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

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General introduction and outline of the thesis

GENERAL INTRODUCTION

Non-invasive imaging has revolutionized the way clinicians evaluate patients with cardiovascular disease. Multimodal non-invasive imaging has facilitated significant advances in the diagnosis of cardiac disease, while also providing new opportunities for the prediction of patient outcomes. In clinical practice, echocardiography remains the first imaging technique of choice to evaluate cardiac dimensions and function. However, in recent years, there has been a shift from use of conventional echocardiographic parameters (such as left ventricular ejection fraction (LVEF) and cardiac chamber volumes) to the use of advanced strain imaging by speckle tracking echocardiography, which provides a more sensitive and robust evaluation of cardiac function[1, 2].

New developments based on strain imaging have allowed for the non-invasive assessment of myocardial work of the left ventricle, providing a deeper insight into myocardial performance and energetics[3, 4]. Indeed, by accounting for afterload and myocardial work efficiency, myocardial work evaluation with left ventricular (LV) pressure-strain loops (Figure 1) has been demonstrated to offer incremental prognostic value over LV global longitudinal strain[5, 6]. Due to the greater afterload dependency of the right ventricle compared to the left ventricle, the evaluation of noninvasive right ventricular (RV) myocardial work could improve the non-invasive understanding of RV performance[7]. However, despite this, current imaging parameters of RV function used in clinical practice, such as tricuspid annular plane systolic excursion (TAPSE), RV longitudinal strain and RV fractional area change (FAC), do not account for RV afterload and do not provide an estimate of mechanical efficiency[8, 9]. RV pressure-strain loop analysis has the potential to non-invasively improve a clinician's understanding of the RV pathophysiology of an individual patient and enhance risk stratification in those with RV pathology, such as patients with pulmonary arterial hypertension. In addition, measurements of myocardial work and strain may be influenced by the type of cardiac remodeling, which may also vary according to the underlying disease[10]. Indeed, greater understanding of cardiac remodeling may improve understanding of concomitant or future changes in myocardial function.

Valvular heart disease accounts for a significant burden of disease in Western countries and likely remains undetected in a significant proportion of the population[11]. Indeed, at present it is estimated that approximately 41 million people worldwide are affected by rheumatic heart disease, with 24 million affected by degenerative mitral valve disease and 9 million by calcific aortic stenosis[12]. There is promise that non-invasive imaging techniques evaluating myocardial remodeling and function may identify patients with valvular heart disease who could benefit most from specific therapies. For example, the use of imaging techniques to establish the extent of cardiac involvement may be particularly important for the development of algorithms that facilitate referral

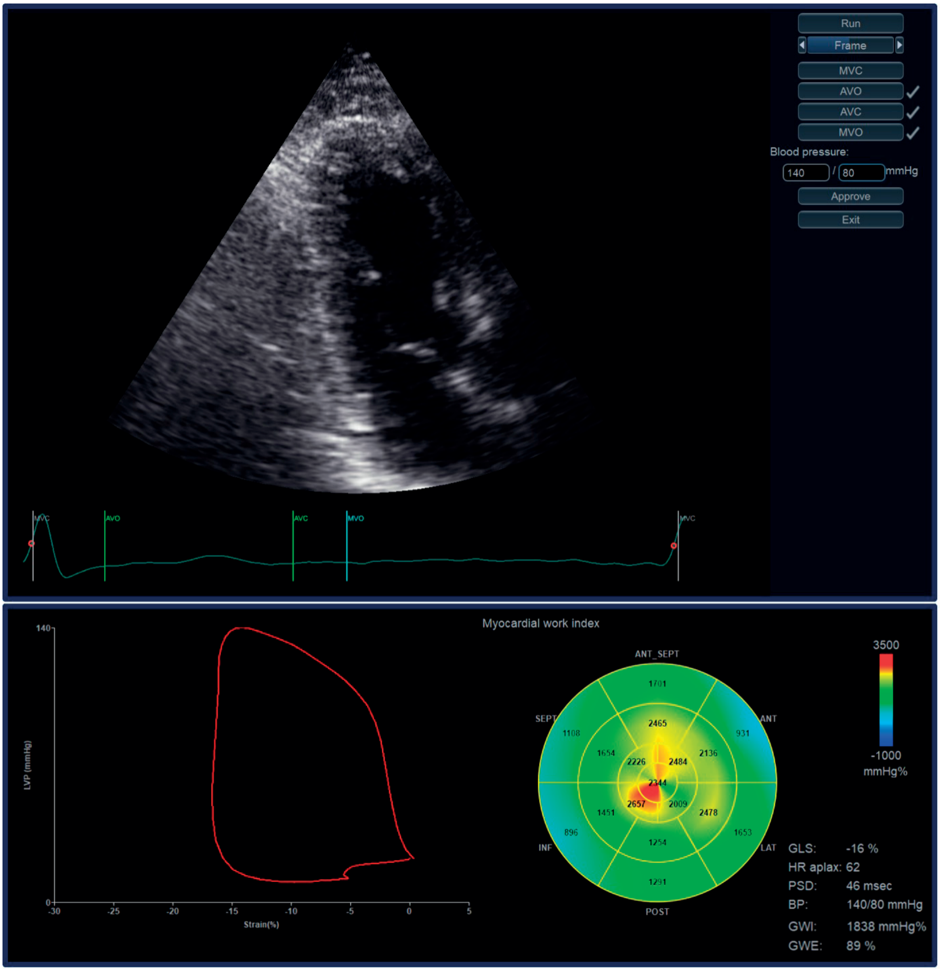

Figure 1: The upper panel demonstrates the synchronization of valvular event timings with LV strain and incorporation of systolic blood pressure. A LV pressure-strain loop (red outline) and bulls-eye plot of LV myocardial work index are displayed in the lower panel. LV pressure strain loops are used to provide a quantitative estimate of LV function that accounts for afterload and mechanical efficiency.

for timely intervention. At present, most guideline recommendations for intervention in valvular heart disease are based on observational data and depend on either the presence of symptoms or specific thresholds of isolated imaging parameters. However, the recognition of high-risk phenotypes with multiple abnormal parameters of cardiac structure and/or function may identify patients at even higher risk than patients who meet the traditional thresholds for intervention. The identification of such a phenotype may also increase the clinician's certainty of the significance of the hemodynamic consequences and severity of the underlying valvular lesion.

In addition, guideline recommendations for patients with bicuspid aortic valve are frequently extrapolated from data from patients with a tricuspid aortic valve. Indeed, despite the availability of extensive data regarding the risk stratification and management of patients with tricuspid aortic valve disease, there is limited data which supports that identical recommendations should be applied to patients with a bicuspid aortic valve, a cohort who are considerably younger, with fewer comorbidities, and whom may have important differences in cardiac remodeling and function[13, 14]. Further understanding of myocardial remodeling and function for this important patient group is urgently needed, to enhance risk stratification and facilitate appropriate timing for intervention.

OUTLINE OF THE THESIS

The objective of this thesis was two-fold: (i) To investigate the utility of the non-invasive evaluation of RV myocardial work and, (ii) to investigate the role of echocardiography for the risk stratification of patients with valvular heart disease. In this thesis, novel and established imaging techniques have provided new insights into the pathophysiology and outcomes of various cardiac diseases.

In **part I**, a novel method of evaluating RV function is described and validated. **Chapter 2** provides a proof of concept for the feasibility of RV myocardial work assessment on 2-dimensional speckle tracking strain echocardiography. This concept was validated in **chapter 3** with hemodynamic parameters and outcome in a population with pre-capillary pulmonary hypertension who underwent right heart catheterization.

Part II includes six chapters focused on novel insights into the risk stratification of patients with valvular heart disease. **Chapter 4** demonstrates the differences and prognostic implications of LV remodeling in different types of bicuspid aortic valve disease, while **chapter 5** shows the association between left atrial enlargement and outcome in patients with aortic regurgitation due to a bicuspid aortic valve. **Chapter 6** evaluates the prevalence and prognostic relevance of mitral regurgitation in patients with a bicuspid aortic valve and **chapter 7** investigates the importance of LV ejection fraction in patients with significant bicuspid aortic stenosis, aortic regurgitation, and mixed aortic valve disease. **Chapter 8** evaluates the mechanisms linking renal function and significant tricuspid regurgitation and associated prognostic implications. **Chapter 9** evaluates the prognostic role of the number of secondary outcome determinants (left atrial enlargement, pulmonary hypertension, tricuspid regurgitation, and atrial fibrillation) on post-surgical survival in patients with degenerative mitral regurgitation.

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