Quantitative cardiac imaging in women with a history of preeclampsia

English summary

Preeclampsia is a maternal gestational hypertensive complication. It is the leading cause of maternal and fetal morbidity and mortality in the western world. Approximately 2-8% of all pregnancies worldwide are affected by preeclampsia and its incidence has been increasing over the past few decades. Preeclampsia is also associated with long-term, maternal, adverse cardiovascular health effects. Among these effects is concentric left ventricular hypertrophy, which is thought to be, at least in part, the myocardial response to increased pressure load with concurrent shallow volume load. This remodeling is necessary to decrease end-diastolic stress while preserving ejection fraction, but it is unfavorable in the long term. In 25% to 40% of cases, these changes do not completely resolve postpartum. Women with a history of preeclampsia have a higher incidence of cardiac disease later in life, including ischemic heart disease, arrhythmias, and heart failure.

The cause of the increased risk of heart failure after preeclampsia is incompletely understood. It may be a result of pre-existing susceptibility, pregnancy induced concentric remodeling, along with co-existing or remaining elevated pressure load along with shallow preload. It is unknown whether preeclampsia predisposes to cardiac disease, or whether the increased cardiovascular risk is caused by shared risk factors. While some myocardial changes have been described in formerly preeclamptic women, among which residual hypertrophy after delivery, diastolic dysfunction, and impaired myocardial strain, these changes appear to describe the symptoms of the cardiac sequelae of preeclampsia rather than the cause.

Because heart failure is more common after preeclampsia than after normotensive pregnancy, these women may benefit from proper cardiovascular evaluation following preeclamptic pregnancy, since heart failure is hardly reversible once it is in its clinical stage. In its preclinical stage, before symptoms of heart failure become manifest, disease progression may be halted, improving quality of life for the women affected by it and reducing hospitalization and disease burden. However, not every formerly preeclamptic woman will develop heart failure. Therefore, it is important to find

biomarkers associated with cardiac abnormalities in women with a medical history of preeclampsia, in order to monitor disease progression and to improve postpartum evaluation in an effective manner allowing efficient treatment.

Cardiac imaging modalities allow safe and minimally invasive assessment of cardiac abnormalities in formerly preeclamptic women. Cardiac imaging has already been employed in research settings to study the aftermath of preeclampsia, but these previous studies were predominantly performed with echocardiography. Cardiac MRI can provide additional information, among which myocardial perfusion and diffuse fibrosis assessment, which are characteristics of endangered functioning and secondary but permanent damage. In addition, previous research only focused onstandard echocardiographic parameters and systolic strain, which is the myocardial deformation in the systolic phase, during which the heart contracts.

Global myocardial perfusion is used as an indirect marker to assess cardiac microvascular health. Coronary microvascular impairment is associated with heart failure, both with and without preserved ejection fraction, and early signs of global changes in myocardial perfusion may serve as an early indicator to detect those at risk of developing heart failure. Global myocardial perfusion dysfunction is more indicative of general microvascular dysfunction, as opposed to a focal myocardial perfusion defect which is more indicative of coronary atherosclerosis. First-pass perfusion imaging is a cardiac MRI technique which measures myocardial perfusion.

Diffuse fibrosis, the deposition of collagen in the extracellular matrix of the myocardium in a dispersed manner, has been associated with left ventricular hypertrophy and heart failure, both with and without a preserved ejection fraction. Diffuse fibrosis is a gradual process in response to dysregulated blood pressure, and early markers of fibrosis may be detectable in the early stages of preclinical heart failure. It can be reliably assessed through cardiac MRI by the use of T1-mapping and extracellular volume calculation. Previous studies have shown that calculated extracellular volume based on T1-mapping strongly correlates with histology, which is the gold standard for fibrosis assessment.

Women are more likely to develop heart failure with preserved ejection fraction, rather than heart failure with reduced ejection fraction, more common amongst males. Heart failure with preserved ejection fraction is often accompanied by diastolic dysfunction, which occurs in the relaxation phase of the cardiac cycle. Strain rate analysis is able to analyze the diastolic phase of the cardiac cycle as well as the systolic phase and may provide further insight into diastolic dysfunction in formerly preeclamptic women. Furthermore, early signs of diastolic dysfunction may present themselves in strain rate analysis before they become apparent in more conventional Doppler echocardiography examinations. Both echocardiography and cardiac MRI can be used as techniques to measure myocardial strain rate in the systolic as well as the diastolic phase.

The goal of this thesis was to investigate whether formerly preeclamptic women show signs of left ventricular changes in terms of myocardial perfusion, diffuse fibrosis formation, and myocardial strain and strain rate.

Chapter 1 provided an overview of our current knowledge of postpartum cardiac changes after preeclampsia and addressed knowledge gaps that needed to be investigated in future research.

The review article in **Chapter 2** further investigated the current knowledge on preeclampsia in relation to postpartum myocardial changes and placed this in the context of quantitative cardiac imaging. It also further identified knowledge gaps, and provided clear direction of the research avenues that were to be pursued to improve our understanding of the postpartum cardiac effects of preeclampsia.

Chapter 3 provided a necessary step to address one of the knowledge gaps, the validation of left ventricular strain assessment. MRI feature tracking was compared with the gold standard, MRI tagging, and ultrasound speckle tracking was in turn compared with MRI feature tracking. This study was performed in a cohort of healthy controls, formerly preeclamptic women, and left bundle branch block patients. Our findings indicated that MRI feature tracking and ultrasound speckle tracking showed good agreement and no biases when myocardial strain was assessed on a global level,

though agreement was less good and accompanied with biases on a segmental level.

Chapter 4 gave an outline of the research design of the DECONNECT study, a study that concurrently explores the role of microvascular dysfunction and its possible sequelae in two vascular regions, the brain and the heart after preeclamptic pregnancy as compared to normotensive gestation. Referring back to the knowledge gaps described in **Chapters 1 and 2**, the cardiac sub-study of the DECONNECT study specifically sought to address these knowledge gaps in an explorative fashion. Specifically, it focused on myocardial perfusion, diffuse fibrosis, and peak strain and strain rates in the left ventricle. The investigation of these parameters was a novel approach, as these potential imaging biomarkers had not yet been examined in formerly preeclamptic women, but may shed light on functional and anatomical abnormalities after a preeclamptic pregnancy.

Chapter 5 showed the results of the cardiac sub-study of the DECONNECT study. This explorative study provided a between-group comparison of myocardial perfusion, diffuse fibrosis, myocardial strain and strain rate, and left ventricular volume, function, and mass. Formerly preeclamptic women were found to have a slightly higher blood pressure. When we corrected for age and postpartum interval, formerly preeclamptic women had a higher absolute circumferential and longitudinal peak strain, comparable left ventricular ejection fraction, higher left ventricular mass-to-volume ratio consistent with the still functional concentric adjustments to modestly increased pressure load, and a smaller indexed left-ventricular end-systolic volume. We were neither able to detect differences in myocardial perfusion, nor able to observe statistically significant fibrotic differences. While the sample size of our study was limited, even at the upper limits of the confidence intervals the between-group differences in myocardial perfusion and diffuse fibrosis were small. This implies that in the first decade after preeclampsia, myocardial perfusion diminishment and diffuse fibrosis formation does not occur in a clinically relevant amount.

Chapter 6 presented the findings of an ultrasound speckle tracking-based study on participants of the Queen of Hearts study, a large cross-sectional study

that investigated the presence of subclinical heart failure or diastolic dysfunction in a cohort of formerly preeclamptic and a control group consisting of women with normotensive pregnancy up to 30 years post-delivery. In a large cohort, longitudinal strain and strain rates, obtained with echocardiography, were examined. A subset of the Queen of Hearts participants was chosen from youngest upward in order to assess myocardial changes early in life and at a short postpartum interval. The novel finding of this study was that early-diastolic strain rate and the early-to-late-diastolic strain rate ratio were impaired in formerly preeclamptic women at a young age and at a short postpartum interval. An impairment of early-diastolic strain rate is an indication of reduced ventricular compliance. As the left ventricle becomes stiffer, its ability to relax passively (due to differences in pressure between the left atrium and the left ventricle) becomes reduced. The volume-independent early-to-late-diastolic strain ratio may be slightly different from the volume-dependent E/A ratio, which is commonly assessed through Doppler echocardiography. As the early-diastolic phase becomes impaired, the late-diastolic phase becomes more pronounced. Although on a tissue level diastolic function was impaired, trans-mitral volume-dependent parameters were comparable between groups, indicating mechanical diastolic impairment in formerly preeclamptic women in the absence of, or preceding, trans-mitral flow impairments. Univariable analysis revealed further differences. Formerly preeclamptic women had a higher interventricular septal wall thickness, posterior wall thickness, relative wall thickness, and indexed left ventricular mass. Furthermore, their septal mitral annular velocity (e') was lower, resulting in a higher ratio between peak early-diastolic transmitral flow velocity and septal mitral annular velocity (E/e'). The overall mean E/e' ratio was also higher, and pulmonary S/D ratio was lower. However, in multivariable analysis, only a lower septal e' and higher septal E/e' remained significantly different, which agrees with the finding of a reduced early-diastolic strain rate, indicating a diminished mechanical relaxation in the early-diastolic phase of the cardiac cycle.

Chapter 7 discussed the findings in this thesis in depth and placed the findings of each chapter in context to the other chapters and to the overall research questions

of this thesis. Future research and clinical perspectives were also discussed.