

# Myocardial creatine metabolism in experimental infarction and heart failure

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2007

## Abstract

The failing heart is characterized by changes in structure, function and metabolism. All these changes are usually defined as pathologic remodelling. An important part of this negative remodelling process is disturbances in the myocardial energy metabolism. It has been demonstrated both in clinical and experimental studies that the failing heart contains low levels of creatine (Cr), phosphocreatine (PCr) and adenosine-triphosphate (ATP). For the heart to be able to function and contract normally, it needs energy in the form of ATP. ATP needs to be transported from sites of energy production to the sites of energy utilization in the myocyte. The Creatine-kinase (CK) system is responsible for this energy transport. Previous studies have shown that Cr depletion results in disturbed energy metabolism, which is associated with decreased PCr content, decreased CK activity and compromised left ventricular dysfunction. But there is still limited knowledge about the role of creatine and myocardial energy metabolism in the diseased heart. It is known that the heart depends on exogenous lipids for the oxidative production of ATP, and thereby for maintenance of normal cellular energy homeostasis. Recent studies have however, reported that the heart synthesizes and releases its own endogenous apolipoprotein B (apoB). It has been proposed that apoB may be involved in cardioprotection by means of elimination of toxic intracellular lipids.

The aim of this thesis were

- To investigate whether measures of intensive cardiac care applied to rats with acute myocardial infarction (MI) would reduce mortality in this small animal model.
- To investigate *in vivo* the effects of Cr depletion in rats on left ventricular function and morphology, energy metabolism, catecholamines and incidence of malignant ventricular arrhythmias during acute myocardial infarction.
- To investigate *in vivo* the effects of Cr depletion in mice on left ventricular function and morphology, energy metabolism and myocardial lipids.
- To investigate importance of endogenous lipoproteins in the heart for cardiac function, morphology and survival in the settings of acute and chronic myocardial infarction.
- To investigate acute and chronic effects of complete heart block (CHB) on cardiac function, morphology and energy metabolism in a rat model.

In paper I we show that by applying simple methods like pre-treatment with anti-arrhythmia, prolonged respiratory support, use of isoflurane gas anaesthesia, and treatment of MVA with electrical cardioversion, the mortality in the rat model of acute MI is decreased by ~70 %.

In the rat model of Cr depletion we show that lack of myocardial Cr leads to disturbances in metabolism, morphology and function of the heart, similar to those found in HF patients. The animals suffering from CR depletion show increased incidence of arrhythmias and increased mortality in the setting of acute MI. We also showed that Cr depletion in mice leads to similar disturbances as in the rat model. One very interesting new finding was the increased accumulation of triglycerides. The most important finding in the mouse model was that the disturbances in the metabolism, structure and function of the heart are completely reversible upon the normalization of the Cr levels. These findings indicate that Cr metabolism may be an important target for pharmacological interventions in order to increase myocardial efficiency and structural integrity of the failing heart.

In paper IV we showed that the over-expression of apolipoprotein B (apoB) in mice increased the survival post-MI, 2-fold. This was associated with improved myocardial function in the apoB mice. It was also determined that the production of endogenous apoB was increased acutely post-ischemia injury, but in long term it decreases to subnormal levels. These findings indicate that the myocardial apoB system may be important in cardioprotection in pathophysiologic settings as myocardial ischemia and HF.

CHB in rats lead to early, pronounced and sustained cardiac remodelling with the development of eccentric hypertrophy. However they did not develop left ventricular dysfunction and showed no signs of disturbed energy metabolism. Future studies are needed here to elucidate the mechanism behind the beneficial cardiac remodelling post-CHB.

Keywords: Energy metabolism, Creatine, Congestive heart failure, Myocardial infarction, Ventricular arrhythmias, Cardiac remodeling, apolipoprotein B, Lipid metabolism

ISBN 978-91-628-7317-2

## **Myocardial creatine metabolism in experimental infarction and heart failure**

Akademisk avhandling

som för avläggande av medicine doktorexamen vid Sahlgrenska akademien vid Göteborgs Universitet  
offentligen kommer att försvaras i föreläsningssalen på våning 3, Guldhedsgatan 10A, Göteborg.

Torsdagen den 18 oktober 2007, kl. 9.00

av

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Department of Physiology, Anatomy and Genetics  
University of Oxford

Avhandlingen baseras på följande delarbeten:

- I Råmunddal T, Lorentzon M, Omerovic E.  
**Decreased mortality in a rat model of acute postinfarction heart failure.**  
*Biochem Biophys Res Commun.* 2006 Mar 10;341(2):459-63
- II Lorentzon M, Råmunddal T., Bollano E., Soussi B., Waagstein F., Omerovic E.,  
**In vivo Effects of Myocardial Creatine Depletion on Left Ventricular Function, Morphology and Energy Metabolism – Consequences in Acute Myocardial Infarction.**  
*J Card Fail.* 2007 Apr;13(3):230-7.
- III Lindbom M, Råmunddal T., Camejo G., Waagstein F., Omerovic E.  
**In vivo effects of myocardial creatine depletion on left ventricular function, morphology and energy metabolism in mice**  
(Submitted)
- IV Råmunddal T., Lindbom M, Scharin-Täng M., Stillemark-Bilton P., Boren J., Omerovic E.  
**Overexpression of apolipoprotein-B improves cardiac function and increases survival in mice with myocardial infarction.**  
(Submitted)
- V Gizurarson S., Lorentzon M, Råmunddal T., Waagstein F., Bergfeldt L., Omerovic E.  
**Effects of complete heart block on myocardial function, morphology and energy metabolism in rats.**  
*Europace.* 2007; 9(6): 411-6.