Phenotyping cardiometabolic disease with magnetic resonance techniques

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CHAPTER

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Current magnetic resonance methods enable detailed phenotyping of the left ventricle and accurate characterization of body fat distribution, by assessment of cardiac morphology and function, myocardial triglyceride content, diffuse fibrosis, and visceral and subcutaneous adipose tissue. The objective of this thesis was to characterize cardiovascular remodeling associated with metabolic disturbances, using several magnetic resonance techniques.

Cardiovascular Remodeling in Type 2 Diabetes

In Chapter 2, we examined the relationship of insulin resistance, an important predictor of type 2 diabetes, to cardiovascular imaging parameters in a middle-aged population-based cohort. Previous large-scale studies have shown that abnormalities in glucose metabolism are associated with impairments in diastolic function, independently of body mass index (BMI) (1,2). However, the cardiovascular effects of insulin resistance and body fat, in particular visceral fat, might not be fully separated by adjustment for BMI. In our population-based study, we confirmed that the relation of insulin resistance to a lower diastolic function is independent of body fat.

In this thesis, we evaluated the role of insulin resistance in obesity-related impairments in diastolic function. However, several other factors such as increased inflammatory cytokines, high levels of circulating fatty acids, microvascular dysfunction and autonomic neuropathy have been implicated in the pathogenesis of HFpEF in obesity and type 2 diabetes (3-5). Accordingly, in our population-based study, insulin resistance was associated with impaired diastolic function, but the associations between adipose tissue and reduced diastolic function were not completely mediated by insulin resistance. Up till now, heart failure treatment options are limited, and the efficacy of therapies developed for HFrEF (such as angiotensin-converting enzyme inhibitors and beta blockers) has been uncertain in patients with HFpEF (6-9). Therefore, hopefully, future research on the contributing factors to diastolic dysfunction in obesity and type 2 diabetes may help to guide the development of new treatment strategies through a better understanding of the pathogenesis of diabetic heart failure.

Furthermore, our population-based results showed that visceral and total body fat are associated with lower and higher left ventricular end-diastolic volumes, respectively, which suggests that the body fat distribution phenotype may influence the cardiac phenotype in obesity. These findings are in keeping with the disparity in the cardiac remodeling types in relation to visceral and subcutaneous fat as reported in previous population-based studies (10-13). Importantly, left ventricular hypertrophy and concentric remodeling, independent of cardiovascular risk factors, have been associated with a higher risk of heart failure events (14). To date, routine use of imaging in type 2 diabetes patients to detect early abnormalities in cardiac function has not been recommended, although functional capacity and natriuretic peptides may be potential markers to identify high-risk patients who may benefit from cardiac screening

(15,16). Interestingly, distinct imaging-based cardiac phenotypes in type 2 diabetes patients have been associated with distinct cardiovascular risks; for example, high cardiac mass and dimensions and low systolic function, despite similar clinical characteristics, have been related to a higher cardiovascular risk (17). Therefore, risk stratification in type 2 diabetes patients based on the cardiometabolic phenotype using imaging techniques may merit further investigation.

Diabetic Cardiomyopathy Phenotype

In Chapter 3, we explored the differences in diabetic cardiomyopathy characteristics between Dutch South Asians and Dutch Europeans. Both the South Asian and the European type 2 diabetes patients demonstrated abnormalities in diastolic function, but the results regarding myocardial tissue characteristics were different between the two study groups. Based on the results of this thesis and previous studies (18,19), we speculate that myocardial lipotoxicity and altered substrate metabolism may be significant contributors to diabetic cardiomyopathy in European populations, whereas increased cardiac mass may be a predominant factor in South Asian ethnic groups. Likewise, findings of previous studies suggest that the etiology of diabetic heart failure may be different in South Asian compared with European ethnicities (20,21). Prospective studies are warranted to confirm the differential impact of type 2 diabetes on myocardial remodeling across ethnic groups. Although several large-scale studies, particularly in the United States (22) and in the United Kingdom (23), have investigated the ethnic disparities in the risk of cardiometabolic disease, the separate effects of genetic and behavioral conditions remain to be elucidated (24).

Cardiometabolic Effects of Type 2 Diabetes Medication

In our study on the effect of liraglutide on ectopic fat in type 2 diabetes patients of South Asian origin residing in the Netherlands, we reported a liraglutide-related reduction in visceral adipose tissue, which was associated with improved glycemic control (Chapter 4). Liraglutide has consistently been documented to reduce body weight, with approximately three to four kilograms (25); however, some studies have described a reduction in visceral fat, while others have reported a decrease in subcutaneous fat (26-28). Interestingly, it has been documented that the glucose-lowering effects of liraglutide are pronounced in South Asian type 2 diabetes patients (29). Our study was the first that assessed the effects of liraglutide on specific fat compartments in type 2 diabetes patients of South Asian ethnicity. The results of this thesis show that liraglutide can be used for glucose regulation in South Asians, and that glucose control might be improved by reduction of visceral adipose tissue.

In contrast to the liraglutide-related improvement of glucose levels and reduction of visceral adipose tissue, liraglutide had no effect on diastolic function and myocardial tissue characteristics in Dutch South Asian type 2 diabetes patients (Chapter 5). Similarly, the liraglutide-placebo controlled trial in Dutch European type 2 diabetes patients did not reveal an improvement of myocardial relaxation parameters in response to liraglutide, although liraglutide was found

to reduce the left ventricular end-diastolic filling pressure (presumably due to vasodilation or diuretic effects) (30). Recent cardiovascular outcome trials have demonstrated that glucagon-like peptide 1 (GLP-1) receptor agonists have no benefit on the incidence of heart failure, in contrast to sodium-glucose cotransporter 2 (SGLT-2) inhibitors which have been shown to reduce hospitalization for heart failure (31,32). In our study, we did not observe amelioration of diastolic function, neither a reduction of the myocardial triglyceride content and myocardial extracellular volume, which are more sensitive cardiac measures than heart failure incidence. Therefore, from our results, together with those of other single-center studies (33,34), we may conclude that liraglutide does not reverse diabetic cardiomyopathy.

Since recently, guidelines have recommended GLP-1 receptor agonists and SGLT-2 inhibitors as part of type 2 diabetes management in patients with overt atherosclerotic disease, whereas in type 2 diabetes patients with manifest heart failure, SGLT-2 inhibitors may be considered (35). Although liraglutide has no beneficial effect on heart failure incidence, liraglutide remains worth considering in South Asian type 2 diabetes patients because of the unfavorable cardiometabolic profile and high risk of atherosclerotic disease within this group, as well as the efficacy of liraglutide for glycemic control and the reduction of visceral adiposity in South Asians, as demonstrated in this thesis. Interestingly, it has been speculated that a combination treatment of GLP-1 receptor agonists and SGLT-2 inhibitors might have synergistic benefits on atherosclerotic and non-atherosclerotic cardiovascular morbidity in type 2 diabetes, which might be investigated in future studies (36).

In our studies we explored the diabetic cardiomyopathy phenotype and assessed the effects of the antidiabetic agent liraglutide. However, lifestyle modifications in type 2 diabetes patients for the regression of diabetic cardiomyopathy have not been addressed in this thesis, although dietary and behavioral therapies may be more efficient for the prevention of type 2 diabetes and the reduction of cardiovascular risk factors (37). In a recent trial, intensive lifestyle intervention did not decrease the rate of cardiovascular events compared with standard type 2 diabetes support and education, but several other positive effects such as less use of cardiovascular medication and improved quality of life were reported in the lifestyle intervention group (38). There is a limited number of studies on the effects of health behavior on the incidence of cardiometabolic disease among different ethnic groups (39,40). Therefore, multi-ethnic studies on the efficacy of lifestyle modification in individuals at risk of type 2 diabetes and diabetic cardiomyopathy seem warranted.

Imaging-based Cardiovascular Risk Stratification after Pediatric Hematopoietic Stem Cell Transplantation

Currently, pediatric hematopoietic stem cell transplantation recipients are selected for patient-specific follow-up programs according to the risk of late complications, based on pre-existing comorbidities, pre-transplant exposures, the transplant-preparative regimen, post-transplant complications such as graft-versus-host-disease, or relapse of the primary

disease (41). There has been limited research on the value of imaging-based cardiovascular risk stratifiers after hematopoietic stem cell transplantation. The results in this thesis suggest that diastolic function parameters, rather than systolic strain, aortic pulse wave velocity, myocardial triglyceride content or native T1, may represent early markers of cardiovascular disease after pediatric hematopoietic stem cell transplantation (Chapter 6). Future longitudinal studies are needed to confirm the predictive value of diastolic function for the development of manifest cardiovascular disease. Also, comparative studies are required to assess the effectiveness of magnetic resonance for the selection of patients who may require frequent follow-up by standard echocardiography.

Imaging-based Cardiovascular Risk Stratification in Ischemic Cardiomyopathy

Patients with prior myocardial infarction are at risk of life-threatening ventricular arrhythmia. Currently, selection for primary prevention implantable cardioverter defibrillator (ICD) therapy is based on left ventricular ejection fraction, but in only 35% patients, ICD therapy is appropriate (42). Most studies have investigated the role of late gadolinium enhancement (LGE) scar characteristics in ventricular arrhythmia risk stratification, whereas in this thesis, we examined the association of cardiac function abnormalities with ventricular arrhythmia. Our results suggest that the extent of impaired systolic strain and the late diastolic strain rate may play a role in the pathogenesis of ventricular arrhythmia, possibly by promoting adverse cardiac remodeling (Chapter 8). This work was a hypothesis-generating study and longitudinal research is needed to demonstrate causality of the relation between functional parameters, adverse remodeling and subsequent ventricular arrhythmia in patients with prior myocardial infarction. Thus far, studies have not demonstrated additional prognostic value of novel imaging markers above left ventricular ejection fraction; yet, advanced imaging markers have not been adopted in current risk stratification guidelines. The complex pathogenesis of ventricular arrhythmia remains uncertain, and further research is required.

Future Role of Magnetic Resonance in Characterizing Cardiometabolic Disease

To date, heart failure in type 2 diabetes patients without coronary artery disease remains overlooked. Although reduced diastolic function in type 2 diabetes patients may be predictive of diabetic heart failure, it is also a characteristic of normal aging and it is related to other conditions than type 2 diabetes as well, such as hypertension. To facilitate the early recognition of diabetic heart failure, researchers should continue to search for markers that are specific for diabetic cardiomyopathy. Possibly, magnetic resonance methods may contribute not only to the mechanistic understanding of diabetic heart failure, but also to the establishment of improved diagnostic criteria for diabetic cardiomyopathy.

In recent cardiovascular outcome trials, the effects of new antidiabetic agents have been evaluated by assessment of the incidence of non-fatal myocardial infarction, stroke, cardiovascular-specific death and heart failure hospitalization. The approval of GLP-1 receptor

agonists and SGLT-2 inhibitors to reduce the risk of cardiovascular events in type 2 diabetes with established atherosclerotic disease has been unique in the history of type 2 diabetes management. Although cardiovascular outcome trials provide essential information on the long-term cardiovascular safety of novel antidiabetic drugs, imaging-based studies will remain important to elucidate the biological actions of glucose-lowering medication on the cardiovascular system.

Cardiac magnetic resonance methods continue to be improved. In our center as well, techniques for the assessment of diastolic function using 4D flow imaging and for myocardial tissue characterization including cardiac T1 mapping and proton-magnetic resonance spectroscopy (^{1}H-MRS) have been optimized over the past years. The ongoing advances in cardiac magnetic resonance may increase the potential of imaging-based risk stratification in cardiometabolic disease, and perhaps in the near future, magnetic resonance parameters may prove to provide additional value above current clinical measures in selected patient groups.

Interestingly, a growing number of population-based studies such as the UK Biobank, but also earlier studies such as MESA, contain a wide variety of detailed imaging-based phenotypic characteristics (22,43). As such, in the coming years, magnetic resonance methods seem to be increasingly exploited in large-scale research on human biology and, hopefully, this will add to the development of efficient personalized strategies for the prevention, but also the treatment of diabetic heart failure and other cardiometabolic diseases.

CONCLUSION

The results of this thesis demonstrate that reduced diastolic function is a common characteristic of myocardial remodeling in cardiometabolic diseases (Chapter 2, 3, 5 and 6) and a potential marker for the detection of patients at increased cardiovascular risk (Chapter 6 and 8). Our findings show that the evaluation of visceral adiposity and myocardial triglyceride content may help to identify distinct cardiometabolic phenotypes in obesity and type 2 diabetes (Chapter 2 and 3), and to better understand the cardiometabolic actions of antidiabetic agents (Chapter 4 and 5). Interestingly, in our study, the GLP-1 receptor agonist liraglutide reduced visceral adipose tissue in South Asian type 2 diabetes patients, but did not improve cardiac function. With the emergence of non-contrast cardiovascular protocols (Chapter 7), magnetic resonance techniques may be increasingly used for cardiometabolic phenotyping in population-based cohorts as well as clinical studies.

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