Med. 2011;124:265-75.

III Transient repolarization alterations dominate the initial phase of an acute anterior infarction.
Lingman M, MD, Hartford M, Karlsson T, Herlitz J, Rubulis A, Caidahl K, Bergfeldt L. *Submitted*

IV The spatial QRS-T area angle predicts increased risk for sudden cardiac death after acute coronary syndromes.
Lingman M, Hartford M, Karlsson T, Herlitz J, Rubulis A, Caidahl K, Bergfeldt L. *Submitted*

Abbreviations

3-D	3-dimensional
AP	action potential
ATP	adenosine triphosphate
AMI	acute myocardial infarction
ACS	acute coronary syndrome
ATRAMI	Autonomic Tone and Reflexes After Myocardial Infarction
CAD	coronary artery disease
CAST	Cardiac Arrhythmia Supression Trial
CHF	congestive heart failure
ECG	electrocardiography
HR	hazard ratio
ICD	implantable cardioverter defibrillator
LAD	left anterior descending artery
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MASTER	Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients
NPV	negative predictive value
PCI	percutaneous coronary intervention
PPV	positive predictive value
ROC	receiver operating characteristic
SCD	sudden cardiac death
STEMI	ST-elevation myocardial infarction
STVM	ST vector magnitude
UAP	unstable angina pectoris
Teigenv	T eigenvalue
T loop	T vector loop
Tp-e	Tpeak-Tend
TWA	T wave alternance
VCG	vectorcardiography
VF	ventricular fibrillation
VG	ventricular gradient
VR	ventricular repolarization
VT	ventricular tachycardia

Introduction

Background

During the second half of the 20:th century coronary artery disease (CAD) became the most common cause of death in the western world.[1] In parallel knowledge about acute coronary disease grew and some basic features were established as facts. The view of acute coronary syndromes (ACS) today is very different from that tought to the doctors trained a few decades ago. It has long been known that the cause of myocardial ischaemic injury is a suddenly impaired blood flow in relation to down stream demands for blood perfusion of the myocardium.[2] The sequence of events can be rapid if the fibrous cap of the plaque ruptures and thereby induces the coagulation cascade with aggregating platelets forming a clot.[3] Some of the established features of ACS are that patients with larger myocardial injuries due to ischemia fare worse than those with smaller extents of damaged tissue [4,5] and that the location of the infarction is of prognostic importance.[6] Also the time from occlusion of a coronary vessel to reperfusion treatment in these patients affects the patient´s prognosis.[7] The preferred approch in this setting is mechanic restoration of blood flow by percutaneous coronary intervention (PCI) [8] without delay.[9] Approximately 30% of all acute myocardial infarctions (AMI) are silent, but carry the same risk for sudden death as the symptomatic ones.[10]

The in-hospital mortality related to ACS in countries with good access to modern treatment is down to a few percent.[11] Despite this progress in cardiovascular medicine cardiovascular mortality remains high. In Sweden 4 out of 10 deaths are cardiovascular [12] and AMI is still the number one killer in the world.[13] The trend is positive but threatened by increasing prevalence of complicating riskfactors such as diabetes and overweight.[14] Along with diabetes several other risk factors for CAD, such as smoking and hypertension, have been well established.[15]

Within the ACS spectrum different diagnoses have different prognoses. There is shift towards a larger proportion non-ST-elevation myocardial infarction (non-STEMI) [16] which seems to have a less favourable long-term outcome when compared to STEMI [17] including an increasing number non cardiovascular death among short term survivors.[18]

In countries like Sweden, the proportion of out-of-hospital cardiovascular deaths is increasing and remains a great challenge.[19] In order to decrease cardiovascular mortality even further in a way that has impact on the general population, focus needs to be put on prevention – primary as well as secondary. Effective prevention requires prognostic tools that allow us to identify individuals who are best served by the interventions that modern medicine can offer. We need to look for markers indicating future risk of arrhythmias as well as fast and slowly progressing pump failure from different underlying causes among which CAD dominate.

Diabetes, hypertension and risk

The increase in risk generated by diabetes is of the same order of magnitude as that of a previous cardiovascular event and diabetes is known to increase risk after an ACS.[20,21] Diabetes can in part be regarded as a vascular disease with progressing atherosclerosis in large and small vessels which eventually causes organ damage. The diabetic patient carries a cardiovascular vulnerability [22] and the diabetic myocardium is more sensitive to ischemia.[23] Paradoxically diabetic patients often present with a more wide spread coronary disease and the reason for this is not known.[24] Possibly diabetics are protected by a slowly developing collateral network.

Diabetes *per se* continues to be associated with considerably increased long-term mortality after an AMI [25] and non-STEMI ACS [21,26,27] and in the ACS group as a whole [28,29] even if the patient is subject to modern treatment.[30] Unfortunately not all patients receive this evidence based treatment.[31]

Along with diabetes hypertension is one of the most common diseases in the western world. It is a well-known risk factor for cardiovascular events, [32,33] and a common cause of heart failure.[34] Left ventricular hypertrophy (LVH) due to hypertension is especially linked to a worse outcome, [35,36] including sudden cardiac death.[37-39] Increased dispersion of repolarization as a response to ischemia may be one link between LVH and sudden cardiac death (SCD).[40] Another link might be the larger infarctions that are seen in LVH patients subjected to myocardial ischemia.[41,42]

The importance of treating hypertension has been known for over fifty years.[43] The effect of pharmacological treatment in preventing patients with

hypertension from complications is indisputable.[43,44] Still compliance to medication is low.

Hypertension has been put foreward as an independent risk factor in AMI patients [45-48] but the evidence are not solid.[49,50] The combined effect of diabetes and hypertension has been described in patients with acute chest pain.[51] Little is known about the combined impact of hypertension and diabetes on the outcome after ACS. This is the topic of my first two papers.

Sudden cardiac death

The yearly incidence of SCD is around 1 per 1000 inhabitants [52] partly depending on definition. It constitutes a major mortality cause in western countries and might make out 1 out of 5 deaths in the modern society.[53 54] A unifying definition is lacking [55] and it has changed over time. One definition used recently reads out unexpected death from cardiovascular causes within 1 hour from the onset of symptoms in patients without known pre-existing heart disease.[56] This definition rules out the important group of patients with known CAD and/or congestive heart failure (CHF).

In order to know the underlying cause of death an autopsy is often needed but relatively rarely performed, which impairs quality of the cause of death end-point in large registries. Therefore SCD as an end-point has and will be subject to criticism. In patients with CHF SCD probably accounts for the majority of deaths.[57,58] However in absolute numbers SCD more often occurs in a person seen as low risk [59] and normally at home. The event is often the first manifestation of heart disease.[52]

Sudden Cardiac Death and Coronary Artery Disease

In 15% of SCD victims the substrate is considered to be a non ischemic cardiomyopathy [56] while CAD is the underlying cardiac disease in up to 80% of the SCD victims.[60] Acute myocardial infarction is regarded as the most common cause of fatal arrhythmias.[61] One link might be the induced dispersion of repolarization across the border zone of ischemia constituting av substrate for re-entry.[62]

From the opposite point of view SCD accounts for more than 50% of cardiovascular deaths.[63] In chronic CAD the development of collateral circulation probably protects in part from cardiac arrest,[64] which might contribute to the relatively good prognosis in stable angina pectoris patients.

The risk of SCD after an AMI is highest during the following year. Some of the risk factors for SCD, such as ventricular arrythmia, left ventricular dysfunction, LVH,[65] smoking,[66] diabetes,[67] overweight, and a family history of SCD,[68] are also risk factors of AMI.[69] Apart from overlapping risk factors between SCD and CAD the association between the two is mirrored by the preventive pharmacological treatment also known to protect from both.[70] This indicates a common pathophysiology. The risk of SCD after an ACS can be reduced by adequate therapy.[71]

Sudden Cardiac Death and left ventricular dysfunction

Severe left ventricular dysfunction has been pointed out as a major risk factor for SCD even though investigations found that it only affects 25-30% of all SCD patients in broad populations.[52,72] Still left ventricular ejection fraction (LVEF) is the only factor recommended for risk stratification [73] even though only a minority of patients with left ventricular dysfunction will be served by an implantable cardioverter defibrillator (ICD) as primary prevention. We lack specific markers of death from arrhythmia in large patient groups [61] and a risk stratification based on LVEF combined with other risk factors of SCD has been requested.[74]

Preventive measures

Even if the cardiac arrest patient receives rapid and adequate treatment the injuries are often extensive and irreversible. Survival to hospital admission after a cardiac arrest is less than 25% and about 10% survive to hospital discharge according to reports from the Swedish Resuscitation Council (www.HLR.nu) and others.[75] The notion of SCD has recently been complicated by data illustrating that we also must take into account that high-degree atrio-ventricular block might be the most powerful predictor of cardiac death.[76]

Interest in the passage of events leading to SCD increased in 1989 when the Cardiac Arrhythmia Supression Trial (CAST) [77] fell short of proving that certain antiarrhythmic drugs prevented patients from suffering an arrhythmic sudden death. Neither class I nor class III antiarrhythmic drugs seem to be able to prevent from SCD.[78]

The combined depolarization delay and repolarization alteration is probably important in the arrhythmogenesis.[79] Abnormal ventricular repolarization is an important risk marker for cardiac death in clinical studies.[80,81] Presumably alterations both of depolarization and repolarization as well as other factors such

as post repolarization refractoriness play roles in the arrhythmogenesis related to ischemia.[82]
Importantly even though ventricular fibrillation (VF) is associated with immediate death early VF is not a marker of worse prognosis in persons surviving an AMI [83-85] regardless of when it appears during the two first days.[86]
The last two papers in the theses is about ischemia, electorphysiological alterations and its relation to SCD.

The electrical cycle of the heart

The electrical cycle of the cardiomyocyte
The transmembrane potential is the result of a difference in the concentrations of sodium, potassium and calcium ions between the inside and outside of the myocardial cell membrane.
Under normal resting conditions the inside of the cell has a negative charge of between -80 and -95 mV in relation to the outside. This difference is sustained by energydemanding Na/K-ATPase pumps transporting sodium out of and potassium into the cell. The energy is supplied in the form of adenosine triphosphate (ATP) in aerobic metabolism. During phase 0 of the AP the cell rapidly depolarizes to a positive charge of about 20 mV by opening voltage-dependent sodium channels (I_{Na}) at -65mV, letting sodium into the cell. Also a slow inward current of calcium (I_{Ca}) is initiated. As the intracellular level of calcium increases by I_{Ca} the ryanodine receptor type 2 (RyR2) channel in the sarcoplsmatic reticulum opens rapidly releasing a larger amount of calcium. Calcium binds to troponin and promotes myofilament contraction. In phase 1 the cell interrupts depolarization by initiating a transient outward current of potassium (I_{to}). The following phase (phase 2) is an electrical plateau where calcium is continued to be let in and potassium is let out (I_{Kr}, I_{Ks}) as a rectifying current balancing each other out. The main repolarization takes place in phase 3 through a rapid outflow of potassium (I_{K1}) ending the AP. In phase 4 the cell is back at its negative resting equilibrium. The reuptake of Ca back into the sarcoplasmatic reticulum is carried out by Ca ATPase. (Figure 1) The impuls is transmitted to the adjacent cells by ions passing through gap junctions.

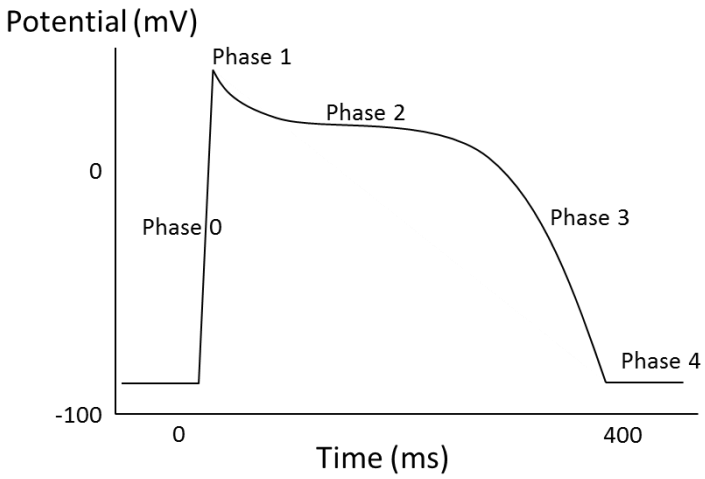


Figure 1. The phases of a model action potential of a cardiomyocyte.

The autonomic nervous system acts on several of the ion channels via acetylcholine´s effect on the muscarinic receptors and adrenergic neurotransmitters´ effect on (α- and) β-receptors.
ECG and VCG reflect the net temporal differences and differences in magnitude of the transmembrane potential of all myocardial cells by recording the body surface potentials. Due to cancellation phenomenons the potential measured reflects only a small part of the potential generated.[87]

The electrical cycle of the heart
Depolarization is initiated in the sinus node. It is then conducted to the apex of the heart through the AV-node and the interventricular septum. The wave front then turns towards the basal inferior regions of the heart through the ventricles. The endocardium is depolarized before the epicardium. Thus the contraction is directed from the inside to the outside of the myocardial wall. The mass of the left ventricle is larger than that of the right and therefore it dominates the reflection of depolarization on ECG.
Repolarization starts directly after depolarization at phase 1 of the AP. During repolarization a new impuls cannot start a depolarization of that cell since the cell is not susceptible.
Repolarization proceeds through the inverse path of that of the depolarization wave front through the heart. Hence repolarization starts at the base of the heart and the epicardium repolarizes first.
The homogeneity of repolarization throughout the heart is warranted by varying repolarization durations making the end of the repolarization occur during a

shorter time period. This results in different AP durations in different regions of the myocardium. Cardiomyocytes activated early have long AP durations and vise versa, making repolarization more homogenous throughout the heart.
The same positive polarity on ECG, as that of depolarization, is the result of the inverse path of repolarization in combination with a change from positive to negative membrane potential.
Even the normal heart shows some global heterogeneity of the AP instants and durations. Differences in AP can be identified between the apex and base,[88,89] between the epicardium and endocardium [90] and between one heart beat and another.[91,92] This normal heterogeneity is probably not arrhythmogenic.
Differences in phase 0 and 1 give rise to the QRS complex and heterogeneity in phase 3 gives rise to the T wave on the ECG.
When the cell cannot be depolarized it is said to be in a refractory state normally corresponding to about 80-85% of the AP. Repolarization and refractoriness are thightly interconnected.
Figure 2 illustrates the relation between AP and ECG tracings.

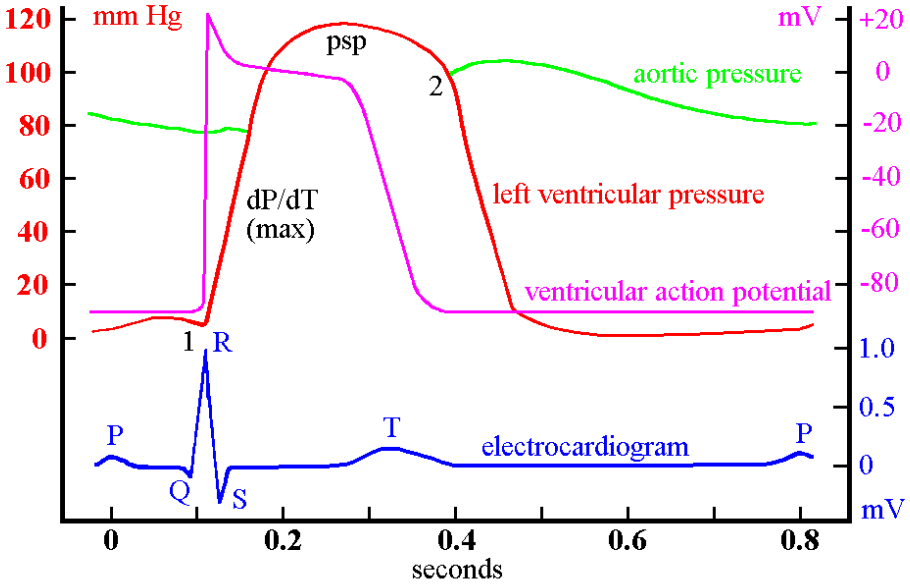
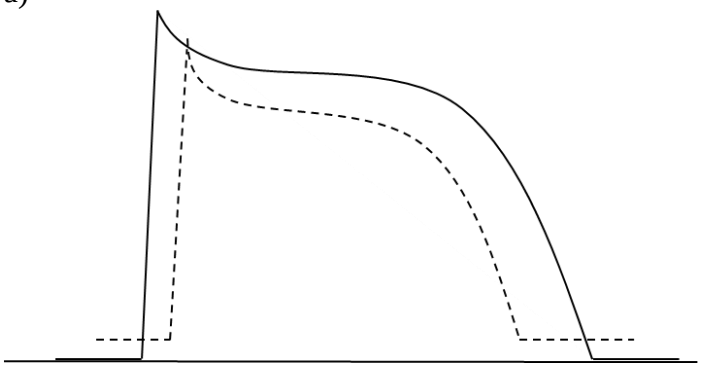


Figure 2. Temporal relation between electrocardiogram, action potential, left ventricular pressure and aortic pressure.

The electrical cycle in the heart during ischemia
Ischemia affects the electrophysiology of the cell in several ways. (Figure 3) An interrupted blood flow immediately causes shortage of oxygen impairing the Na/K-ATPase´s ability to maintain the resting potential. Low intracellular ATP

makes $I_{K(ATP)}$ let potassium out from the cell. Sodium accumulates outside the cell and lactic acid increases inside and outside the cell. Phase 0 is prolonged by inactivation of the sodium channels and the relative influence of the slower I_{Ca} is increased. In contrast to the normal global heterogeneity of repolarization heterogeneity over small areas such as those affected by myocardial ischemia or injuries is arrhythmogenic by constituting a substrate for re-entry phenomenons with a circular propagation of the wave front. An arrhythmia can then be started by an extrasystole or other trigger. This implies that measures of heterogenic repolarization can indicate risk of ventricular arrhythmia of re-entry types.[93]

a)



b)

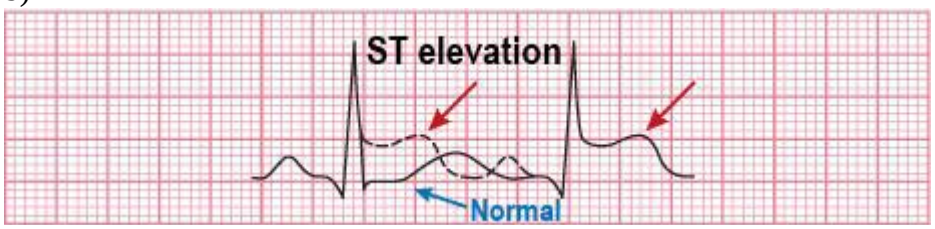


Figure 3. a) When the myocardial cell is subject to ischemia (dotted) the resting potential is affected, phase 0 is somewhat slower, the amplitude is lower and the action potential duration is shortened. b) Corresponding reaction on the ECG.

The local diversification of APs, caused by the gradient of extracellular potassium over the border zone of ischemia, causes local dispersion of repolarization.

The effective refractory period can greatly outlast action potential repolarization. Partly because of *post repolarization refractoriness*. Post repolarization refractoriness is (like Wenckebach periodicity) probably the result of the slow recovery of excitability due to slow deactivation of outward current I_K. In the

ischemic myocardium this dispersion is further increased by particularly high levels of extracellular potassium delaying recovery of excitability, increasing the assymetry of propagation.
Also the threshold of excitation is increased in the center of the ischemic area.[82]

The link to ventricular arrhythmias
Differences (heterogeneity) in refractoriness might act as wave-breakers before the depolarization wave-front and thereby constituting a stubstrate for re-entry. Increased heterogeneity of repolarization by ischemia is associated with ventricular arrhythmias.[62] This information is not new.[94,95] Also conductivity is slowed down by ischemic effects on gap-junctions, changed distribution of extra- and intracellular volume and acidosis. Activation of whole regions can be delayed if Purkinje cells are subject to severe ischemia.
Recently Lund et al. concluded that prolonged depolarization is associated with increased mortality in CHF patients including those with preserved LVEF.[96]

Heterogeneity of repolarization can be measured by invasive techniques assessing APs, but invasive techniques are associated with risks for the patient. Also they are expensive in relation to surface detecting techniques such as ECG and VCG. Invasive techniques are therefore not feasible at a larger scale. Non-invasive measurements of global repolarization and its relation to depolarization by surface detection might be helpful to the clinician in risk stratification.

Information on risk on the ECG
Several ways of extracting information on risk from the ECG have been investigated. Both temporal aspects and morphological aspects have been considered, but they all have low positive predictive value or have shown conflicting results.[74] Many approaches have been investigated to describe altered repolarization on ECG in relation to outcome. Some are presented below.
Nonspecific minor ST-segment and T wave abnormalities according to the Minnesota code has been associated with increased risk of coronary death but not non-fatal AMI in low risk patients suggesting that these alterations indicate an increased risk of arrhythmic death in particular.[97] The latter part of repolarization reflected by the T wave was of greater prognostic importance than the ST-segment in a low risk population.[98]

Interval based markers of risk on ECG

Prolongation of the QRS interval is associated with all-cause mortality in CHF patients.[96]

A prolongation of the QTc is a well known risk factor for death and has been associated with SCD in patients with LVH.[99] A problem with the QT interval as a marker of risk is the need for a valid annotation of the end of the T wave. Tpeak-Tend (Tp-e) (the time from the top of the T wave to its end) has been reported to predict SCD in different populations and ventricular arrhythmias in patients with known heart disease.[100] In 2008 Gupta et al. suggested that a changed time ratio between the Tp-Te and the electric cycle as a whole (Tp-e/QT) indicates an increased risk of ventricular arrhythmias.[101]

Dispersion of intervals such as the QT time on ECG has been proposed to reflect heterogeneity. Increased dispersion on the ECG was reported as a risk factors for arrhythmic death during the two years following an ACS [102] and in patients with impaired left ventricular systolic function.[103] It was measured as the difference between the longest and the shortest QT duration in the 12 leads on the ECG. Increased QT dispersion was associated with susceptibility to VT.[104] Interest in QT dispersion as a prognostic marker decreased by the end of the nineties as its prognostic importance could not be confirmed in ACS patients.[105] It was also discarded as a non-invasive assessment of ventricular repolarization heterogeneity by Malik et al. a decade ago.[106] This, along with difficulties in annotation of the T wave and the fact that the resolution of the T wave is vary in different leads due to varying distances to the heart, has limited clinical implementation.

Temporal repolarization variability

Temporal repolarization instability has been associated with ventricular arrhythmias in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) population [107] and in other studies on patients with CHF.[108] The beat-to-beat variability of repolarization reflected by alternating T wave amplitude on the microvolt level is called T wave alternans (TWA). It is probably caused by abnormal intracellular calcium handling. The presence of TWA on intracardiac electrograms seems to precede ventricular tachycardia (VT) and VF [109] but results from the large Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients (MASTER) trial could not report an association with ventricular tachyarrhythmias in heart failure patients post AMI.[110] Contradicting results and the inability of some patients to perform

the test and problems in the definitions limit its use in the routine clinical setting. Possibly a negative TWA-test can tell us which CHF patient will not benefit from an ICD.[111]

Influence of autonomic tone

The autonomic tone seems to influence prognosis. A high resting heart rate is a well known risk factor for cardiac death including SCD.[112] Heart rate variability has been another area of interest. Studies, such as the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) cohort, report that a low heart rate variability, measured as standard deviation of normal to normal R-R interval (SDNN), indicates increased mortality after an AMI.[113] Heart rate turbulence described as the R-R variability just before and after a premature ventricular beat as a marker of autonomic dysfunction has been identified as a promising marker of risk of SCD in CHF.[108] It is not known whether this mortality is primarily due to arrhythmia. Large studies have not been able to confirm the predictive value of a low SDNN and heart rate turbulence.

Mechanic dysfunction

Along with alterations in the hearts electrical system dysfunction of mechanic aspects of the heart affects prognosis. Today LVEF is the golden standard as a reflector of the mechanic function of the heart.[114]

Vectorcardiography

The vector

The joint temporal and morphological differences in APs of all cardiomyocytes generate an electrical field that can be represented by a vector in space at each time-point. The vector has a magnitude (length) and a direction. On scalar ECG differences of all APs are reflected by the amplitude in each lead. Due to the electrode placement, the ECG leads do not represent all regions of the heart muscle equally – a problem that has to be taken into account for VCG as well. The center of the heart is assumed to be the origin of the vector. During one cardiac cycle the tip of the vector makes three loops in space representing the p wave, the QRS complex and the T wave of the ECG respectively. For practical reasons these 3-D loops are often projected onto three orthogonal planes. In the normal heart the QRS vector points slightly posterior, inferior and to the left while the T vector points anterior, inferior and to the left.

Rationale for using three dimensional registration

The 3-D reflection of the electrical field provides information not only about the magnitude and positive/negative direction of the signal but also about spatial orientation. This is information not achieved on two dimensional ECG. The 3-D VCG gives an anatomic representation of the electrical activity. It has been proven superior to scalar ECG in the diagnosis of carriers of mutations associated with the long QT syndrome and the detection of repolarization changes related to "cardiac memory" after right ventricular pacing and after ablation of the Wolff-Parkinson-White syndrome.[115-117] Over all 3-D analysis of the electric activity is a tool appropriate for assessment of global electrophysiological entities while ECG probably is to be preferred to reflect local aspects. Using 3-D representations of the electrical field does enable us to outline the relation between repolarization and depolarization forces. The dependence on the operator is low since calculations are carried out automatically. Also the vector is not as dependent of breathing motions of the subject. The 3-D representation of the electrical activitity in the heart can also be derived from standard 12-lead ECG.[118]

Our vectorcardiographic approach

In 1995 Badilini et al. concluded that interlead dispersion of the QT time seen on 12-lead surface ECG is also reflected by distortion of the spatial T wave loop.[119] Our group has applied 3-D VCG as suggested by Badilini et al. with a modified Frank orthogonal lead system (Figure 4) to investigate altered depolarization and repolarization and its clinical impact.

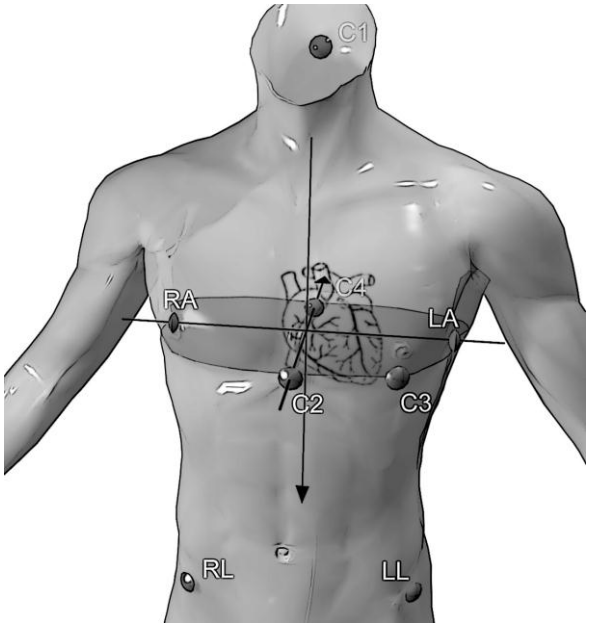


Figure 4. Electrode placement according to a modified Frank setup. Thoracic electrodes are placed at the level of the 4:th intercostal space.

Knowledge of what information that lies in the T vector loop (T loop) formed by the tip of the T vector, in detail described under Methods, has increased gradually. When a left sided coronary vessel is occluded the QT dispersion corrected for heart rate increases as well as the size (Tarea), bulginess (Tavplan) and roundness (Teigenv) of the T loop [120] and the findings are more explicit in hypertensive patients and patients with LVH.[121] In 2009 Odenstedt et al. recognized that Tavplan and heart rate differed from controls minutes prior to VF differed in a close-chest procine coronary artery model.[122]

Prognostic importance T loop and the spatial relation between depolarization and repolarization forces

A wider angle between the main direction of depolarization and repolarization forces is more pathological. In 2006 Perkiömäki et al. concluded that irregular shape of the T loop, but also that the angle between the main QRS and T vectors (called TCRT), predict long term cardiac mortality after AMI.[123] This angle, when measured 1-2 weeks after an AMI, was associated with future risk of ventricular arrhythmia as was the length of the T loop (a concept adjacent to the Tarea) in a study by Korhonen et al. [124] and a similar study by Zabel et al in 2000.[125] In a cohort of CAD patients the angle (here measured as the QRS-T angle using VCG) predicted cardiovascular mortality and Tavplan predicted future AMI [126] confirming results by Triola et al. in women 2005.[127] The ability

of the QRS-T angle to predict cardiovascular death applies also in low risk cohorts [80] and in a general medical population.[128] The QRS-T angle was wider in patients without acceptable blood pressure control.[129]
Recent insights from our group indicate that the reproducibility for QRS-T is not sufficient for use as prognostic marker in the individual (Bergfeldt, unpublished data).

In summary
Cardiac death is predominantly caused by pump failure from mechanical and electrical reasons (acute or progressing heart failure or a ventricular arrhythmia). We know that VT can occur on the basis of macro re-entry or by focal mechanisms. Re-entry can be the result of a heterogeneous refractoriness of the myocardium and several research groups have tried to find ways to identify and quantify this dispersion. We also know that repolarization abnormalities such as prolongation, described as long QT interval on the ECG, is associated with increased risk of ventricular arrhythmias. It would be of great value to find a readily available non-invasive way to identify persons with a deranged depolarization-repolarization sequence throughout the heart and thereby identifying subjects at risk. The latter two papers in this thesis explore VCG reflections of acute myocardial ischemia and VCG markers of future risk after an ACS.
The first two papers deal with high risk populations where we wanted to study the impact of well known cardiovascular risk factors such as hypertension and diabetes. It is known that LVH induced by hypertension constitutes an arrhythmogenic state.
In this thesis we contribute to the identification of patients at risk in a high risk population.

Aims

The overall aim of this thesis was to assess the importance of hypertension, diabetes and VCG measures on long-term risk after ACS and to shed light on the transient nature of VF as a risk factor.

In detail

1. To assess the impact of hypertension and diabetes on future risk of death after ACS.
2. To study the effects of ischemia-reperfusion on global reflections of ventricular electrophysiology in the human setting to shed light on the transient risk for VF in the acute phase.
3. To investigate the prognostic value of the QRS-T area angle and other VCG variables in relation to the future risk of SCD after ACS.

Material and methods

Study populations

Papers I, III and IV

These papers studied patients from a population comprising 2,335 patients <80 years of age with ACS prospectively included during 1995 through 2001 at the coronary care unit at Sahlgrenska University Hospital, Gothenburg, Sweden (the PRACSIS cohort). All patients with an obvious or suspected ACS admitted to the coronary care unit were evaluated for inclusion. Patients were included if symptoms suggestive of myocardial ischemia were supported by ECG changes, biochemical markers of myocardial ischemia or previously recognised CAD. The included patients covered the whole spectrum of ACS.

Paper I deals with 2,329 of the 2,335 patients who received a diagnosis of unstable angina pectoris (UAP) or AMI and with information about hypertension and diabetes on admission.

Paper III deals with 57 men and women who were diagnosed with an anterior STEMI caught on continuous ECG monitoring with VCG registration starting within 4 hours from the onset of chest pain and showing dynamic trends in ST-vector magnitude (STVM). Patients with bundle branch block or pacemaker ECG were excluded as were patients with prior AMI.

Paper IV deals with 643 consecutive ACS patients who were subject to cardiac ultrasound and had continuous VCG registration during hospital stay.

Paper II

In Sweden, 53,320 PCIs were performed between 1 January 2006 and 31 December 2008. They were registered in the Swedish angiography and angioplasty registry (SCAAR). The SCAAR is a national internet based registry of coronary angiographies and PCIs. Each centre provides information on patient characteristics, indications for intervention, procedural data, type of stenosis treated, the type of stent implanted, the presence of restenosis and in-hospital complications. All SCAAR-registered patients undergoing PCI were included if information on pre-existing hypertension was registered. This resulted in 44,268 included patients. As in paper I their diagnoses covered the whole spectrum of ACS, but also stable angina pectoris. Information on prescribed medication during the six months preceding the PCI was obtained.

Clinical data

Paper I, III and IV

Data were collected from hospital records, and while hospitalised, all patients were interviewed in detail by one experienced study nurse. Previous medical history, ongoing medication, as well as clinical features and ECG pattern on admission were recorded. Hypertension and diabetes were defined as previously known disorders. During hospitalisation, 12-lead ECG and VCG changes and clinical complications were documented, along with pharmacological treatment, which was also documented at discharge.

Paper II

Data were collected from the SCAAR registry, The Swedish Hospital Discharge Register and the Prescribed Drug Register. These registries are nation wide (see below).

ECG and VCG data

Papers III and IV used VCG along with ECG data. A MIDA 1000 or MIDA 1200 system (Myocardial Infarction Dynamic Analysis, Ortivus AB, Danderyd, Sweden) was connected to electrodes, positioned according to a modified Frank orthogonal lead system (X, Y, and Z).

The methods for recording, interval measurements, and other analyses followed the same principles and definitions as described by others.[116,120,121,130,131] Like on the ECG, the VCG recordings are generated by temporal differences and differences of the amplitude of the AP of different cardiomyocytes. (Figure 5)

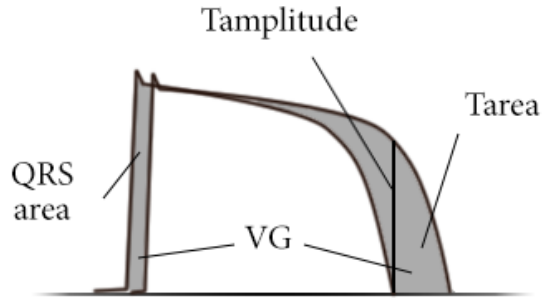


Figure 5. Conceptual model of how the temporal diffence of the action potential of two cardiamyocytes results in selected vectorcardiographic variables. (Adapted from Vahedi et al. Ann Noninvasive Electrocardiol 2011;16:287-94.)

The cycle can be described in 3 dimensions as one loop formed by the tip of the vector representing the atrial depolarization (P-loop), one mainly representing the global ventrical depolarization (QRS vector loop) and one T vector loop mainly describing global repolarization. Averaged 3-D QRST complexes used for analysis were constructed from all cardiac cycles during one to two minutes. The VCG was recorded continuously and used both for analysis of 3-D based QRST intervals and for the QRS and T vector as well as T loop analyses.

The VCG data was mathematically handled and visually presented (Figure 6) by a customized software (Coronet on the MIDA systems).

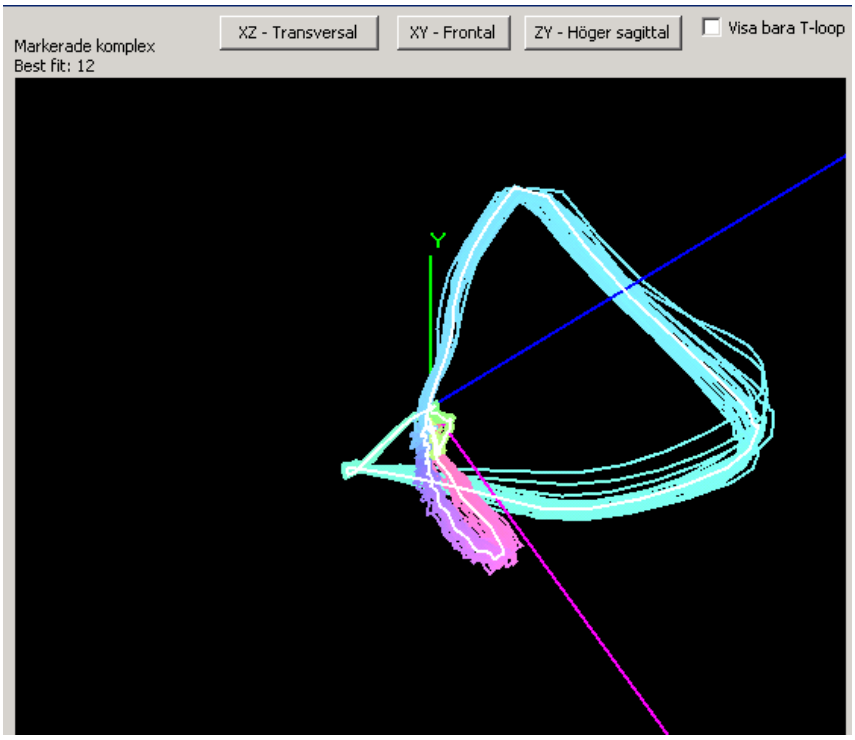


Figure 6. P loop (green, smallest), T loop (pink, pointing down and right) and QRS loop (turquoise, largest) and x, y and z coordinates as presented by the customized software developed for data analysis.

The direction of the maximum T vector was assessed by Televation (º) and Tazimuth (º), and the T loop morphology was evaluated by Teigenvalue (Teigenv) (unitless) and Tavplan (µV). **Tazimuth** is the angle between the maximum T vector projected on the horizontal plane and the positive x-axis which can also be expressed as the angle in the transverse plane (0º left, +90º front, -90º back and 180º right). **Televation** is the angle between the maximum T vector and the negative y-axis. In other words the angle in the cranio-caudal direction defined

from 0º (caudal direction) to 180º (cranial direction). As mentioned the normal human T loop is narrow (elliptical) and situated in one preferential plane pointing downward to the left and forward, and hence with large Teigenv and small Tavplan measures. (Figure 7)

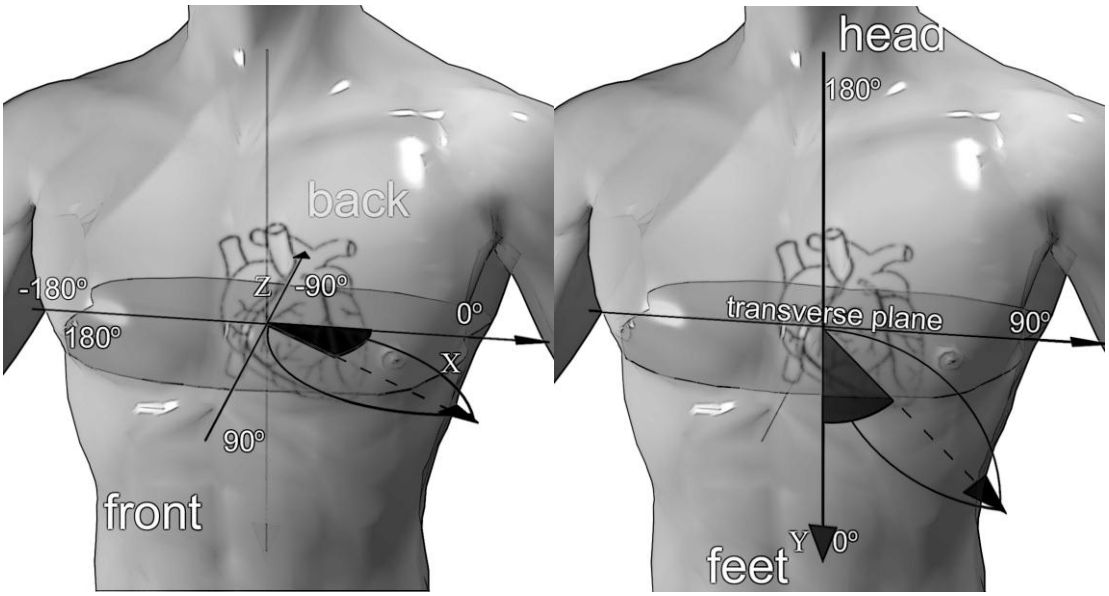


Figure 7. The T loop variables T azimuth (left) and T elevation (right). (Sahlén et al. Heart Rhythm 2009;2:28-34).

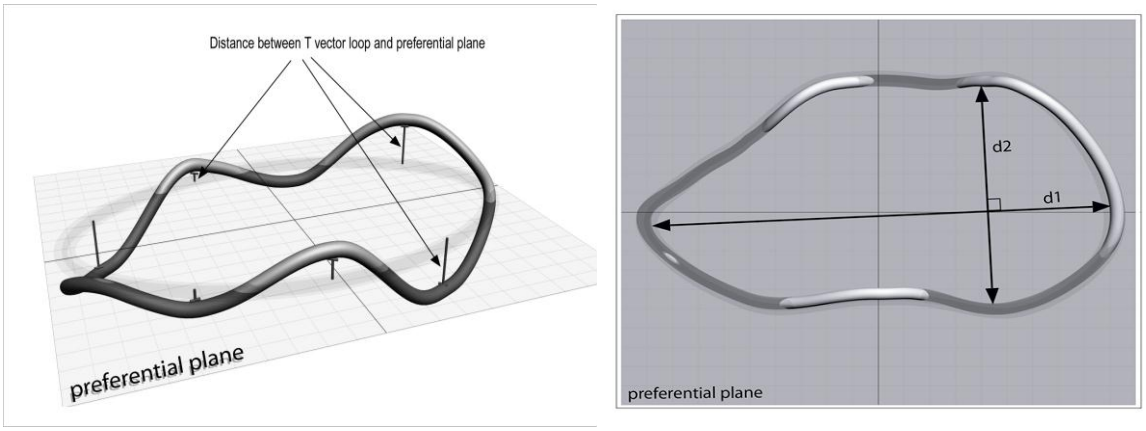


Figure 8. Simplified model of the T loop where Tavplan (left) is given as the mean distance between the loop and a preferential plane and Teigenvalue (right) is the squared quotient between d1 och d2. (Wecke L et al. Heart Rhythm 2007; 4:1477-86.)

Tavplan (µV) describes the bulginess (or irregularity) of the loop as the mean distance from the preferential plane in space. (Figure 8) **Teigenv** (unitless) is the matrix of inertia of the loop or the "roundness" of the loop. (Figure 8)

It is the squared quotient between the two largest perpendicular axes (eigenvalues) of the T loop. A Teigenv equal to 1 indicates a round T loop.
The amplitude (i.e. magnitude) of the maximum QRS and T vectors (mV) in space were defined as well as their spatial orientation in relation to each other, i.e. the QRS-T angle (º). Thus the **QRS-T angle** is the angle between the maximum QRS vector and the maximum T vector (0° to 180°). **Tarea** (µVs) is the abstract "3-dimensional area" between the baseline and the T curve during the JT interval and defined as: $Tarea = (Tx^2 + Ty^2 + Tz^2)^{1/2}$, where Tx is the area under the T wave recorded on the x-axis and Ty and Tz are defined accordingly. Tarea mainly describes the dispersion of repolarization. The QRS complex has a corresponding **QRSarea** (µVs) defined by the QJ interval and hence defined as: $QRSarea = (QRSx^2 + QRSy^2 + QRSz^2)^{1/2}$ mainly reflecting depolarization.
As opposed to the QRS-T angle the **QRS-T area angle** (º) is the angle between the QRS and T area vectors and constitutes a more stable alternative to the QRS-T angle. Unpublished data from our group on 50 adults imply that the coefficient of variance is unacceptably high for QRS-T angle (Bergfeldt, unpublished). Therefore the QRS-T area angle was preferred before the QRS-T angle.
The ventricular gradient (**VG)**, also called the QRSTarea (µVs), is the sum of the QRSarea and Tarea vectors and calculated as: $QRSTarea = (QRSTx^2 + QRSTy^2 + QRSTz^2)^{1/2}$, where QRSTx is the area formed under the VCG curve when plotting the x-lead of the VCG as a function of time from QRS onset to Tend, y and z likewise. It can also be expressed as:
$VG= (QRSarea^2+Tarea^2+2QRSarea*Tarea*\text{cosine } \alpha°)^{½}$. The concept of the VG was developed in the 1930s by Wilson et al. as a way to take into account primary (i.e., heterogeneity of AP morphology throughout the ventricles) and secondary (i.e., heterogeneity in ventricular depolarization instants) factors that afflict the T wave.[132] (Figure 9)

The averaged 3-D QRST complex was used for assessing the QRS, QT, and Tp-e intervals, as in a standard ECG. QT was heart rate corrected.

In paper III QRST complexes and loops were analyzed at 7 time-points during the VCG registration including at maximum and minimum ischemia according to

STVM and at a late stable phase before VCG recording was ended. The samples used for calculations in paper IV were selected at a stage when the STVM had reached a steady state just before the end of the VCG registration.

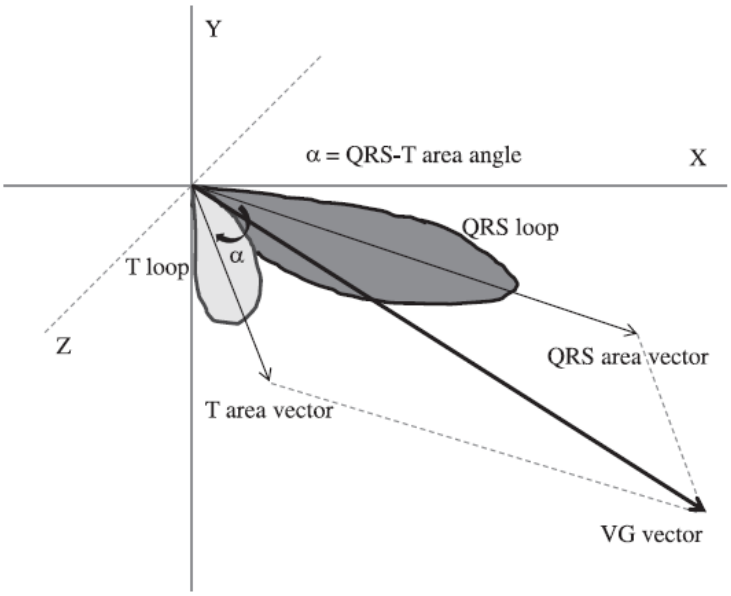


Figure 9. Selected vectorcardiographic measures in a "3-D" model.
(Vahedi F et al. J Appl Physiol 2012;113:368–376)

Quality of data

The validity of VCG STVM has been evaluated by comparison with epicardial ST magnitude in dogs.[133] The quality of the VCG signal is crucial when it comes to detailed analysis. To ensure good signal quality and to eliminate the effects of noise we used averaged QRST complexes on ECG and VCG. On these complexes customized software made automated annotations used for calculations. In order to avoid impact of interference an averaged QRST loop and QRST complex were calculated from every 1-2 minutes of sampling. Then the software eliminated complexes with possible remaining interferences. The number of extrasystoles during the sampling period was counted. Only averaged complexes that were made out of more than 75% of the beats during the sampling period were accepted. Manual control of all complexes used for calculation was done by two of the authors blinded to all other data. Their coefficient of variance was 0.72% when measuring the QT time in 30 cases.

The controlling authors altered annotation points when deemed justified (61% of cases including minimal adjustments). Thereafter all calculations were made automatically by the software.

Background data and clinical data in paper I, III and IV
These data were prospectively collected. Background data was collected by one experienced study nurse ensuring high quality of data input. End-point data was manually verified through hospital records in paper IV.

Registry data
Access to the 5 nationwide registers provided a unique opportunity to validate the data. The high quality of the input data is reflected for example by the fact that there was a discrepancy of only 0.3% between the information on insulin in SCAAR and the number of patients who had purchased insulin from a pharmacy. When the data were analyzed from the opposite perspective, 0.1% of the patients classified as nondiabetic in the SCAAR registry received oral antidiabetics according to the pharmacy registry.
The validity of SCAAR is evaluated on a yearly basis by comparing the SCAAR and original hospital records. All centres have been monitored by comparing 50 variables in 20 randomly selected interventions per hospital. The accuracy of all variables is > 90%.

Follow-up in longitudinal studies (I, II and IV)
In paper I the follow-up on total mortality was concluded with a minimum of 57 months since inclusion. Regarding cardio-vascular mortality the minimum follow-up was 21 months. The survival confirmation or date of death was obtained from the Swedish National Population Register, which is kept by the Swedish national authorities and provides data on death. Information on the cause of death was collected from the Swedish Cause of Death Register, which covers all deaths of Swedish residents, whether they occur in Sweden or abroad. Information regarding any CABG, PCI and re-hospitalisation due to re-infarction after the index hospital discharge was obtained from the Swedish Hospital Discharge Register which provides end-point data according to the International Classification of Diseases from all providers of specialist care in Sweden.

In paper II data were obtained through the following registries:
The Prescribed Drug Register held by the Epidemiological Centre at the Swedish National Board of Health and Welfare, the Swedish Hospital Discharge Register and the National Population Register.
In paper III no follow-up was done.
In paper IV follow-up on death and circumstances around the death was carried out through hospital records 30 months after hospital discharge. Primary end-point was SCD defined as: 1) cardiac death within 24 hours from onset of symptoms or 2) unsuccessful cardiac resuscitation with subsequent death or 3) where circumstances clearly indicated sudden death. Secondary end point was all cardiac deaths (including SCD).

Statistics

Pearson chi-square test was used to find general age-adjusted associations for dichotomous variables and Kruskal-Wallis´ test for ordered and continuous variables in paper I. As in paper I Pearson chi-square test was used for categoric background variables in paper II, but differences in means were assessed using variance tests. In paper III we presented median and ranges in the descriptive statistics and used Wilcoxon´s signed rank test to identify differences in ECG and VCG measures at the different time-points used for measurements.
In paper IV Mann-Whitney U test for ordered variables and Fisher's exact test for categorical variables were used in crude group comparisons. Optimal discriminating cut-offs were identified in ROC curves.
Kaplan-Maier methods were used to describe cumulative events and hazard ratios and its confidence intervals and p-values were calculated using the Cox proportional hazard regression model and adjusted for possible confounders in all longitudinal studies. Non linear variables were logarithmically transformed before calculations.
In paper IV Akaike´s information criterion was used to identify differences between regression models.

Ethical considerations

Paper I, III and IV were approved by the Ethics Committee of the University of Gothenburg (DNR 145/95, 144/95, 465/03) and paper II was approved by the Ethics Committee of Uppsala University (DNR 2006/052/5) accordning to the Swedish law Etikprövningslagen regulating all research. Data was handled

according to applicable laws. The use of registry data can be sensitive since inclusion often is made without consent.
One important ethical task is to ensure that the results from this thesis are implemented in the clinical situation if considered scientifically secured after being scrutinized and confirmed. The publication of papers is one part of this, but medial information and participating and presenting the results in congresses and meetings is also important.

Results

This section is a summary of the results in respective papers, where complete tables are found.

Paper I

A history of hypertension was present in 42%, while diabetes was present in 19% of the patients. Patients with combined diabetes and hypertension had more cardiovascular disorders than patients with diabetes only, followed by patients with hypertension and those who had neither of these diagnoses. Patients with either hypertension or diabetes were older (69±9 years) and more often female (36%). With regard to pharmaceutical out of hospital treatment there were few statistically significant differences between groups.

The diabetes group was in a worse state upon admission with more clinical signs of heart failure and biochemistry indicating a higher risk of cardiovascular events. In contrast ECG signs of acute ischemia or infarction were more frequently found in patients without diabetes or hypertension who consequently were diagnosed with STEMI to a larger extent. (Table 1) The maximum levels of CKMB were highest in patients without diabetes or hypertension, as was the proportion of patients suffering from non-sustained VT.

In a subset of patients (n=571), information on the extent of CAD (based on angiography) showed that triple-vessel disease was most frequent among patients with hypertension and diabetes.

During follow-up the number of deaths was 759. The age-adjusted mortality for diabetics with hypertension was more than twice that for patients with neither diagnosis. (Table 2)

Table 1 Status and ECG pattern on admission to hospital

	Hypertension(HT)/diabetes(DM)				
	HT+ DM n=265	DM n=181	HT n=709	Neither n=1,174	p*
Cardiac arrest prior to admission (%)	2	2	2	3	
Ventricular fibrillation prior to admission or in hospital (%)	3	3	5	6	
Systolic BP (median; mmHg)	160	140	150	145	<.0001
<100 mmHg (%)	3	3	3	5	.04
≥160 mmHg (%)	51	27	43	33	<.0001
Heart rate (median; beats/min)	78	78	71	72	.001
<50	2	3	4	5	
≥100	17	20	14	14	
Killip class >1 (%)	18	18	6	6	<.0001
ECG pattern					
Signs of acute ischemia/infarction	43	49	51	59	<.0001
ST-elevation	24	28	29	37	<.0001
ST depression	24	22	26	30	.009
T inversion	11	16	17	15	
Q-wave	6	9	8	12	.004
Pathological but without signs of acute ischemia	43	30	26	20	<.0001
Without pathological changes	14	20	23	21	

* Age-adjusted p-values for any difference between groups, given if below 0.05

Table 2. Mortality and morbidity in relation to a history of diabetes and hypertension

	Hazard ratio*	95% confidence limits*	p*
Total mortality < 2006-01-01			
No diabetes or hypertension (n=1,174)	1.0		
Hypertension (n=709)	1.18	0.99-1.40	
Diabetes (n=181)	1.74	1.36-2.23	<0.0001
Hypertension+diabetes (n=265)	2.10	1.71-2.57	<0.0001
Multivariate			
Hypertension	1.18	1.02-1.37	0.02
Diabetes	1.79	1.52-2.10	<0.0001
Cardiovascular mortality < 2003-01-01			
No diabetes or hypertension (n=1,174)	1.0		
Hypertension (n=709)	1.07	0.85-1.35	
Diabetes (n=181)	1.96	1.44-2.67	<0.0001
Hypertension+diabetes (n=265)	2.07	1.59-2.70	<0.0001
Multivariate			
Hypertension	1.07	0.88-1.30	
Diabetes	1.95	1.59-2.40	<0.0001

- Age adjusted

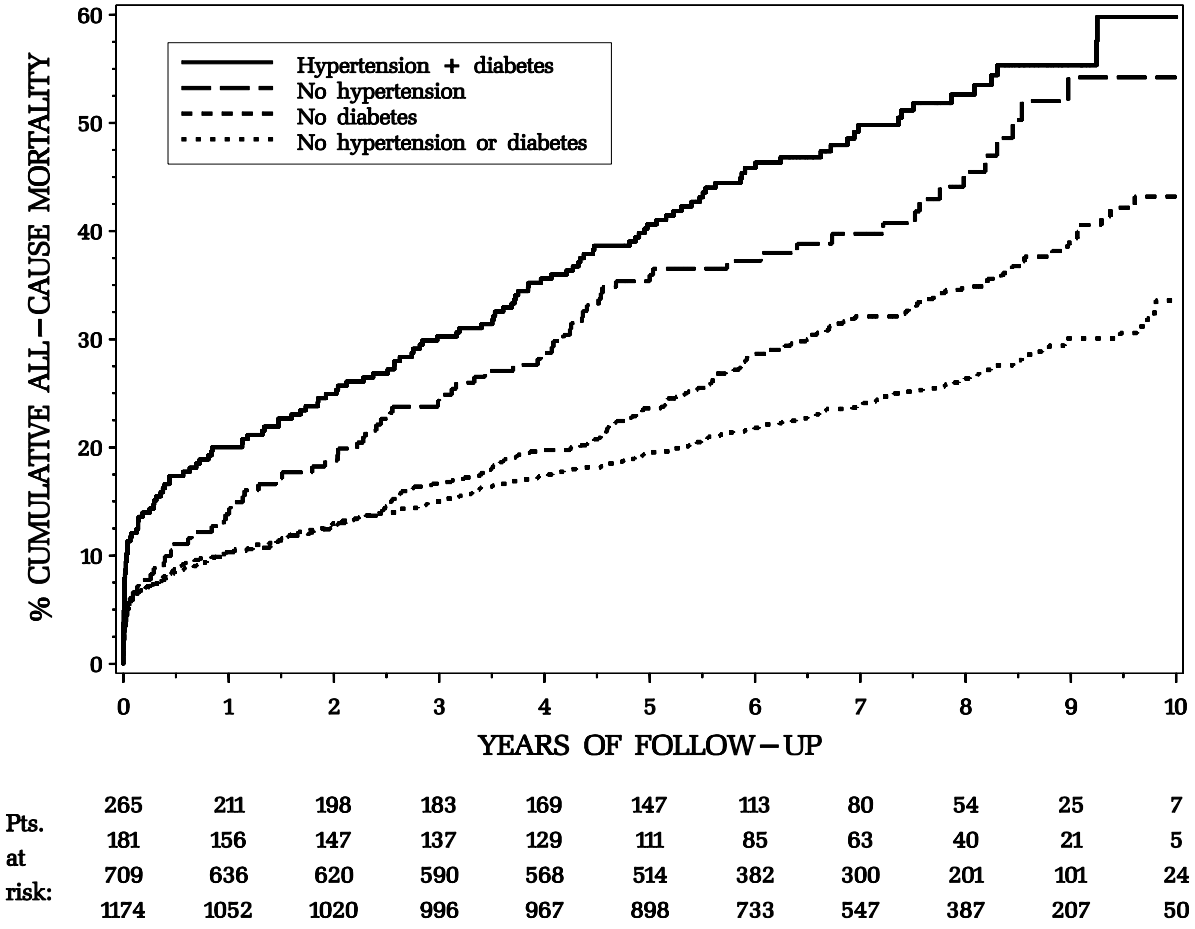


Figure 10. All-cause mortality during follow-up after an acute coronary syndrome in relation to hypertension and diabetes. (Lingman M et al. Int J Cardiol 2009;137:29-36)

Hypertension had a significant impact only when combined with diabetes. (Figure 10)

The overall 10-year mortality was 46% among patients with STEMI, 46% among patients with non-STEMI and 30% among patients with UAP.
In a multivariate analysis of AMI patients adjusting for age, a history of hypertension and diabetes and whether patients had STEMI or a non-STEMI, the results were:
1/ A history of hypertension (HR 1.25; 95% CI 1.06-1.47) was an independent risk indicator for death during eight years, as was a history of diabetes (HR 1.69; 95% CI 1.41-2.03).
2/ A STEMI diagnosis was not a risk indicator for death (HR 1.07; 95% CI 0.91-1.25).
In a more comprehensive multivariate analysis including also tachycardia, signs of acute heart failure, hypotension, left ventricular systolic function and renal

function during hospitalization, a history hypertension and diabetes remained as independent predictors for long-term mortality (HR 1.28; 95% CI 1.06-1.53; p= 0.008) and (HR 1.69; 95% CI 1.38-2.08; p= 0.0001 respectively).

Paper II

Hypertension with or without diabetes was overrepresented among patients with stable CAD. In line with paper I hypertension was less frequent in the STEMI group, in contrast to diabetes and patients with diabetes or hypertension were older (68±0.12 years) and more often female (32% female) than the reference group. The influences of diabetes and hypertension were additively associated with cardiovascular disorders. Diabetic and hypertensive patients had a more wide spread coronary disease.

Patients were followed for an average of 1.9 (±0.9) years. A total of 2,830 deaths (6.4%) occurred during follow-up, on average 3.4% per year. Mortality was highest in diabetic patients regardless of indication of PCI. Hypertension alone did not increase the adjusted mortality risk. (Table 3 and Figure 11)

Table 3 Mortality, stroke, congestive heart failure and myocardial infarction during follow-up.

	HYPERTENSION / DIABETES				
	HT+DM	**HT**	**DM**	**Neither**	**All**
n=	6795	16279	2785	18409	44268
MORTALITY					
Unadjusted mortality					
patients in groups	6630	15869	2704	17969	43198
overall (HR(95% CI))	2.01(1.83-2.22)	1.06(0.97-1.16)	1.73(1.50-1.98)	1	
Adjusted mortality					
overall (HR(95% CI))	1.54(1.38-1.71)	0.90(0.82-0.99)	1.43(1.24-1.64)	1	
In stable CAD subgroup n(%)	1763(19.4)	4204(46.2)	450(4.9)	2692(29.6)	9309(21.0)
overall adjusted (HR(95% CI))	1.29(0.93-1.79)	0.78(0.58-1.04)	1.63(1.04-2.55)	1	
In unstable CAD subgroup n(%)	3445(16.4)	7848(37.5)	1305(6.2)	8356(39.9)	20954(47.3)
overall adjusted (HR(95% CI))	1.68(1.43-1.98)	0.93(0.98-1.08)	1.31(1.04-1.65)	1	
In ST-elevation MI subgroup n(%)	1283(10.4)	3554(28.7)	907(7.3)	6626(53.6)	12360(27.9)
overall adjusted (HR(95% CI))	1.42(1.20-1.69)	0.94(0.82-1.08)	1.51(1.23-1.84)	1	
STROKE					
n stroke in subgroups	209	357	56	272	894
overall adjusted (HR(95% CI))	1.67(1.37-2.04)	1.23(1.04-1.45)	1.23(0.92-1.63)	1	
CONGESTIVE HEART FAILURE					
n CHF in subgroups	988	1324	348	1081	3741
overall adjusted (HR(95% CI))	1.90(1.76-2.09)	1.18(1.09-1.29)	1.79(1.58-2.02)	1	
MYOCARDIAL INFARCTION					
n MI in subgroups	795	1383	278	1334	3790
overall adjusted (HR(95% CI))	1.38(1.26-1.52)	1.10(1.01-1.19)	1.23(1.08-1.40)	1	

CAD=coronary artery disease, CHF=congestive heart failure, CI=confidence interval, DM=diabetes mellitus, HR=hazard ratio, HT=hypertension, MI=myocardial infarction

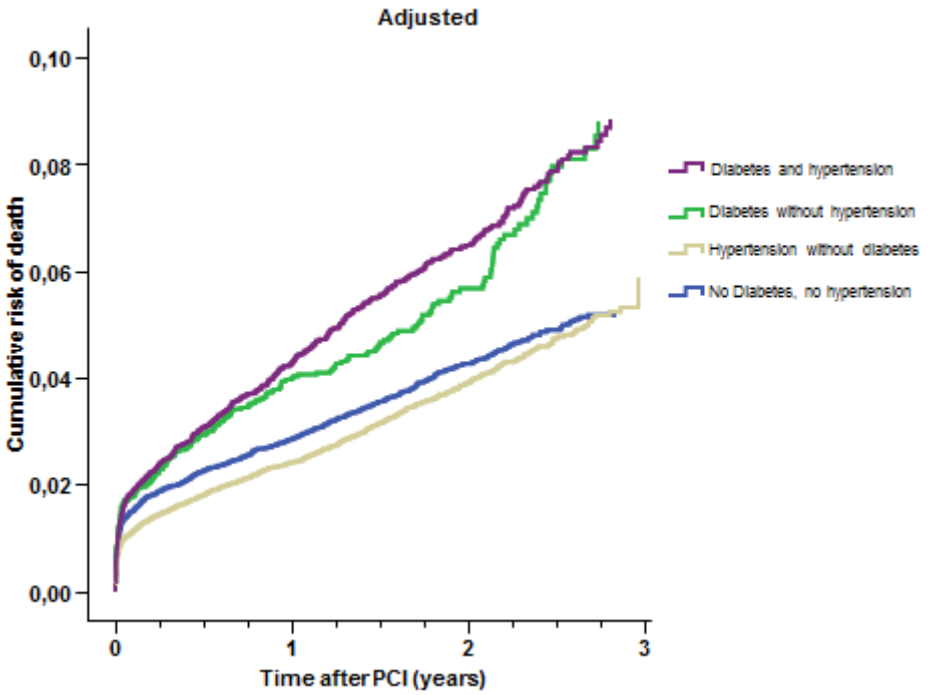


Figure 11. Mortality after percutaneous coronary intervention in relation to hypertension and diabetes. (Lingman M et al. Am J Med 2011;124:265-75)

A combination of hypertension and diabetes increased risk for AMI by almost 40% with a smaller impact of hypertension. (Figure 12) Data on death cause were available for patients who died before January 1, 2008 (of 30,019 patients who underwent PCI), except for less than 50 cases. Among the 1,534 deaths in this group almost 80% were cardiovascular, while 10% died of cancer. Adjusted hazard ratio for cardiovascular death was 1.42 (95% CI 1.20-1.68) in the group with diabetes and hypertension, 0.81 (95% CI 0.70-0.95) in the group with hypertension only, and 1.29 (95% CI 1.04-1.61) in the group with diabetes only, compared with the group with neither hypertension nor diabetes. Hypertension and diabetes were important risk factors for stroke and admission to hospital for CHF.

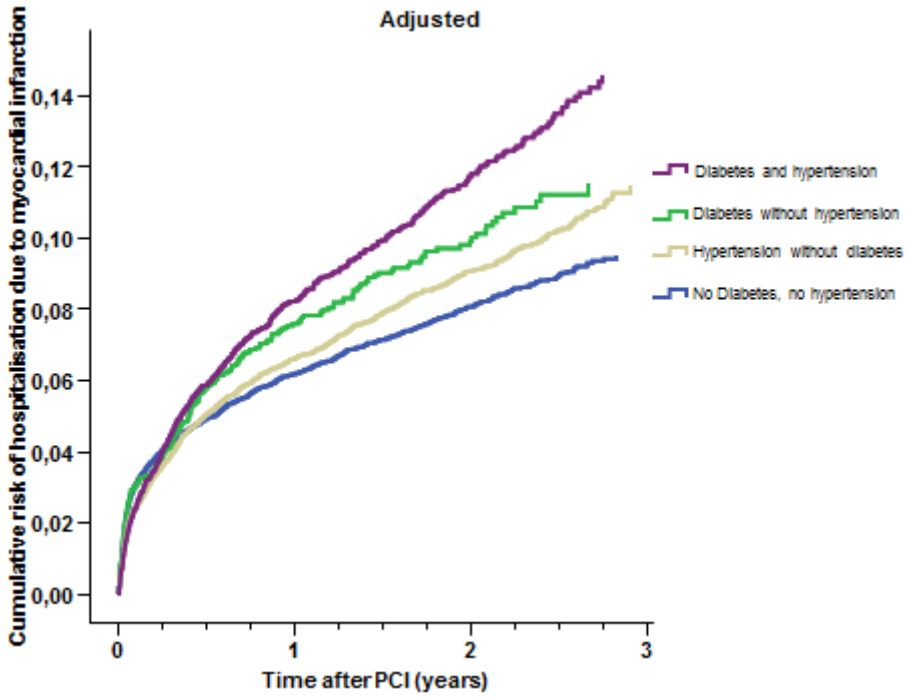


Figure 12. Acute myocardial infarction after percutaneous coronary intervention in relation to hypertension and diabetes. (Lingman M et al. Am J Med 2011;124:265-75)

Paper III

All patients received reperfusion therapy. The median time from symptom onset to hospital admission was 1 hour and 15 minutes and to maximum STVM 3.5 hours, after which STVM decreased. (Figure 1 and Table 2 in paper III) However start of fibrinolysis and primary PCI took place 1.5 to 2 hours before this. After 6 hours from symptom onset STVM reached its minimum.

The T vector turned towards the ischemic area. When comparing depolarization and repolarization parameters at maximum and minimum STVM both differed significantly, but the largest differences were observed regarding different aspects of ventricular repolarization (VR). (Table 2 in paper III)

The Tp-e and QTc intervals were longer and Tp-e/QT larger and both the QRSarea and Tarea were larger at maximum STVM. This was true for the T area in particular. Also other measures of VR dispersion than Tarea and Tp-e were much larger at maximum STVM including VG and Tavplan. The QRS-T angle increased after the most acute ischemic phase.

Paper IV

During 30 months follow-up 12% of the patients died. Almost half of them died from SCD. Among those with non sudden deaths about half were cardiac.

SCD victims were older and had a heavier vascular disease burden as compared with survivors. They were in a worse clinical state upon arrival at the hospital. Their LVEF was almost 10% -points lower than that of survivors. Their final diagnoses at hospital discharge did not differ from patients alive at 30 months.

The magnitude of depolarization forces was larger in SCD victims than in survivors but its duration was not longer. The main direction of repolarization forces pointed in a more upward direction in the SCD group, but its magnitude was smaller as was the VG. The duration of repolarization did not differ when heart rate corrected. The QRS-T area angle was larger in SCD victims. T loop morphology measures did not differ when they were corrected for heart rate. These results remained in univariate regression models where the QRS-T angle and QRS-T area angle had the highest hazard ratios. When adjusting for possible VCG confounders and LVEF the QRS-T angle and the QRS-T area angle remained as independent predictors of SCD. (Table 2 in paper IV)

Based on the receiver operating characteristic (ROC) curve analysis the optimal discriminating value of QRS-T area angle was identified to be 112°. This discriminating value was used to calculate the negative predictive value (NPV) and the positive predictive value (PPV). They were 98% and 13% respectively. The generally accepted LVEF $\leq$35% was used as a discriminator in a separate calculation generating a NPV of 95% and a PPV of 18%.

According to Akaike information criteria, the model including the QRS-T area angle tended to be a better approximation for the risk of SCD than the one including LVEF implying QRS-T area angle to be the better predictor.

The sensitivity was higher for QRS-T area angle while the specificity was higher for LVEF. A combination of LVEF and QRS-T area angle improved risk stratification (data in paper IV).

Discussion

In this thesis we investigated prognostic aspects in patients suffering an ACS. In the first two papers hypertension and diabetes were the foci of interest and we investigated their prognostic importance separately and when combined. In the last two papers focus was turned to electrophysiological markers. The third study was carried out to increase knowledge about the depolarization and repolarization reflected during the acute phase while paper IV investigated the prognostic importance of selected electrophysiological markers when measured after the most acute phase. Below I argue that diabetes is a more important risk factor than hypertension after ACS and that transient alterations in repolarization during acute myocardial ischemia might explain why VF is a transiet risk factor only, in ACS survivors, while altered spatial relationship between depolarization and repolarization forces (not seen during the first hours of ischemia) predicts SCD. The latter makes me question the implantations of primary preventive ICDs in patients with low LVEF but small QRS-T area angles.

Hypertension and diabetes

Main findings

In the first paper in the present thesis I present a prospective study of ACS where patients with a history of hypertension or diabetes or both had a higher mortality rate during a median follow-up of eight years as compared to patients without such a history.

Diabetes was the most important risk factor with a small additive effect from hypertension. Interestingly a history of the risk factors diabetes and hypertension affected prognosis more than the ECG-based final diagnosis. Diabetes affected the all-cause and cardiovascular mortality rate immediately while the adverse effect of hypertension appeared two years after the ACS. This information is not retrieved in short term studies. The impaired long-term prognosis among patients with diabetes and hypertension appears to be related to a more widespread coronary artery disease, according to the angiographies in a subset of patients.

This thesis´ second paper reinforced the picture regarding diabetes from paper I. In this study we assessed the importance of hypertension and diabetes in relation to the prognosis after PCI in a large (40,000) cohort. We found that prognosis of diabetic patients, especially with concomitant hypertension, was much worse

than that of the reference population in terms of mortality, new cardiovascular and cerebrovascular events, and CHF, even after adjusting for relevant background variables. The short-term mortality was higher in diabetic patients. Ten percent of diabetic patients with hypertension died within 30 days of an acute PCI performed for an STEMI. In patients with UAP and STEMI hypertension alone increased the risk of a cardiovascular event.

Overall we conclude that diabetic and hypertensive patients suffering an ACS constitute an older population that is already afflicted by cardiovascular complications from the start. As a group they have a more wide-spread CAD and a poorer long-term outcome after PCI with the main adverse effect of diabetes.

Paper I and II put into perspective

Paper II confirms the high mortality rates during follow-up after PCI reported by Williams et al. in 2006.[134] After adjustment for baseline differences, our diabetic population ran an increased risk of dying during follow-up (HR 1.43; 95% CI 1.24-1.64), which was comparable to that described by Mathew et al. in 2004.[135]

Previous studies on hypertension as a risk factor have shown that hypertensive patients, in low risk cohorts, run an increased risk of cardiovascular morbidity.[136,137] Furthermore hypertensives have a poorer outcome after acute coronary events according to some studies,[46,47,138] also in patients with co-existing diabetes in the 1-year perspective.[139] Therefore our hypertension-related results in paper I were expected and confirmative while, and as opposed to paper I, the results from paper II could not convince us that hypertension is an independent risk factor for death after a coronary event. This result was supported by Ali et al. in 2004.[49]

On the other hand we could confirm that (often treated) hypertension increases the risk of stroke in the long term, but it seems to be conquered out by diabetes as a main risk factor for this cerebral insult. Also, in contrast to diabetes, hypertension accounted only for a small contribution of risk of admission for CHF after adjusting for relevant confounders. It is well known that diabetes is a more important risk factor than hypertension for CHF in low risk cohorts.[140]

Equally interesting was the finding that STEMI did not indicate a risk higher than that of non-STEMI on the long term. Similar data were reported by Sinnaeve et al. 2009 indicating that the STEMI group does not have a higher mortality than non-STEMI after 6 months.[141] This implies that other factors

should be used when assessing long term prognosis. The prognostic importance of diabetes, especially in non-STEMI ACS, was supported by somewhat later data presented in 2007 by Donahoe et al. who still identified a short term importance of the subtype of ACS.[21] A STEMI remains as a risk indicator regarding 30-mortality. Diabetes and possibly hypertension should be included in scoring systems for long term prognosis.

Diabetes and hypertension complicate diagnostics. The symptoms of myocardial ischemia are known to be more diffuse in the diabetic patient and silent myocardial injuries are common.[142] In our studies diabetic and hypertensive patients with no signs of acute ischemia on ECG still had a large percentage of non ischemic pathologies on ECG. On ECGs indicating ischemia the presentation was less often an ST-elevation. The distribution by subtype of ACS within the ACS spectrum reported by us was similar to that reported Sinnaeve et al.[141]

The reason for the adverse effect of diabetes on coronary events in post PCI patients is partly known. For example diabetic patients have an increased risk of stent thrombosis and they respond more poorly to clopidogrel.[143] Apart from death diabetes increased risk of AMI in patients with known CAD in our work. In addition we report that restenosis is more common in the diabetic group. Along with the known adverse effects of diabetes the wide spread CAD might contribute to the association between diabetes and hypertension on the one hand and the requirement for CABG on the other.

Electrophysiology and the ACS

As stated ECG markers of altered repolarization is associated with SCD. Recent reports add that temporal dispersion of depolarization in CAD patients seems to be involved in the process of SCD [144] although the idea has met some criticism.[145] On the other hand increased dispersion of repolarization, also due to acute ischemia, has been linked to ventricular arrhythmias.[94,95] We continued work to identify electrophysiological markers of both depolarization and repolarization that can be measured with acceptable feasibility in the clinical setting.

Electrophysiology in the acute phase of ischemia

In paper III we assessed the electrophysiological alterations associated with ongoing AMI. Like in most previous experimental and human studies we focused on ischemia in the (anterior) region supplied by the LAD due to its known association with arrhythmogenicity and to worse outcome including SCD.[146,147] We used non-invasive continuous VCG recorded with the modified Frank orthogonal lead system. VCG reflects the global electrical conditions at each moment in time registered and has proven to be a suitable method for following ST and QRS vector changes during acute ischemia.[148,149] STVM was used as a dynamic reference marker of the degree of ischemia. The deviation of the ST-segment from the isoelectric line on ECG is considered to represent acute myocardial ischemia and the magnitude of the deviation represents the extent of ischemia or myocardium at risk.[150] The STVM dynamics correlate with the degree of ischemia during coronary artery occlusion.[151] Anterior ST-elevations identify the LAD as the culprit artery with good certainty.[152] We took interest in the early part of ischemia development. During the time span studied a natural course support an on-going occlusion of the coronary artery in a vast majority of patients.[153,154]

We found that VCG parameters reflecting ventricular repolarization showed larger variations than VCG parameters reflecting depolarization related to the STVM development. Importantly global markers of repolarization dispersion (Tarea) and of dispersion of AP morphology (VG) showed the largest variations in the acute phase. This pattern was consistent with ECG derived reflections of ventricular repolarization such as Tp-e and Tp-e/QT. The VG did not vary because of alterations in depolarization.

The results imply that ischemia affects repolarization transiently during the occlusion-reperfusion process while the effect on depolarization was limited. The transient nature of the repolarization alteration might be an explanation why ventricular fibrillation is not a prognostic marker in survivors of the acute ischemic phase as described by Demidova et al. (*accepted*).

The results of paper III state that acute ischemia affects repolarization followed by altered depolarization. Altered repolarization in the acute phase might be the link between acute ischemia and VF and even the portion of SCD associated with acute ischemia where the cardiac arrest is initiated with a VF.

Paper III put into perspective

Recent results from our group show that VG, Tarea and Tamplitude decrease with increasing heart rate, while Tavplan is not heart rate dependent.[131] In paper III the difference in heart rate was so small that it cannot explain the large differences in most other VR parameters.

We found that the bulginess (Tavplan) of the T loop was higher at maximum STVM. In a porcine occlusion-reperfusion model Tavplan was an independent risk factor for ventricular fibrillation.[122] The results are consistent with observations during short-lasting occlusion of the LAD.[121] Other variables such as Tp-e and Tp-e/QT strengthened the view that dispersion of repolarization varies along with ischemia development. Increased Tp-e has been associated with ventricular arrhythmias in high risk patients with organic disease and increased Tp-e/QT has been associated with SCD in certain patient groups.[100,101,155,156] As pointed out in a recently published review post repolarization refractoriness is also an important factor in arrhythmogenesis during acute ischemia but it is probably not reflected by VCG parameters. [82]

From magnetic resonance imaging work by Hedström et al. we know that by the time our group of patients showed evidence of maximum STVM almost 50% of the ischemic myocardium at risk was infarcted.[157] Notably in paper III, maximum STVM was observed one hour after reperfusion therapy was initiated, which is in line with results from the porcine occlusion-reperfusion model, in which the STVM peak during reperfusion was higher than during occlusion.[122] In humans an increase in STVM shortly after reperfusion can occur [158] and it might indicate a larger myocardial injury.[159]

Electorphysiological prognostic markers after an ACS

In paper IV we used the same VCG method as in paper III. Paper IV showed that the QRS-T area angle assessed after the acute phase is a predictor of SCD in patients surviving an ACS. The prognostic information is comparable to and not dependent of that of LVEF dichotomized at ≤ 35% which is recommended for risk assessment in patients with heart failure and selection of candidates for primary prophylaxis with an ICD.[114] Also a smaller VG was seen among SCD victims. This difference was explained by differences in the QRS-T angle and QRS measures and not so much by alterations in repolarization in the late stable phase analysed. Thus altered depolarization, mirrored as a higher QRS area, after an episode of myocardial ischemia affects prognosis negatively as opposed

to repolarization. The alteration of depolarization was merely spatial while it was temporal to a small degree only.
In contrast to previous papers using the QRS-T angle we focused on the QRS-T area angle because its reproducibility with coefficients of variation of 45 vs 15% (Bergfeldt, unpublished data). The strength of the QRS-T area angle lies in the narrow angle implying a low risk (high NPV) but on the other hand it identified too many as high risk (low PPV). The QRS-T area angle and the QRS-T area identified 2 out of 3 SCD while the widely used LVEF (≤ 35%) identified only 1 out of 3 SCD victims. The high NPV gives the doctor a chance to reassure the correct patient of their low risk of SCD during the coming 2.5 years. A low LVEF seemed to be a better predictor of cardiac death in a broader sense.

Choice of method when predicting SCD and rationale of paper IV
One important question when trying to predict SCD is what we can expect from a method that identifies risk of arrhythmic death. This is not clear due to the imminent difficulties concerning the concept of SCD. Since electrophysiological as well as more mechanical parameters, such as left ventricular function and LVH all are independently associated with SCD, the mechanisms behind the event might be multiple.[160] A risk stratification strategy that might be able to combine different pathological findings has also been requested,[161] but such a risk score should only include paramaters that contribute to its predictive value in a relevant way. In our work adding the QRS-T area angle to the LVEF in the model predicting SCD increased the AUC significantly.
There is reason to believe that we underestimate the number of AMI when adjudicating the patients cause of sudden death.[162] On the other hand we might overinterpret the importance of an infarction if the immediate cause of death is the arrhythmia triggered by the infarction, in which case an underlying susceptibility to arrhythmia is of great interest. Findings from Pouler et al. in 2010 [163] indicate that the relative impact of AMI vs arrhythmia changes over time after a coronary event with arrhythmia being more important in later stages (> 3 months) post AMI. In 2001 Huikuri et al. concluded that we lack markers of increased risk of death from arrhythmia.[61] Among patients in whom ICDs are implanted only a minority will benefit from the treatment. Even if the MADIT-II and SCD-HeFT criteria are applied only 1 in 5 patients will receive an appropriate chock.[164] Therefore there is also a need to refine the selection of patients most likely to benefit from treatment. Our group and others have taken interest in SCD in an electrophysiological context. For obvious reasons an invasive measurement of dispersion of repolarization is not feasible in a clinical

setting. Non-invasive methods must be developed but so far tested descriptors of altered electrophysiology have had only limited predictive power in risk populations [165] and implantation of ICD based on risk stratification has not been successful.[166] Today there is a lack of instruments helping us to pinpoint who will have a fatal arrhythmia even in high risk populations.[167] The ICD´s are mainly implanted in patients with failing left ventricular function as a risk factor. Improved identification of people at risk could increase survival since SCD is partly preventable by ICD implantation.[71]

Paper IV put into perspective

Depolarization and repolarization are tightly interrelated. The spatial relation between depolarization and repolarization vectors has been studied by others. Kenttä et al used 12-lead ECG derived vectors when reporting an association between the QRS-T angle and SCD if corrected for heart rate in a cohort with lower risk than ours.[168] Retrospective measurement of this angle was associeated with future ventricular arrhythmias and mortality in a small post AMI cohort.[125] The temporal dispersion of depolarization is also a current focus of interest. Data on the prognostic value of the QRS interval is increasing. Recently Lund et al. reported that QRS duration is associated with all-cause mortality regardless of LVEF.[96] In a general population QRS duration was associated with SCD,[169] which was also the case in persons with CAD.[144] The results from paper IV indicate that QRS duration is associated with cardiac death but not with SCD specifically. On the other hand other measures quantifying dispersion of depolarization (QRS amplitude and the QRS area) implied increased risk of SCD.

In paper IV we could not confirm a predictive value of the Tp-e interval in this clinical setting. Nor did the heart rate corrected QT interval come out as a discriminator between high and low risk patients.

At this point, with the results of paper III and IV at hand and with support from previous studies, we can conclude that there is a prognostic value in QRS and QRS-T alterations not seen during the acute phase of ischemia.

Gender aspects

None of the present studies were primarily designed to identify sex differences of the end-points. All studies included men and women but the included patients

were not equally distributed between the sexes. In the cohort studied I, III and IV the largest proportion of women was found in the group with the highest morbidity and age. The pattern was repeated in the SCAAR database. Results in papers I, II and IV were corrected for these differences in background variables.

Methodological aspects and limitations

AMI diagnosis

In our work we have examined patients with diagnoses where treatment has evolved dramatically over the last decades. For example the diagnosis of AMI is currently based on troponins rather than CKmb as in our work. In addition the diagnostic cut-off of troponin has gradually been lowered. However the fact that the STEMI diagnosis is still based on ECG criteria ensures relevance in a contemporary setting.

Diabetes and hypertension diagnosis

We used "known" hypertension and "known" diabetes as diagnostic criteria. Consequently the patient´s hypertension or diabetes was diagnosed by previously consulted doctors based on clinical data not evaluated by us. Since inclusion in paper I spanned over several years, during which the definitions of hypertension and diabetes were tightened, other definitions than "known" disease would not have been feasible. Defining diabetes by measured blood glucose level, and hypertension by the blood pressure level in the acute setting would have been subject to justified criticism. Also we did not differentiate between type 1 and type 2 diabetes. Previous reports [170] indicate that there might be a significant number of patients with high blood pressure without a diagnosis of hypertension. One can assume that some patients have been adjudicated to the wrong group due to existing diabetes and hypertension that simply had not been diagnosed and therefore were not "known". If all patients would have known about their diabetes or hypertension and thereby correctly adjudicated, differences between groups would probably have been greater. Especially since patients with known hypertension or diabetes seemed to be well treated.

Blood lipids

Lipid levels measured during the acute phase were not investigated as potential prognostic markers or confounders. The rationale for this was that the long term

prognostic impact of lipid depend more on the steady levels of lipids reached after start on secondary prevention than on single values in connection with the AMI, which are falsely low due to the acute inflammatory reaction. Also the numbers of missing values were high.

Revascularization
Regarding treatment of STEMI the fibrinolytic approach is rare in urban settings of today. In fibrinolytic therapy one has to rely on ECG markers to identify successful reperfusion which creates some degree of uncertainty.

"Snap shot measurements"
Making a prediction of the future based on values measured at a single time point does not take into consideration dynamic entities such as electric or anatomic remodelling. In the prospective papers in this thesis the dynamics of variables were not accounted for.

LVH and myocardial scarring
A limitation worth noting is that no data on LVH was available in our patients. In previous studies, however, hypertension and obesity were correlated with LVH and an aggravated clinical presentation of coronary heart disease [171] (although this is still a subject of debate [172] when it comes to the short-term prognosis). According to one study on ACS, LVH was a risk factor for one-year mortality in women but not in men.[173] The lack of data on LVH also limits the understanding of the impact of the QRS-T angle since they are in part interrelated (LVH is associated with a wider angle) [174] and the fact that the VCG response to ischemia is greater in hypertensive patients might affect our results in a way that we cannot give an account for. Pre-existing myocardial injury was only taken into account in one of the studies (paper IV) by the surrogate marker LVEF which only roughly reflects this risk factor.

Narrow inclusion and delayed start of registration
In order to be able to compare clinical data to the experimental settings with LAD occlusion we chose narrow inclusion critera in paper III. The patient group studied had been subject to selection since they all had survived the most acute phase of myocardial ischemia. In future studies this could in part be avoided by starting VCG registrations already when the ambulance arrives on scene at the patient´s side. Pre-hospital VCG could teach us more about the very first phase

of ischemia. The delayed initiation of the start of registration, passed the hyperacute phase of ischemia, unabled us to confirm that early acute T waves with high amplitudes were reflected in the VCG by high Tamplitude.

Global measurements only
The VCG (like ECG) as a method of identifying substrates for re-entry phenomenons and fibrillation is limited to some degree by the fact that it is not expected to reflect post repolarization refractoriness. Identification of global dispersions, by VCG, might rather enable us to single out patients with high risk of VF since re-entry loops maintaining VT can be small and result from minor disturbances not mirrored in global measurements. Vectorcardiography is a simple way to retrieve a 3-D representation of the electrical activity in the heart, but several others exist.

Beat-to-beat variability
Several non-invasive electrophysiological methods of assessing disturbances in ventricular repolarization have been evaluated including temporal QT variability [107] and T wave alternance,[110] which, however, have proven to be of limited value when low to intermediate risk patients have been examined. But hope of a prognostic value in these markers remains. In our work we could not relate to the mentioned markers since the technique used for VCG registration at the time of inclusion did not allow beat-to-beat analysis, but this additional function has now been developed.

Clinical implications

Treating hypertension and diabetes is important. Our data indicate that the importance of hypertension increases after the first two years after an ACS and that the prognostic impairment of hypertension might be reduced by an intensified anti-hypertensive treatment after an ACS as indicated in other studies, but first and foremost there is room for improvement regarding risk reduction among diabetic patients.[175]

The VCG markers of increased SCD risk are likely to be reflections of ischemia induced alterations in ion currents and cell-to-cell coupling. In paper IV mechanical aspects were reflected only by LVEF which is a rough measure of myocardial injury (or preservation) with a low ability to separate high from low risk patients. Most patients suffering a SCD have preserved LVEF. There is a

need for complementary approaches along with morphologic description of myocardial injury in the clinical setting to identify high risk patients. VCG can be one way to improve risk stratification. The present results should stimulate further investigation of the electro-mechanical complex as a link between structural and electrophysiological function to improve the identification of patients who might benefit of preventive measures such as ICDs alternatively is at such a low risk that there is no gain from such a device.

Conclusions

Paper I

Patients with ACS and a history of hypertension and diabetes have a higher age-adjusted mortality risk during long-term follow-up than non-hypertensive, non-diabetic patients. More widespread coronary artery disease is possibly one contributory factor. The increased risk of death appears to be particularly associated with diabetes. Among hypertensive patients, the mortality risk appears to increase after two years. The presence of risk factors such as diabetes and hypertension appears to be more strongly associated with long-term outcome than STEMI vs non-STEMI.

Paper II

This study showed that diabetic patients still run a high risk of a negative outcome after a PCI, especially when combined with hypertension. Our data imply that even greater efforts are needed to improve prognosis, and recent data show that post-intervention protection can be further improved. When treated with modern pharmacotherapy, hypertension does not seem to be associated with a higher mortality rate after PCI when it is not associated with diabetes. However, patients with hypertension run an increased risk of AMI, stroke, and CHF after PCI.

Paper III

VCG is a suitable method for following the electrophysiological events during an AMI in humans. The occlusion-reperfusion process was accompanied by modest depolarization but profound repolarization alterations, including greatly increased dispersion. The alteration of repolarization was transient and may therefore explain why VF is a transient risk factor only during the acute phase of an ACS.

Paper IV

A wide QRS-T area angle measured by VCG during an early but stable phase after an ACS pointed out patients with an increased risk for SCD. This angle might become a future complement to LVEF in risk stratification in high risk patients if confirmed in larger studies.

Future directions

Methodologically more information could be extracted from the VCG. It has already been improved by providing beat-to-beat analysis. Irregularities of the T loop were assessed in relation to a preferential plane but extraction of information could be increased by relating the T loop to a preferential loop in 3 dimensions. Also it would be possible to differentiate the speed and duration of the efferent part of the T loop.
Furthermore a detailed assessment of the relation of VCG variables and left ventricular mass using MRI could teach us more about the increased vulnerability in patients with LVH. A VCG study on patients carrying ICDs would probably shed light on risks of malignant arrhythmias and maybe confirm the QRS-T area angle as a risk factor. Starting VCG registration already on the arrival of the ambulace at pick-up would deliver information about the earlier phase of ischemia and its effects on electrophysiology. A study on pacemaker patients on betablockers with atrial pacing could inform us on the hypothesis that a modestly increased heart rate (at least in non CHF patients) might protect against VF and why it would be so.
Another interesting route in research would be to identify pharmacological agents that inhibit the increase of dispersion of repolarization as they could in theory have a preventive effect on VF related to ischemia. The results from paper IV lead to a hypothesis that drugs narrowing the QRS-T area angle could alos have protective effects against SCD.
Also testing the potentially preventive effect of antiarrhythmics reducing ischemia´s effect on repolarization could confirm the role of dispersed repolarization in SCD.
In future studies it might be settled whether a narrow QRS-T area angle can identify low risk of SCD in a patient pointed out by LVEF to have a high risk.

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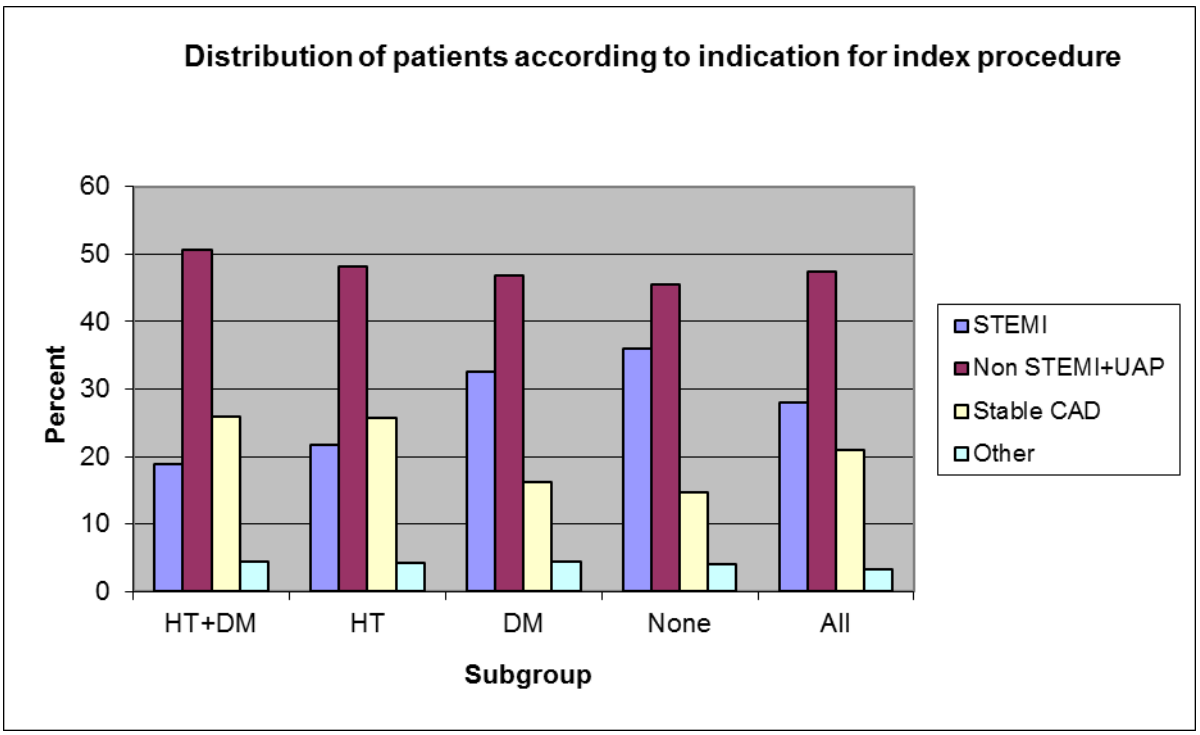
Korrigendum from original papers

Paper II, Figure 1



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