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 (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 20 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 m³/m² vs. 43.9±17.2 m³/m²; p < 0.001). Mean LAVI reduction was 22.5% ± 27.2. There was no significant difference in LAV reduction between mitral repair and replacement groups (22.1±22.6% vs. 23.1±32.8%; p = 0.9). 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 = 0.007). 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: 0.0001) while the delta drop in trans-aortic mean gradient as predictors of LA volume index reduction 3 months after TAVI (p = 0.0001).

Conclusion: TAVI is 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

P1856 | BENCH
Involvement of Monoamine Oxidase a (MAO-A) in mitochondrial fission and autophagy during aging
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Cardiac expression of monoamine oxidase A (MAO-A), an enzyme localized into the mitochondrial external membrane, increases during aging and is considered associated with heart failure. In previous studies, we have observed mitochondrial fission in 2 years old mice and in 30 weeks old MAO-A- transgenic mice. Here we studied the role of fission and autophagy in mitochondrial quality control associated with MAO-A.

Several in vitro and in vivo models were used: (1) cardiomyocytes from neonatal rats or (2) adult rats, infected or not with a MAO-A adenovirus and treated with tyramine, an MAO-A substrate; and (3) an aging model of MAO-A cardiac overexpressing mice (TG-MAO-A) or MAO-A-KO mice. Proteins of interest were studied by western blot and mRNA by Real-Time PCR. In parallel, immunofluorescence and electron microscopy were achieved.

In vitro, we observe an autophagosome accumulation, via a LC3-GFP staining, in neonatal cardiomyocytes infected with MAO-A and treated with tyramine. These results are accompanied with an increased ratio of LC3-II/LC3-I. These effects were abolished by a ROS scavenger (NAC) or an autophagy inhibitor (3-methyladenin). In vivo, 6 weeks old TG-MAO-A mice present an increased DRP1 and Fis1 mRNA, implicated in mitochondrial fission and a decrease of Mfn1 and Opal 1 mRNA, implicated in mitochondrial fusion, compared to littermates. We also observe an increase of Beclin-1 and Parkin proteins in these TG-MAO-A mice at 30 weeks. These variations are correlated with the observation of autophagosomes using electronic microscopy. Conversely, DRP1, Beclin-1 and Parkin proteins remain unchanged in 24 month old MAO-KO mice. This study is the first to explore the role of monoamine oxidase A in mitochondrial quality control during aging.

P1857 | BENCH
Eicosapentaenoic acid mediates mitochondrial fatty acid composition and fusion protein OPA-1 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 ligating 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, myocardial tissues 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 that 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, and -dp/dt, and reduced left ventricular (LV) end-diastolic diameter and pressure.

In addition, histological examination showed EPA significantly suppressed myocardial hypotrophy 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...
P1858 | BENCH
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 pathological processes. Although ROS production is also involved in 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/reperfusion (I/R). The normal mammalian Shc locus encodes three Shc isoforms: p46Shc, p52Shc and p66Shc. The p66Shc is not involved in mitogenic signals as p46Shc/p52Shc, but it functions as a critical mediator of intracellular apoptosis and necrosis. Various studies reported p66Shc to cardiovascular disease; however, few data are available on the role of p66Shc in myocardial I/R.

Methods and results: 8-12-week-old male p66Shc deficient (p66Shc−/−) 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]: 20.46 ± 2.93% of baseline, 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 post-ischemic level of serum cardiac troponin I (cTnI). Moreover, the observed effect on infarct size was 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 translocation factor STR3 – 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.

P1860 | BENCH
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 is still high with age. Current strategies lack a specific therapy for effective treatment of stroke, thus, new approaches in the treatment are essential. Recently, we demonstrated that p66shc knockout mice are protected from Ischemia/Reperfusion (I/R) brain injury by a decreased production of ROS. The present study aimed to investigate the role of p66shc in p66shc silencing in a clinically relevant experimental setup whereby p66shc knockdown was performed after the ischemic episode.

Methods: A transient Middle Cerebral Artery Occlusion (MCAO) was performed to induce I/R brain injury in wild type (C57/Bl6) mice. After 45 min of ischemia and directly upon reperfusion, specific small Interfering RNA (siRNA) for p66shc or scrambled RNA (scRNA) were injected into the ipsilateral striatum. 48 h post-MCAO, stroke size and neurological deficit were determined 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 putative protective mechanisms of in vivo p66shc silencing, p66shc silencing was performed on primary Human Brain Endothelial Cells (HBE) exposed to Hypoxia/Reoxygenation (H/R) and p66shc gene expression was determined in Peripheral Blood Monocytes (PMB) 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=6-7) as well as an improved neurological function (p<0.05, n=11) as compared to scRNA injected mice. Moreover, Evans blue extravasation in p66shc silenced mice was reduced as compared to scRNA injected mice (p<0.05, n=5-6). Additionally, sip66shc mice displayed a 50% increase in survival 6 days after stroke (p<0.05, n=10-11). In HBE, 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 PMB 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 underscores the concrete 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 cardioprotectant 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 (IR) 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 respiration and the generation of reactive oxygen species (ROS) by cardiac mitochondria after IR in anaesthetised rats.

Methods: Male Wistar rats were anaesthetised with pentobarbitone (70 mg/kg, IV), temporarily connected to a ventilator and 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...