

Myocardial ischemia and reperfusion injury, clinical and experimental studies.

Akademisk avhandling
som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinargatan 3.
Göteborg torsdagen den 17 juni 2010 kl. 13.00

av
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The thesis is based on the following papers:

- I. K Åström Olsson, J Harnek, AK Öhlin, N Pavlidis, B Thorvinger, H Öhlin.
No increase of P-malondialdehyde after primary coronary angioplasty for acute myocardial infarction.
Scand Cardiovasc J 2002; 36(4):237-240.
- II. K Åström-Olsson, E Hedström, L Mattsson Hultén, O Wiklund, H Arheden, AK Öhlin, A Gottsäter, H Öhlin.
Dissociation of the inflammatory reaction following PCI for acute myocardial infarction.
J Inv Cardiol 2007;19:452-456.
- III. E Hedström, K Åström-Olsson, H Öhlin, F Frogner, M Carlsson, T Billgren, S Jovinge, P Cain, G.S Wagner, H Arheden.
Peak CKMB and cTnT accurately estimates myocardial infarct size after reperfusion.
Scand Cardiovasc J 2007;41:44-50.
- IV. K Åström-Olsson, L Karlsson, L Mattsson Hultén, P Davidsson, V Mantovani, C Månsson, SO Olofsson, O Wiklund, L Grip.
Myocardial release of FKBP12 and increased production of FKBP12.6 in ischemia and reperfusion, experimental models.
Biochem & Biophysical Res Comm 2009;390:1299-1304.
- V. K Åström-Olsson, L Li, L Akyürek, J Borén, A Gottsäter, H Öhlin, L Grip.
Studies of HL-1 mouse cardiomyocytes regarding viability and release of FKBP12, after hypoxia, energy depletion, acidosis, ROS-activation with or without subsequent reestablishment of physiologic conditions.
Manuscript

Göteborg 2010



UNIVERSITY OF GOTHENBURG

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Abstract

Acute myocardial infarction is the consequence of an occluded nutrient coronary artery. Reperfusion reduces infarct size and enhances the rate of survival. But reperfusion may also, in itself, cause reversible injury, stunning and arrhythmias, as well as irreversible lethal reperfusion injury. The aim of this thesis was to gain knowledge about the complex pathophysiology behind myocardial reperfusion injury.

Two different patient populations with AMI, treated with primary percutaneous coronary intervention were investigated. Presumptive underlying causes for reperfusion injury such as reactive oxygen species (ROS) production, neutrophil activation, signs of inflammation and myocardial cellular damage were studied. In a part of the patient population, delayed-enhanced magnetic resonance imaging (DE-MRI) was performed to estimate infarct size. An experimental porcine infarction with reperfusion was investigated, in which myocardial microdialysis samples and biopsies were analysed with proteomics, Western Blot and real-time-polymerase chain reaction. Mouse cardiomyocytes (HL-1 cells) were analysed after exposition to hypoxia. The HL-1 cells were further investigated with aspects of FKBP12 and FKBP12.6 release in hypoxia, energy depletion, acidosis, ROS activation and re-establishing of physiologic conditions, simulating ischemia and reperfusion at varying durations.

Markers for inflammation increased over time, whereas the markers for ROS production and neutrophil activation were at the maximum level at baseline and during the first day. Biomarkers, showing myocardial injury, were useful for infarct size estimation compared with DE-MRI when obtained correctly. FKBP12 and FKBP12.6, increased during ischemia/hypoxia in both the experimental models. Viability of HL-1 cells matched severity of duration and intensity of ischemia. FKBP12 and FKBP12.6 increased during simulated ischemia, while the mRNA expression was depressed suggesting dissociation from receptors regulating intracellular calcium flows. Clinical symptoms and signs of reperfusion injury may partly be explained by release of FKBP12 and FKBP12.6, this causing disturbance of the intracellular cell contraction. These findings may indicate further important mechanisms in ischemia/hypoxia and reperfusion in the heart.

Keywords: myocardium, ischemia, reperfusion injury, FKBP12, FKBP12.6

ISBN 978-91-628-8100-9

Göteborg 2010