Topic 15 – Myocardial hypoxia, reperfusion, stroke – D

April 25th, Friday 2014

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Fragmented QRS in patients with STEMI undergoing PCI: relation to ST-segment resolution and determinism

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Background: fragmented QRS complex (fQRS) is a marker of myocardial scarring and has prognostic significance. ST-segment elevation acute myocardial infarction (STEMI) is characteristic of tissue reperfusion. This study investigates the relationship between fQRS and STR in STEMI patients undergoing primary percutaneous coronary intervention (PCI) and determines the predictors of fQRS.

Methods: we analyzed the electrocardiograms (ECGs) of 256 patients included in a multicenter prospective STEMI-PCI study. fQRS and ST-segment resolution were evaluated upon arrival in the ambulacne (ECG-amb) and 1 h post-PCI (ECG-post). Major clinical cardiac events were assessed at 30 days and 6 months.

Results: fQRS was present in 33 patients (13.6%) on ECG-amb and in 30 patients (12%) on ECG-post. The presence of fQRS at either time was not associated with STR or clinical outcomes. In a multivariable analysis, the independent predictors of fQRS on ECG-amb were female sex (p = 0.04), cardiac troponin Ic level at 72 h (p = 0.01), TIMI 0-1 flow rate pre-PCI (p = 0.002), and inferior STEMI location (p = 0.04). Patients with fQRS on ECG-amb presented a larger necrosed mass on cardiac MRI than patients without fQRS (p = 0.04). No predictors of fQRS post-PCI were identified.

Conclusion: the presence of fQRS at the time of presentation or 1 h after PCI was not associated with STR. However, fQRS was related to enzymatic infarct size, inferior STEMI location, and low TIMI flow rate.

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TREM-1 modulation improves cardiac function during myocardial infarction in pigs

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Introduction: The widespread use of reperfusion therapy has led to an important improvement in short-term mortality after acute myocardial infarction (MI), but long-term mortality remains high. The Triggering Receptor Expressed on Myeloid cells-1 (TREM-1) belongs to the immunoreceptors superfamily and acts as an amplifier of the inflammatory response triggered by TLRs engagement during both infectious and aseptic inflammatory diseases. We hypothesized that administration of LR12, a synthetic peptide able to inhibit TREM-1 activation, could be beneficial at the acute phase of MI, in a clinically relevant model of experimental MI in pigs.

Materials and methods: MI was induced in fifteen anesthetized and mechanically ventilated pigs weighing 45-55 kg, by inflation of an angioplasty balloon in the proximal left anterior descending (LAD) coronary artery cannulated under X-ray guidance, during 60 minutes. Fifteen minutes before deflation, animals were randomized to receive either LR12 (n=7) or LR12-scramble (n=8). Complete hemodynamic and functional parameters were monitored through arterial line, swan-ganz and intraventricular conductance catheters. Resuscitation was conducted by experienced intensivists according to standard protocols used in clinical practice. The monitoring was prolonged until H18, then survivors were euthanized.

Results: The decrease in mean arterial pressure (MAP) was significantly limited during the monitoring period from H12 to the end (-22.1% vs. -33.9%, p<0.01). Cardiac index and cardiac power index, one of the strongest hemodynamic correlate of mortality in cardiogenic shock, were preserved under LR12 regimen (72% vs 45% from baseline value, p<0.05) as well as SVV02 value (74% vs 62%, p<0.05). Ejection fraction and parameters of systolic function improved under LR12 treatment.

Conclusion: TREM-1 inhibition by LR12 at the acute phase of myocardial infarction in invasively monitored pigs limits reperfusion injury and alteration of ventricular contractility.

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Mitochondrial-dependent cardioprotection during postischemic reperfusion is preserved in isolated aged rodent hearts

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It is widely accepted that with the demographic shift towards an ageing population prevalence of age-related cardiovascular disease will increase. Whether cardioprotective strategies are still effective in elderly is a matter of debate. We have previously demonstrated that magnesium orotate (MO) was cardioprotective in adult rat hearts subjected to acute ischemia/reperfusion (IR) injury. The present study was purported to assess the persistence of the protective effects of MO in old Sprague-Dawley rats. To this aim isolated hearts from old (20-24 mo) vs. adult (4-6 mo) animals subjected to a protocol of 30 min I/120 min R were randomized to receive throughout the postischemic reperfusion: no intervention, MO, MgCl2 and orotic acid (OA). The effects on functional recovery and infarct size were compared to the ones elicited by CsA (0.2 μM), the classic mitochondrial permeability transition pore (mPTP) desensitizer. In a second group of experiments, cardiac mitochondria were isolated at 15 min of postischemic reperfusion for respiratory function and calcium retention capacity assessment. Acute administration of MO, MgCl2, but not OA (5 mM each) at the very onset of reperfusion was associated with a significant recovery of left ventricular developed pressure and infarct size reduction in both adult and old animals; protection was comparable to the one elicited by CsA. In mitochondria energized with complex I (but not complex II) substrates isolated from the old animals, all these pharmacological agents protected against the loss of outer mitochondrial membrane integrity, albeit in a lesser degree compared to adult mitochondria. MO, MgCl2, and CsA also prevented the calcium triggered-opening of the mPTP. In conclusion, magnesium-containing pharmacological agents as well as CsA were effective in protecting mitochondrial function at reperfusion in the aged rodent heart.

This work was supported by a grant of the Ministry of National Education.

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Cardioprotection against ischemia-reperfusion injury by heart rate control

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Myocardial infarction (MI) is the major cause of cardiovascular mortality in western countries. Early reperfusion is the only treatment recommended to reduce infarct size (IS), a crucial prognostic factor of morbidity...
and mortality. However, reperfusion presents also deleterious effects such as ischemia-reperfusion (IR) injury due to irreversible apoptotic death of cardiomyocytes. Heart rate (HR) is also a determinant of cardiac pathology. Most ischemic episodes are triggered by an increase in HR that induces an imbalance between myocardial oxygen delivery and consumption. The BEAUTIFUL clinical trial (Fox et al. The Lancet, 2008) has demonstrated that moderate HR reduction diminishes the frequency of episodes MI in patients with stable coronary artery disease and increased HR at rest. The HCN-mediated If current and the Cav1.3-mediated L-type Ca²⁺ currents play important roles in the generation of automaticity and HR, therefore they are interesting targets for selective control of HR and cardioprotection (reduced IS) during acute MI. The aim of our study was to investigate if targeting Cav1.3 channels could be an efficient strategy to reduce IS. Cav1.3 −/− mice was used as a genetic model of Cav1.3 inhibition because of the lack of selective blocker. Ivabradine (Iva), the selective If-channel blocker, was used for pure HR reduction as a positive control. Results show that selective HR decrease (40%) in an in vivo mouse model of acute MI is associated with reduced IR injury. Ivabradine administration 30 minutes before ischemia significantly reduced IS (35%). Cav1.3 −/− mice presented reduced IS compared to WT mice (30%). In addition, preliminary results show that Girk4 −/− mice, a genetic model of moderate sinus node tachycardia (10%) displayed increased IS compared to control mice (45%). Taken together these results suggest a direct relationship between HR and IR injury and that inhibition of Cav1.3 channels constitutes a promising strategy to reduce both HR and IS.

Impact of admission hyperglycemia on one-year mortality in non-diabetic patients admitted for rescue PCI: data from the "Observatoire des infarctus de Côte d’Or"

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Background: Rescue percutaneous coronary intervention (PCI) is associated with improved clinical outcomes for ST-segment myocardial infarction (STEMI) patients after failed fibrinolysis therapy. Hyperglycemia on admission has been shown to be a powerful predictor of mortality after acute myocardial infarction, particularly in non-diabetic patients. The aim of our study was to assess the predictive value of admission glucose levels on long-term mortality in patients with rescue PCI.

Patients and Methods: From the "Observatoire des infarctus de Côte d’Or" (RICO) survey, 510 consecutive non-diabetic STEMI patients admitted to the intensive care unit for rescue PCI after failed fibrinolysis therapy were included in the study. We analyzed one-year cardiovascular mortality in these patients. Rescue PCI was deemed necessary in patients with ST-segment resolution <50% 90 minutes after lysis, or a thrombolysis in myocardial infarction (TIMI) perfusion grade in the infarct-related artery <3 at the time of angiography in patients with persisting equivocal symptoms. Patients were classified according to admission glycemia: <11 mmol/L (group I, n=452) and ≥11 mmol/L (group II, n=58).

Results: One-year cardiovascular (CV) mortality was 6% in group I and 29% in group II (p=0.001). Patients with hyperglycemia on admission were more likely to develop cardiogenic shock (43% vs. 10%, p=0.001) and to have higher peak CKP (4052(2465-6283) vs. 2667 (1303-4865), p=0.007), reflecting a bigger infarct size than the others, although the revascularization results were similar. By multivariate analysis, glycemia on admission ≥11 mmol/L (odds ratio 6.380, 95% confidence interval 2.075 to 19.617, p=0.001) and GRACE risk score (OR: 1.027, 95% CI 1.012-1.042, p<0.001) were independently associated with 1-year CV mortality.

Conclusion: In non-diabetic patients undergoing rescue PCI after failed fibrinolysis, glycemia on admission is a predictive factor for long-term CV survival. This study suggests that evaluating early glycemic control may be useful in the setting of rescue PCI.