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Preface

The power of metabolism — Linking energy supply and demand with cardiac contractile function☆

Every type of motion requires some sort of energy. In the living world as we know it, this energy is provided by the consumption of nutrients in particular carbohydrates, fatty acids and amino acids. The energy contained within these substrates is converted by metabolic processes into motion and heat. It is therefore no surprise that investigations of biological processes in health and disease often directly contain or end up with recognitions or questions in the field of metabolism. The heart is the most active muscle in mammals with a contraction every second throughout life. Thus, cardiac motion seems the most constant motion known. To support life, the mammalian heart must contract incessantly. As a consequence, the requirement for energy (in the form of ATP) to fuel this function is immense. Interestingly, high energy phosphate storage within the cardiomyocyte is minimal and may support contraction only for a few beats *i.e.* a few seconds. Thus, tight coupling between substrate conversion into ATP and myocardial contraction is essential for normal cardiac function. This has led to the elegant suggestion of a direct and reversible interrelationship between contractile function and metabolic activity as shown on the cover of this issue [1]. Thus, metabolic activity is not simply dictated by contractile activity. In contrast, it may also be used to influence contractile function and therefore overall cardiac performance. The latter recognition is the base for metabolic therapy of diseases such as diabetes or heart failure. This link between energy metabolism and contractile function was the focus of the meeting of the Society for Heart and Vascular Metabolism 2017 in Weimar (Germany). The specific topics discussed during this meeting have led to the generation of this special issue. The following authors describe the current "state of the art" regarding the link between metabolism and function and are summarized as follows:

Volker Adams and his group review the impact of exercise on cardiovascular disease and risk [2]. Exercise is a condition that significantly affects metabolic activity of the organism. Currently it is also clear that exercise affects human health. Again, this change in metabolic activity appears to offer significant therapeutic potential which has not been used to full capacity. They present that with respect to exercise in cardiovascular disease, many concepts have changed and even patients with myocardial infarction are nowadays included into exercise training programs very shortly after the insult.

Exercise intolerance is a frequent condition in heart failure with reduced ejection fraction. Linda Peterson and her group present in their manuscript an overview on the effects of inorganic nitrate on exercise capacity in patients [3]. They indicate why inorganic nitrate has advantages over other sources of NO. Furthermore, they present the mechanisms of action of NO relating to improved exercise performance in heart failure. While there is a larger trial underway, the presented effects may be interesting to follow as they together with the impact of exercise training reported by Volker Adams [2] suggest an intensified effect of exercise therapy in heart failure patients.

The mechanisms for exercise effects on cardiovascular health are still far from clear. Instead, it is known that exercise capacity depends on coupling of ATP generation and contraction in both skeletal muscles and the heart. Central to the coordinated energy transduction function is the mitochondrion. Mitochondria generate not only more than 95% of ATP but also regulate intracellular calcium homeostasis, signaling and cell death. Thus mitochondrial function is of major importance but there are yet limited possibilities to investigate mitochondrial function *in vivo*. In the manuscript of Vera Schrauwen and her group the current knowledge to use magnetic resonance spectroscopy for analysis of cardiac metabolism is discussed [4].

Sina Coldewey and her group describe a new method to assess mitochondrial function *in vivo* in their manuscript [5]. They describe the use of the Protoporpyhrin IX Triplett State Lifetime Technique to determine mitochondrial oxygen delivery, oxygen tension as well as oxygen consumption *in vivo*. The variables influencing mitochondrial oxygen use *in vivo* are described in a pilot study of 26 healthy subjects with and without exercise [5]. This investigation may pave the way for a routine *in vivo* analysis of mitochondrial function.

Such *in vivo* analysis of mitochondrial function expected to be very important in septic patients. Mervyn Singer and his group review the current knowledge [6] on the role of mitochondria in sepsis. Mitochondrial dysfunction has been suggested as a discriminator between survival and death. Importantly, an early analysis in sepsis is indispensable as sepsis rapidly worsens and treatment has to be immediate. Mitochondrial dysfunction has been suggested to contribute to sepsis induced cardiomyopathy as metabolic derangements are central in this disease. The authors describe the pathophysiology underlying myocardial dysfunction in sepsis and focus in their manuscript on mitochondrial processes. The analysis of metabolism and mitochondrial function and preservation of mitochondrial integrity and quality may be a basis for improved treatment in the future.

The second manuscript of Sina Coldewey and her group [7] addresses AMPK signaling in sepsis. This contribution is of interest because sphingosine-1-phosphate signaling in some endothelial cells is mediated by the well-known metabolic sensor AMPK and thereby

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mediates stabilization of the endothelial barrier. In sepsis, breakdown of endothelial barrier is critical for organ failure and endothelial stabilization may thus prevent death. Whether sphingosine-1-phosphate signaling on AMPK affects substrate metabolism simultaneously remains an interesting question in this situation, but may have a high potential to explain metabolic changes in sepsis.

Naturally, mitochondria as the hotspot for ATP generation and substrate use attract further attention in metabolic research. Thus, the article of Yan Burelle and his group [8] presents an overview on mitochondrial quality control pathways. The authors indicate that mitochondrial quality control relies on multiple overlapping mechanisms. Mitochondrial proteases and chaperones process newly imported proteins but degrade non-assembled proteins as well. Protease involvement in mitochondrial unfolded protein response is discussed. Similarly, the ubiquitine-proteasome pathway and mitochondrial dynamics are presented as important quality control mechanisms in mitochondria. Mitochondria derived vesicles as new pathway for quality control is discussed and last but not least mitophagy is presented as well.

Mitophagy pathways are reviewed in detail by Åsa Gustafsson and her group [9]. Canonical as well as non-canonical pathways of mitophagy are discussed and the link of these pathways to cardiac health is explored [9]. This important process selectively removes dysfunctional mitochondria as they may produce high amounts of reactive oxygen species (ROS) or induce apoptosis. The authors discuss mitochondrial membrane dysfunction as an important component in initiating mitophagic processes.

Mitochondrial membranes present with unique properties due to cardiolipin as a major component. The review of Peter Rehling and his group [10] focuses on the role of cardiolipin in cardiac health and disease. The role of cardiolipin in mitochondrial biogenesis as well as morphology is addressed. Cardiolipin as the major membrane component also affects the function of the membrane associated respiratory chain. Furthermore, with its close proximity to places of ROS production, cardiolipin is easily oxidized in case ROS production becomes dysregulated, leading to changes in membrane morphology as well as respiratory chain function.

Oxidative stress not only affects cardiolipin, but is regarded as a main contributor to damage in ischemia and reperfusion as well as in hypoxia. Ischemia/reperfusion is mainly seen in myocardial infarction but is also voluntarily induced in cardiac surgery procedures. A protection of the myocardium against such damages is highly needed as myocardial infarction is a main cause of death in western societies. Petra Kleinbongard and her group address in their review the question whether or not ischemic conditioning has an effect on myocardial contractile function following an acute myocardial infarction [11]. Again, mitochondria play a major role as ischemic conditioning improves respective preserves mitochondrial respiration, ATP production and calcium handling. However, while effects on mitochondria have been shown, the long term effects of ischemic conditioning need further evaluation. The authors review in their manuscript the current knowledge and elucidate where further investigations are needed.

In ischemia, one important signaling molecule is hypoxia signaling factor. Maria Da Luz Sousa Fialho and coworkers [12] address the signaling pathways of HIF and its effect on cardiac metabolism. As HIF is one of the drivers of metabolic changes in ischemia and myocardial infarction the authors summarize the effects of HIF signaling on uptake of fatty acids as well as glucose and analyze the effects on the metabolism of these substrates. The authors present an overview on HIF research and HIF targeting drugs and indicate why HIF may be an attractive target for therapy of cardiac disease.

A different approach to target metabolism in hypoxia is presented by the group of Andrew Murray [13]. In their manuscript the effects of nitrate on tissue oxygenation, fatty acid metabolism and mitochondrial function in skeletal muscle are addressed. The authors present results indicating that hypoxia induces impairment in mitochondrial respiratory function in the soleus. This impairment was abolished when nitrate was supplemented in drinking water and this effect was independent of PPARα signaling. Whether such effect is also present in the heart may be an interesting question with therapeutic potential.

Another unconventional but nevertheless promising approach to target mitochondrial dysfunction in ischemic or hypoxic conditions may represent alternative respiratory chain enzymes. In their manuscript Howy Jacobs and his group [14] present alternative respiratory enzymes as a protection against external stressors. Alternative respiratory enzymes represent enzymes which may replace one or several complexes of the respiratory chain. Thereby they may offer pathways which are not affected by inhibitors of the respiratory chain. As an example, *Ciona intestinalis* alternative respiratory chain enzymes are upregulated by hypoxia. This may reduce oxidative stress and improve survival in this situation. Furthermore, it has been shown that these enzymes may extend lifespan. However, alternative respiratory chain enzymes are not known from vertebrates or drosophila. Thus, their effect in mammals has only partially been investigated and remains a promising field of research.

Taken together, this special issue with reviews and original contributions presenting current knowledge as well as new aspects of cardiac metabolism reflects the importance of cardiac metabolism for contractile function. It strongly supports the view that metabolic ATP-producing and non-ATP producing pathways may be critical regulators of contractile function. Thus, the importance of substrate metabolism to cardiac pump function is beyond the scope of only modulation of energy supply.

Transparency document

The Transparency document associated with this article can be found, in online version.

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Michael Schwarzer is Assistant Professor and Research Director in the Department of Cardiothoracic Surgery at the University of Jena. His research has focused on cardiac substrate metabolism in hypertrophy, heart failure and exercise. The mitochondrion represents the center of his attention as the central organelle for substrate oxidation and a link to contractile function is pursued by linking metabolic findings to contractile function. Various methods to assess substrate oxidation and function *in vivo* and *in vitro* are employed to investigate potential metabolic mechanisms for heart failure development. Dr. Schwarzer demonstrated, for instance, that mitochondrial function in heart failure correlates with the severity stages of heart failure and differs depending on mitochondrial subpopulation. His current interest addresses the influence of intrinsic exercise capacity on several conditions of disease, such as sepsis, pressure overload heart failure or ageing.

Torsten Doenst is Professor of Cardiac Surgery and the chairman of the Department of Cardiothoracic Surgery at the University of Jena in Germany. He is a well-known expert in minimally invasive cardiac surgery and the surgical treatment for heart failure. He actively combines surgical work with a strong interest in basic science. His main interest is the link between myocardial metabolism and contractile function. Specifically, he made relevant contributions for our understandings of the kinetics of glucose uptake in the heart and myocardial insulin sensitivity, the mechanisms of pressure overload induced heart failure and the role of ischemia/reperfusion both in the experimental or the operating room setting. His current projects investigate the effects of genetically-determined exercise capacity on tolerance against pressure overload-induced heart failure.

Christine Des Rosiers is a Professor in the Department of Nutrition of the *Université de Montréal* and Director of the Montreal Heart Institute Research Centre Metabolomic Laboratory and Platform. She is a founding member of the Society for Heart and Vascular Metabolism and has been serving as President from 2015 to 2018. The focus of her research is on the role of metabolic alterations in the pathogenesis of disease, particularly heart disease. She has over 25 years of research experience in metabolic investigations using stable isotopes and mass spectrometric-based methodology. She specifically gained recognition for the development of these methods for the metabolic and functional phenotyping of the *ex vivo* working mouse heart. More recently, she has taken the direction of metabolomic initiatives as part of multidisciplinary translational projects aiming at the discovery of biomarkers of disease development or treatment response in various conditions, which include heart disease, but also diabetes, as well as mitochondrial and inflammatory diseases.

Jan F. C. Glatz is Professor of Cardiac Metabolism at the Faculty of Health, Medicine & Life Sciences (FHML), Maastricht University, the Netherlands. Currently he serves as chair of the Department of Genetics & Cell Biology as well as deputy-chair of the Department of Clinical Genetics (Maastricht University Medical Center+). In the period 2012–2015 Dr. Glatz was President of the *Society for Heart and Vascular Metabolism* (SHVM). Dr. Glatz's major contributions to understanding cardiac metabolism include the disclosure of the molecular mechanism of cardiac fatty acid uptake, especially the role of membrane substrate transporters (in particular CD36/SR-B2) and that of cytoplasmic heart-type fatty acid-binding protein (FABP3), and the unraveling of the significance of altered cardiac fatty acid handling in obesity-induced cardiac insulin resistance and diabetic cardiomyopathy. His main current scientific interest is the regulation of energy metabolism in the healthy and in the diabetic heart with focus on the application of intracellular membrane substrate transporter recycling for so-called metabolic modulation therapy.

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