



Measuring Molecules for Medicine: Quantifying Human Cardiac Metabolic Inflexibility in Diabetic Cardiomyopathy using *in vivo* Magnetic Resonance

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Project outline

Background

Diabetic cardiomyopathy represents a huge future burden to healthcare systems. While Heart Failure with reduced ejection fraction (HFrEF) is a well-known complication of type 2 diabetes (T2D), failure with preserved ejection fraction (HFpEF) has emerged as a larger, significant clinical problem for T2D patients that is poorly understood with no treatment available. Animal studies show that the failing heart is metabolically inflexible, switching from utilising both beta-oxidation and glycolysis, to relying upon glycolysis – inherently deficient in T2D.

Paramount for the fatty acid shuttle into the mitochondrial matrix for beta-oxidation is an amino-acid derivative, carnitine, which in the form of acetyl-carnitine serves also as a buffer of excess acetyl-CoA units in the mitochondria and plays an important role in the pathogenesis of insulin resistance. Previous studies in human skeletal muscle have shown gradually decreasing levels of tissue acetyl-carnitine from athletes through lean and obese sedentary to diabetic subjects. Decreased acetyl-carnitine has been reported in diabetic rat myocardium, and its normalization may have protective effects against HFrEF. The relationship between cardiac acetyl-carnitine and HFpEF is not understood.

Furthermore, it is unclear whether an improvement in insulin sensitivity will lead to increased tissue acetyl-carnitine and in turn in improved fatty acid utilization reversing the substrate utilization inflexibility and potentially improving the clinical symptoms of HF. As one of the confounders of T2D is obesity, it is not surprising that improved insulin sensitivity goes hand-in-hand with weight loss, achieved either through dieting or pharmacologically, with glucagon-like peptide-1 (GLP-1) receptor agonist drugs, e.g., semaglutide. Yet the mechanisms of these effective interventions remain cryptic. This project will build on our previous work, and will non-invasively quantify, and potentially identify a therapeutic target for reversal of this substrate utilization inflexibility in the human heart.

Hypothesis

We therefore propose that cardiac acetyl-carnitine is decreased in HFpEF in comparison to T2D patients and healthy volunteers, both at rest and after low intensity exercise, which would lead to an increase in fatty acid oxidation. This will demonstrate the inflexibility in substrate utilization in HFpEF. Improvement in insulin sensitivity via very low-calorie diet (VLCD) or GLP-1 receptor agonist

administration would then lead to an increase in acetyl-carnitine levels and reverse this inflexibility, improving clinical symptoms of HFpEF and making acetyl-carnitine an exciting therapeutic target.

Aims

- 1) Determine resting and post-exercise human cardiac acetyl-carnitine levels in HFpEF *in vivo*;
- 2) Examine associations between human cardiac acetyl-carnitine and insulin sensitivity;
- 3) Explore the potential of VLED and GLP-1 agonists to increase cardiac acetyl-carnitine concentration and reverse the substrate utilization inflexibility in HF, and potentially explore other relevant measurable metabolites (e.g. myocardial creatine, blood metabolites via MS).

Description of the work

We have developed a new technique to quantify cardiac acetyl-carnitine concentration *in vivo* using magnetic resonance spectroscopy (MRS), which will be extended to allow its absolute quantitation. This hence enables an observational and interventional study, in which cardiac acetyl-carnitine will be compared between groups of diabetics and patients with HFpEF, who will undergo either a 6-week VLCD or a GLP-1 antagonist treatment as a part of their planned healthcare. Two follow-up scans are planned, one after the intervention period and one 6-months later to compare the effects of VLCD and GLP-1 antagonists on cardiac acetyl-carnitine, clinical symptoms of HF and insulin sensitivity, and, through related measurements, the diabetic myocardial metabolome in general.

Supervisor's recent relevant publications:

1. R Klepochová*, **L.Valkovič***, T Hochwartner, C Triska, N Bachl, H Tschann, S Trattnig, M Krebs, M Krššák; Differences in Muscle Metabolism Between Triathletes and Normally Active Volunteers Investigated Using Multinuclear Magnetic Resonance Spectroscopy at 7T. *Front Physiol* (2018). 9:300
2. JJ Rayner, I Abdesselam, MA Peterzan, I Akoumianakis, N Akawi, C Antoniadis, JW Tomlinson, S Neubauer, **OJ Rider**; Very low calorie diets are associated with transient ventricular impairment before reversal of diastolic dysfunction in obesity. *Int J Obes (Lond)* (2019). 43(12):2536-44
3. R Klepochová, **L Valkovič**, M Gajdošík, T Hochwartner, H Tschann, M Krebs, S Trattnig, M Krššák; Detection and Alterations of Acetylcarnitine in Human Skeletal Muscles by 1H MRS at 7 T. *Invest Radiol* (2017). 52(7): 412–8
4. JJ Rayner, R Banerjee, CJ Holloway, AJM Lewis, MA Peterzan, JM Francis, S Neubauer, **OJ Rider**; The relative contribution of metabolic and structural abnormalities to diastolic dysfunction in obesity. *Int J Obes (Lond)* (2018). 42(3):441-7
5. MA Schroeder, HJ Atherton, MS Dodd, P Lee, LE Cochlin, GK Radda, K Clarke, **DJ Tyler**; The cycling of acetyl-coenzyme A through acetylcarnitine buffers cardiac substrate supply: a hyperpolarized 13C magnetic resonance study. *Circ Cardiovasc Imaging* (2012). 5(2):201-9