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Electrocardiographic predictors of clinical outcome in ST-elevation myocardial infarction

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Abstract

Malignant ventricular arrhythmias, particularly ventricular fibrillation (VF), remain an important contributor to mortality in ST-elevation myocardial infarction (STEMI). The size of myocardial injury is one more important factor influencing the prognosis of STEMI patients. The search for new non-invasive markers, which can be relatively simply calculated using conventional ECG recording and can predict the degree of myocardial injury and impending VF, is promising. This work is aimed at investigating cardiac repolarization and depolarization abnormalities and predictors and prognosis of ventricular arrhythmias during the course of STEMI.

The thesis is composed of the experimental part (Studies I, II, III) and clinical register-based retrospective studies (Studies IV and V). Closed-chest porcine model of myocardial infarction (MI) was used in the experimental part. Occlusion of left descending artery (LAD) lasted 40 minutes and was followed by reperfusion, and ECG was continuously recorded. QRS-duration and morphology, dynamics of ST-segment and T-wave alternans (TWA) were calculated, and myocardial area at risk (MaR) and infarct size (IS) were assessed. Predictors and prognostic impact of early VF in STEMI was assessed in a register-based study of 1,718 consecutive patients admitted for primary PCI during 2007-2009 who were followed up for one year.

In experimental MI, the maximal level of TWA during occlusion period was associated with both MaR and IS (Study II). Rapid and marked transient increase in QRS duration associated with appearance of J-wave pattern predicted impending VF in acute ischemia (Study III). Restoration of blood flow in infarct-related artery was accompanied by reperfusion peak in all animals, and the magnitude of ST elevation at reperfusion peak was associated with infarct size (Study I). In clinical studies IV and V, the risk of VF in acute period of STEMI was higher in patients with MI history, cardiovascular risk factors such as smoking and left main stenosis, resulting in a large infarct area. Besides MI history and left main stenosis, the risk of VF at reperfusion was associated with inferior localization of STEMI, hypokalemia, high ST-elevation and shorter symptom-to-balloon time. The magnitude of ST-elevation before PCI for STEMI independently predicted reperfusion VF. Patients successfully resuscitated after VF and alive at 48 hours had higher in-hospital mortality (12% vs. 2%, $p<0.001$). However, in VF patients who were discharged alive, 1-year mortality did not differ compared with patients without VF.

Key words: ischemia, STEMI, reperfusion, PCI, myocardial injury, ventricular fibrillation, J-wave, ECG

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Demidova MM, Smith JG, Höijer C-J, Holmqvist F, Erlinge D., Platonov PG

European Heart Journal: Acute Cardiovascular Care, 2012; 1(4): 302-311

Abbreviations

IS – infarct size

LAD – left anterior descending coronary artery

LCx – circumflex coronary artery

MaR – area at risk

MRI – magnetic resonance imaging

RCA – right coronary artery

SPECT – single photon emission computed tomography

STEMI – ST-elevation myocardial infarction

TWA – T-wave alternans

VF – ventricular fibrillation

Introduction

STEMI – the strategy on reperfusion therapy and individualized approach to risk stratification

The main treatment strategy in ST-elevation myocardial infarction (STEMI) is reperfusion therapy. According to guidelines, reperfusion therapy should be administered to all STEMI patients with symptom onset within the prior 12 hours (I-A) (1) (2), and to patients with symptom onset within 12-24 hours if there is evidence of ongoing ischemia (I-C) (1), (IIa-B) (2). Primary PCI is the recommended method of reperfusion with the goal of 90 minutes or less from first medical contact to balloon (2). If the patient cannot be transferred to a PCI-capable hospital, and primary PCI cannot be performed within 120 minutes of symptom onset, fibrinolytic therapy should be administered in the absence of contraindications (2). When fibrinolytic therapy is chosen as the primary reperfusion strategy, it should be administered within 30 minutes of hospital arrival (I-B) (2).

Immediate restoration of blood flow in infarct-related artery allows to save ischemic myocardium and to limit the necrotic area – the main factor related to prognosis in STEMI. Several studies have shown that infarct size is related to subsequent remodelling, systolic function and prognosis in myocardial infarction (3-5). Every minute of treatment delay in patients with STEMI affects prognosis, not only in thrombolytic therapy, but also in primary angioplasty (6-8). The risk of 1-year mortality increases by 7.5% for each 30-minute delay (9). However, the critical time of reperfusion delay varies considerably in different clinical situations. According to US National Registry of Myocardial Infarction, the critical PCI-related delay is <1 h for an anterior infarction in a patient <65 years of age presenting <2 h after symptom onset, and almost 3 h for a non-anterior infarction in a patient > 65 years of age presenting > 2 h after symptom onset (6). Thus, along with the need to keep within the tight time frame, current guidelines emphasize the importance of an individualized approach to risk stratification in STEMI patients.

The immediate prognosis in patients with acute myocardial infarction is related to the size of ischaemic myocardium supplied by the culprit coronary artery distal to the occlusion, amount of irreversibly damaged myocardium within area at risk, intensity

of ischemia and velocity of ischemia progression, the amount of myocardial reserves, and the presence of the remote ischemia (10). The size of the myocardium at risk depends on the type of coronary anatomy and localization of thrombotic occlusion. In most patients, a part of myocardium at risk is irreversibly damaged by the time of first medical contact. The following progression of ischemia and necrosis depends on collateral flow (11), preconditioning (12) and occlusion character – the presence of incomplete or intermittent occlusion (13). Area at risk is the main factor related to prognosis in patients without prior myocardial infarction and without multiple stenoses in coronary arteries. However, among patients with low myocardial reserves due to previous myocardial infarctions or diffuse fibrosis, even relatively small infarction may be detrimental. Moreover, among patients with advanced diffuse coronary artery disease, a small myocardial infarction may interfere with the delicate balance and induce ischemia in remote segments. Therefore, a need for individualised risk stratification requires the search of new non-invasive markers that can be used for early estimation of the size and degree of myocardial injury before reperfusion.

Reperfusion injury

Restoration of blood flow in infarct-related artery stops ischemic injury, but, paradoxically, causes additional tissue injury, which is called reperfusion injury (14). The concept of reperfusion injury was proposed by Jennings more than 50 years ago, when, in an experiment with isolated reperfused canine hearts, the myocardium after 60 minutes of ischemia-reperfusion corresponded histologically to the necrotic area caused by the 24-hours coronary occlusion (15).

Underlying molecular and cellular mechanisms of reperfusion injury are complex and include oxidative stress, mitochondrial permeability transition pore opening and mitochondrial damage (16-19), calcium overload (20), hypercontracture, apoptosis (21), inflammatory cascade activation (22), platelet activation (23), and endothelial dysfunction (24). Clinical manifestations include four types of cardiac dysfunction: the lethal reperfusion injury - cardiomyocyte death resulting in broadening the necrotic area, microvascular dysfunction, myocardial stunning, and reperfusion arrhythmias (25). Microvascular dysfunction or no-reflow phenomenon is defined as the inability to reperfuse a previously ischemic region due to the impedance of microvascular blood flow encountered during opening of the infarct-related coronary artery (26, 27). Presence of microvascular obstruction independently predicts complications even after adjusting to final infarct size (28-30). Myocardial stunning is a persisting myocardial dysfunction despite restoration of normal or near-normal coronary flow, which usually recovers after several days or weeks (31).

In searching for the ideal mode of reperfusion, modern guidelines emphasize the need to focus not only on fast restoration of epicardial flow, but also on cardioprotection. Simple non-invasive markers are needed for predicting and evaluating reperfusion injury.

Malignant ventricular arrhythmias. Predictors. Prognosis.

Malignant ventricular arrhythmias, particularly ventricular fibrillation (VF), remain an important contributor to mortality in STEMI and are the main contributor to out-of-hospital mortality (32). Ventricular tachycardia (VT) and VF occur during STEMI in 3%-6% (33, 34) to 10% (35). The risk of ventricular fibrillation is very high in the first hour or so after symptoms onset, and declines rapidly thereafter (36).

Success of VF treatment is determined by time elapsed from VF occurrence to administration of medical care. Therefore, the main strategy in relation to life-threatening ventricular arrhythmias during myocardial infarction is their prediction and prevention (37). Although several studies were performed aiming at predicting ventricular arrhythmias in STEMI-settings, the majority of the studies were performed before the routine use of reperfusion therapy or during the thrombolytic era. Data on predictors can be mostly attributed to clinical characteristics; however, some of them are still controversial.

The risk of VF in STEMI is associated with hypokalemia (33, 36, 38-42). The occurrence of VF in patients with hypokalemia was 17.2% in comparison with only 7.5% in normokalemic patients (38). In patients with hypokalemia VF occurs earlier after symptom onset than in patients with normokalemia (33, 38).

The risk of VF in STEMI is strongly associated with the presence and severity of heart failure (33, 34, 36, 43) and depressed ejection fraction (35). Therefore, the term "primary VF" has been introduced and defined as VF in the absence of heart failure. Despite an indirect link between VF and severity of ischemic injury, manifesting in systolic dysfunction and heart failure, the data on the association between VF and the size of myocardial injury in STEMI are scarce.

Available data on the association between VF and cardiovascular history and risk factors are controversial. The link between VF and the history of previous myocardial infarction was found in GUSTO-I (35) but not confirmed in the APEX AMI trial (34). The relationship between VF and hypertension (34, 35, 43), diabetes (34, 35, 43), chronic kidney disease (34, 43) and smoking (33, 34, 44) is controversial.

VF during acute STEMI markedly increases in-hospital mortality (45). In-hospital mortality was markedly higher in VF patients than in patients without malignant

arrhythmias before the reperfusion era (46) and during the thrombolytic era (35). It remains higher still in VF patients treated by primary PCI (43). However, studies performed before the reperfusion era or during the thrombolysis era stated that patients who survive to hospital discharge have a long-term prognosis similar to that of patients who do not experience life-threatening ventricular arrhythmias during the acute phase of STEMI (47, 48). Based on these studies, current guidelines do not advocate implantation of cardioverter-defibrillators (ICD) for survivors of VF during the first 48 hours of STEMI (37, 49). Whether this strategy is still valid today, when thrombolytics are replaced with more efficient percutaneous catheter interventions (PCI), is not fully understood.

Aims

The overall objective of this thesis is to investigate the predictive value of cardiac repolarization and depolarization abnormalities as well as the occurrence and type of ventricular arrhythmias during the course of ST-elevation myocardial infarction (STEMI).

The thesis is composed of the experimental part and clinical register-based retrospective studies. Methodologically different substudies address a common scientific problem in order to prove the value of experimental data in real clinical settings.

The specific aims of the included papers were:

- To assess the association between the ST-segment dynamics during reperfusion and myocardial injury in ST-elevation myocardial infarction (Paper I)
- To investigate the association between T-wave alternans (TWA) and myocardial injury in ST-elevation myocardial infarction (Paper II)
- To find predictors of impending VF in experimental myocardial infarction (Paper III)
- To reveal predictors of ventricular fibrillation at reperfusion in ST-elevation myocardial infarction (Paper IV).
- To assess the predictive value of early ventricular fibrillation in STEMI (Paper V).

Materials and methods

Experimental studies

The experimental model

Healthy domestic male and female pigs weighing 40-50 kg were fasted overnight with free access to water and were premedicated with Ketaminol (Ketamine, Intervet, Danderyd, Sweden), 100mg/ml, 1.5ml/10kg, and Rompun (Xylazin, Bayer AG, Leverkusen, Germany), 20mg/ml, 1ml/10kg intramuscularly 30 min before the procedure. After induction of anesthesia with thiopental 12.5 mg/kg (Pentothal, Abbott, Stockholm, Sweden), the animals were orally intubated with cuffed endotracheal tubes. A slow infusion of 1 µl/ml fentanyl (Fentanyl, Pharmalink AB, Stockholm, Sweden) in buffered glucose (25 mg/ml) was started at a rate of 2 ml/min and adjusted as needed. During balanced anaesthesia, thiopental (Pentothal, Abbott, Stockholm, Sweden) was titrated against animal requirements with small bolus doses. Mechanical ventilation was established with a Siemens-Elema 900B ventilator in the volume-controlled mode, adjusted in order to obtain normocapnia (pCO_2: 5.0-6.0 kPa). The animals were ventilated with a mixture of nitrous oxide (70%) and oxygen (30%). In order to adjust ventilation, analysis of arterial blood gases was performed before initiation of ischemia, at reperfusion, and one hour after reperfusion. Arterial blood pressure was measured using a blood pressure transducer (ADInstruments Inc., Colorado Springs, CO, USA).

Heparin (200 IU/kg) was given intravenously at the start of the catheterization. A 12 F introducer sheath (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted into the surgically exposed left femoral vein. A 0.021-inch guide wire (Safe-T-J Curved™, Cook Medical Inc., Bloomington, IN, USA) was inserted into the proximal inferior vena cava through the introducer. Using the guide wire, a 10.7 F Celsius Control™ catheter (Innercool Therapies Inc., San Diego, CA, USA) was placed into the inferior vena cava with the tip of the catheter at the level of the diaphragm. Body temperature was measured with a temperature probe (TYCO Healthcare Norden AB, Solna, Sweden) placed in the distal part of the esophagus. The catheter and the

temperature probe were connected to the Celsius Control, and the system was set to maintain a normal pig body temperature of 38.0° C (Figure 1).

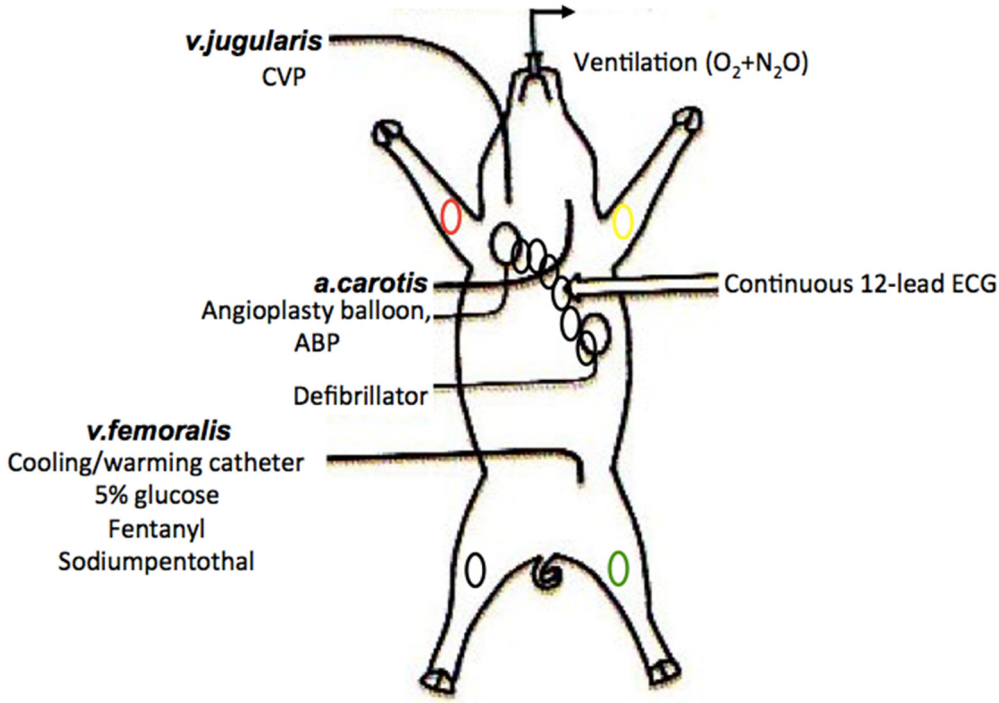

Figure 1
The experimental model. CVP- central venous pressure; ABP- arterial blood pressure. Adapted from (50).

A 6 F introducer sheath (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted into the surgically exposed left carotid artery; thereafter, a 6 F FL4 Wiseguide™ (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted into the left main coronary artery. The catheter was used to place a 0.014-inch PT Choice™ guide wire (Boston Scientific Scimed, Maple Grove, MN, USA) into the distal portion of the left anterior descending coronary artery (LAD). A 3.0-3.5 x 15 mm Maverick monorail™ angioplasty balloon (Boston Scientific Scimed, Maple Grove, MN, USA) was then positioned in the mid portion of the LAD, immediately distal to the first diagonal branch. All radiological procedures were performed at the Biomedical Center (BMC) at Lund University, Lund, Sweden using an experimental catheterization laboratory (Shimadzu Corp., Kyoto, Japan).

Experimental protocol

Ischemia was induced by inflation of an angioplasty balloon for 40 min. An angiogram was performed after balloon inflation and before balloon deflation in order to verify total occlusion of the coronary vessel and correct balloon positioning. ^{99m}Tc-tetrofosmin was administered intravenously at the 20th minute of occlusion for subsequent single photon emission computed tomography (SPECT). After 40 minutes of occlusion, the balloon was deflated, and a subsequent angiogram was performed to verify restoration of blood flow in the previously occluded artery. TIMI-3 flow upon balloon deflation was achieved in all animals. Experiment was terminated after 4 hours of reperfusion. Gadolinium-based contrast agent was administered intravenously 30 minutes prior to removal of the heart for subsequent magnetic resonance imaging (MRI). After 4 hours of reperfusion, the hearts were explanted, and *ex-vivo* SPECT for assessment of area at risk (MaR) and MRI for assessment of IS were performed (Figure 2).

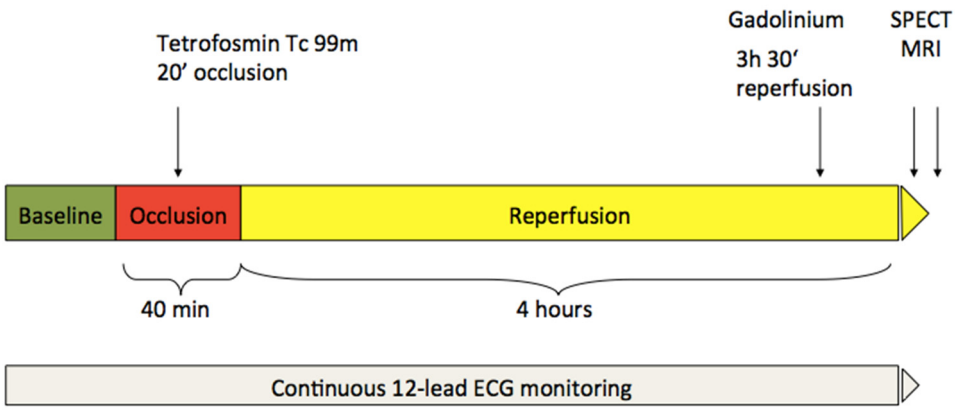

Figure 2
Schematic picture showing the experimental protocol.

In general, 38 experimental animals were involved in experiments performed according to the same protocol during 2009-2011. Of those animals, one pig died during the occlusion period due to thrombosis of the left main coronary artery, large infarction and instability of circulation. Three more experimental animals died during the reperfusion period due to recurrent VF. Imaging was performed on a total of 18 experimental animals. Study I is based on 15 experimental animals, Study II – on 23 experimental animals, and Study III – on 38 experimental animals.

The study conforms to the Guide for the Care and Use of Laboratory Animals, US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and was approved by the local animal research ethics committee.

ECG monitoring

Continuous 12-lead ECG monitoring ("Kardiotechnica-04-8m", Incart, St. Petersburg, Russia) was performed during baseline, occlusion and reperfusion periods. The use of the X-ray negative cable ("MAC LAB", USA) allowed continuous 12-lead ECG-monitoring in angiographic laboratory. The ECG sampling rate was 1024 Hz, and the amplitude resolution was 1.4 μV. Complete analysis of QRS morphology was performed automatically on all QRS complexes with subsequent manual control prior to ST segment analysis so that only QRS complexes of supraventricular origin were included for calculation of ST-segment deviation. The average signal level of 40-20 ms before onset of the QRS complex was referred to as the baseline.

ST segment deviation was measured automatically 40 ms after the J point for each QRS complex with subsequent hysteresis averaging-out. Averaging was based on 30 complexes, but QRS complexes with large deviations from the average were excluded from the analysis. Continuous analysis of ST segment recovery was based on all 12 ECG leads. Maximal ST elevation in a single lead with greatest ST segment elevation, as well as the sum of ST segment deviations (both elevations and reciprocal depressions) were assessed at baseline, during occlusion and reperfusion periods.

QRS-duration analysis

After applying an automatic wavelet-based ECG delineator (51) to precordial leads, beat-to-beat multilead QRS boundaries were computed. For each pig, QRS duration was computed on a beat-to-beat basis as the difference between QRS onset and QRS end marks along a 40-minute occlusion period. These series were then resampled by averaging QRS duration every 10 seconds.

For each animal, dynamic changes in QRS duration during the occlusion period were plotted as a function of time (Figure 3). To quantify QRS-widening, two indices were continuously assessed using a sliding window of 3-min duration: (1) a local QRS duration increase (delta QRS duration), and (2) a maximal absolute QRS duration. Delta QRS duration was calculated as the difference between the QRS duration of the last beat in the window and the narrowest QRS in the 3-min window (52).

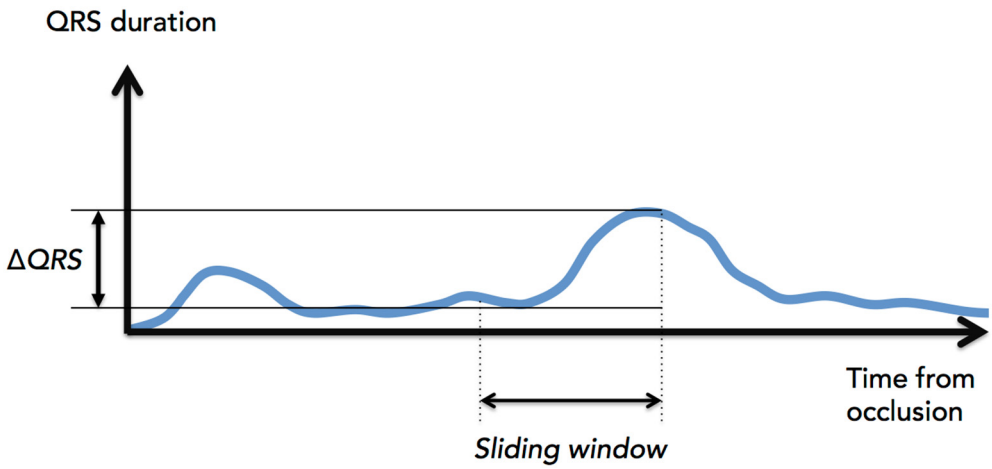

Figure 3
Schematic picture showing the delta QRS duration calculation in the sliding window during the occlusion period. In our study, the sliding window duration was 3 minutes.

QRS morphology analysis

ECGs for each pig at baseline and at the time of maximal QRS duration were independently reviewed for presence of QRS complex notching or slurring (J-wave pattern) (53, 54) in ≥2 contiguous leads by two observers, blinded to VF occurrence. Notching was defined as a positive deflection at the terminal portion of a positive QRS-complex. Slurring was defined as a smooth transition from the QRS-complex to the ST-segment with upright concavity (Figure 4) (54).

The conventional J-wave amplitude criterion could not be applied as the ST-segment was elevated due to complete LAD occlusion. We classified the localisation of the J-wave pattern as present either in the inferior (II, III, aVF), lateral (I, avL, V_4-V_6) or anterior leads (V_1-V_3). Anterior precordial leads reflecting the ischemic zone due to LAD-occlusion were not excluded from the analysis.

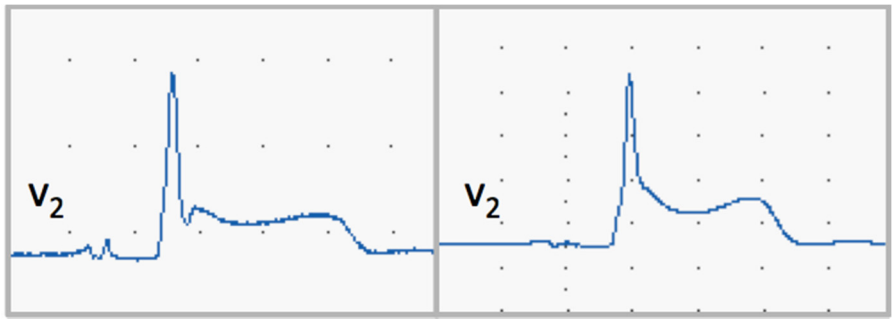

Figure 4
ECG examples in lead V2, illustrating different morphology of the ER pattern. A- notch is present in V2; B- slur is visible in lead V2, ST elevation due to myocardial infarction is present in both A and B.

TWA analysis

In each beat, an interval of 300 ms was selected for TWA analysis (including the ST-T complex). TWA analysis was performed using a sliding 32-beat signal window, applying a multilead processing scheme which uses the technique of periodic component analysis (πCA) for multilead ECG processing combined with the Laplacian Likelihood Ratio method (LLR) in order to detect and quantify TWA (55).

The πCA technique searches for the linear combination of the available leads, which maximizes the desired periodicity in the combined lead. For TWA analysis, we were interested in combining the leads in such a way that the 2-beat periodicity was maximized in the resulting signal. Using this technique, the 8 original independent leads (V1-V6, I, II) were converted into 8 transformed leads (T1. . . T8), where T1 is the lead that maximizes the 2-beat periodicity in the ST-T segment. In order to allow good tracking of the TWA, the optimal combination was obtained for each 32-beat segment, as it depends on how the alternant components and noise are distributed within the ECG leads.

It was shown previously that analysis of πCA-transformed leads allows detecting TWA episodes embedded in noise, which remain undetectable when they are analyzed in the original leads (55). Thus, we used the LLR method explained in (56) to detect and estimate TWA in each of the πCA transformed leads. TWA was considered to be present at the analyzed segment if it was detected in any of the transformed leads. To avoid spurious detections, only stable episodes with duration longer than 64 beats were considered. For segments where TWA was detected, the TWA was estimated in all πCA-transformed leads using the maximum likelihood estimate for Laplacian noise (56). The multilead TWA amplitude was then defined as

the sum of the root mean squared (RMS) values in all transformed leads. When no TWA was detected, the TWA amplitude was considered to be zero. To quantify TWA in the standard leads, we applied the inverse πCA transformation, after setting to zero all transformed leads where TWA was not found. We thus obtained a reconstructed version of the original signal, which kept the TWA content and its lead distribution essentially unaltered while discarding other non-alternant components (55). The RMS value of the TWA amplitude was then estimated in each standard lead using the LLR Method.

Imaging

Magnetic resonance imaging

Magnetic resonance imaging (MRI) was used for assessing final infarct size and delineating the endocardial and epicardial borders of the left ventricle for subsequent MaR assessment in co-registered SPECT images.

The method used to assess IS by MRI has previously been described in detail (57-59). In brief, a gadolinium-based contrast agent (Dotarem, *gadoteric acid*, Gothia Medical AB, Billdal, Sweden) was administered intravenously (0.4 mmol/kg) 30 minutes prior to removal of the heart. After removal, the heart was immediately rinsed in cold saline, and the ventricles were filled with balloons containing deuterated water. MRI was performed using a 1.5 T MR scanner (Intera, Philips, Best, the Netherlands). T1-weighted images (repetition time = 20ms, echo time = 3.2ms, flip angle = 70° and 2 averages) with an isotropic resolution of 0.5 mm covering the entire heart were then acquired using a quadrature head coil.

The endocardial and epicardial borders of the left ventricular myocardium were manually delineated in short-axis *ex vivo* images. This defined the left ventricular myocardium. The infarcted myocardium was defined as the myocardium with a signal intensity >8SD above the average intensity of the non-affected remote myocardium (58). The infarcted myocardium was then quantified as the product of the slice thickness and the area of the hyperenhanced myocardium. The IS was expressed as a percentage of left ventricular myocardium mass.

Assessment of myocardium at risk by ex vivi SPECT

Single photon emission computed tomography was used to assess the MaR as percentage of left ventricular myocardium. 1000 MBq of ^{99m}Tc-tetrofosmin was administered intravenously at the 20th minute of occlusion. *Ex vivo* imaging was performed with a dual head camera (Skylight, Philips, Best, the Netherlands) at 32 projections (40 s per projection) with a 64 x 64 matrix yielding a digital resolution of 5 x 5 x 5 mm. Short and long-axis images were reconstructed. The endocardial and

epicardial borders of the left ventricle that were manually delineated in the MR images were copied to the co-registered SPECT images (Figure 5). A SPECT defect was defined as the region within the MRI-determined myocardium with counts lower than 55% of the maximum counts in the myocardium, and expressed as a percentage of left ventricle mass, as previously described (60).

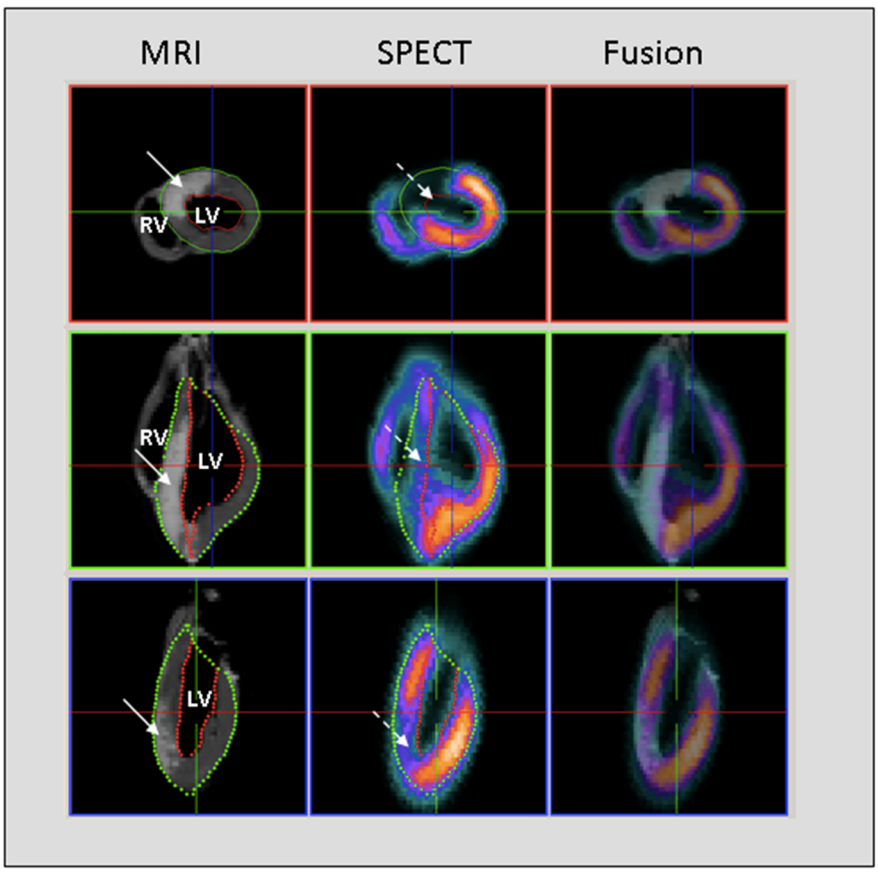

Figure 5
Imaging of myocardium at risk and final infarct size after experimentally induced ischemia by occluding the left anterior descending coronary artery. **Left column:** Magnetic resonance imaging (MRI) performed for visualization of anteroseptal infarction (solid arrows). Dark gray myocardium indicates viable myocardium, and white indicates infarction. **Middle column:** Single photon emission computed tomography (SPECT) used to assess the myocardium at risk by visualization of the anteroseptal perfusion defect (dashed arrows). Warm colors indicate adequate perfusion, and cold/absent colors indicate decreased/lack of perfusion. **Right column:** Fusion of MRI and SPECT images. The upper panel shows a mid-ventricular short-axis slice, and the lower two panels show two long-axis slices. Endocardial and epicardial borders of the left ventricle were manually delineated in the MR images and fused with the co-registered SPECT images. LV=left ventricle, RV=right ventricle.

Cardiac magnetic resonance (CMR) and single photon emission computed tomography (SPECT) images were analyzed using freely available software (Segment v1.700, Medviso, Lund, Sweden, http://segment.heiberg.se) (61).

Clinical studies

In order to assess the prevalence, timing, predictors and prognosis of VF in acute STEMI, we performed a retrospective, register-based single-site cohort study. The study population and relevant clinical information was identified from the Swedish National Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA). Detailed information about the RIKS-HIA registry is available at www.riks-hia.se, and long-term outcome studies using the Register data have been published previously (62-64).

All patients admitted to the Lund University Hospital with acute STEMI during a three-year period from January 1, 2007 to December 31, 2009, were included in the study. For patients with multiple admissions for STEMI during the three-year period, only the first admission was considered.

Patients who underwent cardiopulmonary resuscitation (CPR) or defibrillation for VT/VF during the period from symptom onset through discharge from the coronary care unit or upon in-hospital death, were identified from the RIKS-HIA Register. These patients' medical records were reviewed in order to: verify whether cardiac arrest was caused by haemodynamically unstable VT or VF (VT/VF); estimate the exact timing of arrhythmia with regard to symptom onset and PCI; and reconstruct the sequence of events that lead to VT/VF and defibrillation. Patients in whom VF or VT demanding defibrillation occurred within the first 48 hours of STEMI were identified as the VF Group. All other patients were identified as the No VF Group. VT/VF episodes after 48 hours from symptom onset were considered as study endpoints. In all patients with VT/VF during the index admission, series of electrocardiograms (ECG) were analyzed in order to exclude recurrent ischemic events as possible causes of arrhythmia.

Patients with VT/VF were divided into three subgroups based on the time point of arrhythmia with regard to reperfusion: the first group with VT/VF occurring before the opening of the infarct-related artery (IRA), including both pre-hospital and in-hospital VT/VF; the second group with VT/VF during reperfusion defined as VT/VF occurring during the period from IRA opening to the end of the PCI procedure; and the third group with VT/VF occurring after PCI.

Angiographic characteristics were determined from the Swedish Coronary Angiography and Angioplasty Register (SCAAR). The Register contains information

from all centers performing coronary angiography and PCI in Sweden, and has been described previously (65, 66). Information on implanted cardioverter-defibrillators (ICD) for primary or secondary prevention was obtained from the local hospital register. Medical records were reviewed for occurrence and adequacy of ICD therapy including shocks and antitachycardia pacing.

The study was approved by the Regional Ethics Committee in Lund (# 2010/585, 2010-11-29).

The primary endpoints were in-hospital death; death from any cause at 1 year (total mortality); and a combined endpoint including death from any cause, VT/VF, or appropriate ICD therapy at 1 year.

In total, 1718 consecutive patients admitted for primary PCI during 2007-2009 comprised the study group (Study V), mean age was 66 ± 12 years, 70% males. The population included 61 patients (3.6%) who received pre-hospital CPR, 54 of whom had ongoing mechanical chest compressions with the LUCAS device (Jolife AB, Lund, Sweden) upon arrival at the catheterization laboratory.

To assess the predictors of VF at reperfusion because of their low prevalence, the population was expanded to include all cases of reperfusion VF that occurred during the 6 year period from 2007 to 2012 (Study IV). During this period, 3724 patients were admitted for primary PCI. All patients who suffered from VF at reperfusion during 2007-2012 comprised the rVF group, and 614 consecutive patients without arrhythmias admitted during 2007 were taken as controls (No rVF group).

In the study on the predictors of VF at reperfusion (Study IV), we looked not only for clinical, but also for ECG predictors. ECG stored in digital format in either the GE Marquette MUSE system (GE Medical Systems, Milwaukee, Wisconsin) or in the Infinity MegaCare ECG Management System (Dräger, Lübeck, Germany) databases were analyzed for predictors of VF during reperfusion. We looked for the admission ECG and for a historical ECG that recorded a prior coronary event.

A previously recorded standard 12-lead ECG unrelated to STEMI available for interpretation was defined as the historical ECG. The most recent ECG was used for analysis if several historical ECGs were available. Apart from standard criteria (P, PR, QRS, QT, QTc intervals, presence of right or left bundle branch block (RBBB/LBBB)), we analyzed the presence of J-point elevation at least 1mm above baseline in two contiguous leads – either inferior or lateral.

An ECG recorded after onset of STEMI but prior to coronary intervention was defined as the admission ECG. If several ECGs were recorded prior to PCI, the latest ECG was considered to be the admission ECG. When in-hospital ECG prior to PCI was not taken or not saved in the database, pre-hospital ECG was taken. ECGs with paced rhythm were excluded. ECGs with complete RBBB/LBBB were excluded from analysis of parameters characterizing ventricular repolarization (i.e. ST-level, QT,

QTc). On the basis of the admission ECG, the maximal ST elevation in a single lead with the most prominent elevation (STmax), the sum of ST-deviations in all 12 leads (sumST), including ST-elevation and reciprocal depression, as well as Anderson-Wilkins (67) and Sclarowsky-Birnbaum (10) scores were calculated.

In brief, the Anderson-Wilkins acuteness score (67) takes into account the presence of abnormal Q-waves to the Selvester QRS scoring system (68) and the morphology of T-wave, classified as tall, positive, flat or negative. The acuteness of each standard lead with ST-elevation is classified from no points to 4 points; threafter the total sum in all leads is divided by the number of leads involved in order to correct for the overall extent of myocardial involvement. The Sclarowsky-Birnbaum score (10) assesses depolarization changes during ischemia progression. Tall peaked T-waves are classified as grade I ischemia; ST-elevation is present at grade II; and changes in the terminal part of the QRS complex appear at grade III ischemia. Criteria for grade III include disappearance of S-waves in leads with Rs configuration and J point/R ratio ≥ 0.5 in leads with qR configuration.

Statistics

Normally distributed data are presented as mean values ± standard deviations. Median and interquartile range (IQR) are used in cases of asymmetrical distribution. Statistical significance was accepted at 2-sided $p<0.05$. Clinical factors were compared across groups using chi-square or Fisher's exact test for categorical variables and Student's t-test for continuous variables with an approximate normal distribution, or non-parametric tests, as appropriate.

The Pearson correlation was used to assess relationships between repolarization indices and indices of myocardial injury (Studies I and II).

Receiver operator characteristics curve analysis (ROC curve analysis) was used to identify the optimal cut-off of QRS duration increase for predicting VF during the occlusion period in the experiment (Study III).

In order to identify clinical factors associated with VF (Studies IV and V), relevant and significantly associated covariates were evaluated in univariate logistic regression models with estimation of odds ratios and likelihood-ratio tests. In order to determine independent factors of risk, clinical factors significantly associated with VF in univariate models were included in a stepwise regression analysis with backwards elimination.

The prognostic impact of successful resuscitation for VT/VF during the first 48 hours after onset of ST-elevation myocardial infarction was evaluated from survival

functions calculated using the Kaplan–Meier estimator. Groups were compared using the log rank test (Study V).

All statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, Il, USA).

Results

The size of myocardial injury and ECG predictors (Study I and Study II)

In all experimental animals an anterioseptal infarction developed as a result of LAD occlusion. The MaR was 40±9% (range 28-57%), and the IS was 23±7% (range 10-40%) of the left ventricle.

ST dynamics during occlusion and reperfusion. Reperfusion peak.

ST elevation occurred immediately after balloon inflation and reached its maximum 307±101 seconds after the start of occlusion. The greatest ST elevation was recorded in lead V_2 or V_3 corresponding to the anterioseptal area. The maximal ST elevation during the occlusion was 920±420 μV in a single lead, with the greatest ST elevation (V_2 or V_3) and 2620±1490 μV in the sum of leads with the ST elevation and reciprocal ST depression. Further, the degree of ST elevation decreased during the duration of occlusion, and at the end of the occlusion period it measured 570±220 μV for maximal ST elevation in a single lead and 1681±658 μV for the sum of ST deviations.

The angiografically verified blood flow restoration was accompanied by exacerbation of ST elevation in all cases (see Figure 6). ST elevation started increasing shortly after LAD opening, and reached its maximum 186±102 seconds later. The maximal ST segment elevation during reperfusion was 1300±500 μV in a single lead with the greatest ST elevation. The sum of ST deviations in all 12 leads was 3590±1420 μV (Figure 7). The maximal level of ST elevation during reperfusion exceeded the ST elevation during the occlusion period in 13 of 15 animals. The degree of ST elevation exacerbation in a single lead with the greatest ST elevation was 143±104% (42-370%). The degree of ST elevation exacerbation in the sum of leads with ST elevation and reciprocal ST depression was 126±109% (46-390%). The reperfusion peak was followed by a fast resolution of ST elevation. The time to complete ST resolution was estimated as 55±33 minutes. The residual ST elevation after ST resolution was 90±30 μV in a single lead with the greatest ST elevation, 306±150 μV

in the sum of leads. Upon reaching complete resolution, the ST level remained stable until the end of the experiment.

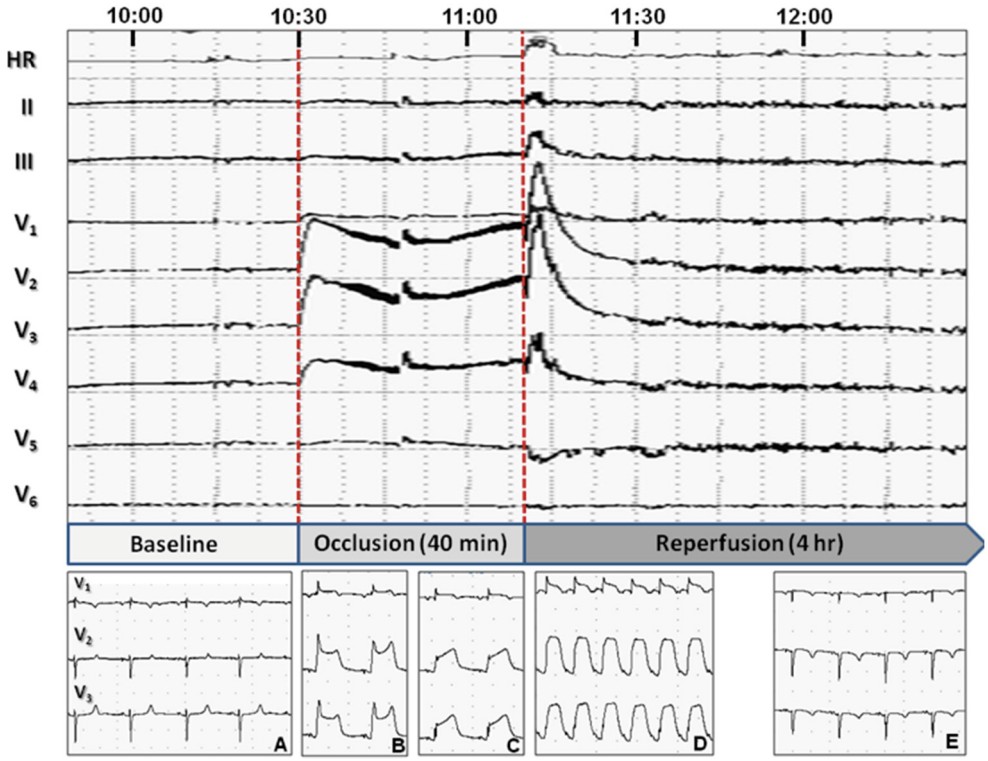

Figure 6
ST segment monitoring during 40-min of LAD occlusion and 4 hours of reperfusion. Transient exacerbation of the ST segment elevation shortly after onset of reperfusion ("reperfusion peak") exemplified in this figure was observed in all animals. HR= heart rate. A-ECG strip at baseline; B- maximum ST elevation during occlusion period; C-ECG at end of occlusion; D- ECG at "reperfusion peak"; E-ECG at the end of the experiment.

ST elevation during the occlusion period was not associated with either MaR or IS (Table 1). The magnitude of transitory ST elevation exacerbation during reperfusion was correlated with IS (r=0.64, p=0.025 for maximal ST elevation in a single lead and r=0.8, p=0.002 for the sum of ST deviations in 12 leads), but was not correlated with MaR (r=0.43, p=0,17 for maximal ST elevation in a single lead and r=0.49, p=0.11 for sum of ST deviations) (Table 1 and Figure 8).

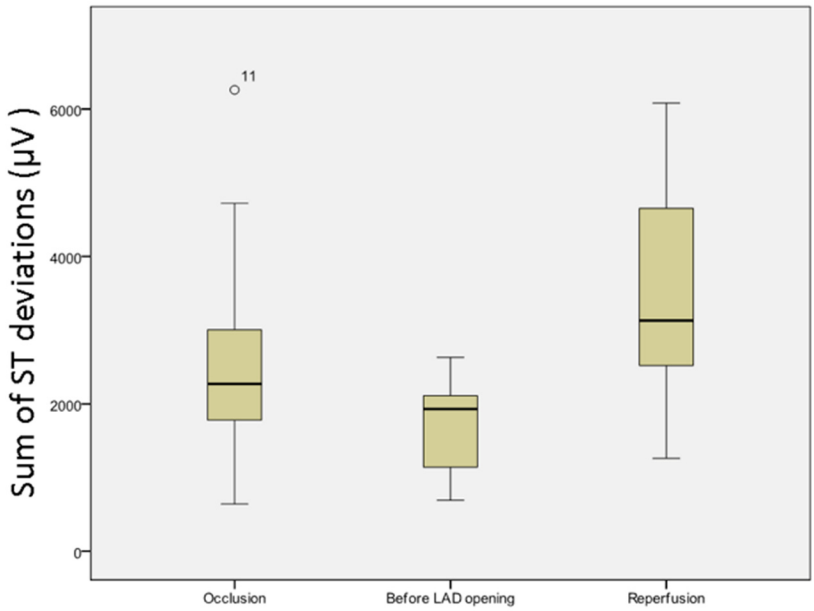

Figure 7
Sum of ST deviations in all leads during occlusion and reperfusion periods.

Table 1
The relationship between ST elevation during occlusion/reperfusion and the myocardium at risk and the final infarct size (Pearson's correlation [p-value])

	Occlusion period		Reperfusion period	
	Myocardium at risk	Final infarct size	Myocardium at risk	Final infarct size
ST max in a single lead	-0.27 [0.40]	-0.45 [0.16]	0.43 [0.17]	**0.64 [0.025]**
Sum of ST deviations	-0.11 [0.74]	-0.21 [0.50]	0.49 [0.11]	**0.80 [0.002]**

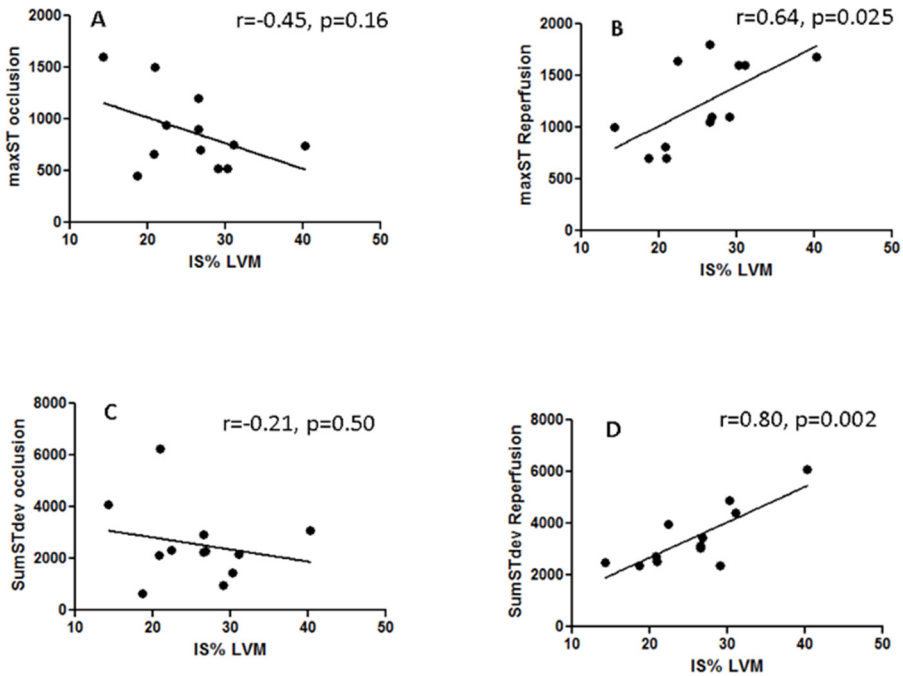

Figure 8
Relationship between final infarct size and maximal ST segment elevation in a single lead with greatest ST elevation and sum of ST deviations during occlusion (A and C) and reperfusion (B and D) periods. IS - infarct size; LVM - left ventricular mass; r - Pearson's correlation coefficient.

T-wave alternans

TWA appeared at 7.2±4.5 (IQ range 3.9-9.6) minutes after occlusion onset, reached its maximum at 12.7±6.3 (IQ range 8.8-17.5) minutes after occlusion onset, and lasted until 26.5±9.2 (range 21.2-32.9) minutes (Figures 9, 10). The amplitude of TWA was maximal in the leads with maximal ST elevation, most often in V_2-V_4. The correlation between maximal ST deviation and maximal TWA amplitude measured in each individual lead was significant for leads V_2-V_6, I and II. However, we did not observe any significant correlation between the maximal T wave amplitude and the maximal TWA in any lead. Maximal TWA was not associated with any significant change in heart rate (75±19 vs 76±21 b.p.m., p=0.575 for heart rate at baseline and during the minute preceding maximal TWA).

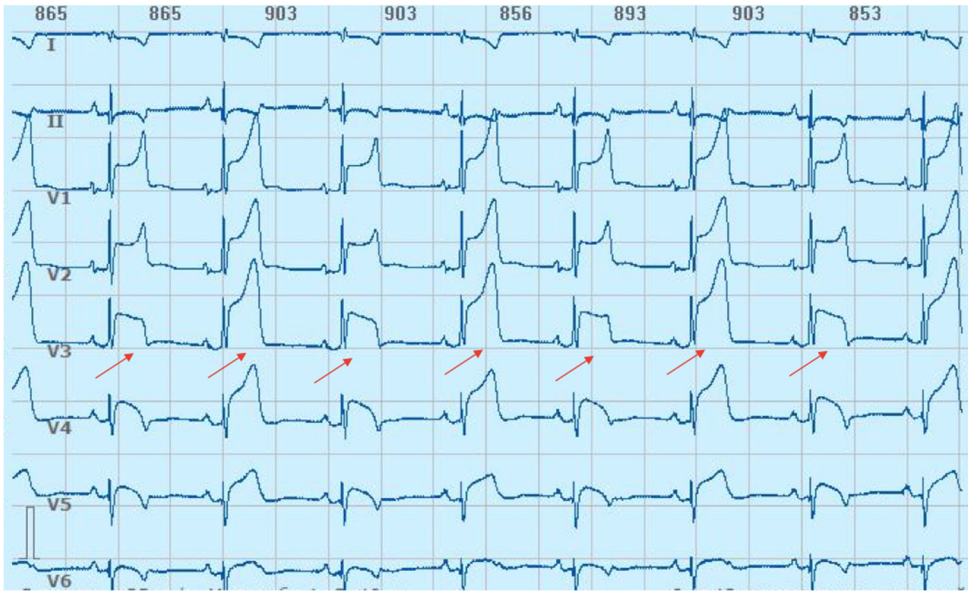

Figure 9
ECG example of visible T-wave alternans during coronary occlusion. ECG at the 12th minute of occlusion. Heart Rate – 68 b.p.m. Arrows show the apparent beat-to-beat alternation of T-wave morphology. The scale (1mV) can be seen in the lower left-hand corner. TWA amplitude is maximal in leads V_2 (302 μV), V_3 (550 μV) and V_4 (446 μV).

The maximal level of TWA in a standard lead was associated with both MaR (r=0.499, p=0.035) and IS (r=0.65, p=0.004) (Figure 11, top panel). When measuring the maximal level of multilead TWA as the sum of the amplitudes in the πCA transformed lead, correlations were stronger with MaR (r=0.58, p=0.012) and IS (r=0.79, p<0.001) (Figure 11, bottom panel).

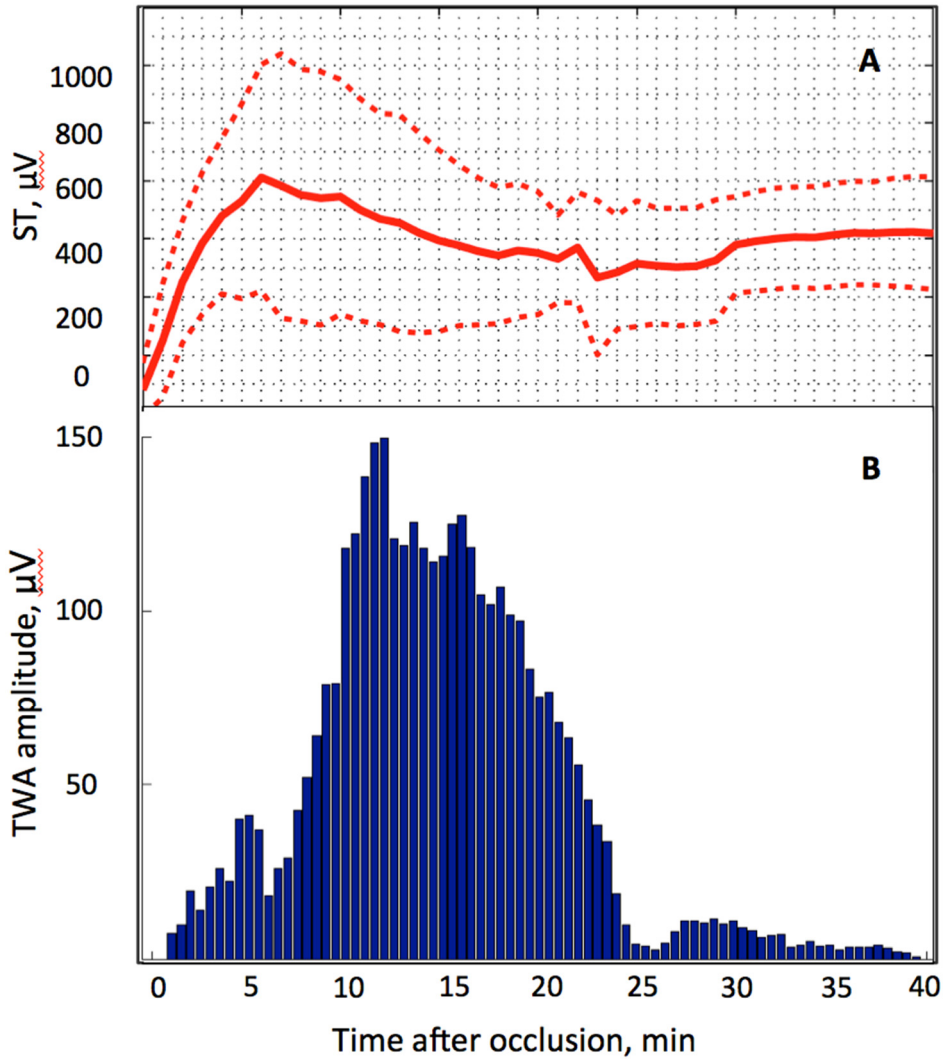

Figure 10
ST dynamics and the time-course of TWA amplitude during occlusion. A. ST dynamics in one lead with most prominent ST elevation during the occlusion period (V_3), group-averaged (Mean (heavy line) ± standard deviation (dotted line)). B. TWA time course during the occlusion period, group-averaged. The standard lead with maximal TWA amplitude (usually V_2-V_4) was used to build the TWA time course. For each animal, the RMS voltage of TWA was averaged every 30 seconds along the 40-min occlusion. Thereafter, the averaged time course of all 21 individual profiles was calculated. Abbreviations: TWA – T-wave alternans; RMS - root mean square.

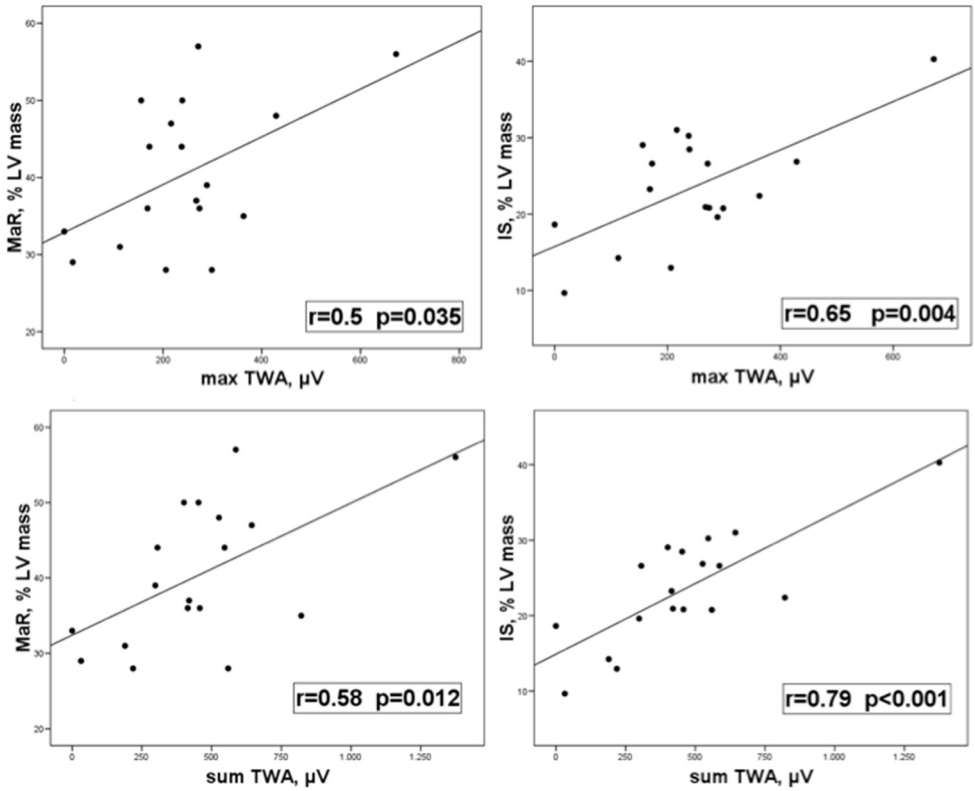

Figure 11.
The association between maximal TWA and the extent of myocardial injury. In the top panels, TWA amplitude is measured as the RMS value in the standard lead with maximal TWA amplitude. In the bottom panels, TWA is given as the sum of RMS amplitudes in transformed leads. Abbreviations: MaR – myocardium at risk, IS - final infarct size, TWA – T-wave alternans; RMS – root mean squared.

VF in experimental myocardial infarction and ECG predictors (Study III)

One experimental animal died during the occlusion period from left main thrombosis, with 37 of 38 pigs surviving the occlusion period. Six pigs suffered from VF during the first minutes of occlusion – on average 2.6±2.1 (range 0.6-7.0) minutes after occlusion start, and 10 pigs – 20.9±4.0 (range 16.8-30.2) minutes after occlusion start (Figure 12).

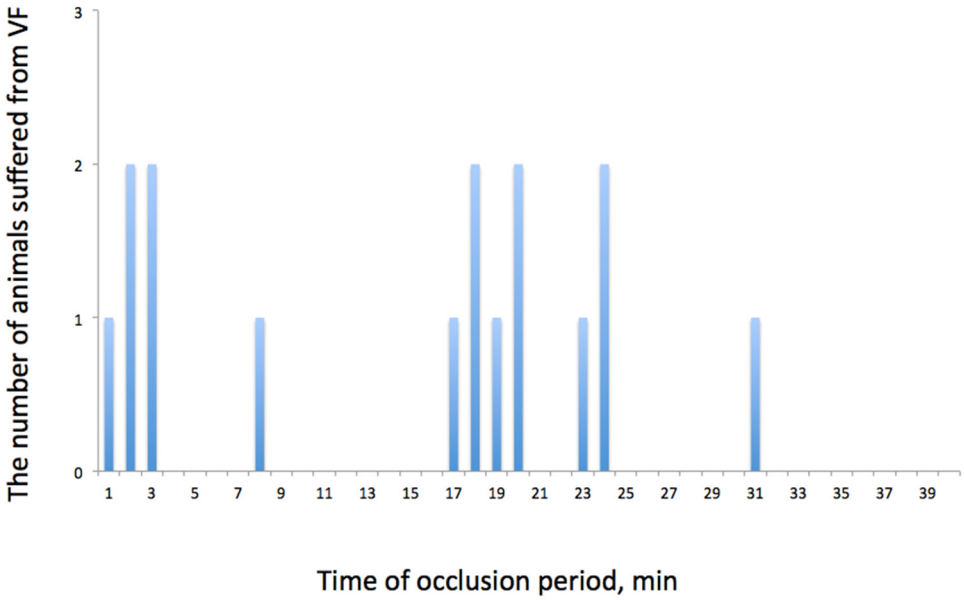

Figure 12.
Time distribution of VF episodes during coronary occlusion. Two distinct peaks of ventricular arrhythmia occurrence were observed and corresponded to Phase 1a (<10 min) and Phase 1b (>15 min).

Dynamics of QRS-duration during coronary occlusion

Five animals were excluded from the QRS duration analysis because of poor-quality signal. All studied animals (n=32) demonstrated similar dynamics of QRS duration changes characterised by the two peaks of QRS-widening: the first peak immediately after LAD occlusion 3.7±1.6 min, and the second peak 19.1±4.0 min after occlusion start (Figure 13). Significant interindividual differences were observed with regard to the magnitude of changes in QRS width. These differences varied from negligible changes in QRS duration to pronounced QRS widening over a short time period, measured as delta in QRS duration over a 3-min window. The QRS duration at baseline was 78±11 ms, at the first peak of QRS widening - 140 ± 21 ms, at the second peak - 124±17 ms, $p<0.001$. The median difference between maximal QRS duration and QRS duration at baseline was 27 (IQR: 16) ms.

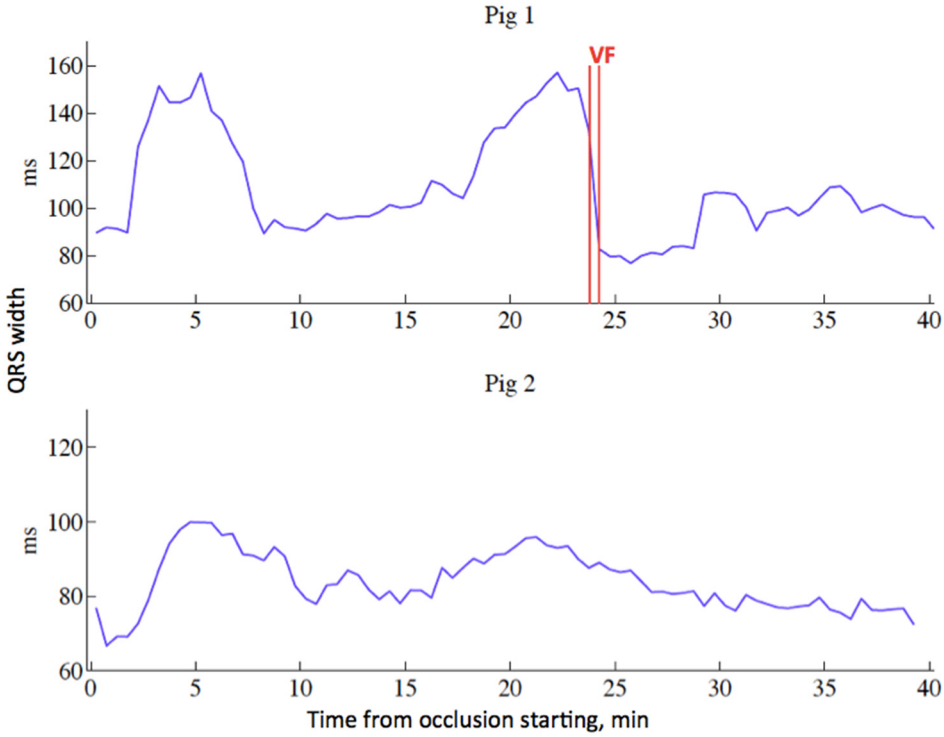

Figure 13.
Dynamics of QRS width thorough 40-minute coronary occlusion. A-marked QRS widening at minutes 2-7 and 17-22 in one pig with VF at 24th minute of occlusion. Vertical line shows the time of VF occurrence. B - slight changes in QRS width in an animal without VF.

Association between QRS widening and subsequent VF onset was studied using the ROC curve analysis. Two thresholds in delta QRS duration showing a reasonable combination of sensitivity and specificity for VF prediction were 28 ms and 36 ms (Figure 14).

QRS widening of ≥28 ms in 3 minutes predicted impending VF with Se=80%, Sp=73%, PPV=57%, NPV=89%, p=0.008. QRS widening of ≥36 ms in 3 minutes predicted impending VF with Se=70%, Sp=95%, PPV=88%, NPV=88%, p<0.001. Thus, marked and fast QRS widening predicted VF (OR 10.7, 95%CI 1.7-65.3, p=0.010 for QRS widening of ≥28 ms in 3 minutes; OR 49.0, 95%CI 4.4-550.7, p=0.002 for QRS widening of ≥36 ms in 3 minutes), while the absolute value of maximal QRS duration had no predictive value (OR 3.3, 95%CI 0.5-19.4, p=0.180 for QRS widening >120ms). In the animals that developed VF, arrhythmia occurred within 2.9±3.8 minutes after reaching maximal QRS duration.

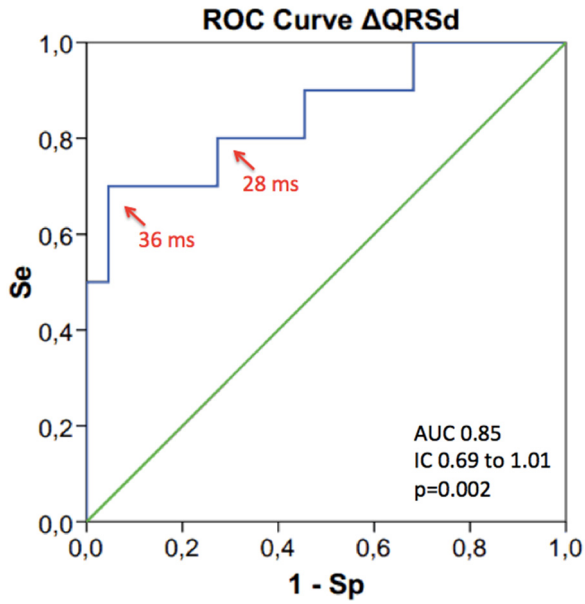

Figure 14.
ROC curve analysis for identifying optimal QRS duration increase cut-off for predicting VF during the occlusion period. Significant points are marked.

QRS morphology during coronary occlusion

At baseline, no animals demonstrated a J-wave pattern in any lead. At maximal QRS duration, J-wave pattern was found in 15 of 32 animals. Figures 15 and 16 show typical QRS morphology dynamics during the experiment. Notching or slurring usually appeared on QRS broadening, and manifested at maximal QRS duration, with subsequent resolution during continued occlusion.

J-wave pattern in anterior leads, which reflected the ischemic zone caused by LAD occlusion, was found in all 15 animals that showed slurring or notching of QRS complexes at their maximal width. In 8 animals, the J-wave pattern in anterior leads was combined with the J-wave pattern in inferior leads; in 2 animals – in lateral leads; while in 5 animals it was confined to anterior leads only. The most commonly observed J-wave pattern was notching of the terminal QRS complex – in 13 animals, while slurring was noted in 2 animals.

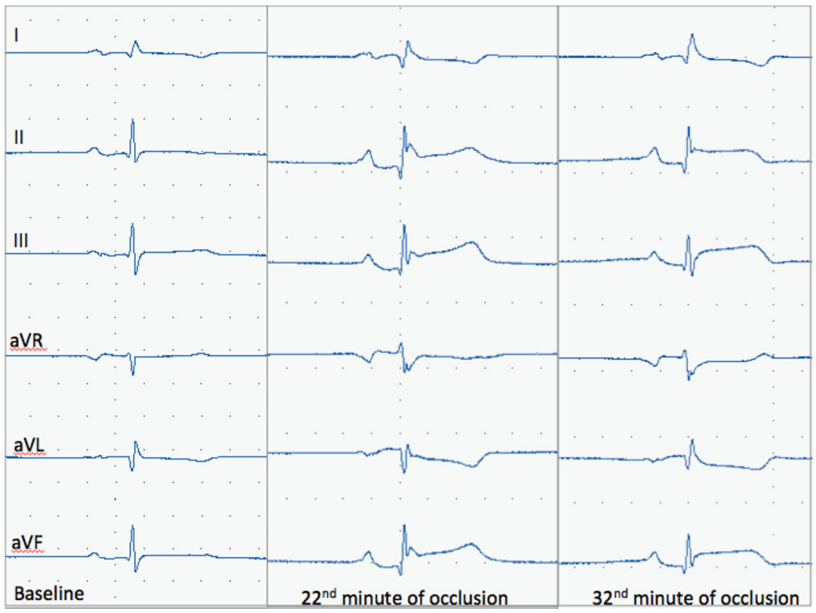

Figure 15.
Apperance of J-wave pattern in inferior leads (notch in II, III, aVF) at 22nd minute of occlusion followed by backward dynamics.

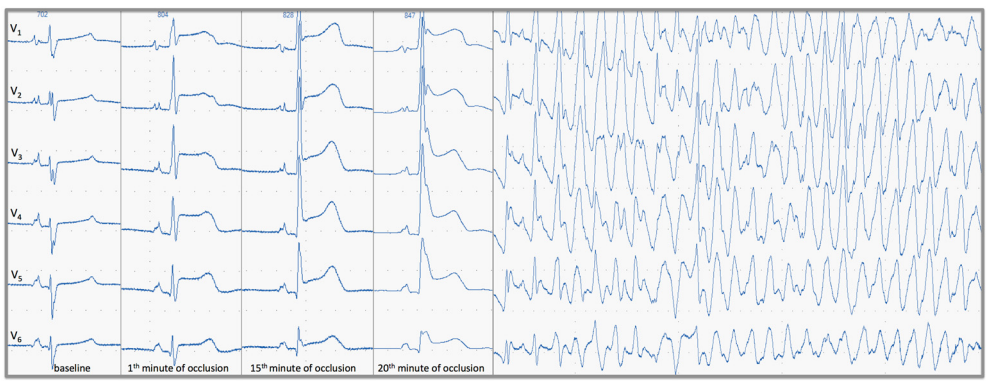

Figure 16.
Apperance of a J-wave pattern in anterior leads at 20nd minute of occlusion, immediately preceding VF episode.

J-wave pattern was observed in 8 out of the 10 pigs that experienced VF, and in 7 out of the 22 pigs without VF, p=0.02. J-wave pattern was found in all 7 animals with QRS duration increase ≥36 ms, and in 10 of 14 animals with QRS duration increase

≥28 ms during a 3-min window. Appearance of a J-wave pattern predicted VF with Se=80%, Sp=68%, PPV=53%, NPV=88% (p=0.02) and remained a significant VF predictor in logistic regression analysis (OR=8.6, 95%CI 1.4-51.4, p=0.020).

VF occurred in 6 out of 8 animals with J-wave pattern in combination of inferior and anterior leads, and only in 2 out of 7 animals with J-wave pattern in isolated anterior leads and combination of anterior and lateral leads (p=0.13) (Se=75%, Sp=71%, PPV=75%, NPV=29%).

Thus, rapid and marked transient increase in QRS duration commonly associated with J-wave pattern appears to predict impending VF in acute ischemic settings, and warrants further clinical studies for monitoring the immediate risk of VF during the acute phase of myocardial infarction.

Prevalence and timing of VF in acute STEMI and its predictors (Study IV and Study V)

VF or VT demanding defibrillation during the first 48 hours of STEMI occurred in 121 of 1718 patients (7.0%). As described in Figure 17, VT/VF was registered before intervention in 73 patients (the "before PCI" group), between restoration of blood flow in IRA and the end of the PCI procedure in 26 patients (the "reperfusion arrhythmia" group), and after PCI procedure in 22 patients, of which 17 occurred within the first 24 hours of STEMI and five occurred during the day after. Thus, in 96% of patients from the VF group, life-threatening arrhythmias occurred within the first 24 hours of STEMI.

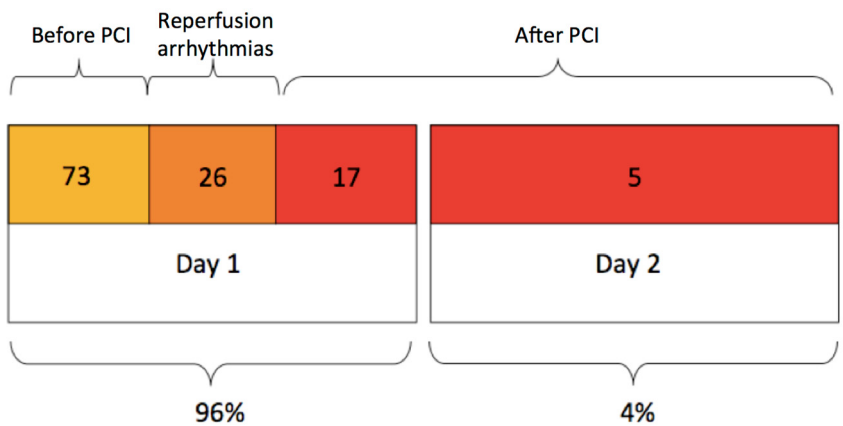

Figure 17
Timing of VT/VF during acute ST-elevation myocardial infarction (STEMI).

In univariate regression analyses, the following factors were associated with increased risk of VT/VF during the first 48 hours of STEMI: current smoking, history of myocardial infarction, use of aspirin, beta-blockers, digitalis and statin, plasma creatinine level and left main coronary artery disease (Table 2). In a multivariate analysis, current smoking, beta-blocker therapy, use of digitalis at admission and left main disease remained independently associated with VT/VF during the first 48 hours. The use of beta-blockers (OR 2.04; p=0.003, 95%CI 1.27-3.27) and digitalis (OR 3.34; p=0.035, 95%CI 1.09-10.22) at admission remained independent predictors of VT/VF before reperfusion.

During the 6-year period from 2007 to 2012, 3724 patients were admitted for primary PCI; 71 (1.9%) of them had reperfusion VF. The rate of occurrence of reperfusion VF was relatively stable over this 6-year period and averaged 1.9%(Figure 18).

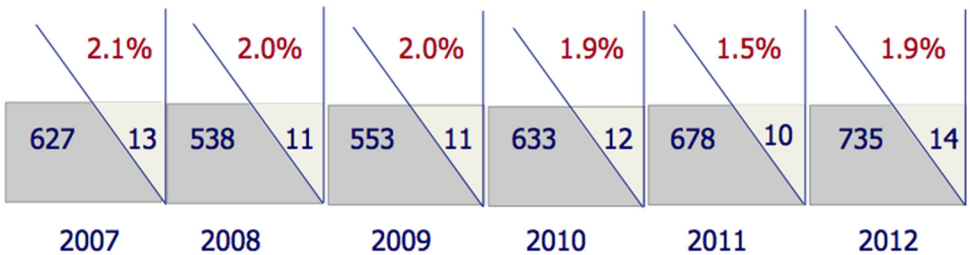

Figure 18
Prevalence of VF during reperfusion in different years.

The following factors were associated with increased risk of VF during reperfusion in univariate analysis: history of myocardial infarction, use of aspirin and beta blockers, VF before PCI, potassium level at admission, left main coronary artery disease, inferior localization of MI, duration of QRS on historical ECG, symptom-to-balloon time of less than 360 minutes, ST-elevation in a single lead greater than 300 μV, and sum of ST-deviations in all leads greater than 1500 μV (Table 3). In a multivariate analysis, the sum of ST-deviations in all leads greater than 1500 μV before PCI and left main stenosis by angiography remained independent predictors of VF during reperfusion.

Table 2 Clinical factors associated with VF during acute STEMI

Characteristics at admission	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Current smoking	1.79	1.06-3.05	0.03	2.82	1.50-5.31	0.001
Previous MI	2.14	1.39-3.30	0.001	-	-	-
Medications:						
Aspirin	2.03	1.38-3.01	< 0.001	-	-	-
Statins	1.78	1.16-2.73	0.008	-	-	-
Beta blockers	2.32	1.57-3.42	< 0.001	2.54	1.59-4.05	<0.001
Digitalis	3.35	1.24-9.06	0.017	4.57	1.54-13.53	0.006
Left main stenosis	2.52	1.44-4.39	0.001	3.04	1.58-5.85	0.001
Creatinine >80 mmol/L	1.63	1.08-2.39	0.019	-	-	-

Abbreviations: MI - myocardial infarction; Left main stenosis - left main coronary artery stenosis

Table 3. Clinical factors associated with ventricular fibrillation during reperfusion

Characteristics at admission	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Previous MI	1.93	1.04-3.58	0.039	-	-	-
QRS duration at historical ECG	1.02	1.003-1.04	0.020	-	-	-
K^+ at admission	0.40	0.22-0.73	0.003	-	-	-
VF before PCI	4.15	1.95-8.81	<0.001			
Medications:						
Aspirin	1.88	1.09-3.22	0.023	-	-	-
Beta -blockers	1.86	1.09-3.19	0.024	-	-	-
Symptom-to-balloon time <360 min	2.19	1.08-4.42	0.029	-	-	-
Left main stenosis	2.60	1.22-5.54	0.013	4.47	1.19-18.80	0.027
Inferior MI	1.89	1.09-3.29	0.023			
ST max >300 μV	4.87	2.34-10.16	<0.001	-	-	-
Sum ST >1500 μV	6.44	2.86-14.53	<0.001	4.00	1.52-10.54	0.005

Abbreviations: MI - myocardial infarction; VF - ventricular fibrillation; PCI - percutaneous coronary intervention; Left main stenosis - left main coronary artery stenosis; ST max – maximal ST in a lead with most prominent elevation, Sum ST - sum of ST deviations in all leads.

Prognostic impact of VF in STEMI (Study IV and Study V)

In-hospital mortality was markedly higher in the VF group (26%) than in the No VF group (3.7%), p<0.001. In-hospital mortality in patients who suffered from VF at reperfusion was 18.3%, and even in patients with reperfusion VF but without VF before PCI it was 16.7% (p<0.001 for comparison with No VF patients).

Long-term prognosis was assessed in patients alive at 48 hours of STEMI (n=1663) (Figures 19, 20). Of these patients, 100 died during one-year follow-up: 13 (12.9%) in the VF group and 87 (5.6%) in the No VF group, p<0.001. The majority of deaths occurred during index hospitalization: 12 patients from the VF group (12%) and 24 patients from the No VF group (1.5%), p<0.001. Of these patients, 18 died from heart failure or cardiogenic shock (12 of 24 No VF patients and six of 12 VF patients), four patients died from mechanical complications of myocardial infarction (interventricular septum rupture, left ventricular free wall rupture, acute mitral insufficiency (all from the No VF group), one patient died from ventricular fibrillation (No VF group), and 13 patients died from other causes.

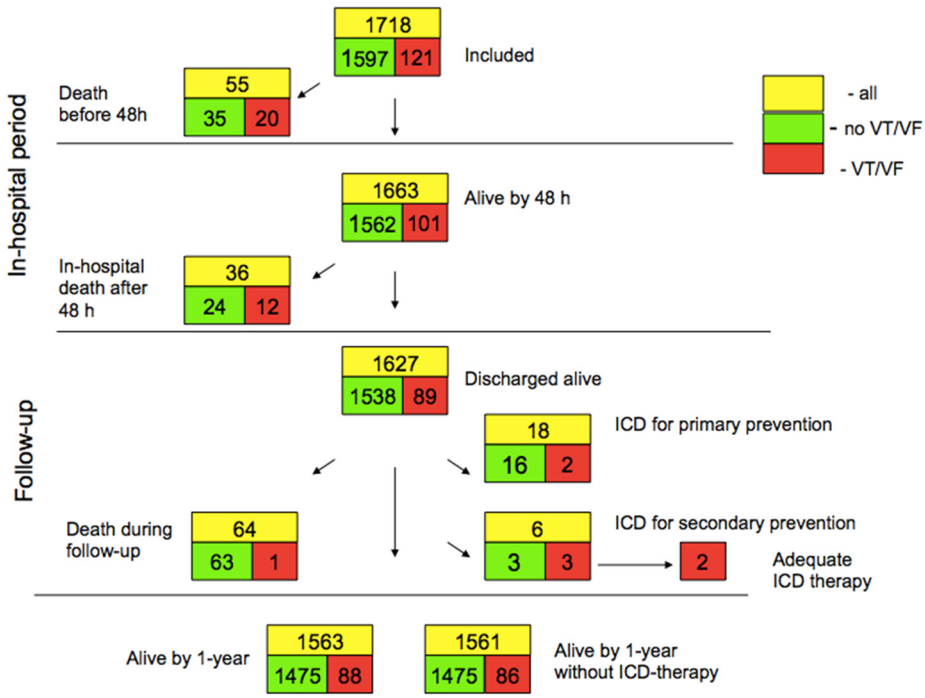

Figure 19 Patient groups chart.

Of the 1627 patients discharged alive, 64 (3.9%) died during the follow-up period. The mortality rate at one year did not differ significantly between the groups: 1.1% in the VF group, and 4.1% in the No VF group (OR=0.27, 95%CI 0.037–1.945, p=0.194, Figure 20(c)).

Of the patients discharged alive, 18 received an ICD for primary prevention and six received an ICD for secondary prevention of sudden death. Three of the six patients in whom ICD was implanted for secondary prevention were from the VF group. In five of the six patients with ICD for secondary prevention, the VT episode which motivated device implantation occurred within the first half-year of STEMI; in four patients it occurred during the first two months. Two patients with ICD implanted for secondary prevention received adequate ICD therapy, both of them received the therapy twice during one year of follow-up. The time from ICD implantation to the first adequate ICD therapy was one month and four months, respectively. None of the patients who received an ICD for primary prevention received adequate ICD therapy by one year of follow-up. In total, 68 patients experienced the combined endpoint of death, VT/VF or appropriate ICD therapy during follow-up: five in the VF group and 63 in the No VF group. Two patients from the No VF group developed sustained VT 18 and 39 days following the date of index admission, respectively. Two additional patients from the VF group received appropriate ICD therapy during follow-up. There were no differences between the two groups with regard to the combined endpoint among those discharged alive (OR=0.85, 95%CI 0.225–2.585, p =0.725 for combined endpoint, Figure 20(d)).

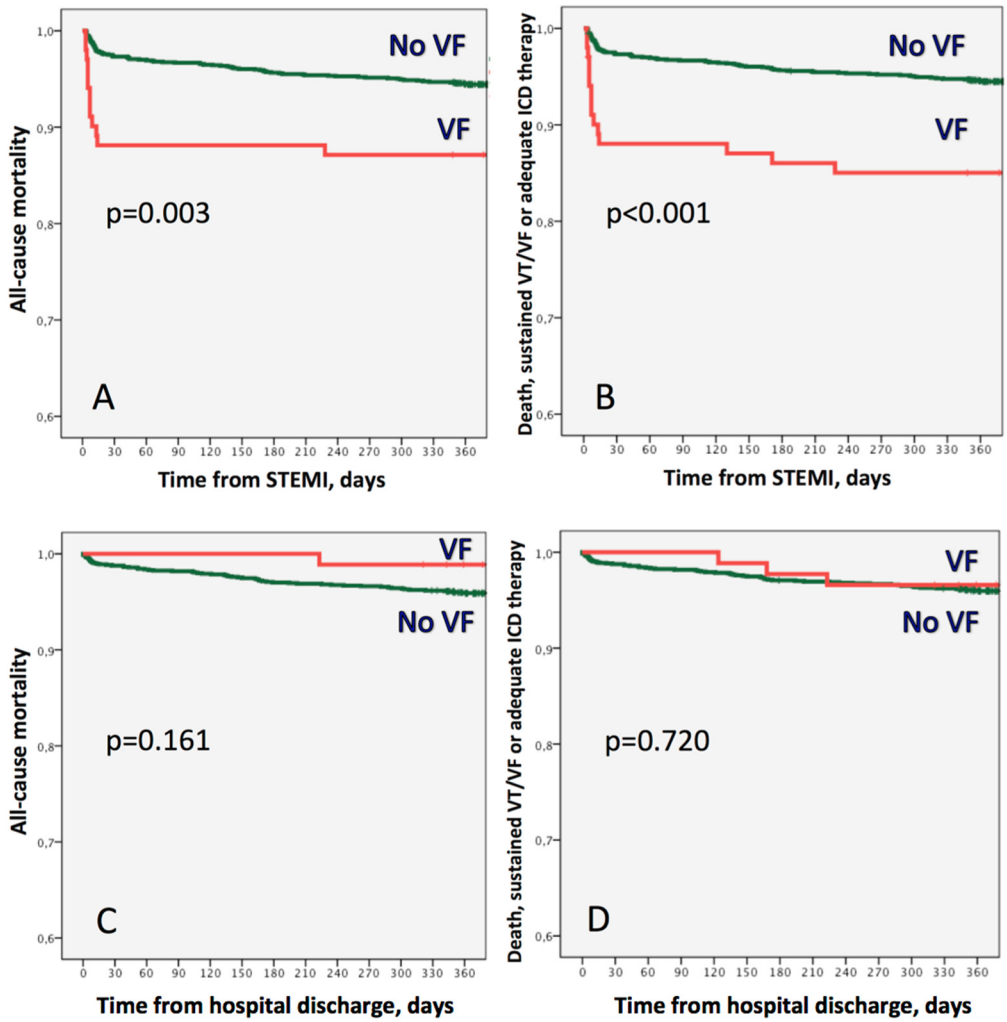

Figure 20. (a) Kaplan–Meier survival analysis with regard to total mortality during follow-up for patients alive at 48 hours of STEMI. (b) Kaplan–Meier analysis with regard to combined endpoint of total mortality, appropriate ICD discharge or new VT/VF during follow-up for patients alive at 48 hours of STEMI. (c) Kaplan–Meier survival analysis with regard to total mortality during follow-up for patients discharged alive. (d) Kaplan–Meier analysis with regard to combined endpoint of total mortality, appropriate ICD discharge, or new VT/VF during follow-up for patients discharged alive.

STEMI: ST-elevation myocardial infarction; VT: ventricular tachycardia; VF: ventricular fibrillation; ICD: implantation of cardioverter-defibrillator

Discussion

The experimental model

The porcine model of myocardial infarction has been chosen for the experimental part of the study. The choice of model was determined by similarity of body weight, cardiac function and anatomy between pigs and humans (69). Pigs have the heart size, heart-to-body weight ratio and coronary artery distribution similar to humans (70-72). Similarly to humans without long-standing coronary artery disease, and in contrast to dogs, pigs have a sparse network of collaterals and a poor ability to recruit new collaterals acutely during an ischemic event (72, 73). Moreover, pigs' electrophysiology and metabolism during ischemia and reperfusion are comparable to those in humans (74, 75).

Using the closed-chest model and induction of myocardial infarction by catheter–based percutaneous intervention allowed us to minimize trauma, operation-induced stress and secondary changes in circulatory physiology (76). Body temperature is a known factor influencing reperfusion injury and final infarct size (59, 77, 78). To avoid spontaneous hypothermia, normal body temperature (38°C) of the experimental animals was maintained throughout the experiment.

The length of the occlusion period in our study was 40 minutes; however, MI progression in pigs is approximately 7 times faster than in humans because of poor collateral flow (79). Therefore, the model corresponded to 4-5 hours of STEMI in humans, which is clinically relevant.

Histologic examination was not performed in our study; however, the correlation of measurements of the size of myocardial injury by MRI and histology was shown earlier (80-82).

In order to create a reproducible myocardial injury during the experiment with a limited number of experimental animals, occlusion of the mid-portion of the left anterior descending artery (LAD) was performed in all animals, and the length of the occlusion period was identical in all cases. Therefore, we were not able to analyze the association between MI localization and ventricular arrhythmia occurrence and the dynamics of depolarization and repolarization indices, which was a limitation of our study.

Our model of antero-septal myocardial injury with final infarct size of 20-30% of left ventricle corresponds in clinic to the group of large anterior infarctions with a high risk of adverse outcome. The myocardial salvage in our model was approximately 40%, which is less than in clinical settings. This can be explained both by faster infarct progression in pigs due to poor collateral flow and greater reperfusion injury due to absence of pre- and post- conditioning in the experiment.

A peculiarity of pigs is their vulnerability to VF in acute ischemic settings (83). 50% of the animals used in this study developed VF during occlusion, while 16% developed VF during reperfusion. The time distribution of ventricular arrhythmias in our study was in agreement with previously published data that describe their occurrence at two distinct periods of ischemia defined as Phases 1a (0-10 min from induction of ischemia) and 1b (15-30 min of ischemia) (84-86) (Figure 21). In clinical settings, Phase 1a arrhythmias usually occur long before the first contact with health-care professionals and remain responsible for high mortality from out-of-hospital cardiac arrest. Phase 1b arrhythmias correspond to approximately 2–2.5 hours of MI in clinical settings, and prediction of VF in this time period may be clinically relevant.

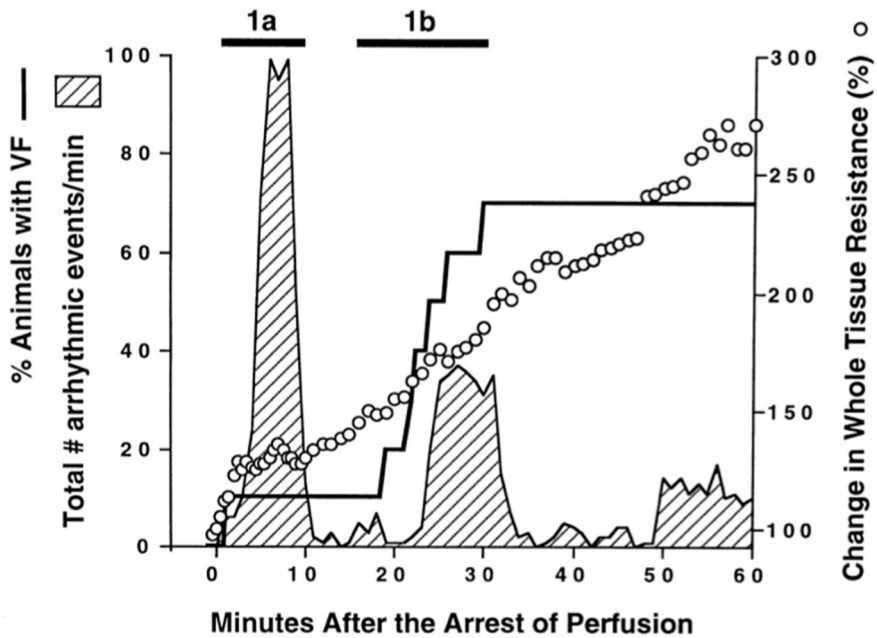

Figure 21
Arrhythmia occurrence in experimental ischemia (reproduced with permission from Smith W.T. et al., 1995)

The ECG predictors of myocardial injury

As was already discussed, the prognosis after myocardial infarction is substantially determined by structural and functional derangement (3). Infarct size (IS) is one of the most important factors related to mortality in ST-elevation myocardial infarction (STEMI) (3, 87). SPECT and MRI, the "gold standard" in evaluating myocardial injury (4, 5), are still far from being a routine clinical examination in patients with STEMI.

The main finding of Studies I and II is that the dynamics of repolarization indices during occlusion and reperfusion can be used for predicting the size of myocardial injury.

T-wave alternans

T-wave alternans, an ECG phenomenon reflecting the spatiotemporal heterogeneity of repolarization, is known to be associated with ventricular vulnerability and risk of death in different categories of patients, particularly in post-myocardial infarction patients (88-90). The negative association between the presence of TWA and ejection fraction has been reported in post-MI patients (91). The hypothesis was that larger infarcts resulted in low ejection fraction and discordant alternans due to considerable extension of abnormal tissue (91). In order to clarify whether TWA is associated with the degree of myocardial impairment, we correlated TWA magnitude with MaR and final infarct size, and we have shown that the maximal level of TWA was associated with both indices of myocardial injury.

To our knowledge, the relationship between repolarization variability and infarct size was previously examined in only one experimental study in a porcine model of subacute myocardial infarction, and in that study no significant correlation between beat-to-beat variability of repolarization and infarct size was found (92). Not only the presence of post-infarction scar, but also acute ischemia seem to be important triggers of TWA. In the above-mentioned study in the settings of the myocardial scar but no acute ischemia, TWA was induced by rapid ventricular pacing and was not observed during intrinsic heart rhythm (92). In clinical practice, exercise tests are often used to reach heart rate acceleration sufficient to enable TWA detection in post-MI patients (93, 94). In our acute STEMI experiment, we observed visible TWA at spontaneous heart rhythm.

TWA is conventionally considered to be a rate-dependent phenomenon that requires certain rate increase in order to induce measurable TWA. Thus, in clinical settings, occurrence of TWA at lower heart rates has been associated with higher risk of ventricular arrhythmias (95). In our experiments mean heart rate was relatively low,

and TWA, including the visually apparent one, occurred without preceding heart rate acceleration. The lack of rate increase can perhaps be attributed to the use of fentanyl-induced general anesthesia in our model. However, the most likely explanation for the TWA that occurred independently of heart rate increase was severe acute ischemia that impaired cellular calcium cycling, permitting alternans to be initiated at slower heart rates (96, 97).

Another important discussion point is the time course of TWA during coronary occlusion. In previous PCI studies with short occlusion times, TWA magnitude increased continuously during the course of the occlusion period (98). In a dog model of ischemia with 10-minute long occlusion, TWA had a tendency to decrease during the last two minutes of the occlusion (99). In our study, TWA decreased abruptly by the 25th minute of occlusion, and became nearly negligible by the end of the 40th minute. The reason for such reduction of TWA amplitude despite continued occlusion is not fully understood, but is perhaps due to progressive loss of living myocytes and development of electrically inactive necrotic tissue in the infarcted area.

To summarize, the revealed association between TWA and indices of myocardial injury suggests that TWA may be a potential marker of prognostic assessment in STEMI patients. TWA is a non-invasive marker and can be calculated relatively simply using conventional holter ECG recording. However, its value for predicting myocardial injury in clinical settings has yet to be determined.

Reperfusion peak and its association with infarct size

ST dynamics analysis during reperfusion therapy is commonly used for noninvasive assessment of reperfusion therapy efficacy (100), estimation of microvascular perfusion and risk stratification of patients with STEMI (101, 102). It has been shown that rapid and complete ST resolution following reperfusion therapy is associated with better left ventricular function (103-105), lower enzyme level and greater myocardial salvage measured by nuclear imaging (103, 106). In clinical settings, the extent of ST-resolution and the time to ST-resolution are usually assessed on the basis of discrete ECG strips only.

Continuous 12-lead ECG monitoring during reperfusion in STEMI permits assessing not only the degree and velocity of ST-resolution, but also the pattern of ST-dynamics during reperfusion. Study II has shown that, in experimental settings, angiografically verified restoration of blood flow in previously completely occluded coronary artery is commonly accompanied by exacerbation of ST-elevation – by reperfusion peak, and the degree of ST elevation at reperfusion peak is associated with final infarct size. This finding may indicate that the reperfusion ST peak is a sign of unfavorable outcome.

Currently, there is no agreement regarding the explanation of the nature of the reperfusion peak. The reperfusion peak may be a pure electrophysiologic phenomenon caused by potassium washout during reperfusion (107, 108). Some observations indicate that the peak is observed in case of severe myocardial injury before the onset of reperfusion associated with marked ST elevation, poor collateral circulation, and larger amount of myocardium involved in the ischemia-reperfusion process (109). Another plausible explanation is that the peak reflects injury caused by the reperfusion, contributing to the final infarct size (110).

In our experimental study, we observed the reperfusion peak in all experimental animals, whereas in clinical settings reperfusion peak is usually found in just 30-40% of cases (111-114). This difference can be explained by the presence of pre- and post-conditioning due to previous ischemic history and incomplete and intermittent coronary occlusions, which are typical for real-life STEMI. In a clinical study of ST-dynamics during primary PCI in STEMI, we found that the presence of a reperfusion peak was associated with complete occlusion of infarct-related artery and prominent ST-elevation before PCI.

A future goal is to clarify whether the reperfusion ST peak represents "injury before reperfusion" or "reperfusion injury". This could be achieved by comparing the area of the impaired myocardial perfusion between the two images produced just before and immediately after reperfusion (115). Also, if the reperfusion ST peak is a marker of injury caused by the reperfusion, it can be modifiable by adjunctive therapies such as hypothermia, which can attenuate reperfusion injury (59, 116).

Predictors of VF in acute STEMI

We analyzed the VF predictors in an unselected population of STEMI patients admitted for primary PCI. In agreement with earlier reports (35, 117), patients from the VF group included in our study had prior MI more often than patients without VF. No other medical conditions such as diabetes or hypertension were associated with VF during acute STEMI, also in line with previous reports (118, 119). The association between early VF and smoking was in agreement with earlier publications (44, 118, 119).

Patients from the VF group more often received beta-blocker treatment, which is likely to be a more sensitive indicator for underlying cardiovascular disease than anamnaestic data. Aside from beta-blockers, digoxin use was independently associated with VF occurrence. The association between digoxin use and early VF in our study is especially noteworthy in the light of recent publications about digoxin. It is well known that digoxin decreases the hospitalization rate but does not decrease mortality

due to congestive heart failure (CHF)(120). Also, digoxin was reported to increase the rate of death from "other causes"(121), presumably due to arrhythmias. Recently, based on a large data sample from the RIKS-HIA registry, it was shown that digoxin is an independent risk factor for death among patients with AF without a history of congestive heart failure (122). The strong association between digoxin use at admission with acute STEMI and early VF is in agreement with the findings of previous trials, thus further supporting the previously-suggested potential hazard of digoxin in acute ischemia settings.

Thrombosis of the left main coronary artery resulting in a large ischemic area was observed more often in the VF group. For the whole group of VF that occurred during the first 48 hours of STEMI, we did not observe any association between VF occurrence and localization of myocardial infarction. However, this association was revealed for the subgroup of reperfusion VF.

Predictors of reperfusion VF

Just as VF at any time within the first 48 hours of STEMI, reperfusion VF was also associated with left main stenosis, which could lead to more intensive ischemia and larger area of myocardium at risk involved in ischemia-reperfusion. We have not found any association between VF at reperfusion with multivessel disease, which is in accordance with the APEX-AMI cohort.(34).

The occurrence of VF at reperfusion in our study was higher in inferior STEMI localization. This is in line with previously published data concerning VF in STEMI but not directly related to reperfusion (34, 123, 124). The higher incidence of VF in inferior STEMI, especially with right ventricular involvement, can be explained by much more prominent I_{to} in the epicardium of the right ventricle than in the left ventricle (125). We also observed a tendency to the prevalence of RCA as IRA that had been previously reported to be predictive for VF (44). Notably, in our cohort, patients with inferior STEMI with higher risk of rVF had lower max ST elevation than patients with anterior STEMI (309±219 vs 501±339 μV, $p<0.001$).

In earlier studies, TIMI 0 before PCI has been reported to be predictive for VF in catheterization laboratory (44). In our study, all 71 patients who suffered from rVF had total acute coronary occlusions, with no cases of non-occlusive stenoses . The rate of thrombectomy in the VF group was 53%, compared to 12% in the No VF group ($p<0.001$).

Hypokalemia is known to be a predictor of VF during STEMI, especially with regard to VF occurring shortly after symptom onset (38, 41). We analyzed the association between potassium level at admission and reperfusion VF, and found that despite differences between the rVF group and the No rVF group, the average potassium

level in both groups was normal. The percentage of patients with hypokalemia at admission tended to be higher in the rVF group vs. the No rVF group (5.8% vs 2.7%), but the difference did not reach statistical significance. Earlier published metaanalysis demonstrated that the weighted mean difference in potassium level between VF patients and patients without VF is rather small (118). It was shown that potassium levels are inversely correlated with catecholamine concentrations during myocardial infarction. It cannot be excluded as a hypothesis that a possible mechanism of lowering potassium concentration is the high catecholamine surge which shifts potassium intracellularly through muscular $beta_2$–receptor stimulation of Na-K-ATPase (126).

The symptom-to-PCI time was shorter in the rVF group than in the No rVF group, in agreement with PAMI trial results (44). Not only the large extent of myocardial injury, but also the presence of viable myocardium by restoration of blood flow seems to be important for reperfusion VF occurrence. VF before PCI was predictive for VF during reperfusion, reflecting interindividual variation in vulnerability to ventricular arrhythmias in ischemia-reperfusion settings. At the same time, 85% of patients who suffered from VF during reperfusion had experienced no VF before reperfusion.

In earlier studies, the sum ST deviation in 12 ECG leads was predictive for VF at any time of STEMI (34, 118), but did not influence the occurrence of postprocedural VF (127). We found that the magnitude of ST-elevation, reflecting ischemia intensity before primary PCI, predicts VF during reperfusion. Since myocardial ischemia affects not only ventricular repolarization but also the depolarization process, we scrutinized admission ECGs for Sclarovsky-Birnbaum ischemia grades. The terminal distortion of QRS-complex corresponding to Grade 3 of ischemia is believed to reflect severe and prolonged ischemia that affects Purkinje fibres (10) and correlates to larger infarct size and less myocardial salvage at reperfusion (128, 129). In our study, the percentage of patients with Sclarovsky-Birnbaum Grade 3 ischemia on admission did not differ between rVF and No VF groups despite the shorter symptom to PCI time in the rVF group. This may be explained by the presence of patients with fast progression myocardial infarction due to poor collateral flow or absence of preconditioning in the rVF group (10).

In earlier studies, the prolongation of PR was found to be predictive for VF (118), especially in RCA occlusions (130). RCA perfuses the AV node in approximately 90% of humans (131), and blockage of RCA flow results in a proximal conduction delay. We found no differences in PQ on admission ECG between patients with reperfusion VF and without reperfusion VF.

In our study, we reviewed not only admission ECGs, but also historical ECGs before STEMI. We have shown that QRS duration before the coronary event is a predictor of VF during reperfusion for subsequent STEMI. This finding is in agreement with

results of Tikkanen (132) on longer QRS duration in future victims of sudden death during an acute coronary event.

Recently, several studies reported the association between the J-wave pattern on historical ECG, life-threating ventricular arrhythmias and sudden death during acute ischemic event (132-135). The association of an initially existing J-wave pattern with future arrhythmic complications during acute STEMI was explained by the presence of heterogeneity of ventricular repolarization as a substrate predisposing to the development of ventricular arrhythmias in the setting of an acute ischemia trigger (136). In our study, J-wave point elevation was observed in 0.2%, which is much lower than in the above-mentioned studies - 11-16% (132, 133), and also lower than the reported early repolarization prevalence in the general population – 4.5% (137). However, early repolarization is known to be an age-dependant phenomenon, and in the age group of 60-70 years, corresponding to the average age at the moment of historical ECG in our study, repolarization prevalence appears to be in the range of 1.5% in women and 2-3% in men (137), which corresponds to our observations. Moreover, according to some literature data, this ECG phenomenon may have an alternating nature, and may show appearance and disappearance on the serial discrete ECGs during follow-up (138).

Dynamic ECG changes in predicting impending VF

Research aimed at predicting VF has been mostly focused on settings outside of ischemia, while data on dynamic electrocardiographic changes that can predict VF, especially VF at reperfusion, are scarce. In our study, we used the advantages of the experimental model of acute myocardial ischemia and infarction, and assessed the time course of QRS duration and morphology which enabled us to reveal predictors of impending VF.

At baseline, QRS was narrow in all experimental animals. During the course of ischemia, QRS duration demonstrated dynamic behavior with two peaks of QRS-widening. Similar QRS-duration dynamics characterised by the two peaks of QRS-widening was observed in all experimental animals, although the magnitude of changes in QRS width varied dramatically. The peaks of ventricular arrhythmias coincided in time with the peaks of QRS-widening (Figure 22).

Marked and fast QRS broadening was associated with VF occurrence. We were able to find quantitative thresholds in delta QRS duration showing a reasonable combination of sensitivity and specificity in VF prediction - QRS widening of ≥28 ms in 3 minutes predicted impending VF with Se=80%, Sp=73%. Notably, the absolute value of QRS duration did not have any predictive value for impending VF.

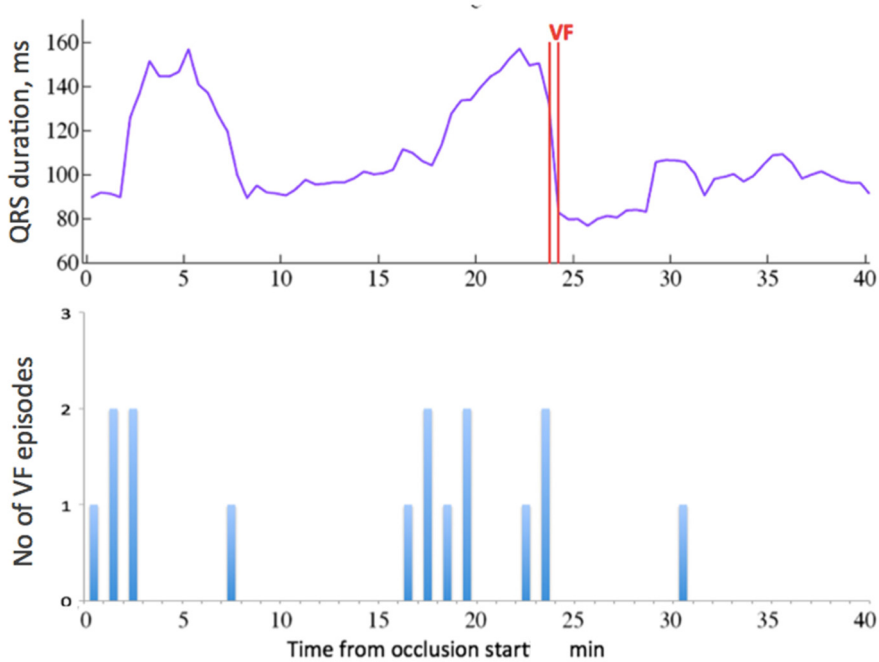

Figure 22
Coincidence of ventricular fibrillation occurrence and periods of QRS broadening.

In a previous study on ECG prediction of ischemic VF with respect to the culprit artery, no differences in QRS duration were found between VF and no VF patients with LAD occlusions (130). QRS prolongation was an independent predictor of VF in LCx occlusions only. LCx perfuses the posteriolateral area of the left ventricle, which was one of the last areas to be activated (139). In non-anterior infarctions caused by RCA occlusions, QRS prolongation was not an independent predictor of VF. The conduction delay due to RCA occlusion will remain hidden within the QRS complex unless it exceeds the activation time of the LCx territory. LAD perfuses the septum, which was shown to be the first area to be activated, and conduction delay due to LAD occlusion may not be recognizable on the surface ECG (131, 139). A plausible explanation of marked QRS prolongation in our study is that the great extent of of ischemia due to proximal LAD occlusion caused a sufficient conduction delay.

In most experimental animals, QRS prolongation was associated with similar changes in QRS morphology. At baseline, QRS did not reveal any signs of J-wave pattern in any of the experimental animals, but QRS broadening was associated with J-wave pattern appearance. J-wave pattern was found in all animals with QRS duration increase ≥36 ms, and in 71% of animals with QRS duration increase ≥28 ms during a

3-min window. Appearance of a J-wave pattern remained a significant VF predictor in multivariate logistic regression analysis.

The association between the J-wave pattern and VF in acute ischemia settings was first been reported in experimental studies (140, 141) and later observed in a handful of reports (142, 143). More recently, the association between the presence of J-wave pattern and myocardial ischemia or infarction was reported in several controlled studies (132-134, 144, 145).

In most studies investigating the predictive value of ER in ischemic patients, the presence of a J-wave-pattern has been assessed on the basis of a historical ECG recorded prior to the ischemic event (132-134). The association of an initially existing J-wave pattern with future arrhythmic complications during acute STEMI was explained by the presence of heterogeneity of ventricular repolarization – i.e. a substrate predisposing to the development of ventricular arrhythmias in the setting of an acute ischemic trigger (136, 146). Other studies attempted to evaluate the J-wave pattern during the subacute phase of STEMI (5th-7th day), i.e. after restoration of blood flow by primary PCI and in the absence of acute ischemia (138, 144, 145). To the best of our knowledge, there have been no reports on the time course of QRS morphology with regard to the occurrence of the J-wave pattern during progression of acute ischemia and infarction.

In one study intended to describe the repolarization ECG characteristics in STEMI complicated by VF, patients were divided into three groups according to the shape of the terminal part of QRS-complex on admission ECG. Downsloping J-ST segment toward T-waves immediately after R defined as type I or "lambda" pattern or "monophasic" pattern was found to be highly predictive of VF (147). Because of QRS complex deformation and elevated ST segment, the detection of J-point in such QRST morphology may be challenging (Figure 23). In order to avoid subjectivity in assessing QRS borders, we chose to use an automatic assessment of QRS duration, which includes terminal slurring and J-wave, if present, as part of the QRS complex (54).

Despite including J-wave or slurring in the QRS complex during automatic QRS delineation, the electrophysiological background of these QRS changes during acute ischemia remains controversial. In our experiment, all animals were on spontaneous sinus rhythm, and we observed no dramatic changes in heart rate during the occlusion period, which could help to differentiate the contribution of repolarization and depolarization abnormalities in the changes in the terminal part of QRS. The exact mechanisms underlying J-wave development associated with ischemia and preceding VF episodes cannot be elucidated from our study based on the closed-chest porcine model of myocardial infarction.

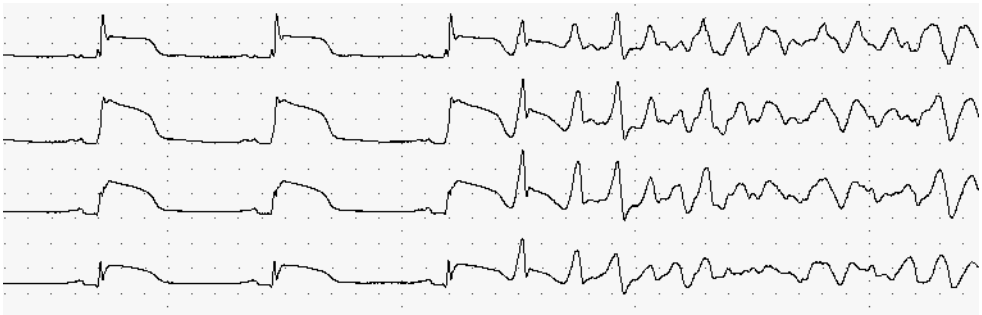

Figure 23
Occurrence of polymorphic VT followed by VF during acute ischemia. The QRS morphology is similar to type I pattern described in (147).

Earlier observations made in an open-chest model suggest that J-wave development is caused by the action potential differences between the epicardial and the endocardial myocardium (148). The decrease in inward currents Ina and Ica and a significant increase in outward currents such as IK-ATP and IKAA resulted in prevalence of outward currents in the epicardium and gave rise to the typical notched configuration of the action potential in the epicardium and the development of prominent J-waves (149). Yan et al. were the first to report the causative association between ischemia-induced I_{to}–mediated changes in action potential leading to the transmural voltage gradient that predispose to Phase 2 reentry (140). These experimental studies suggest that the fundamental mechanisms responsible for ST-segment elevation and initiation of VF are similar in early phases of acute myocardial ischemia and inherited J-wave syndromes (140, 150).

The similarity of morphology and underlying mechanisms raises an important question on genetic propensity for an ischemic J-wave pattern. Whether or not a typical J-wave pattern during acute ischemia is genetically determined is unclear; however, a higher prevalence of familial sudden death has been reported in patients with VF during acute STEMI than in patients without life-threatening arrhythmia (151). This suggests that genetic factors may be involved, and that predisposition to ischemic VF may differ between patients.

Because of presence of marked ST-elevation due to acute myocardial infarction, we did not measure J-point elevation and did not assess the slope of ST-segment, which has been previously reported to have predictive value for arrhythmic events (136, 152, 153).

Several previous studies reported an increased risk of arrhythmic complications in patients with inferior localization of J-wave pattern (133, 134, 136). In our study, a J-wave pattern, when observed, was present in the anterior leads corresponding to the

occluded coronary artery in all affected animals. QRS width varied in different leads, and maximal width was also reached in anterior leads. However, in some of the animals, J-wave pattern in anterior leads was combined with slurring or notching in inferior leads. The J-wave pattern presence in both anterior and inferior leads was associated with higher incidence of VF than J-wave pattern presence in only anterior or anterior and lateral leads, although this association did not reach statistical significance. However, any extrapolation of topical ECG changes observed in experimental animals to clinical settings should be made with extreme caution.

Several studies reported T-wave alternans to be predictive of malignant ventricular arrhythmias and cardiac death (89, 154, 155). In our study, we did not observe any association between the peak amplitude of TWA and VF. VF episodes always occurred after back evolution or disappearance of TWA (Figure 24).

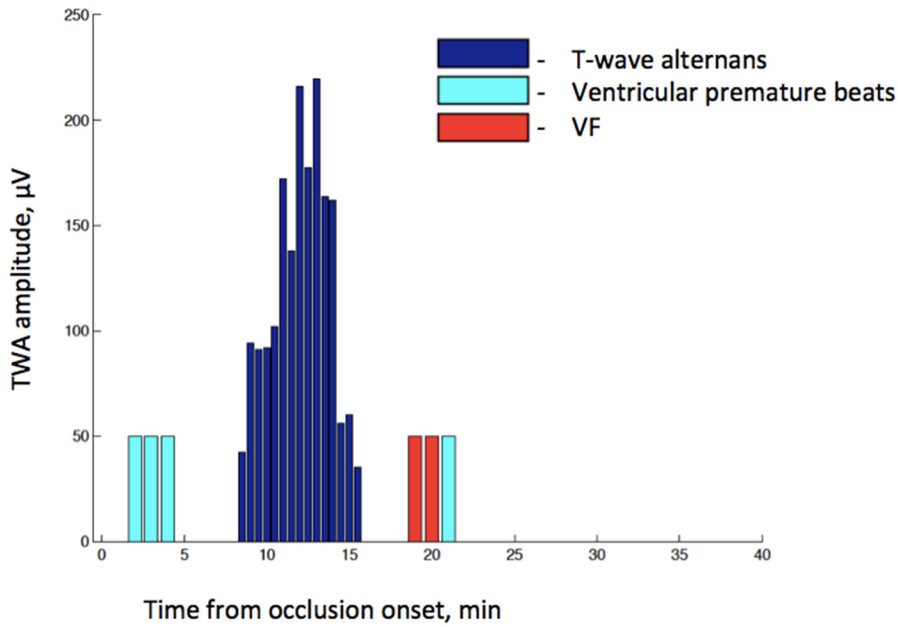

Figure 24
An example of TWA in one experimental animal with respect to VF at the 19th minute of occlusion.

Prognosis of VF in STEMI

Our studies confirmed the data of previous studies regarding poor in-hospital prognosis for VF patients (35, 43, 45, 47). Even reperfusion VF usually occurring after first medical contact is associated with mortality that is five times higher than mortality in No VF patients. The majority of in-hospital deaths in both rVF and No rVF groups was due to heart failure. Other causes included mechanical complications, cerebral injury and reinfarction, which corresponds with published data (44). Predictors of in-hospital mortality are age, MI history, heart failure ≥ Killip 2, multivessel disease, left main stenosis, VF before reperfusion and reperfusion VF.

We observed that long-term outcome among patients discharged alive is not affected by VF early in the course of STEMI. During follow-up, we analyzed not only the cases of death, but also the combined end-point of death, resuscitated cardiac arrest or appropriate ICD treatment, and found no differences between the two groups for this endpoint either. Therefore, our study, performed on a large non-selected population of PCI-treated STEMI, confirmed data from trials conducted before or during the thrombolysis era (33, 45, 47, 156, 157) regarding the absence of VT or VF influence within the first days of STEMI on long-term prognosis. After our results were published, another study based on the FAST MI register with a 5-year follow-up also reported that patients discharged alive after successfully resuscitated VF have the similar prognosis to patients without life-threatening arrhythmia (158).

In modern guidelines, VF occurring within the first 48 hours of STEMI is considered to be an event likely caused by transient reversible cases (159). Therefore, the prognosis of successfully resuscitated and revascularized patients expected to be benign. In general, these patients can receive standard medications for secondary prevention after STEMI with no need for ICD implantation or antiarrhythmics. However it is unclear whether these patients are at a higher risk of recurrent VF in settings of acute ischemia, e.g. in cases of repeated myocardial infarction.

Arrhythmia type may also play a role in choosing treatment strategy (160). For example, revascularization may be sufficient in patients with no MI history surviving VF or polymorphic VT in association with acute ischemia, but sustained monomorphic VT in patients with prior MI likely originating from a myocardial scar may not be affected by revascularization (160, 161). Many patients without clear indication of ICD implantations remain at risk and require individualized decision-making. Despite the absence of recommendations about ICD implantations for this group in guidelines, according to an HRS/AHA consensus document, ICD implantation may be appropriate for patients with single or recurrent VF within the first 48 hours of STEMI if ejection fraction is ≤35%, as well as being appropriate for patients who suffered VF within the first 48 hours of STEMI and nonsustained VT after the 4th day of STEMI and inducible VT/VF during electrophysiological study

after the 4th of STEMI; and for patients with VF within the first 48 hours of STEMI and obstructive coronary artery disease (CAD) with coronary anatomy not amenable to revascularization (162).

Patients who suffered VF after 48 hours of STEMI are at risk of repeated cardiac arrest and should be considered for ICD implantation (159, 161). In most cases, the decision about ICD implantation should be made no earlier than after 40 days of STEMI, after assessing cardiac function recovery. However, the problem of prevention of sudden death during the first month after STEMI remains unsolved (163).

Finally, the 48-hour cut-off is used in current recommendations for sudden death prevention for definition of early VF. We used this cut-off in our study as well. One should keep in mind, however, that the 48-hour cut-off comes from the pre-PCI era. It is not known whether different and possibly shorter cut-offs should be considered for patients undergoing invasive strategy resulting in immediate restoration of coronary flow. In our study, all seven patients who had VT or VF beyond the first 24 hours were alive at 1-year follow-up. While VF incidence during the first day of STEMI is sufficiently high for evidence-based decisions, data on the prognostic importance of in-hospital VF occurring beyond the first day of STEMI are scarce and can hardly be used for evidence-based risk stratification. More studies are therefore needed.

Conclusions

- Exacerbation of ST elevation - reperfusion peak - is common during restoration of blood flow in the occluded coronary artery. The magnitude of the ST elevation at reperfusion peak in experimentally induced myocardial infarction is associated with infarct size.
- The maximal level of TWA during occlusion period in experimental myocardial infarction was associated with both MaR and IS, which further supports the need for evaluating TWA in clinical settings in order to assess its prognostic value in patients with acute coronary syndrome.
- Rapid and marked transient increase in QRS duration commonly associated with the J-wave pattern appears to predict impending VF in acute ischemic settings and warrants further clinical studies for monitoring the immediate risk of VF during the acute phase of myocardial infarction.
- The risk of VF in acute period of STEMI is higher in patients with MI history, cardiovascular risk factors such as smoking and left main stenosis resulting in large infarct area.
- Besides MI history and left main stenosis, the risk of VF at reperfusion is associated with inferior localization of STEMI, hypokalemia, high ST-elevation and shorter symptom-to-balloon time. The magnitude of ST-elevation before PCI for STEMI independently predicts reperfusion VF and should be considered in periprocedural arrhythmic risk assessment.
- In a large non-selected population of STEMI patients treated with primary PCI, VT or VF within the first 48 h of STEMI is associated with increased in-hospital mortality, but does not influence long-term prognosis for patients discharged alive. Therefore, in line with current sudden death prevention guidelines, our data do not advocate ICD therapy for survivors of VF during the first 48 hours of STEMI. The rate of VF events beyond 24 h of STEMI in PCI-treated patients was low, and for these patients results must be interpreted with caution.

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Paper I

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ST-segment dynamics during reperfusion period and the size of myocardial injury in experimental myocardial infarction

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Abstract

Background: Exacerbation of ST elevation associated with reperfusion has been reported in patients with myocardial infarction. However, the cause of the "reperfusion peak" and relation of its magnitude to the size of myocardial damage has not been explored. The aim of our study was to assess the correlation between the ST-dynamics during reperfusion, the myocardium at risk (MaR), and the infarct size (IS).

Methods: Infarction was induced in 15 pigs by a 40-minute-long balloon inflation in the left anterior descending coronary artery. Tetrofosmin Tc 99m was given intravenously after 20 minutes of occlusion, and ex vivo single photon emission computed tomography was performed to assess MaR. Maximal ST elevation in a single lead and maximal sum of ST deviations in 12 leads were measured before, during, and after occlusion from continuous 12-lead electrocardiographic monitoring. A gadolinium-based contrast agent was given intravenously 30 minutes before explantation of the heart. Final IS was estimated using ex vivo cardiac magnetic resonance imaging.

Results: All pigs developed an anteroseptal infarct with MaR = 42% ± 9% and IS = 26% ± 7% of left ventricle. In all pigs, reperfusion was accompanied by transitory exacerbation of ST elevation that measured 1300 ± 500 μV as maximum in a single lead compared with 570 ± 220 μV at the end of occlusion ($P < .001$). The transitory exacerbation of ST elevation exceeded the maximal ST elevation during occlusion (920 ± 420 μV, $P < .05$). The ST elevation resolved by the end of the reperfusion period (90 ± 30 μV, $P < .001$). Exacerbation of ST elevation after reperfusion correlated with the final IS ($r = 0.64$, $P = .025$ for maximal ST elevation in a single lead and $r = 0.80$, $P = .002$ for sum of ST deviations) but not with MaR ($r = 0.43$, $P = .17$ for maximal ST elevation in a single lead and $r = 0.49$, $P = .11$ for sum of ST deviations). The maximal ST elevation in a single lead and the sum of ST deviations during occlusion did not correlate with either MaR or final IS.

Conclusion: In the experiment, exacerbation of ST elevation is common during restoration of blood flow in the occluded coronary artery. The magnitude of the exacerbation of ST elevation after reperfusion in experimentally induced myocardial infarction in pigs is associated with infarct size but not with MaR.

Keywords: Infarct size; ST elevation; Occlusion; ECG monitoring; Reperfusion

Introduction

The main treatment strategy of ST-elevation myocardial infarction (STEMI) is early administration of reperfusion therapy.[1-2] Early reperfusion therapy has been shown to limit myocardial infarct size (IS) and to reduce mortality.[1,3-4]

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It is well known that successful restoration of blood flow in the infarct-related artery is accompanied by a fast ST-elevation resolution[5]; thus, the ECG estimation is a common indirect method for assessing efficacy of reperfusion therapy.[6] Several previous studies have shown a short-term exacerbation of ST-segment elevation followed by complete ST-resolution during reperfusion.[7-10] The cause of this "reperfusion peak" and its relation to the extent of myocardial injury is not fully understood.

Thus, the aim of the present study was to assess the relationship between ST dynamics during reperfusion and size of myocardium at risk (MaR) as well as final IS in experimentally induced myocardial infarction in pigs.

Methods

Experimental protocol

After induction of anesthesia, ischemia was induced by inflation of an angioplasty balloon for 40 minutes. An angiogram was performed after inflation of the balloon and before deflation of the balloon to verify total occlusion of the coronary vessel and correct balloon positioning. After deflation of the balloon, a subsequent angiogram was performed to verify restoration of blood flow in the previously occluded artery. Twelve-lead ECG monitoring was initiated before starting the occlusion and lasted throughout the occlusion and continued until 4 hours after reperfusion when the experiment was terminated. The hearts were then explanted and analyzed by single photon emission computed tomography (SPECT) for assessment of MaR and by cardiac magnetic resonance (CMR) for assessment of IS.

The study conforms to the Guide for the Care and Use of Laboratory Animals, US National Institute of Health (NIH Publication No. 85-23, revised 1996), and was approved by the local animal research ethics committee.

Experimental preparation

Fifteen healthy domestic male and female pigs weighing 40 to 50 kg were fasted overnight with free access to water and were premedicated with Ketaminol (Ketamine, Intervet, Danderyd, Sweden), 100 mg/mL, 1.5 mL/10 kg, and Rompun (Xylazin, Bayer AG, Leverkusen, Germany), 20 mg/mL, 1 mL/10 kg intramuscularly 30 minutes before the procedure. After induction of anesthesia with thiopental 12.5 mg/kg (Pentothal, Abbott, Stockholm, Sweden), the animals were orally intubated with cuffed endotracheal tubes. A slow infusion of 1 μl/mL fentanyl (Fentanyl, Pharmalink AB, Stockholm, Sweden) in buffered glucose (25 mg/mL) was started at a rate of 2 mL/min and adjusted as needed. During balanced anesthesia, thiopental (Pentothal, Abbott) was titrated against animal requirements with small bolus doses. Mechanical ventilation was established with a Siemens-Elema 900B ventilator in the volume-controlled mode, adjusted to obtain normocapnia (P_{CO_2} 5.0-6.0 kPa). The animals were ventilated with a mixture of nitrous oxide (70%) and oxygen (30%). Analysis of arterial blood gases to adjust ventilation was performed before initiation of ischemia, at reperfusion, and at 1 hour after reperfusion. The pigs were continuously monitored by electrocardiogram (ECG). Arterial blood pressure was measured using a blood pressure transducer (ADInstruments Inc, Colorado Springs, CO). Heparin (200 IU/kg) was given intravenously at the start of the catheterization. A 12F introducer sheath (Boston Scientific Scimed, Maple Grove, MN) was inserted into the surgically exposed left femoral vein. A 0.021-in guide wire (Safe-T-J Curved, Cook Medical Inc, Bloomington, IN) was inserted into the proximal inferior vena cava through the introducer. Using the guide wire, a 10.7F Celsius Control catheter (Innercool Therapies Inc, San Diego, CA) was placed into the inferior vena cava with the tip of the catheter at the level of the diaphragm. Body temperature was measured with a temperature probe (TYCO Healthcare Norden AB, Solna, Sweden) placed in the distal part of the esophagus. The catheter and the temperature probe were connected to the Celsius Control, and the system was set to maintain a normal pig body temperature of 38.0° C. A 6F introducer sheath (Boston Scientific Scimed) was inserted into the surgically exposed left carotid artery upon which a 6F FL4 Wiseguide (Boston Scientific Scimed) was inserted into the left main coronary artery. The catheter was used to place a 0.014-in PT Choice guide wire (Boston Scientific Scimed) into the distal portion of the left anterior descending coronary artery (LAD). A 3.0 to 3.5 × 15 mm Maverick monorail angioplasty balloon (Boston Scientific Scimed) was then positioned in the mid portion of the LAD, immediately distal to the first diagonal branch. A 9F introducer sheath (Boston Scientific Scimed) was inserted into the surgically exposed right jugular vein. A 7.5F Continuous Cardiac Output Pulmonary Artery Catheter (Edwards Lifesciences, Irvine, CA) was then inserted into a pulmonary artery. Cardiac Output was continuously recorded using a Vigilance monitor (Edwards Lifesciences). All radiologic procedures were performed at the Biomedical Center at the Lund University, Lund, Sweden, using an experimental catheterization laboratory (Shimadzu Corp, Kyoto, Japan).

Electrocardiographic monitoring

A 12-lead digital ECG monitor ("Kardiotechnica-04-8m," Incart, St. Petersburg, Russia) with a sampling rate of 1024 Hz was used for assessing ST dynamics during occlusion/reperfusion. The use of the x-ray negative cable ("MAC LAB," USA) allowed continuous 12-lead ECG monitoring in angiographic laboratory with sampling frequency of 1000 Hz and amplitude resolution of 1.4 μV.

Complete analysis of QRS morphology was performed automatically on all QRS complexes with subsequent manual control before ST-segment analysis so that only QRS complexes of supraventricular origin were included for calculation of ST-segment deviation. The average level of signal at the area 40 to 20 milliseconds before onset of the QRS complex was referred to as the baseline. ST-segment deviation was then measured automatically 40 milliseconds after the J point for each QRS complex with subsequent hysteresis averaging-out. Averaging was based on 30 complexes, but QRS complexes with large deviation from average were excluded from the analysis. Continuous

analysis of ST-segment recovery was based on all 12 ECG leads. Maximal ST elevation in a single lead with greatest ST-segment elevation as well as the sum of ST-segment deviations (both elevations and reciprocal depressions) were assessed at baseline, during occlusion, and reperfusion periods. The time to complete ST resolution was estimated. ST resolution was defined as complete when residual ST elevation was less than 100 μV in leads I, II, III, aVF, aVL, V_4 through V_6 and 200 μV in V_1 through V_3 and ST stabilization at this level throughout all the period of observation.[11]

Imaging

Ex vivo imaging of the heart was undertaken according to a previously described protocol.[12] Cardiac magnetic resonance and SPECT images were analyzed using freely available software (Segment v1.700, Medviso, Lund, Sweden; http://segment.heiberg.se).[13]

Assessment of MaR by ex vivo SPECT

SPECT was used to assess the MaR as percentage of left ventricular myocardium. One thousand megabecquerel of tetrofosmin Tc 99m was administered intravenously at the 20th minute of occlusion. Ex vivo imaging was performed with a dual-head camera (Skylight, Philips, Best, the Netherlands) at 32 projections (40 seconds per projection) with a 64 × 64 matrix yielding a digital resolution of 5 × 5 × 5 mm. Iterative reconstruction using maximum likelihood-expectation maximization was performed with a low-resolution Butterworth filter with a cutoff frequency set to 0.6 of Nyquist and order 5.0. No attenuation or scatter correction was applied. Finally, short- and long-axis images were reconstructed. The endocardial and epicardial borders of the left ventricle that were manually delineated in the CMR images were copied to the co-registered SPECT images (Fig. 1). A SPECT defect was defined as a region within the CMR-determined myocardium with counts lower than 55% of the maximum counts in the myocardium and expressed as a percentage of left ventricle as previously described.[14]

Infarct size assessed by ex vivo CMR

The method used to assess IS by CMR has previously been described in detail.[12,15,16] In brief, a gadolinium-based

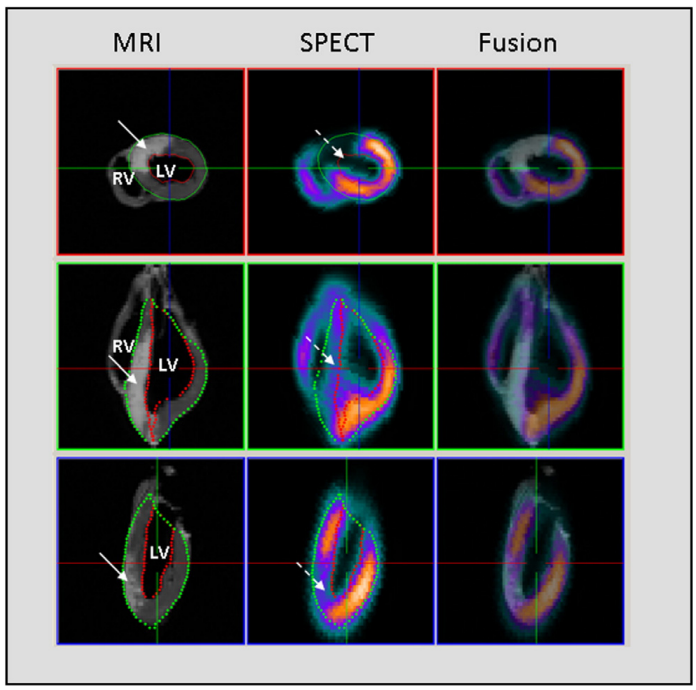

Fig. 1. Imaging of MaR and final IS after experimentally induced ischemia by occluding the LAD. Left column, Magnetic resonance imaging performed for visualization of the anteroseptal infarction (solid arrows). Dark gray myocardium indicates viable myocardium and white indicates infarction. Middle column, Single photon emission computed tomography used to assess the MaR by visualization of the anteroseptal perfusion defect (dashed arrows). Warm colors indicate adequate perfusion and cold/absent colors indicate decreased/lack of perfusion. Right column, Fusion of MRI and SPECT images. The upper panel shows a mid-ventricular short-axis slice and the lower 2 panels show 2 long-axis slices. Endocardial and epicardial borders of the left ventricle were manually delineated in the MR images and fused with the co-registered SPECT images. LV indicates left ventricle; RV, right ventricle.

contrast agent (Dotarem, gadoteric acid, Gothia Medical AB, Billdal, Sweden) was administered intravenously (0.4 mmol/kg) 30 minutes before removal of the heart. After removal, the heart was immediately rinsed in cold saline and the ventricles were filled with balloons containing deuterated water. CMR was performed using a 1.5-T MR scanner (Intera, Philips). T1-weighted images (repetition time = 20 milliseconds, echo time = 3.2 milliseconds, flip angle = 70°, and 2 averages) with an isotropic resolution of 0.5 mm covering the entire heart were then acquired using a quadrature head coil.

The endocardial and epicardial borders of the left ventricular myocardium were manually delineated in short-axis ex vivo images. This defined the left ventricular myocardium. The infarcted myocardium was defined as the myocardium with a signal intensity of greater than 8 SD above the average intensity of the nonaffected remote myocardium.[16] The infarcted myocardium was then quantified as the product of the slice thickness and the area of hyperenhanced myocardium. The IS was expressed as percentage of left ventricular myocardium.

Statistical methods

Data are presented as mean values ± SDs. Pearson correlation was used for assessment of relationships between ST-segment indices and MaR/IS. Paired-samples *t* test was used for comparisons between ST-segment indices at different stages of experiment. Statistical analyses were performed using PASW Statistics 18 (release 18.0.0, July 30, 2009).

Results

Experiment performance and data availability

All 15 animals survived during occlusion and early reperfusion period, despite frequent ventricular arrhythmias. Nine animals received defibrillation for ventricular fibrillation/hemodynamically important ventricular tachycardia during the occlusion period; 7, during reperfusion period.

Ex vivo imaging of the heart was performed in the 13 animals that survived for the 4 hours of reperfusion. Two pigs died during the experiment before the MRI contrast agent was administered. One more animal was excluded

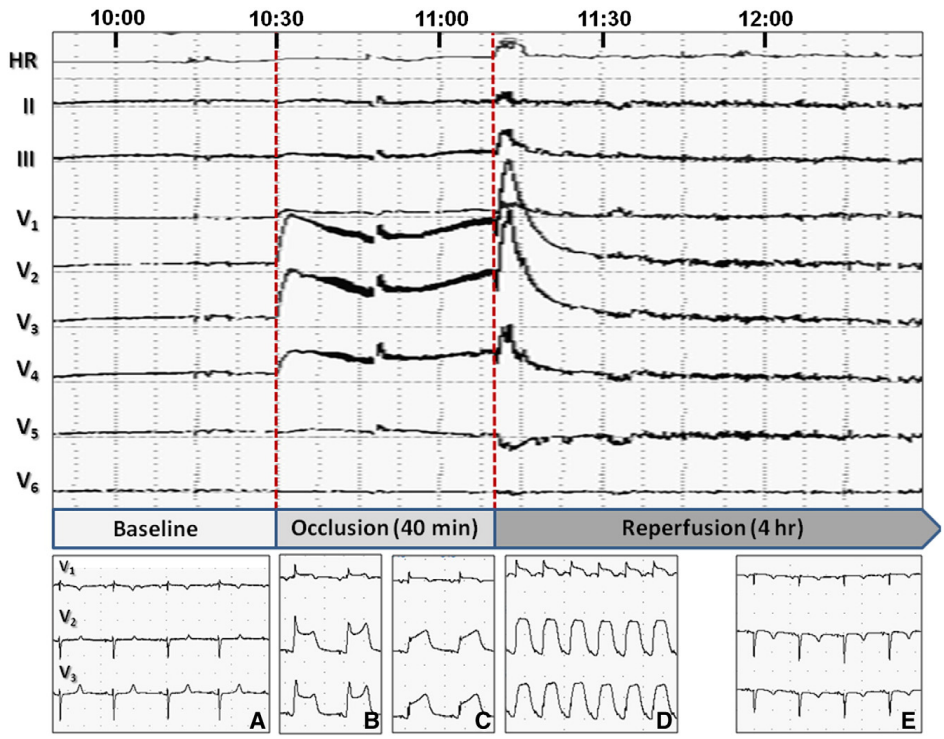

Fig. 2. ST-segment monitoring during 40 minutes of LAD occlusion and 4 hours of reperfusion. Transient exacerbation of the ST-segment elevation shortly after onset of reperfusion ("reperfusion peak") exemplified in this figure was observed in all animals. HR indicates heart rate. A, ECG strip at baseline; B, maximum of ST elevation during occlusion period; C, ECG at the end of occlusion; D, ECG at the "reperfusion peak"; E, ECG at the end of experiment.

Table 1
ST elevation during occlusion and reperfusion periods

	Maximal level during occlusion	Immediately before onset of reperfusion	Maximal during reperfusion ("reperfusion peak")	End of experiment
ST elevation in a single lead (V_2 or V_3) (μV)	920 ± 420	570 ± 220	1300 ± 500*	90 ± 30*,#
Sum of ST deviations in all 12 leads (μV)	2620 ± 1490	1681 ± 658	3590 ± 1420*	306 ± 150*,#

* $P < .001$ for comparison with the ST elevation at the end of occlusion.
\# $P < .001$ for comparison with the ST elevation at the "reperfusion peak."

from the analysis because of anomalous coronary anatomy. Thus, the association between ECG findings and MaR/IS was analyzed in 12 animals, whereas ECG data were analyzed for all 15.

ST dynamics during LAD occlusion

Typical ST dynamics during the occlusion and reperfusion is shown in Fig. 2. ST elevation occurred immediately after balloon inflation and reached its maximum 307 ± 101 seconds after the start of occlusion and decreased during the occlusion period (Table 1, Fig. 3). In all cases, an anteroseptal infarction with the greatest ST elevation in lead V_3 (n = 9) or V_2 (n = 6) developed.

ST dynamics during reperfusion

The angiographically verified blood flow restoration was accompanied by exacerbation of ST elevation in all 15 cases (see Fig. 2). The ST elevation started increasing shortly after LAD opening and reached its maximum 186 ± 102 seconds later. In 13 of 15 animals, the maximum level of ST elevation during reperfusion exceeded the ST elevation during the occlusion period. The maximal ST-segment elevation in a single lead with the greatest ST elevation and sum of ST deviations in all 12 leads during reperfusion are shown in Table 1 and Fig. 3. When maximal ST-segment elevation in a single lead was assessed, it was measured in the same lead (V_2 or V_3) during occlusion and reperfusion periods in all animals. During reperfusion, ST elevation in a single lead increased by 143% ± 104% (42%-370%) compared with ST elevation at the end of occlusion. The sum of ST elevation and reciprocal ST depression increased during reperfusion by 126% ± 109% (46%-390%) compared with the level at the end of occlusion. The reperfusion peak was followed by a fast resolution of ST elevation. The time to complete ST resolution was estimated as 55 ± 33 minutes. Upon reaching the complete resolution, the ST level remained stable until the end of experiment.

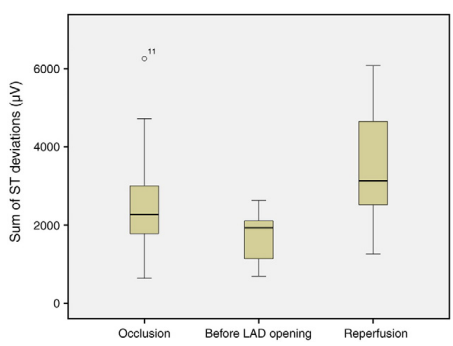

Fig. 3. Sum of ST deviations in all leads during occlusion and reperfusion periods.

Correlation between the ST elevation, MaR, and final IS

The MaR was 42% ± 9% (range, 28%-57%) and the IS was 26% ± 7% (range, 14%-40%) of the left ventricle. ST elevation during the occlusion period was not associated with either MaR or IS. The magnitude of transitory ST elevation exacerbation during the reperfusion was, however, correlated with IS, but not with MaR (Table 2 and Fig. 4).

Discussion

The ST dynamics analysis during the reperfusion therapy is commonly used for noninvasive assessment of reperfusion therapy efficacy,[6] estimation of microvascular perfusion,[17] and risk stratification of patients with STEMI.[18,19] It has been shown that rapid and high-grade ST resolution after reperfusion therapy is associated with better left ventricular function,[20-22] a lower enzyme level, and greater myocardial salvage measured by the nuclear imaging.[20,23] In clinical settings, the extent of ST-resolution and the time to ST-resolution are usually assessed based on discrete ECG strips only. Limited studies using 12-lead continuous ECG monitoring in the settings of STEMI have reported occurrence of short-term ST-elevation exacerbation followed by the complete ST resolution during reperfusion achieved by either thrombolytic therapy[24] or percutaneous coronary intervention (PCI).[11,25]

In the present study, a continuous 12-lead ECG monitoring and angiographic verification of LAD occlusion and complete restoration of blood flow enabled exploration of ST dynamics related to reperfusion in the infarct-related artery. The restoration of blood flow in the infarct-related artery was found to be accompanied by the transient exacerbation of ST-segment elevation in all 15 cases. The ST elevation exacerbated after LAD opening, reached its maximum 2 to 4 minutes later, and returned to the pre-reperfusion level 10 to 15 minutes later. Thereafter, the ST elevation gradually decreased toward complete resolution.

Table 2
The relationship between the ST elevation during the occlusion/reperfusion and the MaR and the final IS (Pearson correlation [*P* value])

	Occlusion period		Reperfusion period	
	MaR	Final IS	MaR	Final IS
ST max in single lead	−0.27 (.40)	−0.45 (.16)	0.43 (.17)	0.64 (.025)
Sum of ST deviations	−0.11 (.74)	−0.21 (.50)	0.49 (.11)	0.80 (.002)

This sharp deflection of the ST curve after reperfusion has earlier been referred to as a "reperfusion peak".[24,26]

In clinical settings, reperfusion peak has been observed in 68% to 75% of patients with STEMI effectively treated with thrombolysis[8,9] and in 23% to 63% of patients undergoing primary PCI.[7,11,25] Some data suggest that the reperfusion peak may be a more common finding during thrombolysis rather than during primary PCI.[27] In fact, the appearance and the magnitude of the reperfusion peak observed in clinical settings and in the present study are similar. In the present study, where all animals showed a reperfusion peak, the occlusion period was 40 minutes. In clinical practice, such short interval from symptom onset to balloon inflation is rarely seen. On the other hand, Terkelsen et al[25] did not find any relation between reperfusion peak presence or absence and time symptom onset to balloon inflation in a previous study addressing this issue. Furthermore, the mode of occlusion and reperfusion in clinical settings and experiment may also play role. The experimental model used in the present study is based on instant and complete mechanical occlusion and reperfusion of LAD. In clinical settings, thrombotic occlusion occurs through an inflammatory and coagulation cascade, often alternates with spontaneous clot lysis, and is associated with distal embolization and vasospasm. These factors may result in intermittent flow obstruction and partial restoration of blood flow contributing to pre- and postconditioning, which might affect the underlying pathophysiology of ST dynamics related to reperfusion.

Currently, there is no agreement in regard to the explanation of the nature of the reperfusion peak. Some data suggest that the peak is a sign of successful reperfusion and is associated with fast ST resolution[8,9,24] and favorable clinical outcome.[8] Several observations indicate that the peak is observed in case of severe myocardial injury before the onset of reperfusion associated with marked ST elevation, poor collateral circulation, and larger amount of myocardium involved in the ischemia-reperfusion process.[28]

Another plausible explanation is that the peak reflects reperfusion injury that contributes to the final IS[29] and caused by distal embolization with clot fragments and leukocyte aggregates, platelet activation, microcirculatory spasm, and edema.[30,31] It is also possible that reperfusion peak is not a consequence of additional myocardial damage but rather a pure electrophysiologic phenomenon caused by potassium washout during reperfusion.[32-34]

Earlier studies demonstrated the relation between the presence of the exacerbation of ST-elevation during reperfusion period and the greater extent of myocardial injury using indirect markers such as maximal level of troponin, ejection fraction, or Selvester ECG score.[11,35] Recently, similar findings were reported using a quantitative assessment of IS by SPECT.[25]

The present study is the first to correlate not only the presence of the peak but also the degree of ST-elevation exacerbation during the reperfusion with both MaR and IS, assessed quantitatively by SPECT and cardiac MRI. The findings indicate that magnitude of ST elevation at

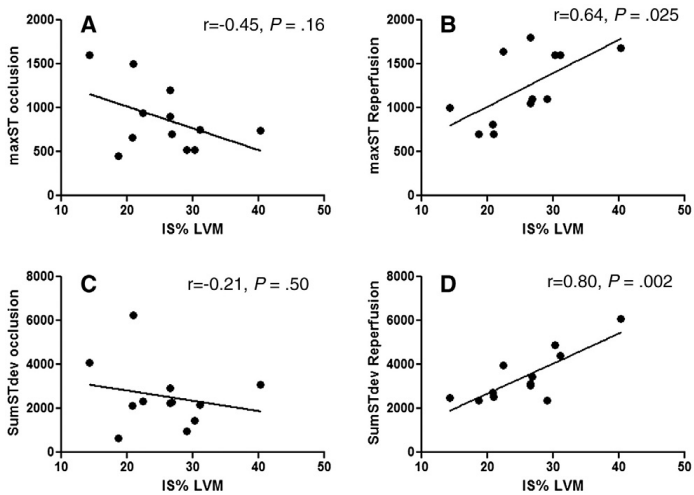

Fig. 4. Relationship between final IS and maximal ST-segment elevation in a single lead with greatest ST elevation and sum of ST deviations during occlusion (A and C) and reperfusion (B and D) periods. LVM indicates left ventricular mass; *r*, Pearson correlation coefficient.

"reperfusion peak" is associated with the IS but not with the MaR. ST elevation during the occlusion period was, however, not associated with either MaR or IS.

The association between the degree of ST elevation at the "reperfusion peak" and IS suggests that assessment of maximal ST elevation during reperfusion may be used for prediction of IS. The sum of ST deviations in all 12 leads appears to be a preferable marker for predicting the IS compared to the ST elevation in a single lead with the highest ST elevation. Further studies are needed to evaluate the usefulness of measurements of ST elevation during reperfusion period to assess its value for IS prediction and risk stratification in patients with STEMI treated with primary angioplasty.

Limitations

The findings in the present study should be interpreted in the light of some limitations. To achieve reproducibility of myocardial lesion in the settings of a limited number of experimental animals, only LAD occlusions were induced and uniform durations of ischemia (40 minutes) were applied. Therefore, evaluation of the effect of variability in duration of ischemia or location of the culprit vessel on the ST-segment deviation pattern and MaR/IS would require substantially greater number of experimental animals and remains to be explored.

As pointed out in the Discussion, the experimental model of myocardial infarction produced by inflation and deflation of the balloon does not fully reflect the course of events during STEMI in humans, which may at least in part explain discrepancy between our findings and clinical observations with regard to the frequency of reperfusion peak observed. Thus, to which extent the findings in the present study reflect the situation in patients with STEMI remains to be explored.

Finally, the timing of clinical CMR examinations for infarct sizing in patients with STEMI is usually much later than 4 hours after reperfusion that was used in the present study. There are observations suggesting that IS measurements using extracellular gadolinium-based contrast agents early after reperfusion may lead to overestimation of actual IS.[36]

Conclusion

Exacerbation of ST elevation is common during restoration of blood flow in the occluded coronary artery. The magnitude of the exacerbation of ST elevation after reperfusion in experimentally induced myocardial infarction in pigs is associated with IS but not with MaR. The prognostic value of this post-reperfusion exacerbation of ST elevation in humans undergoing early reperfusion therapy for STEMI remains to be determined.

Acknowledgment

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Paper II

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T wave alternans in experimental myocardial infarction: Time course and predictive value for the assessment of myocardial damage

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Abstract

Background: T-wave alternans (TWA) is associated with prognosis after myocardial infarction (MI), however its link to the extent of ischemic injury has not been clarified. We analyzed the course of TWA and its relation to myocardial damage in experimental myocardial infarction.
Methods: In 21 pigs, infarction was induced by 40-minute long balloon inflation in LAD under continuous 12-lead ECG monitoring. TWA was assessed in a 32-beat sliding window, using periodic component analysis and the Laplacian Likelihood Ratio method. Myocardium at risk (MaR) and infarct size (IS) were evaluated by SPECT and magnetic resonance imaging respectively.
Results: TWA appeared at 7.2 ± 4.5 minutes of occlusion, reached its maximum at 12.7 ± 6.3 and lasted until 26.5 ± 9.2 minutes. The maximal level of TWA was associated with both MaR ($r = 0.499$, $p = 0.035$) and IS ($r = 0.65$, $p = 0.004$).
Conclusion: TWA magnitude is associated with both MaR and IS in experiment, which encourages further studies in clinical settings.

Keywords: T wave alternans; Myocardial infarction; ST-elevation myocardial infarction

Background

T-wave alternans (TWA), an ECG phenomenon reflecting spatiotemporal heterogeneity of repolarization, is known to be associated with the ventricular vulnerability and risk of death in different categories of patients, particularly in post-myocardial infarction (MI) patients.[1–3] The negative association between the presence of TWA and ejection fraction has been reported in post MI patients.[4] It was supposed that larger infarcts resulted in low ejection fraction and discordant alternans due to considerable extension of abnormal tissue.[4] Infarct size (IS) is one of the most important factors related to mortality in ST-elevation myocardial infarction (STEMI).[5,6] However, the link between TWA and the size of ischemic damage has not been clarified yet. We analyzed the course of T wave alternans (TWA) during coronary artery occlusion and its relation to myocardial damage in experimental myocardial infarction (MI).

Methods

Experimental protocol

A porcine model of myocardial infarction was used in this work. The experimental preparation, study protocol and imaging technique were previously described in detail.[7] In brief, in pigs weighing 40–50 kg, anaesthetised with fentanyl and thiopental, an angioplasty balloon was positioned in the mid portion of the left anterior descending coronary artery (LAD), immediately distal to the first diagonal branch. Twelve-lead ECG monitoring (("Kardiotechnica-04-8 m", Incart, St. Petersburg, Russia) with a sampling rate of 1024 Hz and an amplitude resolution of

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1.4 μV) was initiated before starting the occlusion and lasted throughout all the period of occlusion.

Ischemia was induced by inflation of an angioplasty balloon for 40 minutes. An angiogram was performed after balloon inflation and before balloon deflation in order to verify total occlusion of the coronary vessel and correct balloon positioning. ^{99m}Tc-tetrofosmin was administered intravenously at the 20th minute of occlusion for subsequent single photon emission computed tomography (SPECT). After 40 minutes of occlusion the balloon was deflated and a subsequent angiogram was performed to verify restoration of blood flow in the previously occluded artery. TIMI-3 flow upon balloon deflation was achieved in all animals. Experiment was terminated after 4 hours of reperfusion. Gadolinium-based contrast agent was administered intravenously 30 minutes prior to removal of the heart for subsequent magnetic resonance imaging (MRI). After 4 hours of reperfusion the hearts were explanted and ex-vivo SPECT for assessment of area at risk (MaR) and MRI for assessment of IS was performed.

The study conforms to the Guide for the Care and Use of Laboratory Animals, US National Institute of Health (NIH Publication No. 85-23, revised 1996) and was approved by the local animal research ethics committee.

TWA analysis

The ECG signals were preprocessed, including QRS detection, normal beat labelling and baseline wander attenuation by cubic-spline interpolation. In each normal beat, ST segment amplitude was measured at J point + 40 ms. In each beat, an interval of 300 ms was selected for TWA analysis (including the ST-T complex). Then, TWA analysis was performed automatically on every ECG recording, as explained in the next paragraphs. The person performing the TWA analysis (AMY) was blinded to the rest of the data.

TWA analysis was performed using a sliding 32-beat signal window, applying a multilead processing scheme which makes use of the technique of periodic component analysis (πCA) for multilead ECG processing combined with the Laplacian Likelihood Ratio method (LLR) to detect and quantify TWA.[8]

The πCA technique searches for the linear combination of the available leads which maximizes the desired periodicity in the combined lead. For TWA analysis, we were interested in combining the leads in such a way that the 2-beat periodicity was maximized in the resulting signal. As shown previously,[8] the optimal combination is obtained by solving a generalized eigenvalue problem involving the spatial correlation matrix of the segment as well as the spatial correlation matrix of the non-periodic components. Using this technique we defined a linear transformation, from the 8 original independent leads (V1–V6, I, II) to 8 transformed leads (T1…T8), where T1 is the lead which maximizes the 2-beat periodicity in the ST-T segment. Note that to allow a good tracking of the TWA, the optimal combination was obtained for each 32-beat segment, as it depends on how the alternant components and noise are distributed within the ECG leads.

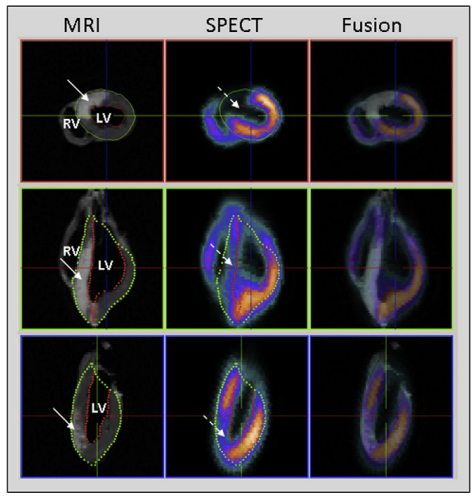

Fig. 1. Imaging of myocardium at risk and final infarct size after experimentally induced ischemia by occluding the left anterior descending coronary artery. Left column: Magnetic resonance imaging (MRI) performed for visualization of the anteroseptal infarction (solid arrows). Dark gray myocardium indicates viable myocardium and white indicates infarction. Middle column: Single photon emission computed tomography (SPECT) used to assess the myocardium at risk by visualization of the anteroseptal perfusion defect (dashed arrows). Warm colors indicate adequate perfusion and cold/absent colors indicate decreased/lack of perfusion. Right column: Fusion of MRI and SPECT images. The upper panel shows a mid-ventricular short-axis slice and the lower two panels show two long-axis slices. Endocardial and epicardial borders of the left ventricle were manually delineated in the MR images and fused with the co-registered SPECT images. LV = left ventricle, RV = right ventricle.
(From Demidova et al. J Electrocardiol 2011; 44 (1):74-81).

We have previously shown that the analysis of the πCA-transformed leads allows the detection of TWA episodes embedded in noise, which remain undetectable when they are analyzed in the original leads.[8] Thus, we used the LLR method explained in Martinez and Olmos[9] to detect and estimate TWA in each of the πCA transformed leads. TWA was considered to be present at the analyzed segment if it was detected in any of the transformed leads. To avoid spurious detections, only stable episodes, with duration longer than 64 beats were considered. For segments where TWA was detected, the TWA waveform (i.e, the median difference between even and odd beats) was estimated in all πCA transformed leads using the maximum likelihood estimate for Laplacian noise.[9] The multilead TWA amplitude was then defined as the sum of the root mean squared (RMS) values in all transformed leads. When no TWA was detected, the TWA amplitude was considered to be zero. To quantify TWA in the standard leads, we applied the inverse πCA transformation, after setting to zero all transformed leads where TWA was not found. In this way, we obtained a reconstructed version of the original signal, which kept essentially unaltered the TWA content and its lead distribution while discarding other non-alternant

components.[8] The RMS value of the TWA amplitude was then estimated in each standard lead using the LLR Method.

Imaging

The imaging technique has previously been described in detail.[10–12] Magnetic resonance and SPECT images were analyzed using freely available software (Segment v1.700, Medviso, Lund, Sweden, http://segment.heiberg.se).[13] In brief, SPECT was used to assess the MaR as a percent of the left ventricular myocardium. The endocardial and epicardial borders of the left ventricle that were manually delineated in the MR images were copied to the co-registered SPECT images (Fig. 1). A SPECT defect was defined as a region within the MRI-determined myocardium with counts lower than 55% of the maximum counts in the myocardium and expressed as a percentage of left ventricle as previously described.[14]

For MRI assessment, after removal, the heart was immediately rinsed in cold saline and the ventricles were filled with balloons containing deuterated water. MRI was performed using a 1.5 T MR scanner (Intera, Philips, Best, the Netherlands). The infarcted myocardium was defined as the myocardium with a signal intensity >8SD above the average intensity of the non-affected remote myocardium.[12] The infarcted myocardium was then quantified as the product of the slice thickness and the area of hyperenhanced myocardium. The IS was expressed as percent of left ventricular myocardium.

Statistical methods

Data are presented as mean values ± standard deviations. Pearson's correlation was used for assessment of relationships between repolarization indices and MaR/IS. Statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Twenty three experimental animals comprised the study group. One pig was lost due to unsuccessful resuscitation after ventricular fibrillation during the occlusion period. In one more animal, TWA could not been assessed due to a poor signal quality. TWA was therefore calculated in 21 pigs. Indexes of myocardial damage could not be measured in three more pigs, which had died during reperfusion period from resistant VF or electromechanical dissociation. Thus data on MaR, IS and TWA were available for 18 of 23 pigs.

TWA appeared at 7.2 ± 4.5 (IQ range 3.9–9.6) minutes after occlusion onset, reached its maximum at 12.7 ± 6.3 (IQ range 8.8–17.5) minutes after occlusion onset and lasted until 26.5 ± 9.2 (range 21.2–32.9) minutes (Figs. 2 and 3). The amplitude of TWA was maximal in leads with maximal ST elevation most often in V_2,–V_4 (Fig. 4). The correlation between maximal ST deviation and maximal TWA amplitude measured in each individual lead was significant for leads V_2–V_6, I and II. However, we did not observe in any lead a significant correlation between maximal T wave

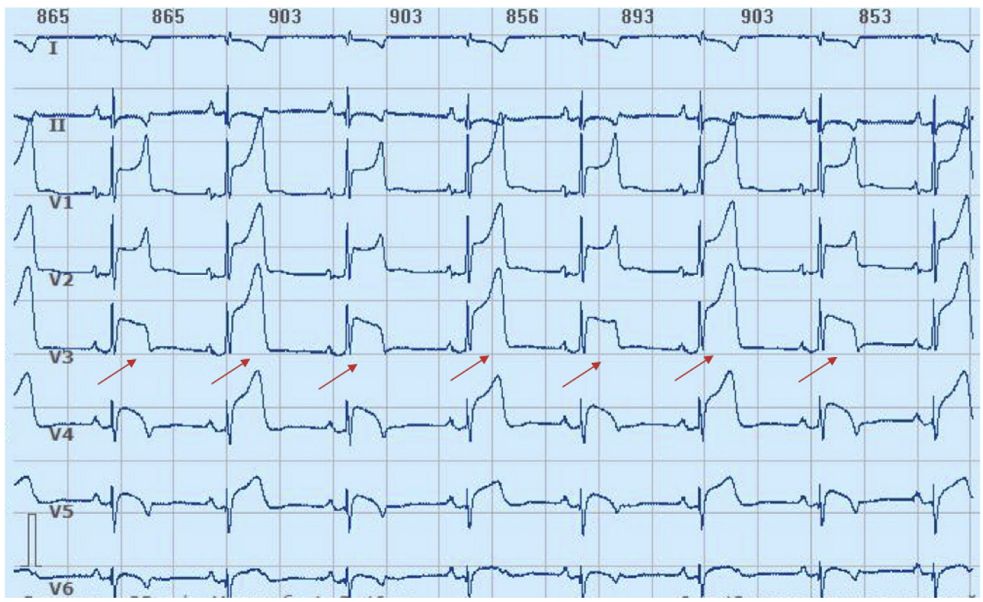

Fig. 2. ECG example of visible T-wave alternans during coronary occlusion. ECG at the 12th minute of occlusion. Heart Rate – 68 b.p.m. Arrows show the apparent beat to beat alternation of T-wave morphology. The scale (1 mV) could be seen in the lower left corner. TWA amplitude is maximal in leads V_2 (302 μV), V_3 (550 μV) and V_4 (446 μV).

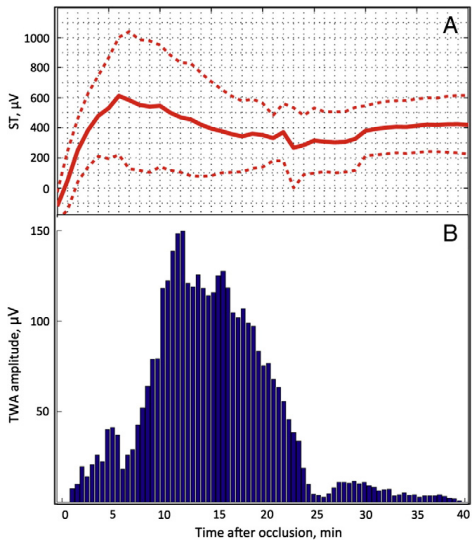

Fig. 3. ST dynamics and the time-course of TWA amplitude during occlusion. A. ST dynamics in one lead with most prominent ST elevation during the occlusion period (V_3), group-averaged (Mean (heavy line) ± standard deviation (dotted line)). B. TWA time course during the occlusion period, group-averaged. The standard lead with maximal TWA amplitude (usually V_2–V_4) was used to build the TWA time-course. For each animal, the RMS voltage of TWA was averaged every 30 seconds along the 40-minute occlusion. Then, the averaged time-course of all these 21 individual profiles was calculated. Abbreviations: TWA – T-wave alternans; RMS – root mean square.

amplitude and maximal TWA. Maximal TWA was not associated with any significant change in heart rate (75 ± 19 vs 76 ± 21 b.p.m., p = 0.575 for heart rate at baseline and during a minute preceding maximal TWA).

Twelve of 21 animals suffered from ventricular fibrillation during two distinct periods during LAD occlusion early (n = 5 at 2.0 ± 0.8 minutes) and late (n = 7 at 16.9 ± 5.8 minutes). All late VF episodes were preceded by TWA, but we did not observe any association between the peak amplitude of TWA and VF occurence.

The MaR was 40 ± 9% (range 28–57%) and the IS was 23 ± 7% (range 10–40%) of the left ventricle. The maximal level of TWA in a standard lead was associated with both MaR (r = 0.499, p = 0.035) and IS (r = 0.65, p = 0.004) (Fig. 5, top panel). When measuring the maximal level of multilead TWA as the sum of the amplitudes in the πCA transformed lead, correlations were stronger with MaR (r = 0.58, p = 0.012) and IS (r = 0.79, p < 0.001) (Fig. 5, bottom panel).

Discussion

We performed quantitative TWA-assessement in the settings of complete and prolonged coronary occlusion, resulting in acute ischemia followed by myocardial necrosis. In earlier studies on TWA caused by ischemia, TWA was observed during exercise stress-test,[15] accompanied ST elevation in patients with Prinzmetal's angina[16] and transitory occlusion of coronary artery during PCI.[17,18] In our study, TWA occurrence was markedly higher (93%) than in studies with even prolonged occlusion during PCI (52%),[19] that could be explained by more severe ischemia and development of necrosis. The 40 minute-duration of occlusion in our experiment corresponds to approximately 4–5-hour of human myocardial infarction because the rate of myocardial infarction progression in pigs is approximately 7-times faster than in humans, presumably due to a poor collateral blood flow.[20] To the best of our knowledge, TWA dynamics during acute long-time coronary artery occlusion has not been described in detail either in experimental or in clinical settings. In previous PCI studies, where the time of occlusion was short, the TWA magnitude increased continuously during all the period of occlusion.[18,19] The prolonged occlusion we could maintain in the experiments as compared

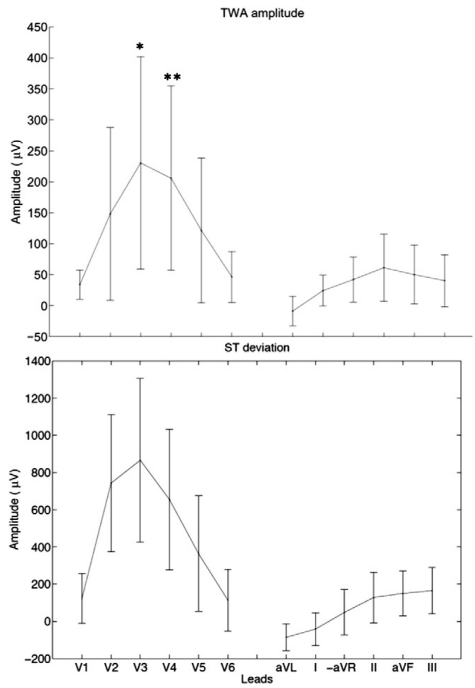

Fig. 4. Averaged TWA lead distribution and average ST distribution profiles, illustrating that maximal TWA corresponds to the area of ischemic injury caused by LAD occlusion. Data from all animals calculated on a per ECG lead basis for each of the 12 standard ECG leads. For each lead, the mean ± standard deviation of the RMS values at the peak of TWA are presented. * - maximal TWA amplitude in V3 was significantly larger than TWA in any other lead excepting V4 (all p < 0.005), and ** - maximal TWA amplitude in V4 was significantly larger than TWA all the leads exept V2 and V3 (all p < 0.005). Abbreviations: TWA – T-wave alternans; LAD – left descending artery; RMS – root mean squared.

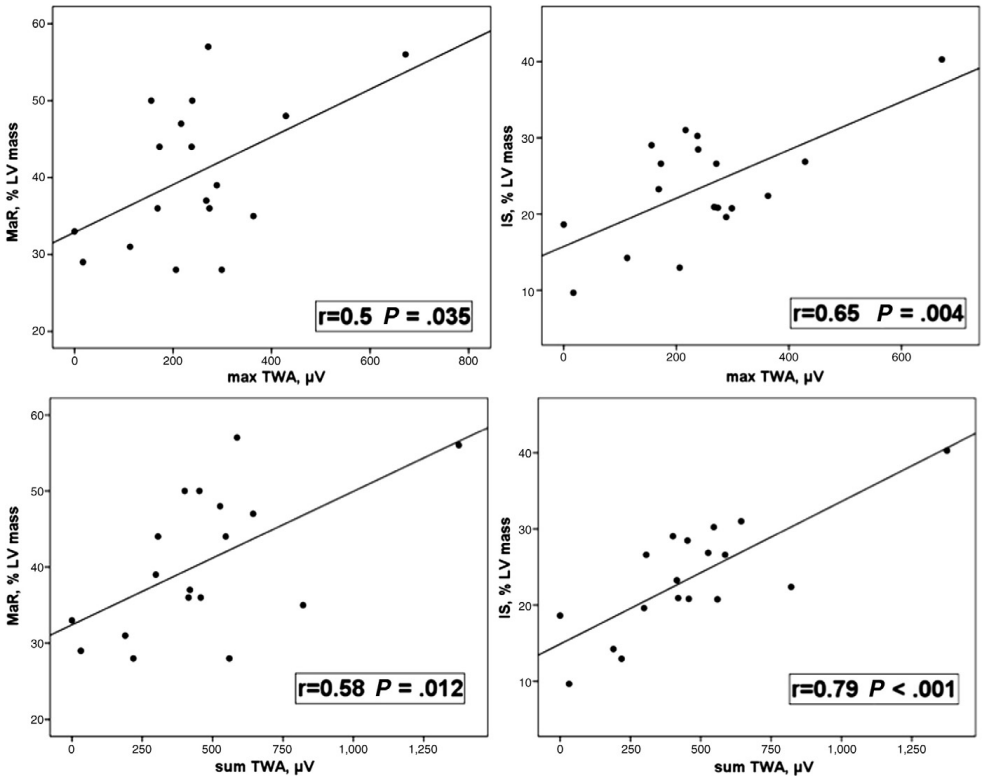

Fig. 5. The association between maximal TWA and the extent of myocardial injury. In the top panels, TWA amplitude is measured as the RMS value in the standard lead with maximal TWA amplitude. In the bottom panels TWA is given as the sum of the RMS amplitudes in the transformed leads. Abbreviations: MaR – myocardium at risk, IS – final infarct size, TWA – T-wave alternans; RMS – root mean squared.

to clinical settings allowed to detect late TWA episodes in some animals (which made the average onset time to delay until 7.2 ± 4.5 min), but the percentage of animals with TWA in the first minutes of occlusion (19% in the first two minutes, 38.1% in the first 5 minutes) as well as their onset times was comparable to those reported in PCI.[19]

In a dog model of ischemia, TWA had a tendency to decrease during the last two minutes of 10-minute long occlusion.[18] Extension of coronary artery occlusion beyond the 10-minute period, at least in the porcine model that was used in our study, leads to a rather abrupt decrease in TWA amplitude by 25th minute and becomes nearly negligible by the end of the 40-minute long occlusion. The reason for such reduction of TWA amplitude despite continued occlusion is not fully understood but may be explained by progressive loss of living myocytes and development of electrically inactive necrotic tissue in the infarcted area.

The intensity of TWA was maximal in leads with maximal ST elevation, most often in V_2–V_4 corresponding the anterio-septal wall – the area supplied by the left anterior descending artery (LAD); SPECT and MRI showed myocardial injury in the same area. The regional nature of TWA was in line with literature data.[18]

Not only the presence of post-infarction scar, but also the acute ischemia seems to be an important trigger of TWA as shown in another experiment, in which the presence of myocardial scar without acute ischemia was not associated with TWA at intrinsic heart rhythm but could be induced by rapid ventricular pacing.[21] In clinical practice, exercise tests are often used to reach acceleration of heart rate sufficient to enable detection of TWA in post MI patients.[22,23] In the acute STEMI experiment, we observed visible TWA at spontaneous heart rhythm.

TWA is conventionally considered a rate-dependent phenomenon that requires certain rate increase in order to induce measurable TWA. In this context, occurrence of TWA at lower heart rates has been associated with higher risk of ventricular arrhythmias in clinical settings.[24] In our series, mean heart rate was relatively low and TWA, including the visually apparent one, occurred without preceding heart rate acceleration. It is possible that the lack of rate increase can be attributed to the use of fentanyl-

induced general anesthesia in our model. However, the most likely explanation for the TWA that occurred independently of heart rate increase was severe acute ischemia that impairs cellular calcium cycling, which would permit alternans to be initiated at slower heart rates.[25,26] Clinical data on TWA occurrence in the acute phase of STEMI are scarce[27,28] while experimental data are limited to mostly the analyses of intracardiac electrograms and open-chest settings[18,29–31] not directly comparable to the closed chest model employed in our study.

Numerous clinical studies demonstrated role of TWA in sudden cardiac death prediction.[1,2,22,32] The majority of them have included patients with a specific substrate for ventricular tachyarrhythmia, such as infarct scar. It is plausible to suggest the existence of relationship between regional inhomogeneities of ventricular repolarization predisposing to ventricular arrhythmias and the size of myocardial damage. To clarify whether TWA is associated with the degree of myocardial injury we correlated TWA magnitude with MaR and final infarct size. To our knowledge, the relationship between repolarization variability and infarct size was previously studied in only one experimental study in a porcine model of subacute myocardial infarction, and no significant correlation between beat-to-beat variability of repolarization and infarct size was found.[21] In the present study, we have shown that the maximal level of TWA was associated with both MaR and IS. This finding suggests that TWA may be a potential marker of prognostic assessment in STEMI patients. SPECT and MRI – the "gold standard" – in evaluating of myocardial injury, are still far from being a routin clinical examination in patients with STEMI. TWA analysis is a non-invasive marker and can be relatively simply calculated using conventional holter ECG recording, but its value in clinical settings remains to be determined.

Limitations

The findings in the present study should be interpreted in the light of some limitations. In order to achieve reproducibility of myocardial lesion in the settings of a limited number of experimental animals, only LAD occlusions with uniformly 40-minutes duration of ischemia were induced, resulted in necrotic area, corresponding approximately 20–30% of left ventricle. Thereby, this experimental model corresponds in clinical settings to MI of high risk of adverse outcome.

Secondly, the experimental model of myocardial infarction produced by inflation and deflation of the balloon does not fully reflect the course of events during STEMI in humans that is characterized by progression through an inflammatory and coagulation cascade to a thrombotic occlusion and commonly occurring spontaneous recanalization or alternating occlusion of the infarct-related artery.

Thirdly, the direct histologic examination has not been performed in this study, but results of several previous studies have shown strong correlation between infarct size assessed by MR-study and histology.[33–35]

Finally, it would be of value to assess TWA in the chronic phase of the MI in this porcine model and evaluate its relationship to the findings obtained in the acute phase. However, due to the acute study settings it could not be performed.

Conclusion

In experimental myocardial infarction induced by LAD occlusion, the maximal level of TWA during occlusion period was associated with both MaR and IS, which further supports the need for evaluation of TWA in clinical settings for assessment of its prognostic value in patients with acute coronary syndrome.

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Paper III

Transient and rapid QRS-widening associated with a J-wave pattern predicts impending ventricular fibrillation in experimental myocardial infarction

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BACKGROUND Certain types of the early repolarization phenomenon, previously considered to be benign, have been reported to be associated with ventricular fibrillation (VF), both in population-based studies and in the myocardial infarction (MI) settings.

OBJECTIVE To analyze whether QRS widening and appearance of a J-wave pattern in experimental MI settings is predictive of VF.

METHODS MI was induced in 32 pigs by 40-minute inflation of an angioplasty balloon in the left descending artery, and electrocardiogram was continuously recorded. Multilead QRS boundaries were computed, and QRS duration was calculated on a beat-to-beat basis during the occlusion period for each pig. An association between QRS widening and subsequent VF was studied using receiver operating characteristic curve analysis. Electrocardiograms at maximum QRS duration were reviewed for the presence of a J-wave pattern.

RESULTS Sixteen animals had VF episodes during the occlusion period. Two peaks of QRS widening were found in all animals: the first peak immediately on left descending artery occlusion and the second peak 19.1 $\pm$ 4.0 minutes later. The magnitude of changes in the QRS width over time had significant interindividual differences. A QRS widening of $\geq$28 ms during a 3-minute time window was observed in 14 animals and predicted impending VF (selectivity 80%, specificity 73%, positive predictive value 57%, and negative predictive value 89%; $P = .008$). In 10 of 14 (71%) pigs, a J-wave pattern appeared at maximal QRS duration. The appearance of a J-wave pattern predicted VF with selectivity 80%, specificity 68%, positive predictive value 53%, and negative predictive value 88% ($P = .02$).

CONCLUSION Transient QRS widening, commonly associated with a J-wave pattern, appears to predict impending VF in acute ischemia settings and motivates further clinical studies for monitoring immediate risk of VF in MI.

KEYWORDS Myocardial infarction; Ventricular fibrillation; Early repolarization; QRS duration; J wave

ABBREVIATIONS **ECG** = electrocardiogram/electrocardiographic; **ER** = early repolarization; **LAD** = left descending artery; **MI** = myocardial infarction; **PPV** = positive predictive value; **NPV** = negative predictive value; **Se** = selectivity; **Sp** = specificity; **STEMI** = ST-segment elevation myocardial infarction; **VF** = ventricular fibrillation

(Heart Rhythm 2014;11:1195–1201)

Introduction

Malignant ventricular arrhythmias, particularly ventricular fibrillation (VF), remain an important contributor to mortality in ST-segment elevation myocardial infarction (STEMI).[1,2] The success of VF treatment is determined by time elapsed between the occurrence of VF and the administration of medical care. Therefore, the main strategy in relation to the life-threatening ventricular arrhythmias during STEMI is their prediction and prevention.[3] Although several studies proposed predictors of ventricular arrhythmias in STEMI settings, most of those predictors can be attributed to

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clinical characteristics[1,2,4] while data on dynamic electrocardiographic (ECG) changes that can predict VF are scarce.

The early repolarization (ER) pattern, including J-point elevation, distinct J wave with or without ST-segment elevation, or slurring of the terminal part of the QRS complex,[5] is generally found in healthy young male individuals and is considered to be a benign ECG phenomenon.[6–8] However, certain types of this J-wave pattern at resting ECG, such as those observed in the inferior leads and associated with the horizontal/descending ST segment, have been linked to an increased risk of ventricular arrhythmias and sudden death.[5,9,10] This association was first reported in animal experiments[11–13] and then in clinic for idiopathic VF.[14]

More recent studies demonstrated that the association of a J-wave pattern with ventricular arrhythmias and sudden death is valid in a broader context of population-based sudden death prediction[9] and in the settings of myocardial ischemia.[10,15–17] Our aim was to analyze the course of QRS morphology and possible appearance of a J-wave pattern during coronary artery occlusion in the experiment as a predictor of VF.

Methods

Experimental protocol

A porcine model of myocardial infarction (MI) was used in this work. The experimental preparation and study protocol have previously been described in detail.[18] In brief, in 38 pigs weighing 40–50 kg, anaesthetized with fentanyl and thiopental, an angioplasty balloon was positioned in the midportion of the left descending artery (LAD), immediately distal to the first diagonal branch. Ischemia was induced by inflation of an angioplasty balloon for 40 minutes, and 12-lead ECG monitoring ("Kardiotechnica-04-8m," INCART, St. Petersburg, Russia) was started before the occlusion and continued throughout the occlusion period. The ECG sampling rate was 1024 Hz, and the amplitude resolution was 1.4 μV. The completeness of coronary occlusion was verified by coronary angiography.

The study conforms to the *Guide for the Care and Use of Laboratory Animals*, US National Institutes of Health (NIH Publication No. 85-23, revised 1996), and was approved by the local animal research ethics committee.

ECG analysis

QRS complexes were automatically detected and then visually and manually checked. After applying an automatic wavelet-based ECG delineator[19] to precordial leads, beat-to-beat multilead QRS boundaries were computed. For each pig, QRS duration was computed on a beat-to-beat basis, as the difference between the QRS onset and the QRS end marks along a 40-minute occlusion period for each experimental animal. These series were then resampled by averaging QRS duration every 10 seconds.

For each animal, the dynamic changes in QRS duration during the occlusion period were plotted as a function of time

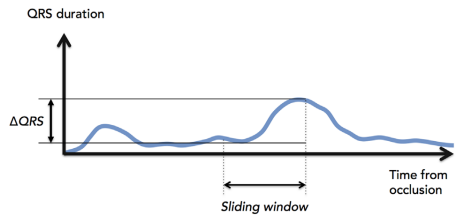

Figure 1 Schematic illustration showing the delta QRS duration in the sliding window during the occlusion period. In our study, the sliding window duration was 3 minutes.

(Figure 1). To quantify QRS widening, 2 indices were continuously assessed using a sliding window of 3-minute duration: (1) a local QRS duration increase (delta QRS duration) and (2) a maximal absolute QRS duration. Delta QRS duration was calculated as the difference between the QRS duration of the last beat in the window and the narrowest QRS in the 3-minute window.[20]

ECGs for each pig at baseline and at the time of maximal QRS duration were independently reviewed for the presence of QRS complex notching or slurring (J-wave pattern)[21,22] in $\geq$2 contiguous leads by 2 investigators (P.G.P. and M.D.) who were blinded to VF occurrence. *Notching* was defined as a positive deflection at the terminal portion of a positive QRS complex. *Slurring* was defined as a smooth transition from the QRS complex to the ST segment with upright concavity (Figure 2).[22] The conventional J-wave amplitude criterion could not be applied as the ST segment was elevated as a result of complete LAD occlusion. We classified the localization of the J-wave pattern as that present in either the inferior (leads II, III, and aVF), lateral (leads I, avL, and V_4–V_6), or anterior (leads V_1–V_3) leads. Anterior precordial leads reflecting the ischemic zone due to LAD occlusion were not excluded from the analysis.

Statistical analysis

Data are presented as mean ± SD or as median and interquartile range in cases of asymmetrical distribution. The Fisher exact test was used for comparisons between study groups.

Receiver operating characteristic curve analysis was used to identify the optimal cutoff of QRS duration increase for predicting VF during the occlusion period. Statistical significance was accepted at $P < .05$ (2-sided). Factors associated with VF were identified in univariate logistic regression models with estimation of odds ratios. Statistical analyses were performed using SPSS 19.0 (SPSS Inc, Chicago, IL).

Results

One pig died during the occlusion period from left main thrombosis. Thus, 37 of 38 pigs survived the occlusion period. Five animals were excluded from the analysis because of the poor-quality signal. Of the remaining

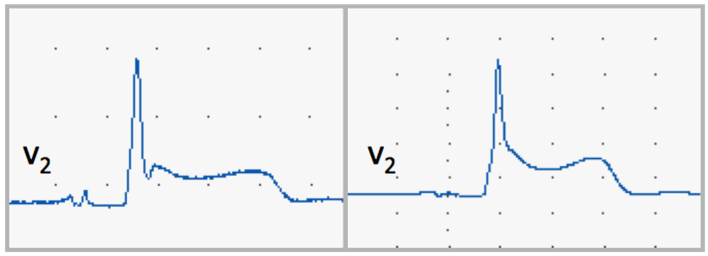

Figure 2 Electrocardiographic examples in lead V_2, illustrating different morphologies of the early repolarizations pattern. **A:** Notch is present in lead V_2. **B:** Slur is visible in lead V_2. ST-segment elevation due to ST-segment elevation myocardial infarction is shown in both panels A and B.

32 pigs, 6 pigs suffered from VF during the first minutes of occlusion, on average 2.6 ± 2.1 (range 0.6–7.0) minutes after occlusion start, and 10 pigs, on average 20.9 ± 4.0 (range 16.8–30.2) minutes after occlusion start (Figure 3). Since ECG-based prediction of VF was not technically feasible during the first minutes of ischemia, this study focused on the occurrence of late VF episodes (occurring after the 15th minute of occlusion).

All the studied animals demonstrated similar dynamics of QRS duration changes characterized by the 2 peaks of QRS widening: the first peak immediately after LAD occlusion 3.7 ± 1.6 minutes and the second peak 19.1 ± 4.0 minutes after occlusion start (Figure 4). Significant interindividual differences were observed with regard to the magnitude of changes in QRS width. These differences varied from the negligible variation in QRS duration to pronounced QRS widening over short time measured as delta QRS duration over a 3-minute window. The value of QRS duration at baseline, at the first (0–10 minutes of the occlusion period) and the second (10–40 minutes of the occlusion period) peaks of QRS widening, and at the end of the occlusion period is shown in Figure 5. The QRS duration at baseline was 78 ± 11 ms, and at the first peak of QRS widening 140 ± 21 ms, and at the second peak −124 ± 17 ms ($P < .001$). The median difference between maximal QRS duration and QRS duration at baseline was 27 ms (interquartile range 16 ms).

At baseline, no animals demonstrated a J-wave pattern in any lead. At maximal QRS duration, a J-wave pattern was found in 15 of 32 animals. Figures 6 and 7 show the typical QRS morphology dynamics during the experiment. Notching or slurring usually appeared on QRS widening and manifested at maximal QRS duration, with subsequent resolution during continued occlusion.

The J-wave pattern in anterior leads, which reflected the ischemic zone caused by LAD occlusion, was found in all 15 animals, which showed slurring or notching of QRS complexes at its maximal width. In 8 animals, the J-wave pattern in anterior leads was combined with the J-wave pattern in inferior leads; in 2 animals, in lateral leads; in 5 animals, it was confined to anterior leads only. The most commonly observed J-wave pattern was notching of the terminal QRS complex in 13 animals, while slurring was noted in 2 animals.

The association between QRS widening and subsequent VF onset was studied using the receiver operating characteristic curve analysis. Two thresholds in delta QRS duration showing a reasonable combination of sensitivity and

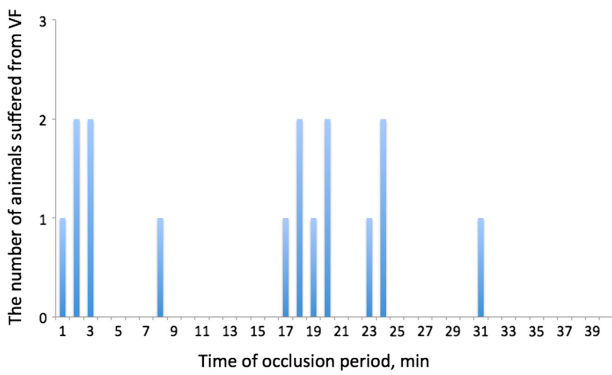

Figure 3 Time distribution of ventricular fibrillation (VF) episodes during coronary occlusion. Two distinct peaks of ventricular arrhythmia occurrence were observed and corresponded to phase 1a (< 10 minutes) and 1b (> 15 minutes).

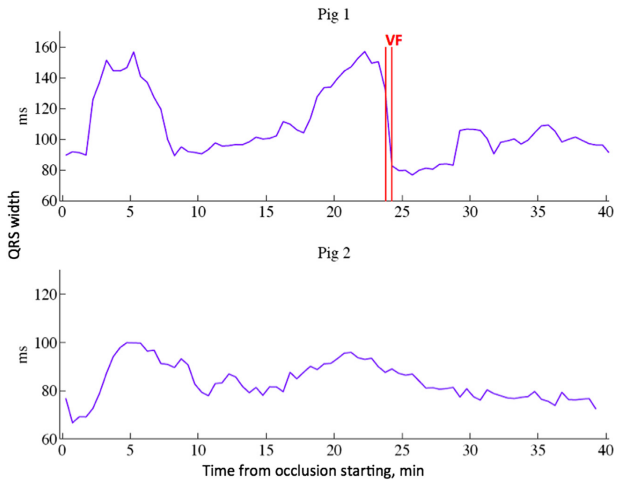

Figure 4 Dynamics of QRS width through 40-minute coronary occlusion. **A:**Marked QRS widening at 2–7 and 17–22 minutes in 1 pig with ventricular fibrillation at the 24th minute of occlusion. Vertical line shows the time of VF occurrence. **B:** Slight changes in QRS width in an animal without ventricular fibrillation.

specificity for VF prediction were 28 and 36 ms, respectively (Figure 8).

A QRS widening of $\geq$28 ms in 3 minutes predicted impending VF with selectivity (Se) 80%, specificity (Sp) 73%, positive predictive value (PPV) 57%, and negative predictive value (NPV) 89% ($P = .008$). A QRS widening of $\geq$36 ms in 3 minutes predicted impending VF with Se 70%, Sp 95%, PPV 88%, and NPV 88% ($P < .001$). Thus, marked and fast QRS widening predicted VF (OR 10.7, 95% CI 1.7–65.3, $P = .010$ for a QRS widening of $\geq$28 ms in 3 minutes; OR 49.0, 95% CI 4.4–550.7, $P = .002$ for a QRS widening of $\geq$36 ms in 3 minutes), while the absolute value of maximal QRS duration had no predictive value (OR 3.3, 95% CI 0.5–19.4, $P = .180$ for a QRS widening of $>$120 ms). In the animals that developed VF, the arrhythmia occurred within 2.9 $\pm$ 3.8 minutes after reaching the maximal QRS duration.

A J-wave pattern was observed in 8 of 10 pigs that experienced VF and in 7 of 22 pigs without VF ($P = .02$). A J-wave pattern was found in all 7 animals with a QRS duration increase of $\geq$36 ms and in 10 of 14 animals with a QRS duration increase of $\geq$28 ms during a 3-minute window. The appearance of a J-wave pattern predicted VF with Se 80%, Sp 68%, PPV 53%, and NPV 88% ($P = .02$) and remained a significant VF predictor in logistic regression analysis (OR 8.6; 95% CI 1.4–51.4; $P = .020$).

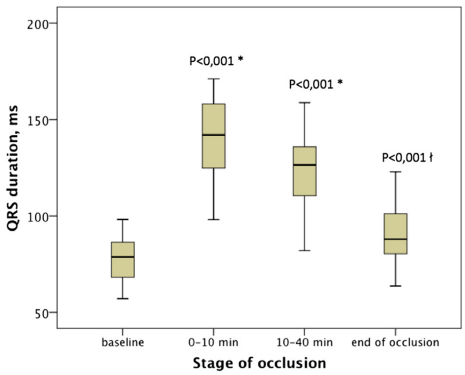

Figure 5 QRS duration at baseline and at the first and the second peak of QRS widening. $^{*}P < .001$ for comparison with the QRS duration at baseline; $^{\dagger}P < .001$ for comparison with the QRS duration at the first and the second peak of QRS widening.

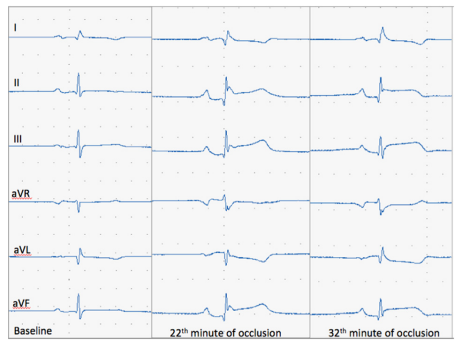

Figure 6 Appearance of a J-wave pattern in inferior leads (notch in leads II, III, and aVF) at the 22nd minute of occlusion followed by backward dynamics.

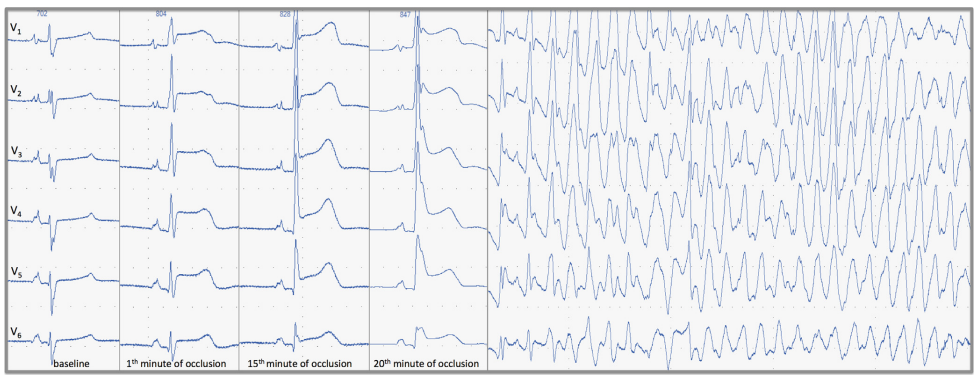

Figure 7 Appearance of a J-wave pattern in anterior leads at the 20th minute of occlusion immediately preceding a ventricular fibrillation episode.

VF occurred in 6 of 8 animals with a J-wave pattern in a combination of inferior and anterior leads and only in 2 of 7 animals with a J-wave pattern in isolated anterior leads and a combination of anterior and lateral leads (Se 75%, Sp 71%, PPV 75%, and NPV 29%; $P = .13$).

Discussion

J-wave pattern in STEMI

The association between a J-wave pattern and VF in the settings of acute ischemia has been first reported in experimental studies[13,23] and later observed in a few case reports.[24,25] More recently, the association between the presence of a J-wave pattern and myocardial ischemia or infarction was reported in several controlled studies.[10,15–17,26]

In most studies investigating the predictive value of ER in ischemic patients, the presence of a J-wave-pattern has been assessed on the basis of a historical ECG recorded before the ischemic event.[10,15,16] The association of an initially existing J-wave pattern with future arrhythmic complications during acute STEMI was explained by the presence of heterogeneity of ventricular repolarization, that is, a substrate predisposing to the development of ventricular arrhythmias in the setting of an acute ischemic trigger.[11,27] Other studies attempted to evaluate the J-wave pattern during the subacute phase of STEMI (5th–7th day), that is, after the restoration of blood flow by primary percutaneous coronary interventions (PCI) and in the absence of acute ischemia.[17,26] To our knowledge, there have been no reports on the time course of QRS morphology with regard to the occurrence of the J-wave pattern during the progression of acute ischemia and infarction.

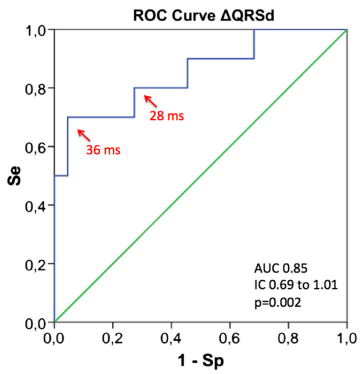

Figure 8 Receiver operating characteristic (ROC) curve analysis for the identification of optimal QRS duration increase cutoff for predicting ventricular fibrillation during the occlusion period. Significant points are marked. AUC = area of the curve; ΔQRSd = delta QRS duration; Se = sensitivity; Sp = specificity.

Ischemia-induced QRS widening and J-wave pattern

At baseline, the QRS complex was narrow without any signs of a J-wave pattern in any of the experimental animals. During the course of ischemia, QRS duration demonstrated dynamic behavior with 2 peaks of QRS widening. Shortening of QRS duration despite the uninterrupted LAD occlusion is in accordance with previously published experimental data.[28]

In order to avoid subjectivity in the assessment of QRS borders, we have chosen to use an automatic assessment of QRS duration, which includes terminal slurring and J wave, if present, as part of the QRS complex.[22] It is well known that the detection of QRS end in the settings of marked ST-segment elevation is a challenging task, and new technical approaches for assessing QRS width have been proposed.[29]

Automatically detected QRS width varied in different leads, and maximal width was reached in anterior leads—the region supplied by LAD, which was the infarct-related artery in our experimental study.

The exact mechanisms underlying J-wave development associated with ischemia and preceding VF episodes cannot be elucidated from our study on the basis of the closed-chest

porcine model of MI. In our experiment, all animals were on spontaneous sinus rhythm and we did not observe any dramatic changes in heart rate during the occlusion period, which could help us differentiate the contribution of repolarization and depolarization abnormalities to the changes in the terminal part of the QRS complex.

Earlier observations made in an open chest model suggest that J-wave development is caused by the action potential differences between the epicardial and the endocardial myocardium.[12] The decrease in inward currents I_{Na} and I_{Ca} and a significant increase in outward currents such as $I_{K\text{-}ATP}$ and I_{KAA} resulted in prevalence of outward currents in epicardium give rise to a typical notched configuration of the action potential in epicardium and the development of prominent J-waves.[5] Yan et al[13] were first to report the causative association between the ischemia-induced I_{to}-mediated changes in action potential, leading to the transmural voltage gradient that predispose to the phase 2 reentry[13]. These experimental studies suggest that the fundamental mechanisms responsible for ST-segment elevation and VF initiation are similar in the early phases of acute myocardial ischemia and the inherited J-wave syndromes.[13,30]

VF during experimental STEMI

Fifty percent of the animals used in this study developed VF during occlusion. The time distribution of ventricular arrhythmias in our study was in agreement with previously published data that describe their occurrence at 2 distinct periods of ischemia, which are defined as phase 1a (0–10 minutes from the induction of ischemia) and phase 1b (15–30 minutes of ischemia).[31,32]

Since phase 1a arrhythmias occurred almost immediately after LAD occlusion, the assessment of the steepness of QRS widening using a 3-minute window was not technically feasible. Nonetheless, upon measuring QRS duration, we found dynamic QRS widening to precede all early VF episodes: QRS duration immediately before VF was 122 ± 11 ms vs 79 ± 13 ms at baseline. QRS widening is unlikely to be due to conduction delay immediately after LAD occlusion.[23] Terminal notching/slurring induced by ischemia appears to contribute significantly to the automatically assessed prolonged QRS duration. This is also supported by the fact that a J-wave pattern was observed in all 6 pigs suffering from early VF.

In clinical settings, phase 1a arrhythmias usually occur long before the first contact with health-care professionals. Since the progression of MI in pigs is approximately 7 times faster than that in humans,[33] 20 minutes of coronary artery occlusion in the porcine model corresponds to approximately 2–2.5 hours of MI in clinical settings and prediction of VF in this time period may be clinically relevant. We found that marked and rapid QRS widening and appearance of a J-wave pattern predicted imminent VF.

Several previous studies have reported an increased risk of arrhythmic complications in patients with the inferior localization of a J-wave pattern.[10,16,27] In our study, a J-wave pattern, when observed, was present in the anterior leads corresponding to the occluded coronary artery in all affected animals. However, in some of the animals, a J-wave pattern in anterior leads was combined with slurring or notching in inferior leads. The presence of a J-wave pattern in both anterior and inferior leads was associated with a higher incidence of VF than did the presence of a J-wave pattern present in only anterior or anterior and lateral leads, even though this association did not reach statistical significance. However, any extrapolation of topical ECG changes observed in experimental animals to clinical settings should be made with extreme caution.

Because of the presence of marked ST-segment elevation due to acute MI, we have not measured J-point elevation and have not assessed the slope of ST segment, which has also been previously reported to have a predictive value for arrhythmic events.[9,14,27]

Conclusion

Rapid and marked transient increase in QRS duration commonly associated with a J-wave pattern appears to predict impending VF in acute ischemic settings and warrants further clinical studies for monitoring the immediate risk of VF during the acute phase of MI.

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Paper IV

Predictors of Ventricular Fibrillation at Reperfusion in Patients With Acute ST-Elevation Myocardial Infarction Treated by Primary Percutaneous Coronary Intervention

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Ventricular fibrillation (VF) during reperfusion (rVF) in ST-segment elevation myocardial infarction (STEMI) is an infrequent but serious event that complicates coronary interventions. The aim of this study was to analyze clinical predictors of rVF in an unselected population of patients with STEMI treated with percutaneous coronary intervention (PCI). Consecutive patients with STEMI admitted to a tertiary care hospital for primary PCI from 2007 to 2012 were retrospectively assessed for the presence of rVF. Admission electrocardiograms, stored in a digital format, were analyzed for a maximal ST-segment elevation in a single lead and the sum of ST-segment deviations in all leads. Clinical, electrocardiographic, and angiographic characteristics were tested for associations with rVF using logistic regression analysis. Among 3,724 patients with STEMI admitted from 2007 to 2012, 71 (1.9%) had rVF. In univariate analysis, history of myocardial infarction, aspirin and β-blocker use, VF before PCI, left main coronary artery disease, inferior myocardial infarction localization, symptom-to-balloon time <360 minutes, maximal ST-segment elevation in a single lead >300 μV, and sum of ST-segment deviations in all leads >1,500 μV were associated with increased risk for rVF. In a multivariate analysis, sum of ST-segment deviations in all leads >1500 μV (odds ratio 3.7, 95% confidence interval 1.45 to 9.41, p = 0.006) before PCI remained an independent predictor of rVF. In-hospital mortality was 18.3% in the rVF group and 3.3% in the group without VF (p <0.001), but rVF was not an independent predictor of in-hospital death. In conclusion, the magnitude of ST-segment elevation before PCI for STEMI independently predicts rVF and should be considered in periprocedural arrhythmic risk assessment. Despite higher in-hospital mortality in patients with rVF, rVF itself has no independent prognostic value for prognosis. **(Am J Cardiol 2015;115:417−422)**

Ventricular fibrillation (VF) during reperfusion for ST-segment elevation myocardial infarction (STEMI) is an infrequent event, but it complicates coronary interventions and subsequent hospital stays.[1] Because of its relatively low incidence, the predictors and prognostic value of VF during reperfusion are usually analyzed together with other VF episodes at any time of acute STEMI.[2−4] Some studies have divided VF into early and late timing,[2,5] and some have dealt with prereperfusion,[6] periprocedural,[1] or postprocedural[7] VF. Although experimental studies have been conducted to search for specific underlying mechanisms of reperfusional arrhythmias at the cellular level, clinical studies focused on VF during reperfusion for STEMI in unselected populations, to the best of our knowledge, are lacking. Most clinical studies have analyzed clinical and angiographic predictors of VF, whereas the data on dynamic electrocardiographic changes that can predict VF, especially VF during reperfusion, are scarce. Our aim was to analyze electrocardiographic characteristics associated with VF during reperfusion in unselected patients with STEMI treated with percutaneous coronary intervention (PCI).

Methods

Consecutive patients with STEMI admitted to Lund University Hospital for primary PCI from 2007 to 2012 were retrospectively assessed for the presence of VF during reperfusion. Information about cardiopulmonary resuscitation or defibrillation for VF was retrieved from the Swedish National Register of Information and Knowledge About Swedish Heart Intensive Care Admissions, and information about reperfusion arrhythmias was obtained from the Swedish Coronary Angiography and Angioplasty Register. Then medical histories of patients were reviewed to cross-check VF occurrence and its timing in relation to infarct-related artery (IRA) opening. Relevant clinical information was taken from the Swedish National Register of Information and Knowledge About Swedish Heart Intensive Care Admissions, and angiographic characteristics were determined from the Swedish Coronary Angiography and Angioplasty Register.

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See page 421 for disclosure information.

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Table 1
Clinical and angiographic characteristics

Variable	VF at reperfusion		p-value
	Yes (n=71)	**No (n=614)**	
Age (years)	68±12	66±12	0.36
Man	52 (73%)	430 (70%)	0.68
Previous myocardial infarction	**15 (22%)**	**80 (13%)**	**0.04**
Hypertension	31 (46%)	244 (40%)	0.36
Stroke	6 (9.0%)	46 (7.5%)	0.63
Chronic heart failure	4 (6.0%)	17 (2.8%)	0.14
Diabetes mellitus	5 (8%)	67 (11%)	0.53
B-blockers	**25 (40%)**	**159 (27%)**	**0.02**
Aspirin	**24 (38%)**	**149 (25%)**	**0.03**
Digitalis	2 (3.2%)	8 (1.3%)	0.24
Past or present smoker	24 (73%)	392 (67%)	0.57
HF at admission Killip>1	7 (13%)	47 (10%)	0.045
Creatinin at admission (mmol/l)	97±51	87±30	0.15
K^+ at admission (mmol/l)	**3.8±0.5**	**3.9±0.4**	**0.002**
Hypokalemia at admission	4 (5.8%)	14 (2.7%)	0.14
VF before reperfusion	**11 (16%)**	**26 (4%)**	**0.001**
Symptom-to-balloon time	**185 (164)**	**227 (254)**	**0,006**
Symptom-to-balloon time <360 min	**51 (84%)**	**359 (70%)**	**0.025**
Multivessel disease	42 (64%)	303 (55%)	0.19
Left main stenosis	**10 (15%)**	**34 (6%)**	**0.02**
RCA as IRA	34 (49%)	226 (41%)	0.2

Categorical variables are expressed as percentages and continuous variables as mean ± SD (if normally distributed) or median (interquartile range).

HF = heart failure; RCA = right coronary artery.

Table 2
Electrocardiographic characteristics

	VF at reperfusion		p-value
	Yes	No	
Historical ECG:			
P duration (ms)	107±28	110±19	0.63
PR duration (ms)	164±30	164±30	0.97
QRS duration (ms)	**102±20**	**96±16**	**0.02**
QTc duration (ms)	421±28	415±26	0.34
J-point elevation in lateral leads	1 (2.1%)	0 (0%)	0.08
Admission ECG:			
P duration (ms)	105±29	110±21	0.3
PR duration (ms)	176±39	171±34	0.45
RBBB	7 (13%)	41 (8%)	0.60
LBBB	6 (11%)	22 (4%)	0.15
Inferior MI localization	**44 (67%)**	**188 (51%)**	**0.02**
ST max (μV)	**498 [330]**	**300 [261]**	**<0.001**
ST max >300 μV	**47 (84%)**	**253 (52%)**	**<0.001**
Sum ST (μV)	**2289 [1933]**	**1518 [1205]**	**<0.001**
Sum ST >1500 μV	**48 (87%)**	**249 (52%)**	**<0.001**
Birnbaum grade 3	13 (45%)	138 (40%)	0.72
Anderson-Wilkins score	2.5±0.9	2.5±1.1	0.94

Categorical variables are presented as percentages and continuous variables as mean ± SD (if normally distributed) or median (interquartile range).

LBBB = left bundle brunch block; MI = myocardial infarction; RBBB = right bundle brunch block; ST max = maximal ST-segment elevation in the lead with the most prominent elevation; Sum ST = sum of ST-segment deviations in all leads.

Electrocardiograms (ECGs) stored in digital format in either GE Marquette MUSE system (GE Medical Systems, Milwaukee, Wisconsin) or Infinity MegaCare ECG Management System (Dräger, Lübeck, Germany) databases were analyzed for predictors of VF during reperfusion. We looked for admission ECGs and historical ECGs recorded before coronary events.

A previously recorded standard 12-lead ECG unrelated to STEMI available for interpretation was defined as a historical ECG. The most recent ECG was used for analysis if several historical ECGs were available. Apart from the standard criteria (P, PR, QRS, QT, and corrected QT intervals and the presence of right bundle branch block [RBBB] or left bundle branch block [LBBB]), the presence of J-point elevation $\geq$1 mm higher than baseline in 2 contiguous inferior or lateral leads was analyzed.

An ECG recorded after the onset of STEMI but before coronary intervention was defined as an admission ECG. If several ECGs were recorded before PCI, the latest ECG was considered the admission ECG, either in-hospital or prehospital ECG (in those cases in which in-hospital ECGs before PCI were not taken or not saved in the database). ECGs with paced rhythm were excluded. ECGs with complete RBBB or LBBB were excluded from the analysis of parameters characterizing ventricular repolarization (i.e., ST level, QT interval, corrected QT interval). On the basis of the admission ECG, the maximal ST-segment elevation in a single lead with most prominent elevation, the sum of ST-segment deviations in all 12 leads, including ST-segment elevation and reciprocal depression, as well as the Anderson-Wilkins and Sclarowsky-Birnbaum scores were calculated.

In brief, the Anderson-Wilkins acuteness score[8] takes into consideration the presence of abnormal Q waves to the Selvester QRS scoring system[9] and the morphology of the T wave, classified as tall, positive, flat or negative. The acuteness of each standard lead with ST-segment elevation is classified from 0 to 4 points, and the total sum in all leads is then divided by the number of leads involved to correct for the overall extent of the myocardial involvement.

The Sclarowsky-Birnbaum score[10] assess depolarization changes during ischemia progression. Tall peaked T waves are classified as grade I ischemia, ST-segment elevation is present at grade II, and changes in the terminal part of the QRS complex appear with grade III ischemia. Criteria for grade III include disappearance of S waves in leads with Rs configuration and J point/R ratio $\geq$0.5 in leads with qR configuration.

To identify clinical factors associated with VF during reperfusion, relevant clinical, angiographic, and electrocardiographic factors were compared across groups using chi-square or Fisher's exact tests for categorical variables and Student's *t* tests for continuous variables with approximately normal distributions, or the Mann-Whitney U test as appropriate. Significantly associated covariates were further evaluated in univariate logistic regression models with estimation of odds ratios and likelihood ratio tests. To determine independent factors of risk, factors significantly associated with reperfusional VF in univariate models were included in

Table 3
Clinical factors associated with VF during reperfusion

Charasteristics at admission	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Previous MI	1.93	1.04-3.58	0.039	-	-	-
QRS duration at historical ECG	1.02	1.003-1.04	0.020	-	-	-
K^+ at admission	0.40	0.22-0.73	0.003	-	-	-
VF before PCI	4.15	1.95-8.81	<0.001			
Medications:						
Aspirin	1.88	1.09-3.22	0.023	-	-	-
B-blockers	1.86	1.09-3.19	0.024	-	-	-
Symptom-to-baloon time <360 min	2.19	1.08-4.42	0.029	-	-	-
Left main stenosis	2.60	1.22-5.54	0.013	4.47	1.19-18.80	0.027
Inferior MI	1.89	1.09-3.29	0.023			
ST max >300 μV	4.87	2.34-10.16	<0.001	-	-	-
Sum ST >1500 μV	6.44	2.86-14.53	<0.001	4.00	1.52-10.54	0.005

CI = confidence interval; MI = myocardial infarction; OR = odds ratio; ST max = maximal ST-segment in the lead with the most prominent elevation; Sum ST = sum of ST-segment deviations in all leads.

Table 4
Clinical factors associated with VF during reperfusion in a subgroup of patients without arrhythmias before PCI (n = 60)

Charasteristics at admission	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Previous MI	2.33	1.22-4.48	0.011	-	-	-
QRS duration at historical ECG	1.02	1.00-1.04	0.014	1.02	1.00-1.05	0.042
K^+ admission	0.40	0.21-0.77	0.006	-	-	-
Medications:						
Aspirin	1.99	1.12-3.54	0.020	2.97	1.29-6.80	0.010
B-blockers	2.12	1.20-3.74	0.009	-	-	-
Symptom-to-baloon time <360 min	2.21	1.05-4.62	0.036	-	-	-
Left main stenosis	2.29	1.01-5.22	0.048	-	-	-
ST max >300μV	4.99	2.29-10.85	<0.001	-	-	-
Sum ST >1500μV	6.80	2.84-16.30	<0.001	4.40	1.57-12.28	0.005

CI = confidence interval; MI = myocardial infarction; OR = odds ratio; ST max = maximal ST-segment elevation in the lead with the most prominent elevation; Sum ST = sum of ST-segment deviations in all leads.

a stepwise regression analysis with backward elimination. A p value <0.05 was considered significant. All analyses were performed using SPSS version 22.0 (SPSS, Inc., Chicago, Illinois).

Results

Among 3,274 patients with STEMI admitted for primary PCI from 2007 to 2012, 71 (1.9%) had VF during reperfusion. The incidence of reperfusion VF did not differ in different years: 13 of 627 (2.1%) in 2007, 11 of 538 (2.0%) in 2008, 11 of 553 (2.0%) in 2009, 12 of 633 (1.9%) in 2010, 10 of 678 (1.5%) in 2011, and 14 of 735 (1.9%) in 2012.

All patients who had VF during reperfusion from 2007 to 2012 constituted the rVF group, and 614 consecutive patients without arrhythmias admitted during 2007 were taken as controls (no rVF group). Clinical characteristics were analyzed for all 685 patients (71 in the rVF group and 614 in the no rVF group), but admission ECGs were not available for 17%, thus leaving 567 patients included in the analysis of electrocardiographic characteristics (55 patients in the rVF group and 512 in the no rVF group). Among them, 108 were ambulance ECGs and 459 in-hospital pre-PCI ECGs. Two patients in the no rVF group were excluded from electrocardiographic analysis because of paced rhythm. Assessment of repolarization, including the level of ST segment and QT interval, was performed in patients without LBBB or RBBB, a total of 489 patients (42 in the rVF group and 447 in the no rVF group).

Historical ECGs were available for 447 patients: 40 from the rVF group and 407 from the no rVF group. The time from historical ECG to STEMI did not differ between groups: 27 ± 32 months in the rVF group and 40 ± 50 in the no rVF group (p = 0.12).

Patients with VF during reperfusion were more likely to have histories of myocardial infarction and more often used β blockers and aspirin than those without VF (Table 1). Patients with VF during reperfusion more often had VF before PCI, either out of hospital, during ambulance transport, or in hospital before balloon inflation. Eleven patients of 71 in the rVF group had VF before and during reperfusion, whereas 60 patients had no VF before reperfusion and had reperfusion VF only. There were no differences

Table 5
Clinical factors associated with in-hospital mortality

Charasteristics at admission	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.08	1.04-1.12	<0.001	1.07	1.04-1.09	<0.001
Previous MI	1.60	1.01-2.54	0.046	-	-	-
HF >Killip1	3.21	1.30-7.91	0.011	3.56	1.98-6.39	<0.001
VF before reperfusion	9.03	4.07-20.04	<0.001	3.38	1.91-6.00	<0.001
VF at reperfusion	4.87	2.39-9.96	<0.001	-	-	-
Left main stenosis	4.97	3.07-8.03	<0.001	2.30	1.23-4.30	0.009
Multivessel coronary disease	1.60	1.10-2.54	<0.001	-	-	-

CI = confidence interval; HF = heart failure; MI = myocardial infarction; OR = odds ratio.

between the groups with regard to age, gender, smoking, presence of hypertension, diabetes, anamnesis of stroke, history of congestive heart failure, using digitalis at admission, proportion of patients with Killip class >I, and serum creatinine at admission. The level of potassium at admission was significantly lower in the rVF group, though within the normal range. Patients with VF during reperfusion had shorter symptom-to-balloon time and more often had inferior localization of myocardial infarction and left main stenosis on angiography. The percentage of multivessel disease and IRA distribution did not differ between groups.

The patients who had VF during reperfusion were more likely to have longer QRS intervals on historical ECGs before their events (Table 2). Only 1 patient from the rVF group had J-point elevation in the lateral leads meeting criteria for early repolarization on the historical ECG. Patients with VF during reperfusion had higher ST-segment elevation before PCI but did not differ in either Anderson-Wilkins acuteness score or Sclarovsky-Birnbaum score compared with the no rVF group. The percentage of LBBB or RBBB and conventional electrocardiographic criteria did not differ between groups.

In a univariate regression analysis, the following factors were associated with increased risk for VF during reperfusion: history of myocardial infarction, aspirin and βa-blocker use, VF before PCI, potassium level at admission, left main coronary artery disease, inferior localization of myocardial infarction, duration of QRS on historical ECG, symptom-to-balloon time <360 minutes, ST-segment elevation in a single lead >300 μV, and sum of ST-segment deviations in all leads >1,500 μV (Table 3). In a multivariate analysis, sum of ST-segment deviations in all leads >1,500 μV before PCI and left main stenosis by angiography remained independent predictor of VF during reperfusion.

Because prereperfusional VF appeared to be a strong predictor of rVF, we also performed a separate analysis of the predictors of lone VF during reperfusion in patients who did not have VF before IRA opening (Table 4). In the univariate regression analysis, the following factors were associated with increased risk for lone VF during reperfusion: history of myocardial infarction, aspirin and β-blocker use, low potassium level at admission, left main coronary artery disease, duration of QRS on historical ECG, symptom-to-balloon time <360 minutes, ST-segment elevation in single lead >300 μV, and sum of ST-segment deviations in all leads >1,500 μV. In a multivariate analysis, sum of ST-segment deviations in all leads >1,500 μV, aspirin use, and QRS duration on historical ECG remained independent predictor of lone VF during reperfusion.

In-hospital mortality in the whole rVF group was 18.3%. In-hospital mortality in patients with lone VF during reperfusion was found to be 16.7% compared with 3.3% in patients with no VF before and during reperfusion ($p < 0.001$ for both comparisons). In the univariate analysis, age, history of myocardial infarction, Killip class >I at admission, VF before reperfusion, VF during reperfusion, left main stenosis, and multivessel disease were associated with increased in-hospital mortality (Table 5). In the multivariate analysis, age, heart failure at admission, VF before reperfusion, and left main stenosis were independent predictors of poor in-hospital prognosis. However, reperfusion VF was not an independent predictor of in-hospital mortality.

Discussion

The occurrence of VF during reperfusion in our study (ranging from 1.5% to 2.1% in different years) was lower compared with previously reported incidence of periprocedural VF in patients with STEMI. In the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial, which enrolled 5,745 patients with STEMI, periprocedural ventricular tachycardia (VT) or VF occurred in 180 patients (3.1%).[11] In the Primary Angioplasty in Myocardial Infarction (PAMI) trial, which included 3,065 patients, 133 (4.3%) had VT or VF in the cardiac catheterization laboratory.[1] These differences can be explained by several factors that distinguish our study from these earlier studies. First, we took into consideration only VF and VT demanding defibrillation, not all sustained VT and VF, as in the previous investigations.[1,4,11] Second, we considered only VF occurring after IRA opening, not all periprocedural VF, as in Mehta et al.[1] Also, these studies included patients with STEMI admitted within 6 hours (n = 11) or 12 hours (n = 1) from symptom onset, and APEX-AMI included high-risk patients with STEMI only, whereas we analyzed an unselected STEMI cohort. In our previous study, we showed that reperfusion VF accounted for 22% of VF occurring during the first 48 hours after STEMI treated by primary PCI.[3]

The occurrence of VF during reperfusion in our study was higher in patients with inferior STEMI localization. This is in line with previously published data concerning VF in STEMI but not directly related to reperfusion.[11–13] The higher incidence of VF in inferior STEMI, especially with right ventricular involvement, can be explained by much more prominent I_{to} in the epicardium of the right ventricle than the left ventricle.[14] We also observed a tendency toward a prevalence of the right coronary artery as the IRA, which previously had been reported to be predictive of VF.[1] Notably, in our cohort, patients with inferior STEMI with higher risk for rVF had lower maximum ST-segment elevation than patients with anterior STEMI (309 ± 219 vs 501 ± 339 μV, $p < 0.001$).

In earlier studies, Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 before PCI was reported to be predictive of VF in the catheterization laboratory.[1] In our study, all 71 patients with VF during reperfusion had total acute coronary occlusions, while there were no cases of nonocclusive stenoses in this group. The rate of thrombectomy in the VF group was 53% compared with 12% in the no VF group ($p < 0.001$).

We have not found any association of VF during reperfusion with multivessel disease, which is in accordance with the APEX-AMI trial, concerning VF not directly related to reperfusion.[11] Patients with reperfusion VF were more likely to have left main stenosis, which could lead to more intensive ischemia and a larger area of myocardium at risk involved in ischemia-reperfusion. We believe that the higher rate of β-blocker and aspirin treatment in the VF group should be considered as a more sensitive indicator of underlying cardiovascular co-morbidities than anamnestic information.

Hypokalemia is known to be a predictor of VF during STEMI, especially with regard to VF occurring shortly after symptom onset.[15] We analyzed the association of potassium level at admission and reperfusion VF and found that despite the differences between the rVF group and the no rVF group, the average potassium level was normal in the 2 groups. The percentage of patients with hypokalemia at admission tended to be higher in the rVF group (5.8% vs 2.7%), but the difference did not reach statistical significance. The symptom-to-PCI time was shorter in the rVF group, in agreement with the results of the PAMI trial.[1] VF before PCI was predictive of VF during reperfusion, reflecting interindividual variation in vulnerability to ventricular arrhythmias in the settings of ischemia-reperfusion. At the same time, 85% of patients who had VF during reperfusion had experienced no VF before reperfusion.

In earlier studies, the sum of ST-segment deviations on electrocardiography was predictive of VF at any time of STEMI[11] but did not influence the occurrence of postprocedural VF.[7] We found that the magnitude of ST-segment elevation, reflecting ischemia intensity before primary PCI, predicted VF during reperfusion. Because myocardial ischemia affects not only ventricular repolarization but also the depolarization process, we scrutinized admission ECGs for Sclarovsky-Birnbaum ischemia grades. The terminal distortion of QRS complex corresponding to grade 3 of ischemia is believed to reflect severe and prolonged ischemia that affects Purkinje fibers[10] and correlates with larger infarct size and less myocardial salvage at reperfusion.[16,17] In our study, the percentage of patients with Birnbaum ischemia grade 3 on admission did not differ between groups despite the shorter symptom-to-PCI time in the rVF group. We believe this might be explained by the presence of patients with fast progression myocardial infarction due to poor collateral flow or absence of preconditioning in the rVF group.[10]

We reviewed not only admission ECGs but also historical ECGs before STEMI. We demonstrated that QRS duration before the coronary event is a predictor of VF during reperfusion for subsequent STEMI. This finding is in agreement with results of Tikkanen et al[18] on longer QRS duration in future victims of sudden death during acute coronary events.

Recently, a number of studies have reported the association between J-wave pattern on historical ECG and life-threatening ventricular arrhythmias and sudden death during acute ischemic events.[18–21] The association of an initially existing J-wave pattern with future arrhythmic complications during acute STEMI was explained by the presence of heterogeneity of ventricular repolarization as a substrate predisposing to the development of ventricular arrhythmias in the setting of an acute ischemia trigger.[22] In our study, J-wave point elevation was observed in 0.2%, which is much lower than in the aforementioned studies, at 11% to 16%,[18,19] and lower than the reported prevalence of early repolarization in the general population (4.5%).[23] However, early repolarization is known to be an age-dependent phenomenon, and in subjects aged 60 to 70 years, corresponding to the average age at the time of historical electrocardiography in our study, its prevalence appears to be in the range of 1.5% in women and 2% to 3% in men,[23] thus being in line with our observations.

In-hospital mortality in the rVF group was 5 times as high as in the no rVF group, as earlier reported by others.[2,6,24] Most cases of in-hospital death in the rVF and no rVF groups were due to heart failure; other causes included mechanical complications, cerebral injury, and reinfarction, in accordance with a review of the published research.[1] Despite markedly increased in-hospital mortality in the rVF group in our study, reperfusion VF has not been found to have an independent prognostic value for in-hospital mortality.

Because of the low prevalence of reperfusion VF in PCI-treated STEMI, we chose to compare the unselected cohort of patients admitted with STEMI during 2007 with all those who had reperfusion VF from 2007 to 2012, which may affect the interpretation of our findings, because standards of care might have been modified over the 6-year period. However, an invasive strategy as the first-choice approach in patients with STEMI was adopted long before 2007, and the annual incidence of reperfusion VF and symptom-to-balloon time remained similar during the study period, thus suggesting that this would affect study findings to a limited extent.

Disclosures

The authors have no conflicts of interest to disclose.

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Prognostic impact of early ventricular fibrillation in patients with ST-elevation myocardial infarction treated with primary PCI

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Abstract

Aims: Current guidelines do not advocate implantation of cardioverter-defibrillators (ICD) for survivors of ventricular fibrillation (VF) during the first 48 hours of ST-elevation myocardial infarction (STEMI). However, contemporary studies in a real-life setting with long-term follow-up are lacking. We assessed the prognostic impact of early VF in a non-selected population of STEMI patients treated with primary percutaneous coronary intervention (PCI).

Methods and results: Consecutive STEMI patients admitted to a Swedish tertiary care hospital during 2007–2009 were identified from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (*n*=1718, age 66±12 years, 70% male). Patients with VF were identified from the register, and medical records were reviewed to determine the time point of VF. Patients surviving VF in the first 48 hours after symptom onset were compared with patients without VF for one-year mortality and a combined endpoint of death, resuscitated VF or appropriate ICD therapy. VF within 48 hours occurred in 7% of STEMI patients (*n*=121). In patients alive at 48 hours (*n*=1663), VF patients (*n*=101) had higher in-hospital mortality (12% *vs.* 2%, *p*<0.001). However, in VF patients discharged alive (*n*=89), mortality was low (1%) and combined endpoint rate (3%) did not differ compared with patients without VF (*n*=1538; 4% and 4% respectively).

Conclusion: In a large non-selected population of STEMI patients treated with primary PCI, VF during the first 48 hours after STEMI is associated with increased in-hospital mortality but does not influence the long-term prognosis for those discharged alive.

Keywords
Ventricular fibrillation, myocardial infarction, primary PCI, prognosis

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Introduction

Ventricular fibrillation is common in the acute phase of ST-elevation myocardial infarction (STEMI)[1,2] and markedly increases in-hospital mortality.[3–6] However, it is suggested that ventricular tachycardia (VT) and ventricular fibrillation (VF) occurring on the first days of STEMI is a poor predictor of arrhythmia recurrence.[4] Patients who survive to hospital discharge are believed to have a similar long-term prognosis to that of patients who do not experience life-threatening ventricular arrhythmias during the acute phase of STEMI.[2–4,7,8] Accordingly, current guidelines from the ESC/ACC/AHA on the management of

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STEMI do not recommend implantation of cardioverter-defibrillator (ICD) in patients with sustained VT or VF within the first 24–48 hours of STEMI[9–11] and there is no data that would support ICD use in these circumstances.

However, most of the scientific evidence on which current understanding of the prognostic value of early ventricular arrhythmias is based dates back either to the era before reperfusion therapy became widely adopted or to the thrombolysis era.[3,12] It is not fully known whether this strategy is still valid today, when thrombolytic therapy has been replaced with more efficient percutaneous coronary interventions (PCIs). Even though several earlier studies assessed the impact of early VF on the short- or long-term outcomes in selected patient groups,[6,13,14] a large-scale long-term outcome analysis performed in non-selected STEMI patients, to the best of our knowledge, is lacking. Therefore, our aim was to assess the prognostic value of life-threatening ventricular arrhythmias occurring within the first 48 hours after symptom onset in a large non-selected population of STEMI patients treated by primary PCI.

Methods

Study population

We performed a retrospective, register-based single-site cohort study. The study population and relevant clinical information was identified from the Swedish National Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA). Detailed information about the RIKS-HIA registry is available at www.riks-hia.se, and long-term outcome studies using the register data have been published previously.[15–17]

All patients admitted to the Lund University Hospital with acute STEMI during a three-year period from 1 January 2007 to 31 December 2009 were included in the study. Patients not covered by the Swedish social security system (n=24) were excluded from analysis due to lack of follow-up data. For patients who had multiple admissions for STEMI during the three-year period, only the first admission was considered.

Patients who underwent cardiopulmonary resuscitation (CPR) or defibrillation for VT/VF during the period from symptom onset through discharge from the coronary care unit, or upon in-hospital death, were identified from the RIKS-HIA Register. Medical records of these patients were reviewed in order to: verify whether cardiac arrest was caused by haemodynamically unstable VT or VF (VT/VF); estimate the exact timing of arrhythmia in regard to symptom onset and PCI; and reconstruct the sequence of events that led to VT/VF and defibrillation. Patients in whom VT/VF occurred within the first 48 hours of STEMI were identified as the VF Group. All other patients were identified as the No VF Group. VT/VF episodes after 48 hours from symptom onset were considered as study endpoints. In all patients with VT/VF during the index admission, medical records that include review of ST-segment monitoring and series of electrocardiograms (ECGs) were analysed to exclude recurrent ischaemic events as possible causes of arrhythmia. One patient, who did not have VT/VF initially, developed VF due to reinfarction caused by in-stent thrombosis during the second day of STEMI. Due to uncertainty in regard to group allocation, he was excluded from the analysis.

Patients with VT/VF were divided into three subgroups based on timepoint of arrhythmia in regard to the reperfusion: a first group of VT/VF occurring before intervention on infarct-related artery (IRA), defined as 'before PCI' including both pre-hospital and in-hospital VT/VF; a second group of VT/VF during reperfusion defined as VT/VF occurring during the period from restoration of blood flow to the end of the PCI procedure; and a third group of VT/VF occurring after PCI. Patients who had more than one VT/VF episode during the index admission were classified according to the latest episode.

Angiographic characteristics were determined from the Swedish Coronary Angiography and Angioplasty Register (SCAAR). The register contains information from all centres performing coronary angiography and PCI in Sweden, and has been described previously.[18,19] Information on implanted ICDs for primary or secondary prevention was obtained from the local hospital register. Medical records were reviewed for occurrence and adequacy of ICD therapy which was defined as ICD shocks and/or antitachycardia pacing due to ventricular arrhythmias.

The study was approved by the Regional Ethics Committee in Lund (# 2010/585, 2010-11-29).

Study endpoints

The primary endpoints were in-hospital death; death from any cause at one year (total mortality); and a combined endpoint including death from any cause, VT/VF, or appropriate ICD therapy at one year.

Statistical analysis

The prognostic impact of successful resuscitation for VT/VF during the first 48 hours after onset of the ST-elevation myocardial infarction was evaluated from survival functions calculated using the Kaplan–Meier estimator. Groups were compared using the log rank test.

To identify clinical factors associated with VT/VF, relevant clinical factors were compared across groups using chi-square or Fisher's exact test for categorical variables and Student's t-test for continuous variables with an approximate normal distribution, or non-parametric tests, as appropriate. Significantly associated covariates were further evaluated in univariate logistic regression models

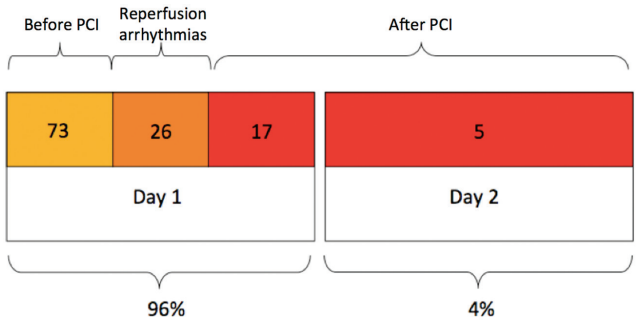

Figure 1. Timing of VT/VF during acute ST-elevation myocardial infarction (STEMI).
PCI: percutaneous coronary intervention

with estimation of odds ratios and likelihood-ratio tests. To determine independent factors of risk, clinical factors significantly associated with VT/VF in univariate models were included in a stepwise regression analysis with backwards elimination. All patients were included in analyses of clinical correlates of VT/VF, whereas only patients alive by 48 hours of STEMI were included in prognostic analyses.

p-values <0.05 were considered significant. All analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

The study population comprised 1718 unique STEMI patients admitted to the Lund University Hospital for primary PCI during a three-year period (mean age 66±12 years, 70% males). The population included 61 patients (3.1%) who received pre-hospital CPR, 54 of whom had ongoing mechanical chest compressions with the LUCAS device (Jolife AB, Lund, Sweden) upon arrival to the catheterization laboratory.

VT/VF during the first 48 hours of STEMI occurred in 121 patients (7.0%). As described in Figure 1, VT/VF was registered before intervention in 73 patients ('before PCI' group), between restoration of blood flow in IRA and the end of the PCI procedure in 26 patients ('reperfusion arrhythmia' group), and after PCI procedure in 22 patients, of which 17 occurred within the first 24 hours of STEMI, and five occurred during the day after. Thus, in 96% of patients from the VF group, life-threatening arrhythmias occurred within the first 24 hours of STEMI. Reperfusion arrhythmias were registered in patients with acute coronary occlusion.

Patients with VT/VF were more likely to have a history of myocardial infarction and to use beta-blockers, aspirin and statins than those without VT/VF (Table 1). The proportion of patients with left ventricular ejection fraction < 30% and Killip class IV was higher in the VF group. Patients with VT/VF more often received an intra-aortic balloon pump and mechanical chest compressions with the LUCAS device. Symptom-to-balloon time was shorter in the VF group than in the No VF group (167 (IQR=130) *vs*. 215 (IQR=249) min, p=0.019).

Coronary angiography findings

Coronary angiography was performed in all patients. Angiographic findings are shown in Table 2. Patients with VT/VF were less likely to have single-vessel disease (33.9% *vs*. 43.9% in the group without VT/VF, p=0.04) and more often had left main disease (14.8% *vs*. 6.5%, p=0.001). The proportion of patients with two-vessel and three-vessel disease did not differ between the groups.

Left main artery was the IRA more often in the VF group (2.6% *vs*. 0.3%, p=0.008) (Table 2). No difference was observed between the two groups in regard to left anterior descending coronary artery (LAD), right coronary artery (RCA) or left circumflex artery (LCX). The majority of patients in both groups had acute occlusion of IRA defined as occlusion that occurred within three months[18] prior to coronary angiography at STEMI admission (70% in No VF group and 78% in VF group, p=0.126).

PCI was not performed in 111 of 1718 patients (6.4%) due to technical difficulties or uncertain culprit lesion. Forty-one of these patients (2.5% in the VF group and 2.4% in the No VF group) underwent subsequent coronary artery bypass graft surgery (CABG). For patients undergoing primary angioplasty, the procedure was successful in 89.6% for VF patients and in 97.6% for the No VF group (p<0.001).

Independent predictors of early VT/VF

In univariate regression analyses, the following factors were associated with increased risk of VT/VF during the

Table 1. Clinical characteristics.

Characteristic	No VF group (*n*=1597)	VF group (*n*=121)	*p*-value
Age, years	64.9±11.6	65.1±11.4	0.657
Male sex, *n* (%)	1115 (69.8%)	88 (72.7%)	0.501
BMI	27.0±4.5	26.2±4.4	0.616
Medical history:			
Prior MI	**221 (13.8%)**	**31 (25.6%)**	**<0.001**
Prior PCI	154 (9.6%)	16 (13.2%)	0.204
Prior CABG	62 (3.9%)	8 (6.6%)	0.146
Prior CHF	46 (2.9%)	5 (4.1%)	0.436
Prior stroke	104 (6.5%)	10 (8.3%)	0.460
Hypertension	637 (40.0%)	52 (43.0 %)	0.522
Diabetes mellitus	196 (12.3%)	9 (7.5%)	0.118
Current smoker	526 (34.4%)	42 (43.3%)	0.093
Smoked earlier	511 (33.4%)	33 (34%)	
Medications at admission:			
Beta-blockers	**397 (25.5%)**	**50 (44.2%)**	**<0.001**
ACE or ARB	319 (20.0%)	25 (20.7%)	0.856
Digitalis	**21 (1.3%)**	**5 (4.3%)**	**0.011**
Aspirin	**377 (24.0%)**	**45 (39.1%)**	**<0.001**
Statins	**282 (18.0%)**	**32 (28.1%)**	**0.007**
Nitroglycerin	55 (3.5%)	6 (5.2%)	0.342
Anterior MI	470 (48.8%)	54 (47.0%)	0.708
Symptom-to-balloon time	**215 (249)**	**167 (130)**	**0.019**
AF at admission	97 (6.2%)	11 (10.4%)	0.092
Heart rate at admission	75 (24)	74 (29)	0.551
Systolic blood pressure	**144 (35)**	**120 (40)**	**<0.001**
IABP	**58 (3.6)**	**24 (19.8%)**	**<0.001**
LUCAS	**22 (1.4)**	**32 (26.4%)**	**<0.001**
Killip class IV at admission	**17 (1.3%)**	**9 (10.0%)**	**<0.001**
EF < 30	**110 (8.0%)**	**16 (16.2%)**	**0.005**
Laboratory parameters:			
Creatinine, median (IQ)	**79 (25)**	**81 (28)**	**0.023**
CRP, median (IQ)	5.0 (11)	3.0 (16)	0.936
Glucose, median (IQ)	**7.0 (2.3)**	**7.3 (3.9)**	**0.001**
Hb	139 (22)	139 (23)	0.344

Continuous variables are presented as mean ± standard deviation (SD) or as median and interquartile range if asymmetric distribution. Categorical variables are presented as frequencies and percentages. Data are presented in average ± SD, or median (IQ) in the case of abnormal distribution. VF: ventricular fibrillation; BMI: body mass index; CABG: coronary artery bypass graft surgery; CHF: congestive heart failure; CRP: c-reactive protein; EF: ejection fraction; Hb: haemoglobin; IABP: intra-aortic balloon pump; MI: myocardial infarction; PCI: percutaneous coronary intervention

first 48 hours of STEMI: current smoking, history of myocardial infarction, aspirin, beta-blockers, digitalis and statin use, plasma creatinine level and left main coronary artery disease (Table 3). In a multivariate analysis, current smoking (odds ratio (OR) 2.82, p=0.001, 95% confidence interval (CI) 1.49–5.32), beta-blocker therapy (OR 2.47, p<0.001, 95%CI 1.54–3.96), digitalis at admission (OR 4.70; p=0.005, 95%CI 1.58–13.94) and left main disease (OR 3.11; p=0.001, 95%CI 1.61–5.98) remained independently associated with VT/VF during the first 48 h. Beta-blockers (OR 2.04; p=0.003, 95%CI 1.27–3.27) and digitalis (OR 3.34; p=0.035, 95%CI 1.09–10.22) at admission remained independent predictors of VT/VF before reperfusion.

Prognostic impact of early VT/VF

Fifty-five of the 1718 STEMI patients died within 48 h of symptom onset (3.2%, age 76±11 *vs*. 66±12 years in survivors, p<0.001). The remaining 1663 patients alive at 48 hours of STEMI were studied with survival analysis, and included 101 patients from the VF group (age 66±12 years, 27% female) and 1562 patients from the No VF group (age 66±12 years, 30% female, n.s.). Of these 1663 patients, 100 died during one-year follow-up: 13 (12.9%) from the VF group and 87 (5.6%) from the No VF group, p=0.0001 (Figure 2 and Figure 3(a)). The vast majority of deaths occurred during index hospitalization: 12 patients from the VF group (11.9%) and 24 patients from the No VF group

Table 2. Angiographic characteristic.

Characteristic	No VF group	VF group
IRA:		
LAD	628 (43.4%)	47 (40.9%)
LCX	221 (15.3%)	12 (10.4%)
RCA	570 (39.4%)	52 (45.2%)
LM	**5 (0.3%)**	**3 (2.6%)***
Graft	22 (1.5%)	1 (0.9%)
Characteristic of stenosis:		
Occlusion in IRA < 3 month[a]	1036 (70.0%)	91 (77.8%)
Non-occlusive stenosis in IRA	416 (28.4%)	24 (20.5%)
Chronic occlusion[b]	12 (0.8%)	2 (1.7%)
Number of vessels with stenosis:		
One-vessel disease	**638 (43.9%)**	**39 (33.9%)†**
Two-vessel disease	398 (27.4%)	31 (27.0%)
Three-vessel disease	285 (19.6%)	24 (20.9%)
LM	**95 (6.5%)**	**17 (14.8%)***
No stenosis	36 (2.5%)	4 (3.5%)

[a]Acute IRA occlusion (less than three months prior to admission). [b]Chronic occlusion (more than three months before admission), as defined by SCAAR registry. *$p<0.01$ †$p<0.05$ IRA: infarct-related artery; LAD: left anterior descending coronary artery; LCX: left circumflex artery; LM: left main stenosis; RCA: right coronary artery

Table 3. Clinical factors associated with VF during acute STEMI.

Characteristics at admission	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-value	HR	95% CI	*p*-value
Current smoking	1.79	1.06–3.05	0.03	2.82	1.50–5.31	0.001
Previous MI	2.14	1.39–3.30	0.001	–	–	–
Medications:						
Aspirin	2.03	1.38–3.01	< 0.001	–	–	–
Statins	1.78	1.16–2.73	0.008	–	–	–
Beta-blockers	2.32	1.57–3.42	< 0.001	2.54	1.59–4.05	<0.001
Digitalis	3.35	1.24–9.06	0.017	4.57	1.54–13.53	0.006
Left main stenosis	2.52	1.44–4.39	0.001	3.04	1.58–5.85	0.001
Creatinine >80 mmol/L	1.63	1.08–2.39	0.019	–	–	–

VT: ventricular fibrillation; STEMI: ST-elevation myocardial infarction; HR: hazard ratio; CI: confidence interval; MI: myocardial infarction; Left main stenosis: left main coronary artery stenosis

(1.5%), $p<0.001$ (Figure 2 and Figure 3(a)). Among patients who were alive at 48 hours but died during hospital stay, 18 died from heart failure or cardiogenic shock (12 of 24 No VF patients and six of 12 VF patients), four from mechanical complications of myocardial infarction (interventricular septum rupture, left ventricular free wall rupture, acute mitral insufficiency (all from No VF group), one from ventricular fibrillation (No VF group), and 13 from other causes.

Among patients from the VF group who were alive at 48 hours, the in-hospital mortality was 11.3% in patients where VT/VF occurred before PCI, 9.1% in patients with reperfusion arrhythmias and 17.6% in patients with VT/VF after PCI ($p=0.696$).

The length of hospital stay was 6.12±8.14 days in the VF group and 5.38±9.9 days in the No VF group ($p=0.421$).

Among the 1627 patients discharged alive, 64 (3.9%) died during follow-up. The mortality rate at one year did not differ significantly between groups: 1.1% in the VF group and 4.1% in the No VF group (hazard ratio (HR) =0.27, 95%CI 0.037–1.945, $p=0.194$, Figure 3(c)).

Among patients discharged alive, 18 received an ICD for primary prevention and six for secondary prevention of sudden death (Figure 2). Three of the six patients in whom ICD was implanted for secondary prevention were from the VF group. In five of the six patients with ICD for secondary prevention, the VT episode which motivated device implantation occurred within the first half-year of STEMI; in four

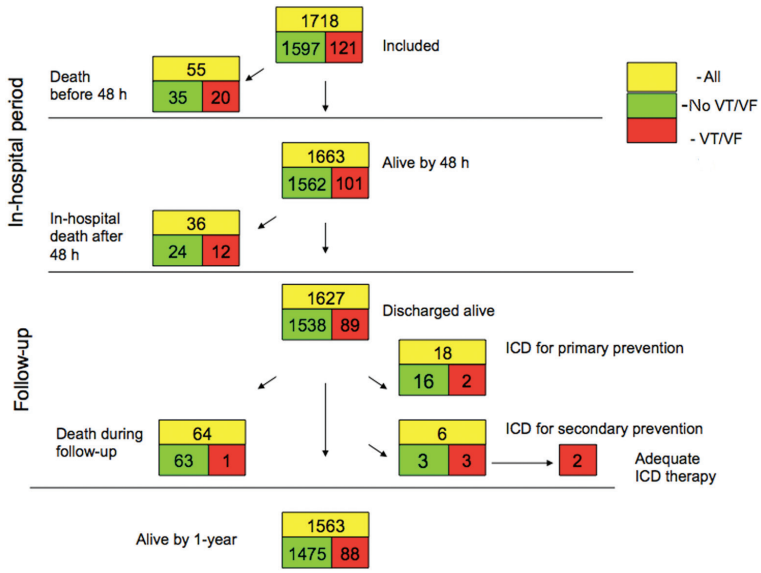

Figure 2. Patient groups chart.
VF: ventricular fibrillation; VT: ventricular tachycardial; ICD: implantation of cardioverter-defibrillator

patients it occurred during the first two months. Two patients with ICD implanted for secondary prevention received adequate ICD therapy, both of them twice during one year of follow-up. The time from ICD implantation to the first adequate ICD therapy was one and four months, respectively. None of the patients who received an ICD for primary prevention received adequate ICD therapy by one year of follow-up.

In total, 68 individuals experienced the combined endpoint of death, VT/VF or appropriate ICD therapy during follow-up: five in the VF group and 63 in No VF group. Two patients from the No VF group developed sustained VT 18 and 39 days following the date of the index admission, respectively. Two additional patients from the VF group received appropriate ICD therapy during follow-up. There were no differences between the two groups in regard to the combined endpoint among those discharged alive (HR=0.85, 95%CI 0.225–2.585, p=0.725 for combined endpoint, Figure 3(d)).

Discussion

Current standards in clinical practice for STEMI patients are based on the premise that VF during the first two days of STEMI is benign in terms of long-term prognosis if the patient survives to discharge from the hospital and the lack of proven ICD efficacy for prevention of sudden death in survivors of VT/VF early during STEMI. However, most data concerning the prognostic significance of early VT/VF for long-term outcome were obtained during or even prior to the thrombolysis era (Table 4). Few prior studies have evaluated VT/VF among patients undergoing primary PCI for acute STEMI; the most important of them were the PAMI trial and the APEX AMI trial.[6,13,14,20]

APEX AMI was the largest trial, enrolling 5745 patients. However, it did not include patients admitted beyond the first six hours of STEMI and those with isolated inferior STEMI. Moreover, the length of follow-up was limited to 90 days.[14] The PAMI trial assessed long-term one-year prognosis and included 3065 patients; however, those with renal failure, cardiogenic shock and patients with contraindications for antiplatelet therapy were excluded.[13]

Our study included all patients admitted for primary PCI during a three-year period. Being a register-based study, our analysis did not exclude the most severe patient categories such as those who underwent pre-hospital resuscitation (3.5%) or arrived at the catheterization laboratory with ongoing mechanical chest compressions with LUCAS (3.1%). The more inclusive nature of our study may explain the differences in malignant ventricular arrhythmia occurrence between our study (7.2%), the PAMI trial (4.3%)[13] and the APEX-AMI trial (5.7%).[14] Furthermore, these earlier studies included VF and any sustained VT episode, whereas our study included only VF and VT necessitating defibrillation.

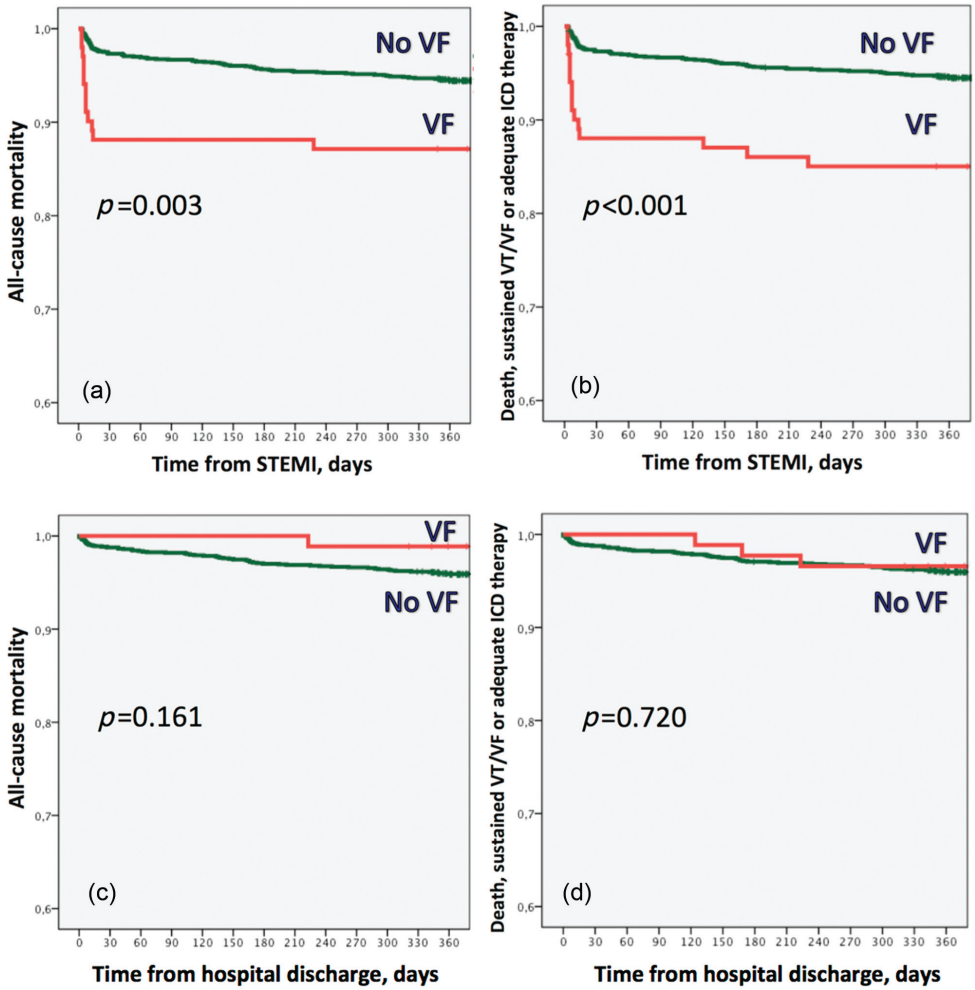

Figure 3. (a) Kaplan–Meier survival analysis in regard to total mortality during follow-up for patients alive at 48 hours of STEMI. (b) Kaplan–Meier analysis in regard to combined endpoint of total mortality, appropriate ICD discharge or new VT/VF during follow-up for patients alive at 48 hours of STEMI. (c) Kaplan–Meier survival analysis in regard to total mortality during follow-up for patients discharged alive. (d) Kaplan–Meier analysis in regard to combined endpoint of total mortality, appropriate ICD discharge or new VT/VF during follow-up for patients discharged alive.
STEMI: ST-elevation myocardial infarction; VT: ventricular tachycardia; VF: ventricular fibrillation; ICD: implantation of cardioverter-defibrillator

In regard to the type of ventricular arrhythmias reviewed in earlier trials, the PAMI trial focused on ventricular arrhythmias in the PCI laboratory only and disregarded potential additional events that could have occurred during the prehospital stage or after PCI. In our material, 62 of 121 qualifying VT/VF episodes occurred before patient admission to the catheterization laboratory and did not recur during PCI. This patient category was not included in the PAMI analysis. In the APEX study, pre-catheterization VT/VF accounted for 7.5% (25 of 329) of all events, which is in contrast to our study population.

Table 4. Clinical trials on prognostic impact of VF during acute STEMI.

Authors	Year of publication	Treatment strategy	Population type	Sample size	Arrhythmia	Time of follow-up
Schwartz et al.[12]	1985	No reperfusion therapy	Non-selected	7486	Primary VF	5 years
Behar et al.[3]	1990	No reperfusion therapy	Non-selected	5839	Primary VF	1 year
Nicod et al.[7]	1988	No reperfusion therapy	Non-selected	2088	Primary VF	1 year
Volpi et al.[8]	1989	Thrombolysis	GISSI	6337	Primary VF	1 year
Newby et al.[5]	1998	Thrombolysis	GUSTO I	40,895	Sustained VT, VF	1 year
Piccini et al.[6]	2008	Primary PCI	Non-selected	9015	Sustained VT, VF	In-hospital
Mehta et al.[14]	2009	Primary PCI	APEX AMI	5745	Sustained VT, VF	90 days
Mehta et al.[13]	2004	Primary PCI	PAMI	3065	Sustained VT, VF	1 year

STEMI: ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; VF: ventricular fibrillation; VT: ventricular tachycardia

Through medical histories of patients we were able to verify all VT/VF episodes, to analyse in detail the timing and circumstances of VT/VF in the studied population. In the majority of cases (60%), malignant ventricular arrhythmias occurred before balloon inflation, while 23% of cases accompanied restoration of blood flow in IRA, and only 17% were registered after the end of PCI. In general, 96% of life-threatening arrhythmias occurred within the first 24 hours of PCI treated STEMI. In previous studies, which were conducted before the routine use of reperfusion therapy or during the thrombolysis era, the proportion of patients having VF after the first day of STEMI was generally higher. However, the exact timing of VF within the first 48 hours of STEMI has not been reported in previous studies.[2,21] In the GUSTO-I study, 86% of VF occurred within the first 48 hours of thrombolysis-treated STEMI, and 15% occurred after the first 48 hours.[5]

In our study, patients from the VF group more often had prior myocardial infarction (MI), which is in agreement with earlier reports.[5,20] We did not observe any association between MI localization and occurrence of VT/VF, which is in contrast to previously published data[13,14] that reported higher risk of malignant ventricular arrhythmias in inferior and RCA-related infarctions. However, thrombosis in the left main coronary artery was observed more often in the VF group. Otherwise, aside from beta-blocker treatment, which is likely to be a more sensitive indicator for underlying cardiovascular disease than anamnaestic data, only current smoking and digoxin use were independently associated with VF occurrence. The association between early VF and smoking has been reported earlier.[13] The association between digoxin use and early VF in our study is especially notable in light of recent publications about this drug. It is well known that digoxin decreases the hospitalization rate but does not decrease mortality due to congestive heart failure (CHF);[22] at the same time, digoxin was reported to increase the rate of death from 'other causes',[23] presumed to be due to arrhythmias. Recently, based on a large data sample from the RIKS-HIA registry, it was shown that digoxin is an independent risk factor for death among patients with AF without a history of congestive heart failure.[24] The strong association between digoxin use at admission with acute STEMI and early VF is in agreement with the findings of previous trials, thus further supporting the previously suggested potential hazard of digoxin in the setting of acute ischaemia. However, interventional studies are needed to establish the causality as our findings can also be explained by more severe underlying congestive heart failure in patients treated with digoxin.

In our study, in-hospital mortality was higher in the VF patients, which is in agreement with previous studies.[3–6] Moreover, we analysed the timing of VF according to IRA opening and did not find any significant differences between arrhythmias occurring before, during or after PCI.

A considerable number of patients surviving STEMI fulfils criteria for primary prevention ICD implantation during follow-up. Appropriate ICD therapy can in some cases prevent sudden death; however, earlier studies in similar patient populations, such as APEX AMI or PAMI, did not analyse ICD therapies during follow-up. In our study, we analysed not only the cases of death but also the combined end-point of death, resuscitated cardiac arrest or appropriate ICD treatment, and found no differences between the two groups for this endpoint either. So, this study performed on a large non-selected population of PCI-treated STEMI confirmed the data from trials conducted before or during the thrombolysis era[2–4,7,8] regarding the absence of influence of VT/VF within the first days of STEMI on the long-term prognosis.

Limitations

Our approach of retrospective analysis based on the information on VT/VF available through the RIKS-HIA registry is likely to underestimate the true prevalence of clinically relevant VT/VF as occasions with ventricular arrhythmias during the acute phase of STEMI that lasted longer than 30 seconds and resolved either spontaneously or converted using pharmacological interventions may not have been documented. Our findings should therefore be considered

as referring the most severe arrhythmias as haemodynamically unstable VT or VF.

Information on electrolyte status at admission would potentially further improve our understanding of VF mechanisms during the early phase of STEMI, but it was not available for analysis.

Finally, while we intended to include all patients admitted with STEMI to a high-volume tertiary care hospital during three-year period, the study population and the actual number of study endpoints might be considered low in comparison with large-scale trials (see Table 4) and have to be acknowledged. However, we believe that this limitation has been balanced by the high level of detail concerning arrhythmic events and study endpoints available through direct access to medical records and ECG archive.

Conclusion

In a large non-selected population of STEMI patients treated with primary PCI, the incidence of VT/VF within the first 48 h of STEMI is associated with increased in-hospital mortality, but does not influence the long-term prognosis for those discharged alive. Therefore, in line with current sudden death prevention guidelines, our data does not advocate ICD therapy in survivors of VF during the first 48 hours of STEMI. The rate of VF events beyond 24 h of STEMI in PCI-treated patients was low and for these patients the results must be interpreted with caution.

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Conflict of interest

None declared.

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