Advanced echocardiographic imaging in valvular and systemic diseases

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CHAPTER 8

Summary, conclusions and future perspectives

SUMMARY

This thesis describes the additional value of advanced echocardiographic techniques in patients with primary cardiac disease, resulting in mitral regurgitation (MR), and secondary cardiac disease caused by a systemic disease. In this thesis we focussed on patients with mitral regurgitation (MR), specifically primary MR and functional MR (FMR), and patients with Systemic Sclerosis (SSc). The general introduction provides a background of MR and cardiac involvement in SSc and how conventional 2-dimensional (2D) echocardiography is currently used. The potential role of 2D speckle tracking echocardiography and 3-dimensional (3D) echocardiography together with customized software to create 4-dimensional (4D) mitral valve models is introduced. This thesis aims to provide new insights in diagnosis, disease progression and risk stratification in patients with MR and patients with SSc with the implementation of advanced echocardiographic techniques.

Part I: Utility and implications of advanced echocardiography in mitral regurgitation

In the first part of this thesis, patients with primary MR, caused by degenerative mitral valve disease, and FMR were studied. Fibroelastic deficiency (FED) and Barlow's disease (BD) are the main aetiologies of primary MR. It remains unknown, however, whether they are two distinct disease processes or part of one spectrum. Furthermore, the impact of various factors, such as mitral annulus dynamics, on MR quantification has yet to be explored. In **Chapter 2,** the differences in regional left ventricular (LV) contraction in FED and BD using 2D speckle tracking echocardiography were assessed. Patients with moderate and severe, primary MR (62 FED and 42 BD) and control subjects (n=40) were evaluated using 2-dimensional (2D) trans thoracic echocardiography (TTE). LV longitudinal strains of the basal, mid and apical segments were assessed with 2D speckle tracking echocardiography. FED and BD showed distinct patterns in regional LV mechanics: in FED, LV strain of the basal segments is impaired and enhanced in apical segments whereas in BD the basal segments are enhanced. In addition, in **Chapter 3**, the mitral annulus dynamics in primary MR (n=92), FMR (n=31) and control subjects (n=29) were assessed using 3D transoesophageal echocardiography (TEE) and dedicated offline software to create 4D

mitral valve models. With the use of 3D colour Doppler TEE data, the effective regurgitant orifice area (EROA) and 3D regurgitant volume (Rvol) were measured, calculated and compared to conventional 2D EROA and Rvol. We found that the mitral annulus in FMR was enlarged but stiff. Whereas, in patients with BD (n=40), the dimensions and dynamics of the mitral annulus were significantly larger compared with controls and patients with FED (n=52). The annular dynamics were increased in patients with primary MR and particularly in BD. Findings in patients with BD showed: 1) a characteristic late systolic overexpansion of commissural width leading to an exaggerated flattening of the mitral annulus at late systole, 2) 2D analyses underestimated MR when compared with 3D measurements resulting in more severe MR and 3) this was more pronounced in patients with late systolic MR, which only occurred in BD (48%). Furthermore, increased dynamics of the annulus height and AHCWR were significantly associated with the amount of 3D Rvol. The findings of Chapter 2 and 3 both suggest that MR in FED may exclusively be a valvular problem whereas in BD the underlying pathology mainly affects the mitral annulus which is subject to LV forces: the hyper-enhanced LV basal segments together with increased late systolic annular dynamics may cause late systolic MR and thereby a secondary, functional prolapse. This in turn may lead to an increase of shear stress on the mitral valve leaflets resulting in leaflet thickening and elongation. Preserving or restoring mitral annular dynamics is essential for treatment and to prevent MR recurrence. Therefore, implantation of (customized) annuloplasty rings in BD may restore annulus dynamics, while, in FED the addition of a ring is debatable if the mitral annulus is not dilated and the dynamics are normal. Furthermore, better quantification of MR in patients with BD with 3D imaging techniques may result in earlier referral to surgery.

The final two chapters of part I focus on patients with MR undergoing minimally invasive transcatheter mitral valve repair (TMVR) using a MitraClip device (Abbott Vascular, Menlo Park, CA). Surgical mitral valve repair is the first choice in patients with primary MR as it improves prognosis. However, there is no survival benefit in patients with FMR undergoing surgical mitral valve repair, although it is likely to alleviate symptoms. However, the development of LV reverse remodelling (LVRR) varies amongst these patients and its occurrence is associated with improved survival. Furthermore, baseline LV dimensions were reported to be associated with LVRR and prognosis. When surgical risk is high, TMVR may be considered. **Chapter 4** assessed the development of LVRR in patients (n=107, 79% FMR)

undergoing TMVR and whether the occurrence is also associated with improved prognosis. LVRR, defined as a reduction of ≥10% in LV end-diastolic diameter (LVEDD) after 6 months, occurred in 34 (32%) patients. Patients who developed LVRR had a better event free survival (all-cause mortality or cardiovascular hospitalisations). Furthermore, a baseline LVEDD <65mm was independently associated with LVRR and better event-free survival at 3 years of follow-up after TMVR. Therefore, the capability of developing LVRR after TMVR with the MitraClip device is limited by the extent of myocardial wall stress, depicted by LV dilatation, prior to intervention. This is most likely due to the over exhaustion of the Frank-Starling mechanism and extent of myocardial fibrosis. Assessment of baseline LV dilatation, in turn, may improve patient selection for TMVR. In **Chapter 5,** the extent of myocardial wall stress and changes after TMVR is further evaluated using N-terminal pro-brain natriuretic peptide (NT-proBNP) and 2D speckle tracking echocardiography in 65 patients (89% FMR). Little is known about the association between changes in NT-proBNP and changes in LV and LA dimensions and function. Similar to development of LVRR, changes in NT-proBNP after TMVR vary widely. Therefore, patients were divided according to the 6-month NT-proBNP tertiles. In patients who showed a reduction in NT-proBNP, reductions in LA volumes and improvement in LV global longitudinal strain (GLS) and LA strain were observed. In contrast, patients who showed an increase in NT-proBNP exhibited impairment in LV GLS and LA strain suggesting an increase of myocardial wall stress. Most likely, the extent of fibrosis in the LA and LV myocardium is an important determinant for response to TMVR, since in patients with more myocardial fibrosis, relief of myocardial wall stress may not occur. Moreover, the relative increase in the transmitral gradient, caused by the MitraClip device, may impact the LA function which may be severely diseased at baseline. An integrated use of NT-proBNP with LV GLS and LA strain may improve assessment of changes in myocardial wall stress in patients undergoing TMVR. In turn, risk stratification may also be improved.

Part II: The role of advanced echocardiography in the assessment of cardiac involvement in Systemic Sclerosis

In the second part of this thesis, the role of advanced echocardiography, in particular 2D speckle tracking echocardiography, was evaluated in patients with SSc. Clinical manifestation of cardiac involvement in SSc occurs at a late stage of the disease and represents one of the main causes of death. Early detection of myocardial dysfunction and

changes in cardiac performance in SSc patients using conventional echocardiographic techniques has been challenging. In **Chapter 6** changes of LV function, measured by LV GLS, over time in a prospective cohort of 234 patients with SSc (165 limited SSc, median time since diagnosis 5.2 years) were assessed. After a median follow-up of 2.3 years, LV GLS significantly worsened while LV ejection fraction (LVEF) did not change. In particular, 39 patients showed a significant deterioration of LV GLS as defined by a ≥15% decrease, which was accompanied by concomitant worsening of disease activity seen in other organs. Baseline parameters associated with ≥15% deterioration in GLS were proximal muscle weakness, decreased diffusing capacity of carbon monoxide (DLCO) and LV diastolic dysfunction. These parameters may, therefore, identify patients at risk for progressive LV systolic dysfunction and in need of closer cardiac monitoring. Assessment of LV function with 2D speckle tracking echocardiography may lead to better risk stratification and earlier detection of cardiac involvement. To improve risk stratification, **Chapter 7** aimed to identify clinical and echocardiographic parameters, including LV GLS, associated with all-cause mortality and cardiovascular hospitalisation in 408 patients with SSc in a multi-centre setting. After a follow-up of 39 months, the endpoint occurred in 84 patients. LV GLS was found to be independently associated with all-cause mortality and cardiovascular hospitalisations, together with age, DLCO and NT-proBNP. Comparing patients according to median LV GLS and the upper value of normal NT-proBNP, endpoint-free survival was worse in patients with impaired LV GLS *and* elevated NT-proBNP.

Chapters 6 and 7 demonstrate that LV GLS is not only a useful tool for detecting subtle LV myocardial involvement in SSc, but also for identifying patients at higher risk for mortality and cardiovascular events. It may therefore be of use in optimising risk stratification. In particular, an integrative approach using LV GLS and NT-proBNP may improve the detection of cardiac involvement and optimize patient management. Additionally, earlier detection may lead to appropriate therapeutic measures at an earlier stage of the disease.

CONCLUSIONS AND FUTURE PERSPECTIVES

Advancements in medical technology, such as advanced echocardiographic techniques and minimally invasive procedures like TMVR by implanting a MitraClip device (Abbott Vascular, Menlo Park, CA) continue to improve healthcare worldwide. Using 2D speckle tracking echocardiography and 3D echocardiography with dedicated software,

significant differences in mitral annulus dynamics were observed in functional and primary MR (especially between FED and BD). This consequently improved our understanding of pathophysiological differences between FED and BD. Mitral annulus dynamics have important implications for MR quantification. Particularly in patients with BD, 3D echocardiographic techniques for quantification of MR were found to be superior to the conventional 2D techniques. MR assessment with 3D echocardiographic techniques may as a consequence result in earlier referral to surgery. Furthermore, better understanding of mitral annulus dynamics may result in the development of surgical techniques that aim to restore the normal dynamics of the annulus. More research and experience is needed to explore these issues.

To further improve treatment options, TMVR using a MitraClip device has been introduced and is now part of daily practice for patients with significant MR but with high surgical risk. However, evidence of survival benefit remains absent. As seen in surgical patients with FMR, the occurrence of LVRR varies and has an important impact on survival. This thesis supports these findings in patients undergoing TMVR and shows that the development of LVRR is limited by the extent of LV dilatation prior to intervention. It needs to be further explored whether LVEDD may guide clinicians to first try to achieve smaller dimensions or help detect patients in whom TMVR would be futile. Most likely, the extent of fibrosis in the LA and LV myocardium is an important determinant for response. Therefore, this thesis suggests that the response to TMVR and changes in myocardial wall stress may be monitored by an integrated use of NT-proBNP with LV GLS and LA strain. Prospective studies need to explore whether these parameters can further improve risk stratification in patients undergoing TMVR. Furthermore, recent development of several new interventional procedures may further improve outcome and may be taken into account during early decision making. For example, simultaneous direct annuloplasty with for example the Cardioband may be beneficial and needs further investigation.

Primary cardiac involvement in patients with SSc is related with increased mortality. However, timely detection of cardiac involvement in patients with SSc is challenging using conventional echocardiographic parameters such as LVEF. This thesis demonstrates that progression of LV systolic dysfunction over time was detected by LV GLS but not by LVEF. Moreover, progression was correlated with disease activity in other organs at baseline. In

addition, baseline LV GLS was independently associated with all-cause mortality and cardiovascular hospitalisations. This thesis also suggests that an integrative approach using LV GLS and NT-proBNP at baseline may improve detection of cardiac involvement. Whether these findings can be implemented in clinical practice to improve risk stratification, and help identify which patients need closer cardiac monitoring, needs to be further investigated.