Metabolic and functional evaluation of diabetic cardiomyopathy using MR Spectroscopy and MR Imaging

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Chapter 11

Summary

Nederlandse samenvatting

List of publications

Curriculum vitae

Summary

Type 2 diabetes mellitus (T2DM) patients have an increased risk of adverse cardiovascular complications.T2DM increases the risk of coronary artery disease and myocardial infarction which can result in heart failure and death. In addition, T2DM patients without coronary artery disease also have an increased risk of heart failure. This type of heart failure is called diabetic cardiomyopathy. Diabetic cardiomyopathy is characterized by left ventricular hypertrophy and (predominantly) diastolic dysfunction, i.e. heart failure with preserved ejection fraction (HFpEF). The pathophysiology of diabetic cardiomyopathy involves insulin resistance, impaired myocardial energy metabolism, myocardial steatosis and fibrosis. Cardiac magnetic resonance imaging (MRI) and Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) have proven useful to assess these cardiovascular complications in T2DM.

Part 1. Technical advances in MRS and MRI to evaluate diabetic cardiomyopathy

In part 1 of this thesis we examined whether the MR techniques used to image and quantitatively assess cardiovascular complications of T2DM could be further optimized.

In **chapter 2**, we reviewed the current standings of clinical application of cardiac ^{1}H-MRS in ischemic heart disease and diabetic cardiomyopathy. Furthermore, we aimed to describe the technological hurdles that need to be overcome to improve quality and speed of cardiac ^{1}H-MRS acquisition. In literature, the use of cardiac ^{1}H-MRS has predominantly shown that increased myocardial triglyceride content (i.e. myocardial steatosis) is a hallmark of diabetic cardiomyopathy. The lipotoxicity hypothesis causally links myocardial steatosis with left ventricular diastolic dysfunction. One important challenge appeared to be the low signal-to-noise ratio of cardiac ^{1}H-MRS, which impairs spectral quality and contributes to long acquisition time.

Therefore, in **chapter 3**, we aimed to improve signal-to-noise ratio of cardiac ^{1}H-MRS in a study with healthy human volunteers. We hypothesized that a high

permittivity pad (with a barium titanate suspension) placed on the subject's chest could increase signal-to-noise ratio. We found that the pads ameliorated the main magnetic field and the transmit field, thereby increasing signal-to-noise ratio by 60%. This improvement can be used either to boost spectral quality or to reduce scanning time. The high permittivity pads were used for the studies described in part 2 of this thesis.

In **chapter 4**, it was investigated whether coronary MR angiography could be performed with a very high spatial resolution. A previous study had shown that MR angiography using ultrahigh field MR (7 Tesla) yielded higher signal-to-noise ratio and blood vessel edge sharpness as compared to 3 Tesla. In 24 healthy volunteers, we tested whether the increased signal-to-noise ratio could be used to image with a very high spatial resolution (0.31 x 0.31 x 0.60 mm voxels) at 7 Tesla. When compared to a lower spatial resolution imaging sequence, high resolution images had a significantly higher mean blood vessel edge sharpness while vessel conspicuity was preserved. Future research will need to focus on the diagnostic accuracy of coronary MR angiography to detect coronary artery disease in T2DM patients.

In **chapter 5**, we focused on MR imaging of myocardial infarction. The image quality of an in-house developed three-dimensional high resolution late-gadolinium enhancement MR sequence that can be acquired during free-breathing was compared with a traditional sequence that needs to be acquired while the patient is holding his breath. A retrospective study was performed in 51 cardiac patients. The myocardial scars imaged with the two MR sequences were compared in terms of scar edge sharpness and scar mass. The high resolution images had, as expected, higher scar edge sharpness while scar mass was lower when compared to the traditional images. Since previous studies had found that the traditional images overestimate scar mass, we speculate that the novel MR sequence approach actual scar mass more precisely.

Part 2. Clinical application of MRS and MRI in diabetic cardiomyopathy

The second part of the thesis used state-of-the-art MR techniques to assess efficacy of therapeutic interventions to reverse diabetic cardiomyopathy. The MAGNA VICTORIA trial aimed to investigate the effect of the glucagon-like-peptide-1 receptor agonist liraglutide in T2DM patients. To this end, liraglutide treatment was compared with placebo added to standard diabetes care. In addition to this pharmacologic intervention, a lifestyle intervention study was performed in another trial with T2DM patients.

Chapter 6 describes the primary endpoints of the MAGNA VICTORIA study. In total, 23 participants were treated with liraglutide and 26 with placebo. We found that liraglutide did not improve indices of active diastolic relaxation of the left ventricle. However, liraglutide treatment significantly lowered estimated left ventricular filling pressure. Left ventricular systolic function reduced slightly but remained within normal values. We concluded that liraglutide did not directly improve diabetic cardiomyopathy. However, the reversal of increased left ventricular filling pressure may beneficially affect the progression from asymptomatic diastolic dysfunction to heart failure with preserved ejection fraction. Future studies with longer follow-up are needed to test this hypothesis.

Secondary endpoints of the MAGNA VICTORIA study are described in **chapter 7**. Using MRI and cardiac ^{1}H-MRS the effect of liraglutide on ectopic fat accumulation was investigated. Despite moderate weight loss in the liraglutide group as compared to placebo, visceral fat, hepatic steatosis and myocardial steatosis did not decline. The fact that myocardial steatosis and active left ventricular diastolic relaxation both remained unchanged was in keeping with previous studies that had shown strong association of myocardial triglyceride content and diastolic function. The results of the MAGNA VICTORIA study must be viewed in the context of the LEADER trial which has shown reduced incidence of major adverse cardiovascular events in liraglutide-treated T2DM patients, probably driven by a modifying atherosclerosis. This highlights that cardiovascular complications of T2DM have various pathophysiologic paths.

One important hallmark of T2DM is hyperglycemia. In **chapter 8**, we aimed to investigate whether liraglutide could help reaching target glycemic goals in the most severely affected patients: T2DM with increased glycated hemoglobulin level despite using multiple daily insulin injections. The results of the MAGNA VICTORIA trial were pooled with the same trial performed in T2DM patients of South Asian descent. In total, 47 participants were included in the analysis. Only 5% reached target HbA1c in the placebo group, versus 41% in the liraglutide group, which was a significant difference. Liraglutide did not increase the risk of hypoglycemia.

The effect of a lifestyle intervention was investigated in **chapter 9**. Eleven obese insulin-dependent T2DM patients with long-standing diabetes and with a high rate of diabetic and musculoskeletal complications underwent a 12-week eSupported lifestyle coaching intervention. Combined metabolic and MR assessment revealed that insulin requirements had decreased dramatically, in parallel with improved insulin sensitivity and hepatic and myocardial steatosis. However, beta-cell function, pancreatic fat and cardiac function did not improve. These data, although sample size was small, suggest that insulin-dependent T2DM can be complicated by irreversible damage of beta-cells and myocardial tissue.

This thesis shows that collaboration of basis scientists and physicians can result in technological improvement of MR techniques resulting in higher robustness, spatial resolution and quality. Combining cardiac MR with MRS shows the complexity of the interplay between cardiac function and metabolism, in response to therapeutic interventions. Moderate weight loss with liraglutide did not combat ectopic fat accumulation while cardiovascular function did change. Paradoxically, more progressive weight loss upon a lifestyle coaching intervention resulted in significantly reduced ectopic fat accumulation, including myocardial steatosis, but cardiac function remained unchanged. Whether this discrepancy is caused by study population characteristics or has to do with the intervention, remains to be established in future studies.