Topic 8 – Aging – B

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0397

Age-related changes in rodent myocardial perfusion reserve in response to adenosine: longitudinal follow up with ASL-MRI

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Introduction: In clinical routine, myocardial perfusion MRI is generally performed with a stress/rest protocol using adenosine as a stressor to visualize ischemic risk zones in the myocardium. Changes in the vasodilator responses to adenosine with age have been reported in the rat thoracic aorta and the isolated-perfused rat heart. This study assesses the effect of maturation on the vascular relaxant action of adenosine in vivo on rats.

Methods: We used a fast imaging procedure (cine-ASL) to non-invasively quantify myocardial blood flow (MBF) and myocardial perfusion reserve (MPR) at rest and during adenosine-induced stress. Adenosine was injected via the tail vein at a rate of 420 µg/kg/min. MBF and maximal MPR were monitored on 10 healthy Wistar rats at 4.7T, from young to mature rats at five different time points during growth (2, 8, 10, 13, and 15 months).

Results: Myocardial perfusion was measured in a region of interest covering the entire myocardium. No statistical differences in mean group MBF at rest were found across time (5.3±0.6mL/g/min). MPR, defined as the ration of stress MBF over rest MBF, was 2.3±0.3 at M2, 2.2±0.4 at M8, 2.0±0.5 at M10, 1.7±0.3 at M13, and 1.7±0.2 at M15 (Fig.1). In rats, maximum MPR to adenosine was found to be at early stage of growth, while a continuous decrease in coronary response was observed as the animals became mature (significantly different at M13 and M15).

Conclusion: This study focuses on age-related changes in coronary response to adenosine as an infused vasodilator. These changes might be due to alterations in the adenosine receptor sites and a decrease in vascular elasticity. Such measurements give more detailed insight into changes of rodent coronary reserve occurring with growth and are of interest for studying myocardial stress response in rodent heart disease models across time.

0400

Levels of oxidative stress and markers of senescence in the internal mammary artery of aged cardiac bypass surgery patients with respect to the presence of hypertension and diabetes

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Endothelial cell senescence promoting endothelial dysfunction has been suggested to contribute to the development of age-related vascular disorders. Senescence is characterized by an irreversible cell cycle arrest involving the p53/p21 pathway and oxidative stress. The present study has evaluated the level of vascular senescence and oxidative stress in internal mammary artery segments from 20 aged patients undergoing bypass surgery with or without risk factors including hypertension and diabetes.Patients were 60 to 85 years old. After removal, the internal mammary artery segment was incubated in a physiological salt solution, transported at room T°C to the laboratory and processed within 3 h. Segments were cleaned of fat and connective tissues and cut into rings of 3-4 mm length. Rings were then embedded in OCT tissue Tek, stored at -80°C for subsequent analysis. Senescence markers were assessed by immunofluorescence staining, and the level of oxidative stress using the redox-sensitive probe dihydroethidine in 14 µm sections. In normotensive and non-diabetic patients, a low level of both oxidative stress and p53 and p21 was observed throughout the arterial wall including the endothelium and neointima. These markers were increased in sections of hypertensive patients and was most pronounced in hypertensive and diabetic patients. The present findings indicate that oxidative stress and senescence are observed in the internal mammary artery of aged patients and that these effects are more pronounced in patients with risk factors including hypertension and diabetes.

0292

Endothelial protein tyrosine phosphatase 1B deficiency reduces both endothelial and cardiac dysfunction of in a mouse model of aging

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I**ntroduction:** Aging is associated with an endothelial dysfunction, characterized by a decrease of nitric oxide (NO) production, which is a risk factor of development of cardiovascular diseases. However, the direct link between endothelial dysfunction and aggravation of cardiac function in aging is not established. We reported previously a new potent therapeutic approach of cardiovascular disease, based on inhibition of protein tyrosine phosphatase 1B (PTP1B), which both increases NO production (*via* restored PI3K/Akt/eNOS signaling) and reduces cardiac dysfunction in both post-ischemic heart failure and aging, however the exact role of endothelial PTP1B in this setting is unknown. To evaluate the endothelial and cardiac consequences of endothelial PTP1B deficiency (endoPTP1B$^{-/-}$) in a mouse model of aging.

Material and methods: EndoPTP1B$^{-/-}$ mice were developed by crossing LOX-P PTP1B mice with mice expressing CRE under the control of the endothelial promoter Tie2, or wild-type (WT). The evolution of cardiac function was assessed by echocardiography at different time points and the vascular function was evaluated *ex vivo* at 24 months.

Results: Compared to young (3 month-old), WT mice aged (24 month-old) showed a markedly impaired flow-mediated dilatation of isolated mesenteric arteries (3 months: 40±4%; 24 months: 1±1%; p<0.001), which was improved in endoPTP1B$^{-/-}$ mice (17±3%; p<0.001 vs. WT 24 months). This restored response in aged endoPTP1B$^{-/-}$ mice was abolished by a NO-synthase inhibitor, suggesting a restored NO production. In WT mice, aging decreased stroke volume (3 months: 0,070±0,002%; 24 months: 0,065±0,005%; p<0.001) and cardiac output (3 months: 37±1%; 24 months: 29±2%; p<0.001) and these parameters were improved in endoPTP1B$^{-/-}$ mice (24 months: 0.081±0,011% and 34±2%; respectively, p<0.05).

Conclusion: In aged mice, endoPTP1B deficiency induced an improvement of endothelial function, and also tended to improved cardiac function. These results provide a direct demonstration of the beneficial effect of endothelial protection in aging.

0144

Depression and anxiety in coronary artery bypass grafting patients: comparisons with percutaneous intervention

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Background: Anxiety and depression are two common psychic entities among coronary patients. They are often sub-diagnosed. Several studies demonstrated that they aggravated the morbi-mortality of the coronary patient. The objective of this study was to quantify the anxiety and the depression in coronary artery bypass grafting patients (CABG), to determine the effect of the revascularisation and to find a relation between depression and morbi-mortality.

Method: 64 patients were admitted for a coronary event and divided in two groups. PTCA (N = 34) and CABG (N = 30). The anxiety and the depression were measured by two scales of psychological self-assessment (HAD, BDI) in three time; T1 (To the announcement of the disease), T2 (3 weeks

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after the revascularisation) and T3 (3 months later). A comparative study between 2 groups was realized.

Results: Two groups were comparable on the sociodemographic plan and the risk factors. The cardiovascular histories of myocardial infarction and coronary angioplasty were frequent in the PTCA groups and CABG. The average of the day number of hospitalization was of 7.5±3.9 days for the PTCA group and 10.3±7.4 days for the CABG group. The psychological evaluation in the admission showed scores of anxiety raised in two groups and depression raised only in the group CABG. The myocardial revascularisation had a positive effect on the psychological state of the patients of the groups PTCA and CABG. The evolution of the psychological scores showed that the patients of the group surgery were more depressed and that the patients of the group angioplasty were more anxious. For the group PTCA, the average duration of survival without revascularisation was of 26 months in the absence of depression, against 21 months in its presence. For the group CABG, the average duration of survival without revascularisation was of 27 months in the absence of major depressive episode, against 16 months in its presence.

Conclusion: The depression and the anxiety are two frequent symptoms in the ischemic heart disorder. The depression is a factor of bad forecast at CABG patients. The early screening is important for setting up appropriate therapeutic.

0359

Cyclosporine A prevents the induction of replicative senescence in cultured coronary artery endothelial cells: role of eNOS-derived NO and the p53/p21 and p16 pathways

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Background: Clinical studies have indicated a higher incidence of heart failure and death following myocardial infarction with increasing age, and that cyclosporine A limits myocardial infarction size. Since aging is associated with the induction of vascular and endothelial senescence, an irreversible cell cycle arrest involving an increased activity of p53 and its downstream effector p21, and p16, and a reduced expression of endothelial nitric oxide synthase (eNOS), the possibility that cyclosporine A prevents endothelial senescence was evaluated using cultured porcine coronary artery endothelial cells, and, if so, the underlying mechanism was characterized.

Material, Methods: Replicative senescence was induced by sequential passaging of primary cultures of endothelial cells up to the fourth passage (P4). Endothelial senescence was assessed by senescence-associated β-galactosidase (SA-β-gal) activity, and protein expression by Western blot analysis.

Results: Passaging of cultures of endothelial cells was associated with a gradual increase in SA-ß-gal activity, a down-regulation of eNOS protein and an up-regulation of p16, p21 and p53 protein level in cells from P1 to P4. Cyclosporine A prevented the increase in SA-β-gal activity at concentrations as low as 0.3 μg/ml. The eNOS inhibitor, L-N^G-nitroarginine methyl ester, increased SA-β-gal activity in cells at P1, and prevented the protective effect of cyclosporine A in cells at P3 and P4. Cyclosporine A prevented the down-regulation of eNOS and the upregulation of p16, p21 and p53 in cells at P3.

Conclusion: the present findings indicate that cyclosporine A delays endothelial cell replicative senescence most likely by preventing the down-regulation of eNOS expression and the up-regulation of the p53/p21 and p16 pathways leading to cell cycle arrest.

0156

Heart failure in the elderly: comparison between reduced ejection fraction and preserved ejection fraction

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Introduction: Heart failure is a common problem in elderly people. In the elderly population, heart failure with preserved ejection fraction (HFPEF) has been increasingly recognized. The aim of this study was to compare clinical features and clinical outcomes between HFPEF and HFREF in patients older than 65 years.

Methods: We enrolled 30 patients over 65 years old, who were admitted for heart failure between April 2009 and February 2010. We retrospectively analysed the clinical features including laboratory data and echocardiography parameters.

Results: In 19 patients (63%) left ventricular ejection fraction was preserved. Acute pulmonary edema (74% vs 27%) is the most frequent presentation in patients with HFPEF. Those patients have thicker left ventricular wall (68% vs 27%). The ischemic heart diseases as background disease is more frequent in HFREF (46% vs 5, 2%). There was no difference in short-term outcomes between HFPEF and HFREF.

Conclusion: Our study has shown that more than the half of the CHF patients over 65 years of age had HFPEF. Left ventricular hypertrophy was one of the risk factors for HFPEF, and the short-term outcomes of HFPEF in this population were not different from that of HFREF.

0348

Telomere length measurement and comparison in skeletal muscle, adipose tissue, skin and leukocytes: methodological aspects and preliminary results

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The prevailing view in telomere epidemiology is that leukocyte telomere length (LTL) is associated with atherosclerosis since it serves as a biomarker of inflammation and oxidative stress during adult life. Our recent results however, indicate that telomere length (TL) is mainly determined at birth and childhood. Since short telomeres antecede atherosclerosis, we hypothesize that TL is not just a marker, but a determinant of arterial aging. This hypothesis cannot be tested by measurements of LTL alone, LTL reflecting TL at birth and its age-dependent attrition. We propose a model that examines different elements of TL dynamics in different tissues: leukocytes, skeletal muscle, adipose tissue and skin in patients with or without atherosclerosis. The method for TL measurement in epidemiologic studies is Telomeric Restriction Fragment Southern Blot (TRF). It requires high quality telomeric DNA therefore DNA extraction step is very important. Telomeric DNA is sensible to degradation and variations in extraction protocol can result in differences in TRF measurement. There are several DNA extraction protocols according to origin of extracted tissue. Since extraction method can influence TL and we want to compare TL between tissues, we have to choose one protocol giving high quality DNA with the 4 tissues. Three protocols were tested: phenol/chloroform/isoamyl alcohol extraction, Miller salting out procedure and Qiagen Puregene kit. Two type of tissue grinding were also tested: automatic bead grinder and manual grinding in liquid nitrogen. Concentrations of DNA obtained were quantified by spectrophotometry at 260 nm, contaminations with proteins and solvents by 260/280 and 260/230 ratios. DNA were checked for integrity on agarose gel and TL measured by TRF method.Quality of DNA obtained with different protocols and TRF measurement make us choose phenol extraction and nitrogen grinding despite their drawbacks, time consumption for nitrogen grinding and toxicity for phenol.