Muscle like muscle? Uncovering the links between impairment in cardiac and skeletal muscle metabolism in heart failure using in vivo magnetic resonance

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Project outline

Background: Heart Failure with preserved ejection fraction (HFpEF) has recently emerged as a significant clinical problem for type II diabetes mellitus patients. Breathlessness, fatigue on exertion and exercise intolerance are all key features of HFpEF. Besides central (cardiac) metabolic impairment, peripheral (skeletal muscle) impairment is simultaneously occurring, with the latter often being more restrictive to the patient’s quality of life. This makes skeletal muscle exercise an appealing way to improve performance in HFpEF, however, whether the potential effects are only local or systemic remains to be uncovered.

Cardiac metabolic impairment in heart failure manifests as a reduced ability to switch between the utilization of fatty acids and glucose for energy generation leading to a decrease in energetic reserves in cardiac tissue. This switch can be potentially explored through the observation of changes in cardiac acetyl-carnitine, which plays an important role in the transfer of fatty acids into the mitochondria for oxidation, as well as the buffering of acetyl units which can inhibit the oxidation of glucose. Gradually decreasing levels of acetyl-carnitine have been observed in skeletal muscle between athletes, lean and obese sedentary control subjects and people with diabetes. However, the link between cardiac and muscle acetyl-carnitine and its contribution to exercise intolerance in heart failure is not well understood.

Other potential linking mechanisms include deposition of lipids, which has been related to insulin sensitivity in the heart as well as in skeletal muscle. Also, peripheral tissue perfusion and oxygen delivery, which is vital for normal oxidative metabolism and mitochondrial function, is closely linked to cardiac function. All these and more provide potential therapeutic targets that allude identification because the underlying mechanism is severely under investigated.

Hypothesis: We therefore propose that, due to the metabolic link between skeletal and cardiac muscle, improvements in cardiac metabolism induced through exercise intervention will also lead to improvements in peripheral muscle function. By uncovering and investigating this likely bi-directional mechanism, we will be able to identify skeletal muscle metabolic targets responsible for the potential improvement of cardiac function and metabolic inflexibility in HFpEF.
Aims

1. Assess resting and post-exercise human cardiac and skeletal muscle metabolism in HFpEF;
2. Explore the effects of exercise training in HFpEF on skeletal and cardiac muscle metabolism and function.
3. Investigate markers of improved metabolism and function of untrained muscle induced via an asymmetrically loaded muscle exercise intervention in HF

Description of the work: Using our latest techniques, based on magnetic resonance spectroscopy and imaging (MRS and MRI), we will investigate the cross-talk between skeletal and cardiac muscle metabolism non-invasively in vivo. In particular, together with tissue lipid accumulation, we will quantify skeletal muscle and cardiac acetyl-carnitine levels in vivo. Utilizing exercise inside the MR scanner, we will also directly probe muscle mitochondrial metabolism, tissue perfusion and oxygenation, as well as cardiac energetics in response to increased workload. We will use all these parameters in our observational and interventional study to describe the impairments in cardiac and skeletal muscle metabolism in HFpEF in detail. Since common exercise interventions fail to separate the local and systemic effects, we will use asymmetrically loaded exercise, i.e., one legged exercise. Since only one leg is actively involved in the exercise, higher exercise intensities can be achieved, significantly improving central function while keeping the other leg untrained. The benefits observed in metabolism and/or perfusion in the untrained muscles will be caused by the cross talk with central cardiac function.

Supervisor’s recent relevant publications (5 max per supervisor):
