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

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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 (PALS) 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 = 0.9). Besides the increase 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 = 0.29; 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, LA PLS and age were all significant predictors of LA reverse remodeling.

Conclusion: Left atrial peak longitudinal strain measured by 2D STI, in conjunction with preoperative LAVI and age is a predictor of LA reverse remodeling in patients undergoing surgery for severe mitral regurgitation. We suggest that in this patient population LA GLS may also be used as a prognostic protective marker.

Atrial remodelling after TAVI

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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 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 study 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, a 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-methyladenine). In vivo, 6 weeks old TG-MAO-A mice present an increased DRP1 and Fi1 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.

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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 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, mitochondrial complexes 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 myocyte hypertrophy 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, MI decreased optic atrophy-1 (OPA-1) protein, a mitochondrial fusion protein, without any effect on the 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 protection and improves outcomes after ischemia-reperfusion injury. These findings provide a potential therapeutic strategy for the treatment of ischemic stroke and set the basis for follow-up clinical studies.

**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 was injected intracranially. 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 putative protective 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=6-7) as well as an improved neurological function (p < 0.05, n=11) as compared to siScr injected mice. Evans blue extravasation after p66shc silenced mice was reduced as compared to siScr injected mice (p < 0.05, n=10-11). 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.

**Conclusion:** The present study together with previously published own work underlines 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.