Atrial longitudinal strain parameters predict left atrial reverse remodeling after mitral valve surgery: a speckle tracking echocardiography study


**Purpose:** Volume overload in chronic severe mitral regurgitation causes left atrial remodeling. MV surgery usually results in left atrial (LA) volume reduction. In patients undergoing mitral valve surgery, LA reverse remodeling was related to better postoperative clinical outcome and survival previously. However, only few clinical and echocardiographic parameters were suggested to be associated with LA reverse remodeling. In this study we investigated the relationship between LA peak longitudinal strain (reservoir strain) assessed with 2-dimensional speckle tracking imaging (2D STI) and LA reverse remodeling.

**Methods:** 53 patients (24 females and 29 males, mean age: 45.7±13.5 years) with severe mitral regurgitation and preserved left ventricular systolic function were included in the study. All patients had normal sinus rhythm. The etiology of mitral regurgitation was mitral valve prolapse (MVP) in 37 patients and rheumatic valvular disease in 16 patients. Mitral valve repair was performed in 30 patients while 23 underwent mitral valve replacement. Echocardiography was performed before the surgery and six months later. Left atrial peak longitudinal strain (PLS) was assessed with speckle tracking imaging. LA reverse remodeling was defined as a percent of decrease in LA volume index (LAVI).

**Results:** Left atrial volume index significantly decreased after surgery (58.2±16.6 ml/m² vs. 43.9±17.2 ml/m²; p < 0.001). Mean LAVI reduction was 22.5% ± 27.2. There was no significant difference in LAVI reduction between mitral repair and replacement groups (22.1±22.6% vs. 23.1±32.8%; p > 0.05). Besides decrease in LAVI was also similar in patients with MVP and rheumatic valve disease (24.4±26.8% vs. 18.2±28.9%; p > 0.4). Correlates of LAVI reduction were pre-operative LAVI (r: 0.28 p: 0.039), LA PLS (r: 0.36 p: 0.001) and age (r: -0.36 p: 0.001). Furthermore, in multivariate linear regression analysis, preoperative LAVI, operative LAVI (r: 0.28 p: 0.039), LA PLS (r: 0.36 p: 0.001) and age (r: -0.36 p: 0.001) were significant predictors of LA reverse remodeling. In patients undergoing mitral valve surgery, LA reverse remodeling was related to better postoperative clinical outcome and survival previously. However, only few clinical and echocardiographic parameters were suggested to be associated with LA reverse remodeling. In this study we investigated the relationship between LA peak longitudinal strain (reservoir strain) assessed with 2-dimensional speckle tracking imaging (2D STI) and LA reverse remodeling.

**Conclusion:** TAVI was associated with significant recovery of LA structure and function suggesting a reverse cavity remodeling. Such functional recovery is determined by the severity of pre-procedural valve stenosis.

**MITOCHONDRIA: BEYOND ENERGY METABOLISM IN CARDIAC PATHOPHYSIOLOGY**

P1858 | BENCH

Eicosapentaenoic acid mediates mitochondrial fatty acid composition and fusion protein OPA1 in association with preservation of oxidative phosphorylation after myocardial infarction

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**Purpose:** Eicosapentaenoic acid (EPA) is a first line drug in the management after myocardial infarction. Mitochondria are major contributors to energy metabolism and recent mounting evidence suggests that mitochondrial dynamics, such as fusion and fission, has a pivotal role in regulating mitochondrial function. This study was designed to determine whether oral EPA mediates mitochondrial fatty acid composition, dynamics, and oxidative phosphorylation, leading to the attenuation of cardiac remodeling after myocardial infarction (MI).

**Methods and results:** Anterior MI was produced in male rats by ligation the left anterior descending coronary artery (MI group). In the EPA-treated group, EPA (1,000 mg/kg/day) was administrated for 12 weeks after coronary ligation (MI+EPA group). Myocardial infarct size and blood pressure were comparable between groups. At 12 weeks after MI, mitochondria were isolated in non-infarcted myocardium and mitochondrial fatty acid composition was determined using gas chromatography mass spectrometry. In EPA+MI group, mitochondrial EPA content was approximately 10 times higher than in untreated-MI group. Cardiac function was assessed by echocardiography and 2F micro-manometer-tipped catheter at 12 weeks of MI. EPA significantly improved fractional shortening, +dP/dt, -dP/dt, and reduced left ventricular (LV) end-diastolic diameter and pressure. In addition, histological examination showed EPA significantly suppressed myocardial fibrosis and interstitial fibrosis in non-infarcted myocardium by 15% and 30%, respectively. Levels of ATP in cardiac tissue were measured by high-performance liquid chromatography and mitochondrial oxidative phosphorylation was assessed by O2 consumption using isolated mitochondria. After 12 weeks after MI, ATP contents in non-infarcted myocardium were significantly decreased, and mitochondrial complex II, III, and IV activities were also impaired, while EPA...
Treatment significantly preserved mitochondrial complex activities, as a consequence of an increase in myocardial ATP content. Furthermore, M1 decreased optic atrophy-1 (OPA-1) protein, a mitochondrial fusion protein, without any effect on the parallel-related protein-1 (Drp-1) protein, a mitochondrial fission protein, leading to attenuation of mitochondrial damage.

Conclusion: These results suggest that oral EPA administration mediates mitochondrial protein expression, preserves mitochondrial fusion protein OPA-1 and function of oxidative phosphorylation, leading to the attenuation of left ventricular remodeling after MI.

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Genetic deletion of p66shc adaptor protein leads to increased myocardial infarction by inhibiting RISK and SAFE prosurvival pathways
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Background: Formation of reactive oxygen species (ROS) contributes to many postischemic pathological processes. Although ROS production is also involved in many physiological processes, the imbalance between their generation and removal, i.e. oxidative stress, plays a major role in particular in myocardial injury caused by ischemia and reperfusion. The normal mitochondrial protein p66shc encodes three mitochondrial forms: p66shc, p52shc and p56shc. The p66shc is not involved in mitochondrial signals as p46Shc/p52Shc, but it functions as a critical mediator of intracellular oxidative stress.

Methods and results: 8-12-week-old male p66shc deficient (p66shc/-/i) mice and corresponding C57Bl/6 wild-type (WT) control mice were subjected in vivo to different durations of ischemia (30, 45 and 60 min) followed by 24h of reperfusion. Infarct size was assessed morphologically and by MRI. After 30 min of ischemia, p66shc+/+ mice developed markedly larger infarcts as compared to WT (infarct size at risk (IAR): 24.5±0.05% vs. 7.72±1.31%, n=18, p<0.05). This effect was confirmed by in vivo silencing of p66shc prior to I/R. Both genetic deletion and silencing of p66shc displayed an increased ROS in ischemic heart (I/R). However, the observed differences in infarct size were limited to 30 min of ischemia since by increasing ischemia duration to either 45 or 60 min infarct size did no longer differ between p66shc+/+ and WT mice. Moreover, differently from WT, infarct size in p66shc−/− was not significantly larger with increasing duration of ischemia (from 30 to 60 min). On the molecular level the observed effect was linked to the inhibition of activation by phosphorylation of protein kinase Akt and transcription factor STAT3 – two key members of prosurvival pathways RISK and SAFE, respectively.

Conclusions: Our data suggest that genetic deletion of p66shc leads to an increased sensitivity to myocardial infarction with larger infarcts with shorter, but not prolonged ischemia, and that RISK and SAFE prosurvival pathways are involved. Therefore, activation of p66shc may provide resistance to ischemia and represent a novel therapeutic target in the early phase of myocardial infarction.

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Post-ischemic in vivo p66shc silencing as a therapeutic strategy for ischemia/reperfusion brain injury

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Purpose: Stroke is a leading cause of morbidity and mortality, and its incidence increases with age. Currently, there is no specific therapy that can be applied for ischemic stroke. Therefore, genetically modified mice were used in the present study to investigate the role of p66shc in stroke in a clinically relevant experimental setup whereby p66shc knockdown is performed after the ischemic episode.

Methods: A transient Middle Cerebral Artery Occlusion (MCAO) was performed to induce I/R brain injury in wild type (C57Bl/6) mice. After 45 min of ischemia and directly upon reperfusion, specific small Interfering RNA (siRNA) for p66shc (sip66shc) or scrambled siRNA (siScr) were injected intravenously. 48 h post-MCAO, stroke size and neurological deficit were analyzed using magnetic resonance imaging (MRI) and RotaRod test as well as Bederson test, respectively. Moreover, blood brain-barrier permeability was assessed by measuring Evans blue extravasation. Long-term benefit was studied by analyzing survival up to 6 days. In parallel, to test the human relevance of the data observed in mice, and to characterize the protective putative mechanisms of in vivo p66shc silencing, p66shc silencing was performed on primary Human Brain Endothelial Cells (HBEc) exposed to Hypoxia/Reoxygenation (H/R) and p66shc gene expression was determined in Peripheral Blood Monocytes (PBMC) of patients who suffered an ischemic stroke.

Results: Post-ischemic in vivo silencing of p66shc resulted in a reduction in stroke size (p<0.01, n=6) as well as an improved neurological function (p<0.05, n=11) as compared to sip66shc injected mice. Moreover, Evans blue extravasation in p66shc silenced mice was reduced as compared to siScr injected mice (p<0.05, n=6). Additionally, sip66shc mice displayed a 50% increase in survival 6 days after stroke (p<0.05, n=10). In HBEc, H/R increased superoxide anion (O2−) production (p<0.05, n=6) and reduced Nitric Oxide (NO) bioavailability (p<0.01, n=6). Silencing of p66shc blunted H/R-induced O2− generation (p<0.05, n=7) and restored NO bioavailability (p<0.05, n=6). Lastly, in PBMC of ischemic stroke patients we found an increased p66shc gene expression as compared to age-matched control subjects.

Conclusions: The present study together with previously published own work underlines the potential for p66shc to become a novel target for the treatment of ischemic stroke and set the basis for follow up clinical studies.

P1861 | BENCH
The cardioprotective 3',4'-dihydroxyflavonol inhibits the mitochondrial permeability transition pore
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Purpose: 3',4'-Dihydroxyflavonol (DIOH) reduces injury caused by myocardial ischemia and reperfusion (I/R) in association with a reduction in oxidative stress. Oxidative stress contributes to the opening of the mitochondrial permeability transition pore (mPTP), a key event in myocardial IR injury. The aim of this study was to determine the effect of DIOH on mPTP, as well as mitochondrial morphology and the generation of reactive oxygen species (ROS) by cardiac mitochondria after I/R in anaesthetised rats.

Methods: Male Wistar rats were anaesthetised with pentobarbital (70 mg/kg i.p. administered 20 min before ischemia) and mechanically ventilated. Through a left thoracotomy the left main coronary artery was occluded for 30 min and then reperfused for 15 minutes. The heart was then rapidly removed, cooled and the area at risk of ischemia homogenised and centrifuged for the isolation of mitochondria. In sham experiments the rats were

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