Quantitative cardiac imaging in women with a history of preeclampsia

Scientific and Societal Impact

Preeclampsia is one of the leading causes of pregnancy-related morbidity and mortality in both mother and child. It affects 2-8% of all pregnancies worldwide. In Europe, it occurs in 2-5% of the pregnancies resulting in roughly 200,000 women each year. Women who had preeclampsia have a four times higher chance to develop subclinical heart failure within 10 years after delivery. While heart failure is currently hardly accessible to treatment in the stage when patients already show clinical symptoms, the progression towards symptomatic heart failure may still be halted if it is detected before it becomes symptomatic. In order to do this, we need to assess cardiac changes after preeclampsia. Once these changes are established, we can examine women who had preeclampsia after the pregnancy to establish their current cardiac health and the progression towards heart failure. In this thesis, we evaluated whether cardiac imaging by MRI and ultrasound can help in determining abnormal cardiac changes after preeclampsia.

First, we summarized previous cardiac imaging studies on cardiac changes in women who had preeclampsia in a review article **(Chapter 2).** In this review, we also identified knowledge gaps in current literature. We concluded that quantitative cardiac MRI and ultrasound-based analysis of myocardial deformation (strain) and rate of deformation (strain rate) may give us more insight in the cardiac health of formerly preeclamptic women. In addition, more information on changes in the microvasculature of the heart and fibrotic development in the myocardium are required. The scientific impact of this chapter is that it clearly describes where additional research needs to be performed.

Following this review, we investigated if two methods for strain assessment which were to be used in this thesis, MRI feature tracking and ultrasound speckle tracking, were suitable and accurate (Chapter 3). In order to validate these techniques, MRI feature tracking was compared to the gold standard for strain assessment, MRI tagging. In turn, ultrasound speckle tracking was compared to MRI feature tracking. Validating measurement techniques is important for both research and clinical practice, as it determines whether two different techniques show similar results. MRI feature tracking and ultrasound speckle tracking are based on routinely acquired images, and therefore they do not increase the examination time for the patient. In addition, these techniques have a higher temporal resolution than MRI tagging, so that subtle changes over the cardiac cycle can be detected more easily. This makes the implementation of MRI feature tracking and ultrasound speckle tracking more convenient than MRI tagging, which may remove an obstacle for further implementation of myocardial strain assessment in research and clinical practice. In this validation study, we showed that for global strain assessment, where the entire left ventricle of the heart is examined, MRI feature tracking and ultrasound speckle tracking show comparable results. However, for segmental strain assessment measurements do correlate, but there are biases

between these techniques that should be taken into account for the implementation of reference values, or when comparing different studies. Our validation of MRI feature tracking and ultrasound speckle tracking has shown that these methods can be reliably used in both research and healthcare settings. Ultrasound speckle tracking is cheaper and more readily available. On the other hand, MRI feature tracking has superior image quality, and is more suitable for the quantification of the strain in all three directions. MRI feature tracking and ultrasound speckle tracking provide information about the contraction and relaxation of the heart, which may assist doctors in their diagnoses and clinical decision-making. Furthermore, the validation of these techniques allows their application in new studies to describe strain and strain rate patterns in different cardiac diseases. These findings may improve our understanding of different cardiac diseases, improve our detection of these diseases, and provide a way to determine if the treatment for these diseases are effective.

Following the previous two chapters, we described our research plan for investigating cardiac function in women after preeclampsia, and to fill in the knowledge gaps that previous studies had not yet investigated **(Chapter 4)**. In this research design article, we discussed our methods in-depth. The impact of this paper is two-fold. First, it serves as the groundwork for the results-focused paper that followed, as well as a way to assure that we performed the actual research as initially described. Second, it serves as a guiding document for future studies. Follow-up studies can benefit from this article as a guidance for their own research into the cardiac imaging after preeclampsia.

Next, using quantitative cardiac MRI, we investigated cardiac microvascular function in women who had preeclampsia **(Chapter 5)**. We also investigated myocardial mass and function, and diffuse fibrosis formation. Finally, through MRI feature tracking, we assessed peak strain, and the systolic, early-diastolic, and late-diastolic strain rates, providing us more information about both the systolic and diastolic cycles of the heart. Our study showed no differences in cardiac microvascular function and fibrosis between women who had preeclampsia compared to women who had an uncomplicated pregnancy. We did find that women who had preeclampsia have a smaller left ventricular end-systolic volume, and that their left ventricular mass-to-volume ratio was higher. Also, women who had preeclampsia had higher absolute myocardial peak strain, which was unexpected, but possibly due to the smaller left ventricular end-systolic volume, and due to the increased thickness of the heart muscle. This implies that systolic function is not reduced in women who had preeclampsia, and may be overcompensated. A limitation of this study was the small sample size. However, the observed effect and sizes and their confidence intervals show that it is unlikely that larger studies will detect clinically relevant effects on microvascular dysfunction and fibrosis in this patient population. This study uses for the first time comprehensive cardiac MRI techniques that can also be used to investigate cardiac

function after preeclampsia in larger cohorts and at different postpartum intervals in future studies. Insights from the present and future studies is necessary in order to direct future therapeutic or preventive interventions.

With cardiac ultrasound, we have also investigated left ventricular strain and strain rate 10 years postpartum **(Chapter 6)**. The most important result of this study was that even at a relatively young age, and 10 years after giving birth, women who had preeclampsia already show subtle signs of reduced diastolic function compared to women who did not have preeclampsia. These findings show that women who had preeclampsia have a slightly reduced ventricular compliance. This stiffening did not affect the actual flow of blood into the left ventricle of the heart, meaning that it can occur without affecting filling rates in the diastolic phase, or that this stiffening happens at a moment in time before the filling becomes affected. The finding that women who had preeclampsia already show such stiffening of the heart at an early age and 10 years after birth provides us a new way to examine cardiac health after preeclampsia. With this method, we can examine if these changes can predict the development of heart failure in future studies. Also, it was found that ventricular stiffening does not affect the left ventricular filling rates, or that it may precede filling rate impairment. This gives us another question to be answered by future research, namely about how cardiac wall deformation and the flow of blood into the left chamber are correlated.

This thesis has given us more insight in cardiac changes after preeclampsia. By finding more of these cardiac changes, we are closer to understanding how preeclampsia might lead to heart failure, and we gain further insight into where we need to perform more research in the future. The successful treatment of heart failure before it becomes symptomatic after preeclampsia depends on how early we can detect it. Future studies, like the upcoming TREASURE trial, initiated by our research group, focuses on the early treatment of asymptomatic heart failure and reduced diastolic function with antihypertensive medication, ACE inhibitors, or angiotensin receptor blockers over the course of two years. This study may show us the importance of timely detection and treatment to recover cardiac health. The findings of this thesis have given us the first steps towards cardiac follow-up examination in women who had preeclampsia. However, our current understanding, still does not lead to clinical implementation of these new imaging-based techniques after preeclampsia, but provides valid protocols and research questions for future studies. Future studies should focus on whether these cardiac imaging techniques might inform doctors on who to treat after preeclampsia to prevent heart failure, and it is expected to provide tools to evaluate whether these treatments are effective or not.