

Effects of physical activity on the physiopathology of cardio- and cerebrovascular disorders: role of oxidative stress

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Sickle cell disease (SCD), atherosclerosis and hypertension are three distinct diseases that share similar underlying characteristics. Sickle cell disease is a hemoglobinopathy characterized by a genetic mutation which causes the normal blood cells to become rigid and weak. The resulting pathophysiological effects, including sickling, vaso-occlusion, and adhesion, involve the production of oxidative stress and inflammation. Atherosclerosis is a chronic inflammatory disease that is characterized by plaque buildup within the vessel walls. An initial step in the pathogenesis of this disease involves the oxidation of lipids, which not only produces inflammation, but more oxidative stress as well. Finally, there is increasing evidence to implicate an important role of oxidative stress in the pathogenesis and progression of arterial hypertension. Indeed, an increase in reactive oxygen species may decrease nitric oxide (NO) bioavailability in the vasculature and further lead to the endothelial dysfunction at the origin of the disease.

In other hand, exercise training is an important mechanism for the beneficial modulation oxidative stress and inflammation through several adaptive pathways: antioxidants, shear stress, vasodilatation, and anti-inflammatory cytokines. Therefore, the purpose of this presentation is to present the beneficial effects of exercise training in oxidative stress, vascular adhesion, NO metabolism and inflammation in two mice model of sickle cell trait and atherosclerosis and in subjects at risk for hypertension (i.e. post menopausal women).

The first experiment of this presentation shows that exercise training decreases pulmonary adhesion, oxidative stress and improves NO metabolism in SCD mice submitted to an acute stress that usually triggers vascular occlusive crises (i.e. hypoxia-reoxygenation paradigm)

Our second study looked at the effects of voluntary wheel running on a mice model of atherosclerosis that present signs of neurologic disorders as paraplegia or hemiplegia in more than 10% of the mice. The exercise training significantly decreased the mortality rate by 50%. Using MRI, we found that exercise training reduced the vessel wall area of the aorta and changed aortic plaque composition. In the brain, exercise training reduced macrophage infiltration, oxidative stress, and inflammation. We demonstrated that exercise training can be beneficial in reducing the complications in advanced atherosclerosis.

Finally, the last study of this presentation demonstrates, in post menopausal women, that regular physical activity beneficially modulates arterial pressure and cerebrovascular resistance via oxidative stress and NO mediation.

Overall, exercise training by modifying the production of oxidative stress, nitric oxide and inflammation, physical activity can limit the cardio- and cerebrovascular pathologies associated with a large broad of diseases.

Muscle fiber diversity and muscle regeneration

Dr pascal Maire

Département Génétique et développement, équipe génétique et développement des muscles

Le Grand et al (2012) J Cell Biol, 198 : 815-832

Richard et al (2011) Dev Biol 359 : 303-320

Endurance training in elderly : why, how, results ?

Professeur honoraire Jean Lonsdorfer

BIEN VIEILLIR – Centre de Prévention Agirc – Arrco - Alsace

Regular physical exercise has an increasingly recognized role in preserving not only cardiovascular and muscular but also brain and cognitive health during ageing and older adults sedentarity.

The number and the diversity of the exercise beneficial consequences suggest that the process' biological regulation is located at a transcriptional level.

Recent investigations and to day Pr. V. Pialoux and Dr P. Maire topics demonstrate the role of the oxidative stress on the genes encoding energy metabolism, protein synthesis, mitochondrial biogenesis, angiogenesis, which underlie the subject's physiological functions.

Free radicals production increases with acute or high intensity exercises, and also during an incremental step exercise when continued above the subject's anaerobic threshold. But training below this threshold does not alter the antioxidant defenses ; more over regular exercise training at the subject's optimal aerobic intensity stimulates his defenses : this level is the subject's ENDURANCE intensity. For several years we observed that patients though after cardiac or lung transplantation had a persisting altered quality of life due to unconstant results on their ENDURANCE capacity after conventionnal rehabilitation programs.

Thus we have developped a training program which uses the patient's accurate ENDURANCE threshold intensity : the PEP'C (Programme d'Endurance Personnalisé sur ergoCycle) or IWEP, a short-term personalized Intermittent Work Exercise Program on bicycle.

The exercise consists on a 30 min. cycling session, twice a week, for 9 weeks. A session consists of 4 min cycling at the patient's Endurance power output (ventilatory threshold, VT1), called Base, then 1 min. at a submaximal "Peak" at 80% of the VO₂max. Base and Peak and their target heart rate values are previously determined during a maximal incremental exercise test led to exhaustion. During the sessions THR decreases, thus BASE intensity can be augmented.

A the end of the 18 sessions training results in a significant increase of ENDURANCE (+30% an often more) ; maximal O₂ intake, VO₂max, (15 to 25%) and arterial blood O₂ extraction by the muscles.

Physiological and clinical benefits will be discussed.

Organization and collaboration between the CENTRE BIEN VIEILLIR (Dr I. CHAPARD Strasbourg) and the CONSULTATION de l'APTITUDE PHYSIQUE du SENIOR, CAPS (Pr. Th. VOGEL Pôle de Gériatrie des HUS) will be presented.

High throughput sequencing platform

Stephanie Le Gras

IGBMC, Illkirch

The IGBMC microarray and deep sequencing platform is dedicated to provide a full service for gene expression-, genomics- and epigenetic-profiling from quality check of starting material up to data analysis. Three complementary technologies are offered: Affymetrix GeneChips, Agilent microarrays and Illumina deep sequencing. The platform recently acquired a Biomark HD and a C1 Single-Cell Auto Prep Systems. These advanced microfluidic systems enable Single cell genomics, gene expression, genotyping and digital PCR.

PCBIS: an open access platform to researchers

Pascal Villa

UMS 3286 CNRS-University of Strasbourg

Since 1999, the "Plate-forme de Chimie Biologique Integrative de Strasbourg" (PCBIS) developed an expertise in the field of chemical biology (www.pcbis.fr, ISO 9001:2008 approved by LRQA).

This presentation will show which technologies and instrumentations are available at PCBIS, and what kind of project can be developed.

- **Technologies:** luminescence, fluorescence, absorbance, FRET, time-resolved fluorescence (TRF & HTRF), fluorescence polarization, DLS, Epic (label-free detection platform for biochemical & cell-based assays), wound healing, etc.
 - **Instrumentations:** liquid handling robotic stations, microplate readers, microplate-format cell transfection apparatus, microfluidics system, etc.
 - **ADME-Tox:** Physicochemical properties (Solubility, Lipophilicity, pKa, Chemical stability), Pre-clinical ADME (Plasmatic protein binding, Permeability (Caco-2, PAMPA), *in vitro* metabolism (liver microsomes, S9 fraction), CYP phenotyping); *in vivo* pharmacokinetic (PK) and blood-brain barrier (BBB); Cytotoxicity
 - **Biological model development:** cellular or molecular models
 - **Chemical libraries:** compounds & associated assays
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NovAliX

Denis Zeyer

BioParc Bld Sébastien Brant Illkirch

Founded in 2002 as a spin-off from the Strasbourg University, NovAliX is focusing on the development of enabling chemistry and biophysical technologies to support the pharmaceutical industry's outsourcing needs from discovery to manufacturing.

A case study on the discovery and development of a novel inhibitor targeting the Pim1 kinase using biophysical technologies will be presented.

<http://www.novalix-pharma.com/>