

### Pathophysiological significance of trimethylamine N-oxide in heart failure.

The aim of this study is to evaluate the biological effects of trimethylamine N-oxide (TMAO) on the circulatory system. Heart failure is a leading cause of death and disability in adults. Some evidence suggests that intestinal bacteria produce methylamines, such as trimethylamine and its oxide, which may affect pathogenesis of cardiovascular diseases. For example, recent clinical studies have shown a positive correlation between an elevated plasma level of TMAO, a methylamine produced by bacteria, and an increased risk of myocardial infarction, stroke and death. TMAO concentration increase may result from diet intake, impairment of alimentary tract function and disturbances in intestinal bacterial flora. TMAO is a metabolite of phosphatidylcholine and L-carnitine, both abundant in red meat. For this reason, TMAO has been proposed to constitute a link between diet and cardiovascular diseases. On the other hand, it is well-established that TMAO plays a protective role in cell homeostasis in marine animals. Moreover, a number of physicochemical studies point out that TMAO may exert protective actions towards protein molecules. Therefore, it is sound to assume that increase in TMAO plasma concentration might not be a cause of cardiovascular diseases but a protective mechanism which protects circulatory homeostasis against harmful influence of risk factors. Furthermore, TMAO-rich seafood, which is an important source of protein and vitamins in the Mediterranean diet, has been considered to have a beneficial effect on the circulatory system. Therefore, it is unknown whether TMAO plays a role of mediators (triggers) of cardiovascular diseases or whether they may serve as protecting agents.

We will check the effect of TMAO on mechanisms regulating the circulatory system in rats. Specifically, the rats will receive for drinking either tap water or water solution of TMAO for almost a year. Afterwards we will evaluate heart performance as well as metabolic and biochemical parameters such as blood cholesterol and glucose levels.

The proposed project will clarify the role of gut-derived TMAO in the circulatory system in health and disease, in particular in heart failure. It will be important for assessing feasibility of developing new drugs which may exert beneficial effects by changing the synthesis of TMAO and other methylamines produced by bacteria in human intestines.