Advanced echocardiographic imaging in valvular and systemic diseases

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CHAPTER 1

General introduction and thesis outline

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Mitral regurgitation (MR) is the second most prevalent valve disease in Europe[1]. It can be caused by degenerative changes of the valve apparatus which may lead to excessive motion of the leaflets (primary MR), or secondary to structural abnormalities of the left ventricle (LV) or the left atrium that dilate the mitral valve annulus and restrict the motion of the leaflets in systole causing functional MR (FMR)[2] (Figure 1). Severe MR is associated with increased mortality and morbidity[3].

Figure 1: Carpentier´s Classification of Mitral Regurgitation

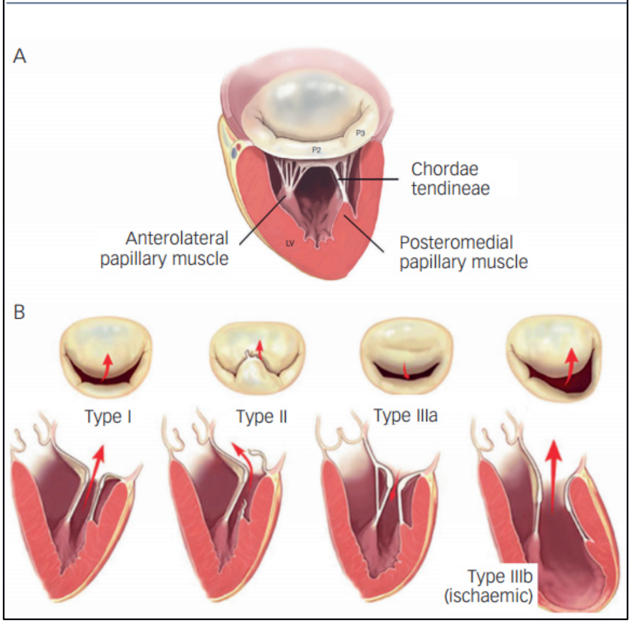

Figure 1. Panel A: *Normal mitral valve anatomy.* ***Panel B*** *Causes of mitral regurgitation according to Carpentier's classification: Type I, Normal leaflet motion with Mitral annulus dilatation or leaflet perforation. Type II, increased leaflet motion due to degenerative mitral valve disease (leaflet prolapse). Type IIIa, restricted motion of leaflets during systole and diastole caused by e.g. rheumatic heart disease or mitral valve calcification. Type IIIb, restricted leaflet motion during systole (restricted leaflet closure) due to a structurally abnormal left ventricle.*
** Modified from Carpentier A, Adams DH, Filsoufi F.* **Carpentier's Reconstructive Valve Surgery. From Valve Analysis to Valve Reconstruction**. *2010 Saunders Elsevier*

Systemic sclerosis (SSc), also known as scleroderma, is a connective tissue disease which is characterised by generalised microangiopathy and fibrosis affecting multiple organs, and is associated with increased mortality[4]. SSc affects women more often than men and occurs most commonly between 30 and 50 years. It is traditionally classified based on the extent of skin involvement (limited to diffuse SSc) and the accompanying pattern of internal organ involvement such as heart, lungs, kidneys and the gastrointestinal tract. Prognosis is determined by the form of the disease and the extent of organ involvement. Death is most often caused by lung, cardiac, or kidney involvement. Cardiac involvement is common in SSc and can occur in up to 70% of patients as reported in autopsy series[5]. Particularly, myocardial fibrosis may lead to diastolic and systolic dysfunction and to conduction abnormalities[6-8]. Once clinically evident, cardiac involvement represents one of the main causes of death in SSc patients[9, 10]. Therefore, identification of cardiac involvement, ideally at a pre-clinical stage, is of crucial importance for optimal patient management.

In both patients with MR and SSc, accurate assessment of size and function of the cardiac structures is essential for diagnosis, risk assessment, therapeutic decision making and follow-up. For these purposes echocardiography is the most important non-invasive imaging modality which is used worldwide in clinical practice. For these echocardiographic assessments a list of conventional parameters, including the biplane Simpson LV ejection fraction (LVEF) as a measure of LV systolic function, are currently recommended[11]. However, these conventional indices have shown inherent variability and lack of sensitivity for subclinical dysfunction cannot be detected. Previous studies have shown preserved LVEF despite subclinical LV systolic dysfunction, measured by global longitudinal strain (GLS), in patients with MR and SSc[12-14]. Another challenging aspect in echocardiography is the saddle shaped mitral apparatus which is a complex 3-dimensional (3D) structure. Accurate evaluation of size, shape and function using 2-dimensional (2D) echocardiography is challenging. Therefore, advanced echocardiographic modalities, such as 4-dimensional (4D) imaging have been developed to provide an anatomically sound display of heart valve geometry and function[15-17]. Also, compared to conventional 2D echocardiography, 3D colour Doppler data allows for more accurate measurements of the effective regurgitant orifice area (EROA) after which the regurgitant volume can be calculated[17].

Two-dimensional speckle tracking echocardiography is an offline technique that measures deformation of the myocardium by tracking 'speckle' artefacts which occur naturally in the myocardial tissue. These speckles are followed in every frame throughout the cardiac cycle which allows us to measure the amount of longitudinal, circumferential and radial shortening and lengthening of the myocardial segments. After offline processing, the relative change in myocardial length is calculated and presented as a percentage, strain, which accurately reflects myocardial contraction. The LV systolic function is depicted as global longitudinal strain (GLS) which is the average of the peak longitudinal strain values of 17 segments displayed in a bulls-eye plot (Figure 2).

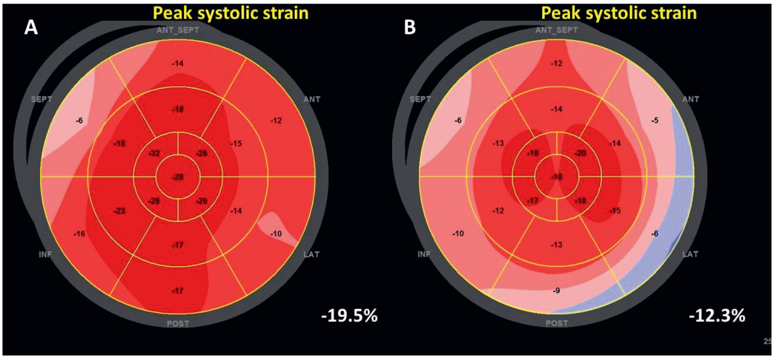

Figure 2. *Bulls eye plots of a patient with preserved left ventricular (LV) global longitudinal strain (GLS) in panel* ***A*** *and impaired LV GLS in panel* ***B***

Using 3-dimensional (3D) echocardiography, customized software has been developed to obtain not only static measurements but also a dynamic assessment of the mitral valve apparatus geometry throughout the cardiac cycle. The software semi-automatically tracks placed landmarks in all frames during the cardiac cycle in order to create a dynamic 4D mitral model. After processing, the software provides several measurements of the mitral valve geometry at any point in the cardiac cycle and the extentof saddle shape is calculated by the annulus height to commissural width ratio (AHCWR) (Figure 3).

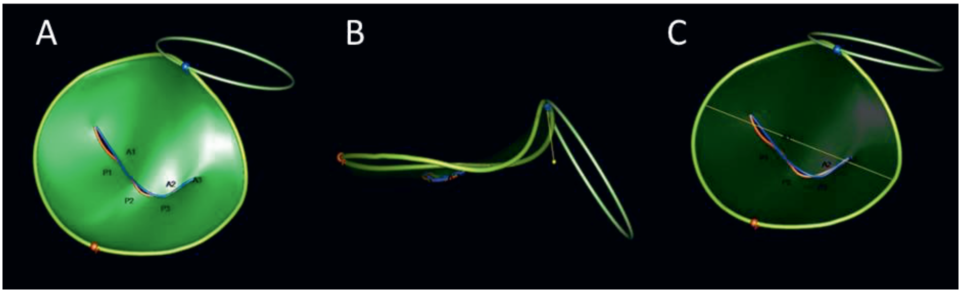

Figure 3. *Examples of 3D reconstruction of a mitral valve annulus, A depicting the annulus area with its six scallops and coaptation lines of the mitral valve leaflets, B depicting the measurement of annulus height, C shows the commissural width*.

Mitral regurgitation, aetiology and implementation of advanced echocardiography

Mitral regurgitation may be primarily due to abnormalities of mitral valve apparatus (primary MR) or secondary to structural abnormalities of the LV, caused by e.g. coronary artery disease or dilated cardiomyopathy, that restrict the motion of the leaflets causing functional MR (FMR) [2]. Primary MR is most commonly caused by degenerative mitral valve disease and encompasses a spectrum from fibroelastic deficiency (FED) to Barlow's disease (BD). FED is defined as a single-segment prolapse and is characterized by thin leaflet tissue or limited thickening and a ruptured chord and is seen primarily in older people. BD is characterized by large and thickened leaflets, with excessive tissue and elongated and frequently ruptured chords and occurs more often in younger patients[18] (Figure 4)**.** Studies have mainly focused on the excessive leaflet motion in primary MR and the mechanisms of leaflet malcoaptation. However, as clinical presentations differ between FED and BD, it remains unclear whether they are part of a spectrum or different phenotypes with distinctly different disease processes. It has been suggested that in BD the underlying pathology affects the mitral annulus, which is subject to LV forces, leading to annular dilatation, mitral annular disjunction and the systolic outward motion of the annulus. This in turn may lead to an increase of shear stress on the mitral valve leaflets resulting in leaflet thickening and elongation of the leaflets and chords[19-21]. Furthermore, in primary MR the mitral valve annulus has shown to be more flexible and dynamic whereas in FMR the annulus is more rigid with structural and functionally normal valves[20, 22-24]. The impact of pathological mitral annular dynamics per aetiology on MR quantification has not yet been sufficiently studied.

Using 2D speckle tracking echocardiography for regional wall assessment and 3D echocardiography with 4D mitral valve assessment, these dynamical differences can be observed per aetiology and can be of assistance in optimising surgical mitral valve repair. Studies have shown that the saddle shape configuration of the mitral valve annulus relieves shear stress on the mitral valve apparatus during systole[25]. Therefore, maintaining this saddle shape with an annuloplasty ring or band may delay recurrence of MR[26, 27]. There are various types of annuloplasty rings and bands which each have their own characteristics, such as in rigidity or flexibility, maintaining the saddle shape and its dynamics[27].

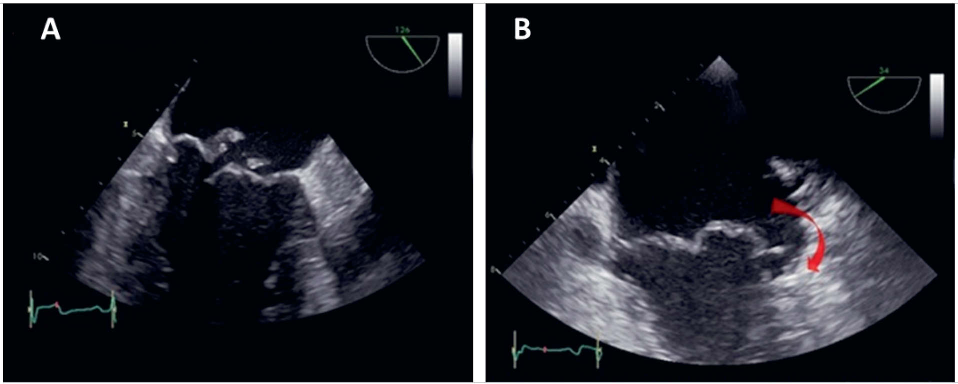

Figure 4. *Transoesophageal echocardiographic views of in* ***panel A:*** *a patient with fibroelastic deficiency (FED) with flail of the posterior mitral valve leaflet and in* ***panel B*** *a patient with Barlow's disease (BD) with bi-leaflet mitral valve billowing and systolic mitral annular disjunction (red arrow).*

Mitral valve surgery improves prognosis significantly in patients with primary MR, however, there is no conclusive evidence for a survival benefit, with such an intervention, in patients with FMR [28]. Studies on valvular surgery in FMR have mainly shown to alleviate symptoms. However, studies have shown that the development of LV reverse remodelling (LVRR) after surgery has shown to benefit survival in FMR patients, but the occurrence of LVRR varies widely amongst these patients[29]. Mitral valve surgery is recommended in patients with severe FMR with an indication for CABG and may be considered in patients who continue to be symptomatic despite optimal medical therapy (including cardiac resynchronization therapy, CRT) or who have a low surgical risk when revascularization is not indicated[3]. However, when surgical risk is high, transcatheter mitral valve repair (TMVR) using a MitraClip device (Abbott Vascular, Menlo Park, CA) may be considered to improve symptoms, functional capacity and quality of life[30]. TMVR may induce hemodynamic unloading and LVRR with a significant reduction of both LV and left atrial (LA) volumes, however, changes in LV systolic function measured by LVEF varies[31, 32]. It is therefore important to determine which baseline parameters are associated with a beneficial response to TMVR which may in turn improve patient selection. Conventional echocardiographic parameters such as LVEF and LV or LA dimensions may not be sensitive enough to reflect myocardial dysfunction. Assessment using 2D speckle tracking strain has been shown to reflect LV myocardial fibrosis in heart failure patients and impaired LV systolic function than LVEF in patients with MR[6, 33-35]. Therefore, assessment of myocardial function with 2D speckle tracking strain may be a valuable tool to characterize the changes in LV and LA function in patients treated with MitraClip.

Systemic Sclerosis and the role of advanced echocardiography

Several multi-centre studies have shown that cardiac involvement is one of the most important causes of morbidity and mortality in SSc patients[9, 36]. Furthermore, the risk of developing cardiovascular disease has been shown to be significantly higher in SSc patients as compared to the general population[37]. The incidence of cardiovascular disease is increasing in this population as SSc patients are less likely to die of SSc-specific complications because of improvements in the treatment of renal disease and pulmonary hypertension[37]. Detection of cardiac involvement at an early stage remains challenging however[12, 38]. Recommendations are usually based on clinical symptoms or conventional echocardiography. Cardiac involvement is frequently described as the presence of arrhythmias and/or LV dysfunction, and/or pericardial effusion [12, 39-41]. Particularly, LV diastolic dysfunction is often observed in SSc patients, even at a young age[7, 39-41]. However, impaired LV systolic function, as measured by conventional LVEF, is not frequently observed in SSc patients. This is mainly due to the low sensitivity of the currently practiced techniques for detecting subtle myocardial systolic dysfunction[38]. It has been demonstrated that advanced 2D speckle tracking echocardiographic analysis is more sensitive in the detection of LV systolic dysfunction. Little is known about when LV systolic dysfunction may occur or how it may progress since we lack sequential echocardiographic studies. LV systolic dysfunction is more prevalent than initially described and is associated with reduced functional capacity and diffusing capacity of carbon monoxide (DLCO%)[12.]. Identification of patients at high risk for cardiovascular events is challenging due to the heterogeneous clinical presentation and prognosis of SSc. Risk stratification tools, specifically for cardiovascular outcomes, are limited and mainly include LVEF measurements, pulmonary artery pressure estimations and heart failure symptoms. However, an impaired LVEF and development of heart failure symptoms represent an advanced stage of cardiac involvement. Risk stratification should ideally help identify patients at an earlier stage of the disease in which timely treatment can change the course and prognosis. Therefore, novel cardiac-specific prognostic markers are needed to improve risk stratification. 2D speckle tracking echocardiography is a promising tool to improve detection of LV systolic dysfunction in SSc patients to further improve risk stratification.

Aim and outline of thesis

The aim of this thesis is to provide new insights in diagnosis, disease progression and risk stratification in patients with primary cardiac disease, resulting in MR, and secondary cardiac disease caused by SSc by the implementation of advanced echocardiographic techniques.

Part 1 of this thesis focusses on the utility of advanced echocardiography for the understanding of disease processes, and risk stratification in patients with primary MR and FMR. In **Chapter 2**, the differences of tracking differences of regional LV wall contractility between patients with FED and BD using advanced 2D speckle tracking echocardiography are explored. In **Chapter 3** the differences of mitral valve annulus dynamics between FED, BD and FM and its impact on MR quantification using 3D echocardiography and 4D mitral valve assessment software are further investigated. In **Chapter 4** of this thesis conventional LV dimension as a parameter for further risk stratification in patients undergoing TMVR is assessed. **Chapter 5** further explores the hemodynamic effects of TMVR on LV and LA function and wall stress using 2D speckle tracking echocardiography and its association with N-terminal pro-brain natriuretic peptide (NT-proBNP).

Part 2 focusses on the use of 2D speckle tracking echocardiography to improve diagnosis of LV systolic dysfunction and risk stratification in patients with SSc. **Chapter 6** assesses LV systolic function over time measured by 2D speckle tracking echocardiography in patients with SSc. **Chapter 7** explores the association of clinical and echocardiographic parameters with all-cause mortality and cardiovascular outcomes in patients with SSc.

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