

## **Adaptations of cardiac myocyte energy metabolism in atherosclerosis - implication for pathology and therapeutic strategies**

The main objective of the planned research is to see whether lipid disorders that are a known to cause the formation of atherosclerotic plaques in the blood vessel wall could also cause other disorders such as adverse metabolic adaptations in the heart even before the blood flow in the coronary arteries become restricted. Excessive supply of fat can cause mitochondrial dysfunction, increased oxidation of fat and reduced oxidation of glucose in the cells of the heart. These changes can result in increased oxygen consumption with the same amount of accumulated energy. In this situation, the sudden closure of the blood supply, as occurs in myocardial infarction will cause much more damage than if these metabolic changes would not occur. This is a situation other than during the gradual, progressive development of coronary insufficiency, when heart cells are able to adapt to hypoxia. Therefore, the aim of this proposal is to study how heart cells convert energy at different stages of atherosclerosis, both in the laboratory and in patients. In addition, the possibilities of simple and early detection of these adverse changes will be examined as well as experiments to determine the optimal treatment.

The project will include experimental studies and testing in patients. In experimental studies a mice that develop atherosclerosis will be applied. They will be studied at different ages from 1 to 18 months. Material derived from these animals will undergo the analysis of proteins, metabolites and RNA as well as the detailed analysis of mitochondrial function. After determining the age at which atherosclerotic mice inefficiently uses oxygen, and age of adaptation to oxygen depletion the effectiveness of drugs in both stages will be tested. Further studies will be conducted in patients with familial hypercholesterolemia and in healthy subjects. Non-invasive test <sup>31</sup>P NMR spectroscopy of the human heart will be performed, which will allow to check whether patients have similar changes of energy related processes to that observed in animals. Blood samples will be examined in the same direction. The analysis will be carried out before and three months after the start of treatment to lower blood lipids.

Atherosclerosis is a serious challenge to contemporary medicine contributing the majority of mortality and morbidity in the world. The proposed experiments will allow a better understanding of the changes taking place in the heart at the different stages of atherosclerosis and consequences for the degree of damage in the heart during infarct. This project aims to confirm the concept that atherosclerosis is not only a disease of the vessel, but also causes the early adverse changes in the cells of the heart. Understanding these processes may contribute to a more effective treatment for patients that should be directed not only to prevent changes in the vessels but also for better preparation of heart cells for the conditions of infarct.