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Novel imaging insights into cardiac remodeling, myocardial function and risk stratification in cardiovascular disease

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Summary, conclusions and future perspectives

Samenvatting, conclusies en toekomstperspectieven

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SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

SUMMARY OF PART I: Non-invasive right ventricular myocardial work analysis

Contemporary echocardiographic methods of evaluating right ventricular (RV) function, including RV longitudinal strain and tricuspid annular plane systolic excursion (TAPSE), do not adequately account for RV afterload and mechanical efficiency in their quantification. In **chapter 2**, a novel echocardiographic method of evaluating RV function with RV pressure strain loops was developed, utilizing software originally designed for the assessment of left ventricular (LV) function. In 22 patients with heart failure and reduced ejection fraction undergoing right heart catheterization, the evaluation of RV myocardial work derived from RV pressure-strain loops was demonstrated to be feasible, with excellent reproducibility. Furthermore, two parameters of RV myocardial work, RV global work index and RV global constructive work, but not conventional parameters of RV systolic function (RV longitudinal strain, TAPSE, RV fractional area change), were shown to be moderately correlated with stroke volume index measured invasively during right heart catheterization.

Chapter 3 demonstrated that parameters of RV myocardial work were also associated with several invasive hemodynamic parameters, including RV stroke work index and pulmonary vascular resistance, in a cohort of patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. In addition, RV global work index and RV global constructive were demonstrated to be significantly and non-linearly associated with all-cause mortality, whereas standard echocardiographic parameters related to RV function (pulmonary artery systolic pressure, RV strain, TAPSE, and RV fractional area change) were not.

SUMMARY OF PART II: New insights into risk stratification of patients with valvular heart disease

In part II, **chapter 4** demonstrated that LV remodeling is dependent on the underlying bicuspid aortic valve pathology, with important differences in LV remodeling observed between patients with significant ($\geq$ moderate) isolated aortic stenosis, isolated aortic regurgitation, and mixed aortic valve disease. In addition, the prognostic significance of LV geometric patterns and LV hypertrophy varied according to the type of aortic valve disease. The presence of concentric remodeling, concentric hypertrophy and eccentric hypertrophy were independently related to a composite endpoint of aortic valve repair/replacement and all-cause mortality in patients with isolated AS, while concentric hypertrophy and eccentric hypertrophy were independently associated with the combined endpoint for patients with isolated aortic regurgitation. Unexpectedly, there was

no adjusted association observed between indices of LV remodeling and outcome in patients with mixed aortic valve disease.

Chapter 5 showed that left atrial dilation is present in approximately one-third of patients with significant aortic regurgitation due to bicuspid aortic valve and was independently associated with a combined endpoint of aortic valve repair/replacement and all-cause mortality. The presence of left atrial dilation in significant aortic regurgitation may identify patients with worse subclinical LV diastolic function, who are more likely to develop symptoms, thus requiring surgical intervention. **Chapter 6** demonstrated that the prevalence of significant mitral regurgitation in patients with bicuspid aortic valve was 5%. In addition, patients with a type 1 raphe with left and non-coronary cusp fusion were shown to be significantly more likely to have $\geq$ moderate mitral regurgitation due to prolapse of the anterior mitral valve leaflet when compared to other bicuspid aortic valve phenotypes. Interestingly, following adjustment for important confounding variables, significant mitral regurgitation was not associated with adverse prognosis, except for the patient subgroup with moderate to severe aortic regurgitation. Nonetheless, when stratifying by the etiology of mitral regurgitation, the presence of significant mitral regurgitation not due to aortic valve disease was independently associated with increased all-cause mortality. This suggests that consideration of the etiology of significant MR is essential in the setting of treatable aortic valve disease. **Chapter 7** demonstrated increased mortality with a LV ejection fraction below 60% in patients with significant bicuspid aortic valve disease, providing data supporting recent guideline recommendations for aortic valve replacement if the LV ejection fraction is $<60\%$ in patients with severe aortic stenosis and aortic regurgitation. Importantly, data supporting those recommendations was previously based almost entirely on studies of patients with a tricuspid aortic valve. Given the younger age and vastly different comorbidity profile of patients with bicuspid aortic valve, the results of this study are important, suggesting that similar recommendations may also be applied to this patient group. Ideally, randomized controlled trials will be performed to determine if asymptomatic patients with severe BAV disease and LV ejection fraction $<60\%$ benefit from early aortic valve replacement.

Chapter 8 demonstrated that of the pathophysiological mechanisms (including tricuspid regurgitation [TR] regurgitant volume, RV size, pulmonary artery systolic pressure, right atrial pressure) identified by echocardiography that are associated with significant secondary TR, only severe RV dysfunction was independently associated with the presence of significant renal impairment. It is possible that previous associations observed between significant renal impairment and the TR grade were indicative of the increased incidence of RV dysfunction observed with increasing TR severity. In addition, the presence of severe RV dysfunction was shown to be associated with reduced overall survival in patients with stage 1-3 chronic kidney disease, but not in patients

with stage 4–5 chronic kidney disease. **Chapter 9** showed that the number of secondary outcome determinants (left atrial volume index $\geq 60 \text{ ml/m}^2$, atrial fibrillation, pulmonary artery systolic pressure $\geq 50 \text{ mmHg}$ and $\geq$ moderate TR) are strongly independently associated with post-surgical survival in patients with degenerative mitral regurgitation, likely identifying patients with high-risk cardiac phenotypes. Furthermore, the presence and number of secondary outcome determinants demonstrated better outcome discrimination than traditional Class I indications for surgery, including the presence of symptoms, LV ejection fraction $\leq 60\%$, or LV end-systolic diameter $\geq 40 \text{ mm}$. This study suggests that a paradigm shift in guideline recommendations could be considered: In addition to the use of clinically established thresholds of individual imaging parameters for intervention, accounting for the overall cardiac phenotype represented by the presence of multiple prognostically important parameters may improve discrimination and therefore, patient selection for early surgery. Furthermore, the presence of multiple prognostically important parameters probably warrants a stronger recommendation for intervention than any single parameter in isolation.

CONCLUSIONS AND FUTURE PERSPECTIVES

RV myocardial work analysis with RV pressure-strain loops holds much promise for improving the non-invasive understanding of RV pathophysiology for an individual patient. Although this thesis has demonstrated the utility of RV myocardial work for the risk stratification of patients with pre-capillary pulmonary hypertension, larger prospective studies are required to confirm these results and facilitate extensive multivariable analyses. Future research is also needed to examine the prognostic value of RV myocardial work in patients with significant TR, significant mitral regurgitation, left ventricular assist devices, heart failure with preserved ejection fraction and for heart transplant recipients. The potential for improving risk stratification in these important patient groups by providing a more complete quantification of RV function that accounts for RV afterload and mechanical efficiency, represents many exciting research opportunities.

The evaluation of myocardial remodeling and function is essential in valvular heart disease. Indeed, imaging parameters are a direct reflection of the hemodynamic burden imposed by a particular valvular lesion. However, opportunities for improving risk stratification and refining the selection of patients for intervention requires both the development of novel imaging techniques and the use of methods for the identification of patients with high-risk cardiac phenotypes. In addition, further research is desperately needed for patients with a bicuspid aortic valve, in whom accurate selection for intervention is paramount due to their young age and the associated ramifications of early aortic valve replacement. For this cohort in particular, randomized data is needed to inform current clinical practice, which until now, has been driven by a combination of observational data and expert opinion.

