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

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Chapter 10

General discussion and future perspectives

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

In **chapter 2**, we described that the combination of MRS and MRI in cardiac MR has proven useful to gain insight into the tight relation between cardiac metabolism, morphology and function. In research settings, cardiac MRS has provided evidence for the role of myocardial steatosis as a contributing factor in the development of diabetic cardiomyopathy. Intervention studies have shown that diabetic cardiomyopathy can be reversed in certain settings, making cardiac MRS a valuable tool to examine the effect of therapeutic interventions on diabetic cardiomyopathy in study populations. However, for cardiac MRS to be of additional value in a clinical setting, important technological limitations such as low spectral and temporal resolution have to be overcome. There are various technical opportunities to achieve this goal. First, by using higher field MR systems (>3 T), the advantage of increased SNR could result in better resolution and reproducibility[1]. Furthermore, development of improved shimming algorithms, pulse sequences, and receiver coils could aid in achieving higher spatial resolution MRS.

In **chapter 3** we aimed to improve the SNR of cardiac ^{1}H-MRS with the use of a high permittivity pad. In this prospective observational study, cardiac ^{1}H-MRS was performed in 22 healthy volunteers with and without the high permittivity pad placed on the subject's chest. The proton spectra acquired with the high permittivity pad had a mean increase in SNR of 60%, while MTGC content itself was not affected. Further results showed that the homogeneity of the main magnetic field (B_0) and the transmit field (B_1^+) had improved by using high permittivity pads. Translating this increase in SNR into acquisition of less signal averages (thereby generating proton spectra of comparable quality), scanning time could be reduced from five to approximately two minutes. A limitation of this study was that overweight or obese subjects were not included. Although intrinsic SNR of cardiac proton spectra is expected to be higher in obese T2DM patients[2], increased body size poses other challenges to spectral quality. Therefore, for the study described in chapters 8 and 10 we performed cardiac ^{1}H-MRS with the permittivity pad, but without decreasing the number of signal averages. As

such, we aimed to minimize the number of unsuccessful proton spectra in those studies.

Chapters 4 and 5 Improving MR assessment of ischemic heart disease

In **chapter 4** we described a study performed in 24 healthy volunteers. This study aimed to investigate the effect of high spatial resolution (HR) coronary MRA on SNR, CNR and vessel edge sharpness. For this study, MRA of the right coronary artery (RCA) was performed using an ultrahigh field (7 Tesla) MR system. The HR sequence had a voxel size of 0.31 x 0.31 x 0.60 mm and was compared with a low resolution (LR) sequence with 0.82 x 0.82 x 1.00 mm voxels. Both sequences used a spectrally selective adiabatic inversion recovery (SPAIR) sequence generating bright blood with suppression of the perivascular fat. Image quality was assessed in an objective manner by generating a straightened reformat of the RCA. From this reconstruction, SNR, CNR and vessel edge sharpness (VES) were assessed. As expected, SNR and CNR were lower in the HR images but vessel conspicuity was preserved. HR images had a significantly higher mean VES as compared with the LR images. Future studies should focus on the diagnostic accuracy of coronary MRA in patients with known stenosis and should be compared with that of computed tomography angiography (CTA) and invasive coronary angiograms. In addition, the technical challenges of imaging the left coronary artery have to be overcome in future experiments.

The retrospective study described in **chapter 5** investigated an in-house developed 3D high spatial resolution LGE-CMR sequence (voxel size 0.91 x 0.91 x 0.91 mm) acquired during free breathing (FB) at 3 T. This sequence was compared to the traditional LGE-CMR sequence that requires breath-holds (BH) during acquisition. In total, 51 patients were included of which 48 were suitable for analysis. The study population comprised 34 patients with ischemic cardiomyopathy and 14 with non-ischemic cardiomyopathy. Using image post-processing techniques, scar mass and image quality in terms of SNR, CNR and scar edge sharpness (SES) of the FB-3D LGE-CMR images were first compared with BH by generating a normal spatial resolution (FB-NR) reconstruction of the free-breathing 3D images. Subsequently, FB-NR was compared to the high spatial resolution reconstruction (FB-HR). BH and FB-NR images yielded comparable scar mass thereby validating the FB-3D LGE-CMR sequence. FB-

NR had significantly higher SNR and CNR than BH. When compared to the FB-HR images, FB-NR images had a higher mean scar mass. Since FB-HR images had higher SES over the scar border, we hypothesized that FB-NR images overestimated scar mass. As such, FB-HR would more closely approach actual histological scar mass. In support of this hypothesis, an ex vivo validation study has shown that normal resolution LGE-CMR indeed overestimates histological scar mass[3]. A future prospective study should investigate the added diagnostic value of increased image sharpness of the FB-3D HR LGE-CMR sequence.

The studies described in part 1 show that technical issues related to MR physics can be overcome by collaboration of basic scientists and physicians. By means of developing new innovative technological solutions and rapid implementation into a clinical research setting, the quality and applicability of MRI and MRS can improve substantially. Yet, many steps have to be made before a comprehensive MR exam including cardiac ^{1}H-MRS, coronary MRA and LGE-CMR can be applied routinely in T2DM patients. On one hand, there are MR-related hurdles such as scanning time, availability of proton spectra acquisition and post-processing and technical challenges to perform whole-heart coronary MRA. On the other hand, important clinical questions need to be answered: 1. To which T2DM patients should these innovative MR techniques be offered? 2. How should the findings be interpreted? 3. How should T2DM management be modified when abnormalities have been detected? The ultimate goal in answering these research questions would be to enable cost-effective interventions, thereby improving CV outcome of the patient with T2DM in general.

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

Chapters 6, 7 and 8 The MAGNA VICTORIA study

The MAGNA VICTORIA study was a randomized placebo-controlled trial that aimed to include 50 Western European patients with T2DM and BMI > 25 kg/m^2 that had inadequate glycemic control despite the use of metformin and/or sulphonylurea derivatives and/or insulin. Participants were treated with the GLP-1RA liraglutide (1.8

mg daily) or placebo for six months. Importantly, the study protocol required that concomitant medication was titrated on the basis of ambulant blood sugar measurements and glycated hemoglobin level at three months. As such, the trial can be regarded as having an active comparator placebo arm. This was reflected by increased use of sulphonylurea derivatives and insulin in the placebo group as compared with liraglutide-treated participants. As a result, there was no significant between-group difference in terms of change from baseline glycated hemoglobin.

In **chapter 6** the primary endpoints LV diastolic and systolic function were described. The intention-to-treat analysis encompassed 23 participants treated with liraglutide and 26 with placebo. According to previous studies[4,5] the average cardiac phenotype at baseline was characterized by mild LV diastolic dysfunction evidenced by a decreased early (E) to late (A) transmitral peak filling rate ratio (E/A ratio) while LV systolic function (ejection fraction) was normal. The results showed that LV diastolic function in terms of active relaxation: E decreased and peak mitral annular longitudinal motion (Ea) did not improve by liraglutide treatment. However, another index reflecting diastolic filling properties, LV filling pressure (E/Ea ratio), was found to be significantly reduced in the liraglutide group as compared with placebo. Since elevated LV filling pressure is an independent predictor of progression from asymptomatic LV diastolic dysfunction to HFpEF[6], this can be regarded as a beneficial surrogate outcome. Increased LV filling pressure probably plays a causal role in the development of HFpEF by mechanisms such as wall stress, diffuse cardiac fibrosis and LV hypertrophy[7]. LV systolic function slightly decreased as reflected by lower LV stroke volume and a slight reduction of LV ejection fraction, which still remained within normal values. Cardiac output remained unchanged because heart rate significantly increased, which is an effect that has been appreciated previously with liraglutide[8]. Because our study was not designed to unravel the mechanism of the observed effects of liraglutide on the heart, we can only speculate on potential mechanisms. We hypothesize that hemodynamic changes outside the heart, such as natriuresis[9] and vasodilation[10], decreased cardiac preload. A consequence of this hypothesis would be that patients with more severe stages of heart failure, might be at risk for decompensated heart failure if liraglutide therapy is started. As such, initiation of

liraglutide in NYHA class III or IV heart failure should be avoided, which is in agreement with current FDA/EMA warnings. Future studies should focus on the long-term effect of liraglutide therapy on LV function and morphology. An interesting study would be to investigate whether decreased LV filling pressure could result in reduced cardiac fibrosis as assessed by T1-mapping.

Secondary endpoints of the MAGNA VICTORIA study involved assessment of ectopic fat accumulation, the results of which were described in **chapter 7**. It is interesting to note that cardiac ^{1}H-MRS was performed with the high permittivity pad described in chapter 3. By using the pad in combination with acquisition of 32 signal averages the success rate of cardiac ^{1}H-MRS in the MAGNA VICTORIA study was 96%. Liraglutide treatment resulted in a mean 4.5 kg weight loss as compared to placebo. Surprisingly, this moderate weight loss was not associated with decreased visceral fat, hepatic fat, myocardial fat or epicardial fat. This is surprising because moderate weight loss induced by a diet has been shown to reduce visceral fat[11]. Because the study was not powered on these endpoints, results should be interpreted with caution. To speculate on potential explanation why liraglutide failed to reduce visceral fat accumulation: it could be that liraglutide has differing effects on subcutaneous versus visceral adipose tissue in terms of affecting lipogenesis:lipolysis ratio. Alternatively, action of liraglutide in the central nervous sytem[12] might, at least in theory, influence body fat distribution[13]. The absence of an effect on myocardial steatosis is in line with the observations described in chapter 7 because previous studies have shown that increased E/A ratio and reduced myocardial steatosis are tightly linked[14,15]. 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 CV events in liraglutide-treated T2DM patients[8]. As was also suggested by the authors of the LEADER trial, it seems unlikely that the cardioprotective effect of liraglutide is caused by glycemic control or reduced body weight. Based on the LEADER trial and our study, the cardioprotective properties of liraglutide might be exerted by a direct effect on atherosclerotic plaque formation. Several mechanisms have been described using rodents, including macrophage phenotype modulation[16], and decreased leucocyte adhesion and extravasation into the vascular wall[17].

In **chapter 8** the results of the pooled analysis of Western European (n=49) and South Asian (n=47) participants were described. The subgroup of patients on an MDI-regimen at baseline consisted of 43 participants (22 liraglutide; 21 placebo), of which 30 were of South Asian descent. Whereas in the placebo group only one participant (5%) reached target HbA1c, nine participants (41%) in the liraglutide group reached target HbA1c (*p*=0.005). Importantly, the risk of hypoglycemia was not significantly different between treatment arms. These results should be interpreted with the notion that inadequate glycemic control was amongst the inclusion criteria to participate in the study. In other words, the results of this study do not mean that MDI treatment should routinely be combined with liraglutide. This study does however suggest that liraglutide treatment should be considered in T2DM patients that fail to reach target HbA1c despite MDI.

To conclude, the MAGNA VICTORIA study has provided several important insights. First, the effect on diabetic cardiomyopathy seems relatively modest, at least after six months. However, the reduced LV filling might have a beneficial effect on long term progression to HFpEF warranting future studies with longer follow-up. Second, liraglutide seems to have no additional beneficial effect on ectopic fat accumulation when compared to placebo added to standard care. And, third, the addition of liraglutide should be considered in MDI-treated T2DM patients that have inadequate glycemic control.

Chapter 9 eSupported lifestyle intervention in insulin-dependent T2DM

In **chapter 9** we describe a prospective one-arm intervention study performed in eleven insulin-dependent T2DM patients with a median BMI of 34 kg/m^2 at baseline. Diabetes duration was long (median 11 years) and most participants had microvascular and macrovascular diabetes complications at baseline. The participants were subjected to a 12-week eSupported lifestyle coaching intervention after which a final follow-up assessment took place at 50 weeks from baseline. Glucose metabolism, ectopic fat accumulation (visceral fat, liver fat, pancreas fat and myocardial fat) and cardiac morphology and function (LV diastolic and systolic function) were assessed

using oral glucose tolerance testing (OGTT) and MRI/MRS respectively, at baseline, week 12 and week 50. Median weight loss was 9 kg after 12 weeks and did not change significantly thereafter. After 12 weeks, median daily insulin dose reduced dramatically with 53 IU/day and whole-body insulin sensitivity improved significantly, in parallel with hepatic steatosis. However, beta-cell function and pancreatic fat did not improve. Consequently, diabetes remission was not achieved in any participant. Despite sustained reduction of myocardial fat, cardiac morphology and function did not change accordingly (both at week 12 and week 50). Surprisingly, despite stable body weight and insulin dose between week 12 and 50, HbA1c had increased dramatically. These data, although sample size was small, suggest that insulin-dependent T2DM can be complicated by irreversible damage of beta-cells and myocardial tissue. Furthermore, close monitoring should be continued once weight has stabilized after a lifestyle intervention in insulin-dependent T2DM patients.

Thesis conclusion

This thesis shows that collaboration of basis scientists and physicians can result in clinically relevant technological improvement of MR techniques. The studies performed have shown feasibility of MR data acquisition with higher robustness, spatial resolution and quality. Combining CMR 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.

References

1. Stephenson MC, Gunner F, Napolitano A, et al. Applications of multi-nuclear magnetic resonance spectroscopy at 7T. *World J Radiol* 2011; **3**(4): 105-13.
2. Rijzewijk LJ, van der Meer RW, Smit JW, et al. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. *J Am Coll Cardiol* 2008; **52**(22): 1793-9.
3. Jablonowski R, Nordlund D, Kanski M, et al. Infarct quantification using 3D inversion recovery and 2D phase sensitive inversion recovery; validation in patients and ex vivo. *BMC Cardiovasc Disord* 2013; **13**: 110.
4. Liu JE, Palmieri V, Roman MJ, et al. The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. *J Am Coll Cardiol* 2001; **37**(7): 1943-9.
5. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *Jama* 2003; **289**(2): 194-202.
6. From AM, Scott CG, Chen HH. Changes in diastolic dysfunction in diabetes mellitus over time. *Am J Cardiol* 2009; **103**(10): 1463-6.
7. Lekavich CL, Barksdale DJ, Neelon V, Wu JR. Heart failure preserved ejection fraction (HFpEF): an integrated and strategic review. *Heart Fail Rev* 2015; **20**(6): 643-53.
8. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; **375**(4): 311-22.
9. Skov J, Pedersen M, Holst JJ, et al. Short-term effects of liraglutide on kidney function and vasoactive hormones in type 2 diabetes: a randomized clinical trial. *Diabetes Obes Metab* 2016; **18**(6): 581-9.
10. Koska J, Sands M, Burciu C, et al. Exenatide Protects Against Glucose- and Lipid-Induced Endothelial Dysfunction: Evidence for Direct Vasodilation Effect of GLP-1 Receptor Agonists in Humans. *Diabetes* 2015; **64**(7): 2624-35.
11. Chaston TB, Dixon JB. Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review. *Int J Obes (Lond)* 2008; **32**(4): 619-28.
12. Kooijman S, Wang Y, Parlevliet ET, et al. Central GLP-1 receptor signalling accelerates plasma clearance of triacylglycerol and glucose by activating brown adipose tissue in mice. *Diabetologia* 2015; **58**(11): 2637-46.
13. Kreier F, Kap YS, Mettenleiter TC, et al. Tracing from fat tissue, liver, and pancreas: a neuroanatomical framework for the role of the brain in type 2 diabetes. *Endocrinology* 2006; **147**(3): 1140-7.
14. Hammer S, Snel M, Lamb HJ, et al. Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases myocardial triglyceride content and improves myocardial function. *J Am Coll Cardiol* 2008; **52**(12): 1006-12.
15. Hammer S, van der Meer RW, Lamb HJ, et al. Short-term flexibility of myocardial triglycerides and diastolic function in patients with type 2 diabetes mellitus. *Am J Physiol Endocrinol Metab* 2008; **295**(3): E714-8.
16. Bruen R, Curley S, Kajani S, et al. Liraglutide dictates macrophage phenotype in apolipoprotein E null mice during early atherosclerosis. *Cardiovasc Diabetol* 2017; **16**(1): 143.
17. Rakipovski G, Rolin B, Nøhr J, et al. The GLP-1 Analogs Liraglutide and Semaglutide Reduce Atherosclerosis in ApoE(-/-) and LDLr(-/-) Mice by a Mechanism That Includes Inflammatory Pathways. *JACC Basic Transl Sci* 2018; **3**(6): 844-57.