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

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Abstract

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 infarct size (IS).

In 15 pigs infarction was induced by a 40-min long balloon inflation in the left anterior descending coronary artery (LAD). ^{99m}Tc-tetrofosmin 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 ECG monitoring. A gadolinium-based contrast agent was given intravenously 30 min prior to explantation of the heart. Final infarct size was estimated using *ex vivo* cardiac magnetic resonance imaging.

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 to 570±220 µV at the end of occlusion, $p<0.001$. The transitory exacerbation of ST elevation exceeded the maximal ST elevation during occlusion (920±420 µV, $p<0.05$). The ST elevation resolved by the end of the reperfusion period (90±30 µV, $p<0,001$). Exacerbation of ST elevation after reperfusion correlated with the final infarct size ($r=0.64$, $p=0.025$ for maximal ST elevation in a single lead and $r=0.80$, $p=0.002$ for sum of ST deviations) but not 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). The maximal ST elevation in a single lead

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and the sum of ST deviations during occlusion did not correlate with either MaR or final infarct size.

In 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 MaR.

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 and to reduce mortality (1, 3-4).

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 infarct size (IS) in experimentally induced myocardial infarction in pigs.

Methods

Experimental protocol

After induction of anaesthesia, ischemia was induced by inflation of an angioplasty balloon for 40 min. An angiogram was performed after inflation of the balloon and before deflation of the balloon in order 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. 12-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 40-50 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%). Analysis of arterial blood gases in order to adjust ventilation was performed before initiation of ischemia, at reperfusion and one hour after reperfusion. The pigs were continuously monitored by electrocardiography (ECG). 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. A 6 F introducer sheath (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted into the surgically exposed left carotid artery upon which 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. A 9 F introducer sheath (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted into the surgically exposed right jugular vein. A 7.5 F Continuous Cardiac Output Pulmonary Artery Catheter™ (Edwards Lifesciences, Irvine, CA, USA) was then inserted into a pulmonary artery. Cardiac Output was continuously recorded using a Vigilance™ monitor (Edwards Lifesciences, Irvine, CA, USA). All radiological procedures were performed at the Biomedical Center (BMC,) at Lund University, Lund, Sweden using an experimental catheterization laboratory (Shimadzu Corp., Kyoto, Japan).

ECG monitoring

An 12-lead digital ECG monitor (“Kardiotechnica-04-8m”, Incart, St. Petersburg, Russia) with a sampling rate 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 1000 Hz and amplitude resolution 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 level of signal at the area 40-20 ms before onset of the QRS complex was referred to as the baseline. ST segment deviation was then 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 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 went below 100 μV in leads I, II, III, aVF, aVL, V_4-V_6 and 200 μV in V_1-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 (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)(13)

Assessment of myocardium at risk by ex vivo SPECT

Single photon emission computed tomography was used to assess the MaR as percent 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. Iterative reconstruction using maximum likelihood-expectation maximization (MLEM) was performed with a low-resolution Butterworth filter with a cut-off 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 (Figure 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 cardiac magnetic resonance

The method used to assess IS by cardiac magnetic resonance has previously been described in detail (12, 15-16). 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. CMR 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 (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 percent of left ventricular myocardium.

Statistical methods

Data is presented as mean values ± standard deviations. Pearsons's 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 of frequent ventricular arrhythmias. Nine animals received defibrillation for ventricular fibrillation (VF)/hemodynamically important ventricular tachycardia (VT) during the occlusion period, 7 – during reperfusion period.

Ex vivo imaging of the heart was performed in the 13 animals which 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 from the analysis because of anomalous coronary anatomy. Thus, the association between ECG findings and MaR/IS was analyzed in 12 animals, while ECG data were analyzed for all 15.

ST dynamics during LAD occlusion

Typical ST dynamics during the occlusion and reperfusion is shown in Figure 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, Figure 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 angiografically verified blood flow restoration was accompanied by exacerbation of ST elevation in all 15 cases (see Figure 2). The ST elevation started increasing shortly after LAD opening and reached its maximum 186±102 second 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 Figure 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 to 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 to 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.

Correlation between the ST elevation, myocardium at risk and final infarct size

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 Figure 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 following 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 on the basis of 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 following LAD opening, reached its maximum 2-4 minutes later and returned to the pre-reperfusion level 10-15 minutes later. Thereafter the ST elevation gradually decreased towards complete resolution. 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 68-75% of STEMI patients effectively treated with thrombolysis (8-9) and in 23-63% 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 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 infarct size (29) and caused by distal embolisation with clot fragments and leukocyte aggregates, platelet activation, microcirculatory spasm and oedema (30-31). It is also possible that reperfusion peak is not a consequence of additional myocardial damage but rather a pure electrophyiological 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 infarct size 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 "reperfusion peak" is associated with the IS but not 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 with 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 in order to assess its value for IS prediction and risk stratification in STEMI patients treated with primary angioplasty.

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 were induced and uniform durations of ischemia (40 min) 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 post reperfusion that was used in the present study. There are observations suggesting that IS measurements using gadolinium-DTPA 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 infarct size but not MaR.

The prognostic value of this post-reperfusion exacerbation of ST elevation in humans undergoing early reperfusion therapy for STEMI remains to be determined.

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Tables

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<0.001 for comparison with the ST elevation at the end of occlusion

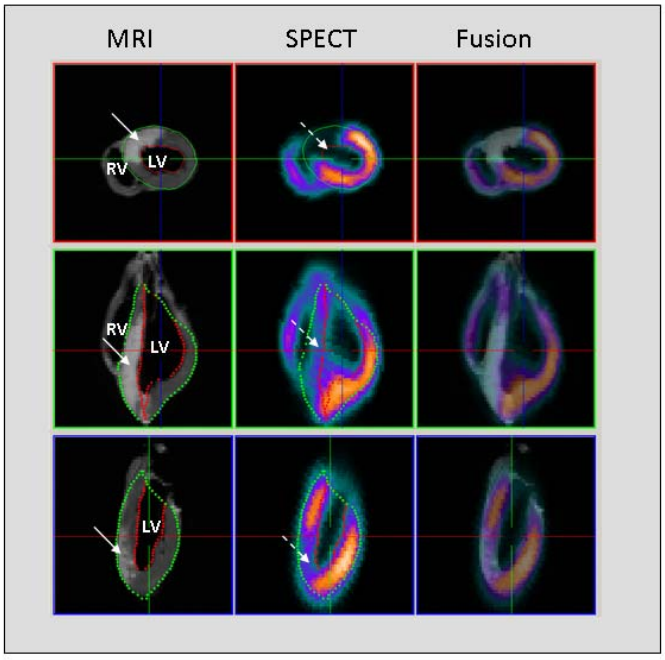
- p<0.001 for comparison with the ST elevation at the “reperfusion peak”

Table 2 The relationship between the ST elevation during the 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 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 legends

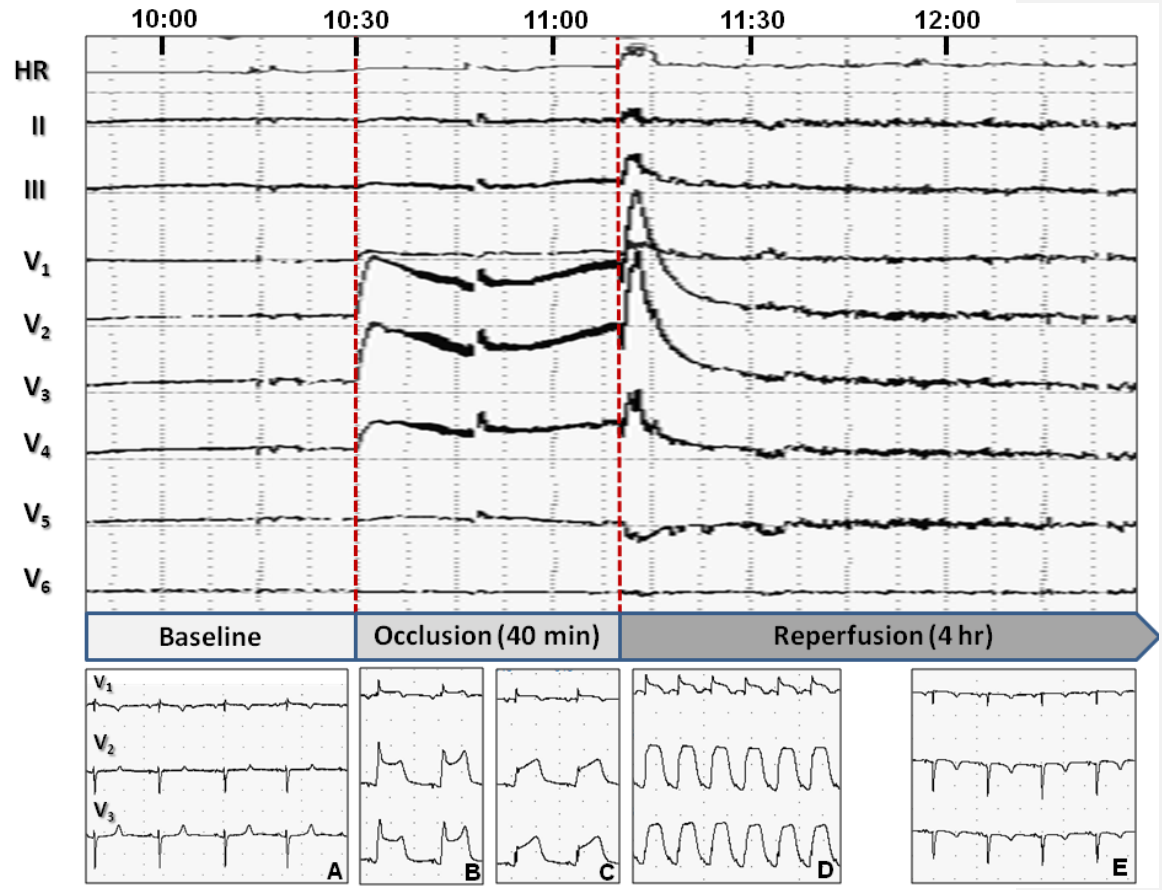
Figure 1



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

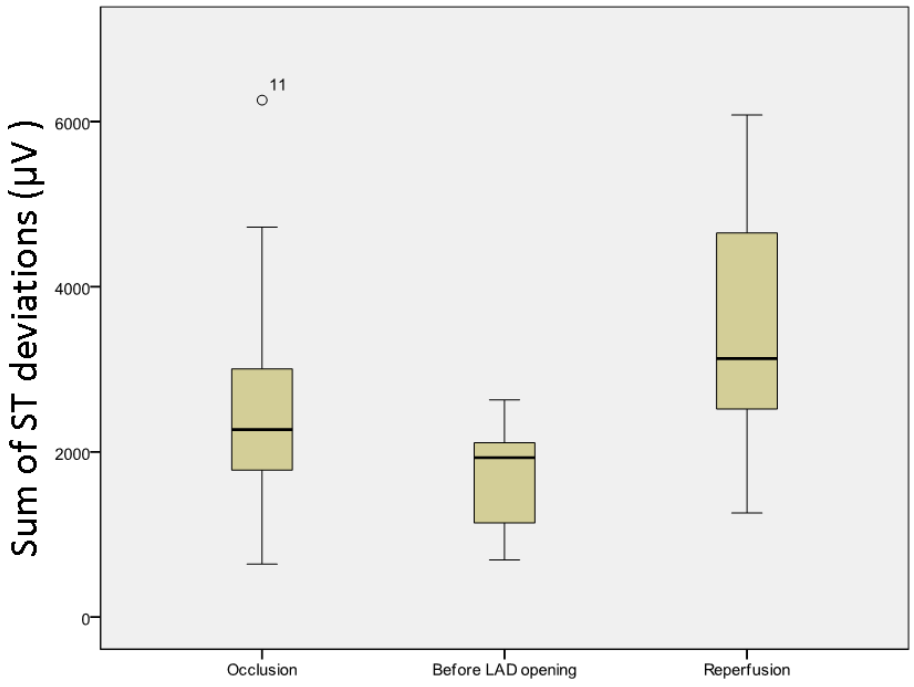
the lower two panels show two long-axis slices. Endocardial and epicardial borders of the left ventricle were manually delineated in the MR images and fused with the co-registered SPECT images. LV=left ventricle, RV=right ventricle

Figure 2



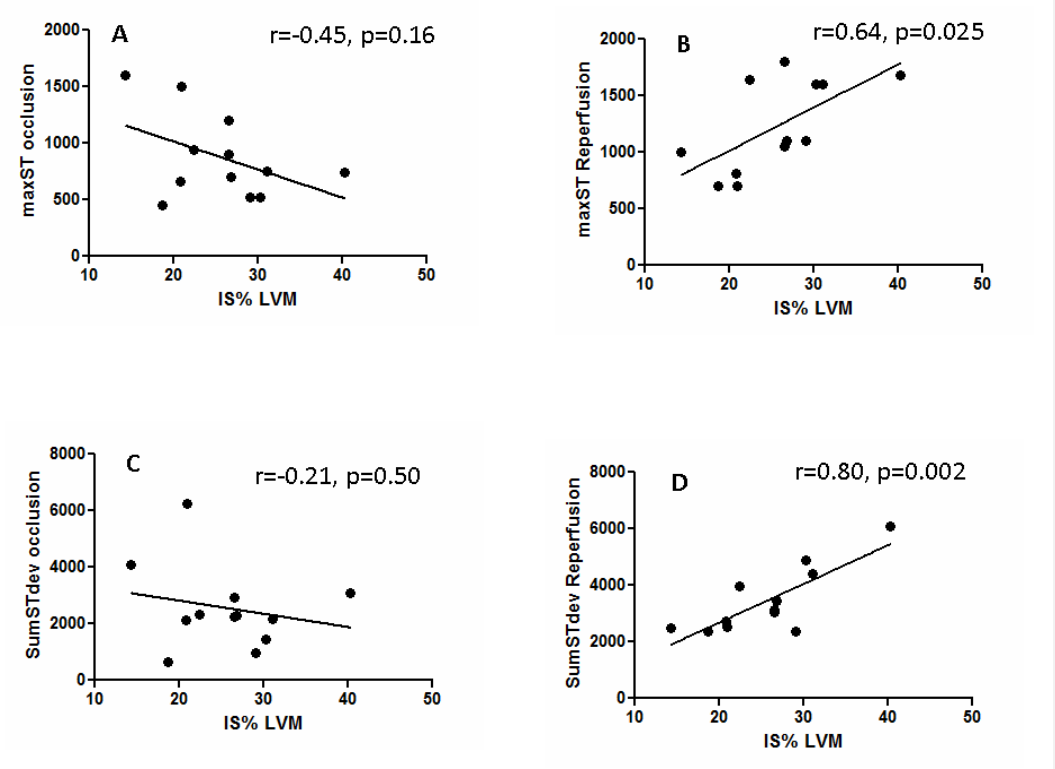
ST segment monitoring during 40-min of LAD occlusion and 4 hours of reperfusion. Transient exacerbation of the ST segment elevation shortly after onset of reperfusion ("reperfusion peak") exemplified in this figure was observed in all animals. HR= heart rate. A-ECG strip at baseline; B- maximum of ST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

Figure 3



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

Figure 4



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.