

Metabolic aspects of cardiac arrhythmias

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The thesis is based on the following papers,

- I. Sigfus Gizurarson, Malin Lorentzon, Truls Råmunddal, Finn Waagstein, Lennart Bergfeldt, Elmir Omerovic. **Effects of complete heart block on myocardial function, morphology, and energy metabolism in the rat.** *Europace*. 2007 Jun;9(6):411-6.
- II. Truls Råmunddal, Sigfus Gizurarson, Malin Lorentzon, Elmir Omerovic. **Antiarrhythmic effects of growth hormone—in vivo evidence from small-animal models of acute myocardial infarction and invasive electrophysiology.** *J Electrocardiol*. 2008 Mar-Apr;41(2):144-51.
- III. Sigfus Gizurarson, Yangzhen Shao, Azra Miljanovic, Truls Råmunddal, Jan Borén, Lennart Bergfeldt, Elmir Omerovic. **Electrophysiological effects of lysophosphatidylcholine on HL-1 cardiomyocytes assessed with a microelectrode array system.** Submitted
- IV. Sigfus Gizurarson, Marcus Ståhlman, Anders Jeppsson, Yangzhen Shao, Björn Redfors, Lennart Bergfeldt, Jan Borén, Elmir Omerovic. **Atrial Fibrillation in Patients Admitted to Coronary Care Units in Western Sweden - The Role of Obesity and Lipotoxicity.** In manuscript



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Metabolic aspects of cardiac arrhythmias

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Cardiac arrhythmias are an important cause of mortality and morbidity in patients with cardiac diseases. Sudden death due to ventricular tachycardia and fibrillation (VT/VF) in the setting of acute myocardial infarction (AMI) and heart failure (HF) is a frequent cause of premature death. Another recognized cause for sudden cardiac death is acquired complete heart block (CHB), a condition where the heart must quickly adapt to volume overload and increased wall stress to maintain normal hemodynamics. In the pre-pacemaker era this was a condition with a very high mortality mostly due to sudden death and progressive HF. The most common sustained arrhythmia, atrial fibrillation causes significant morbidity and is associated with stroke, heart failure and risk of premature death.

The heart is an electro-mechanic pump that metabolizes mostly fatty acids for energy generation. Most of the energy is fuelling contractile work but approximately one-third is designated for ion pumps that maintain the electrochemical homeostasis of the cardiomyocyte, and give rise to the cell depolarization and repolarization. As the ATP pool is completely turned over every 10s, effective metabolism is imperative for the maintenance of electrical stability in the cell. In different pathophysiological states, i.e. obesity and diabetes, there is a mismatch between uptake and utilization of fatty acids leading to intracellular lipid accumulation. This may lead to the production of toxic lipid metabolites (e.g. lysophosphatidylcholine (LPC), diacylglycerol (DAG) and ceramides) and is referred to as lipotoxicity. LPC is also generated during myocardial ischemia and has been proposed as a contributor to the generation of ventricular arrhythmias during AMI. An important metabolic regulatory hormone, growth hormone (GH), has been shown to exert various positive effects in post-infarction HF.

Aims

- I. To evaluate the short- and long-term effects of CHB on cardiac function, morphology and energy metabolism in the rat
- II. To investigate the effects of GH on ischemic and non-ischemic arrhythmogenesis in the rat
- III. To set up and validate an *in vitro* experimental system for studies of the effects of LPC on electrophysiological parameters in beating cardiomyocytes.
- IV. To evaluate associated risk factors for having AF in patients admitted to cardiac care units and to evaluate the role of lipid metabolism in the pathophysiology of AF.

Results and conclusions

- I. Rats with CHB compensate for the reduction in heart rate by doubling the stroke volume and thereby maintaining cardiac output. Increases in wall tension leads to eccentric left ventricular hypertrophy. After long-term CHB there were no hemodynamic or metabolic signs of HF.
- II. GH reduced the occurrence of spontaneous VT/VF in rats with induced AMI as well as reducing induced VT/VF in anesthetized rats. This adds to previously described beneficial effects of GH in HF and AMI, and we suggest that the effect is partly mediated via decreased sympathetic stimulation.
- III. LPC induced prompt and pronounced electrophysiological alterations that may underlie its observed pro-arrhythmic properties. Our model may be a useful tool for preclinical studies of electrophysiological effects of various pathophysiological concepts.
- IV. In a multivariate analysis we found that obesity was associated with AF, but diabetes was not. AF was associated with quantitative and qualitative alterations in atrial lipid content but not with signs of lipotoxicity. Polyunsaturated DAG may play a role in pathophysiology of AF.