Aortic valve disease: multimodality imaging for risk stratification and evaluation of therapy

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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

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INTRODUCTION

AORTIC valve disease, i.e., aortic stenosis (AS) and aortic regurgitation (AR), is the most common cause of native valvular heart disease and a major cause of cardiovascular morbidity and mortality [1, 2]. Recently, the EURObservational Research Programme Valvular Heart Disease II survey [3] showed that AS was present in 41% of patients referred with severe native valvular heart disease. Aortic regurgitation was present in 5% of patients. Importantly, aortic valve disease was shown to be of a predominantly degenerative pathogenesis (>90% in AS and >40% in AR, respectively) [3]. Therefore, with the increasing age of the general population worldwide, aortic valve disease will become a more prevalent health issue.

Both AS and AR are regarded as diseases of the aortic valve and the left ventricle (LV), but differ in pathophysiology. In AS, only a pressure overload is imposed on the LV, while AR induces both a pressure and volume overload. These abnormal hemodynamic states induce different LV remodelling responses in order to normalize wall stress: eccentric remodelling and LV dilatation occur in AR due to growth of cardiomyocytes and addition of new sarcomeres in series, and concentric hypertrophy is seen in AS due to increased diameter of muscle fibers and parallel addition of myofibrils (Figure 1) [4]. However, in both valvular diseases, overload conditions may cause irreversible formation of myocar-

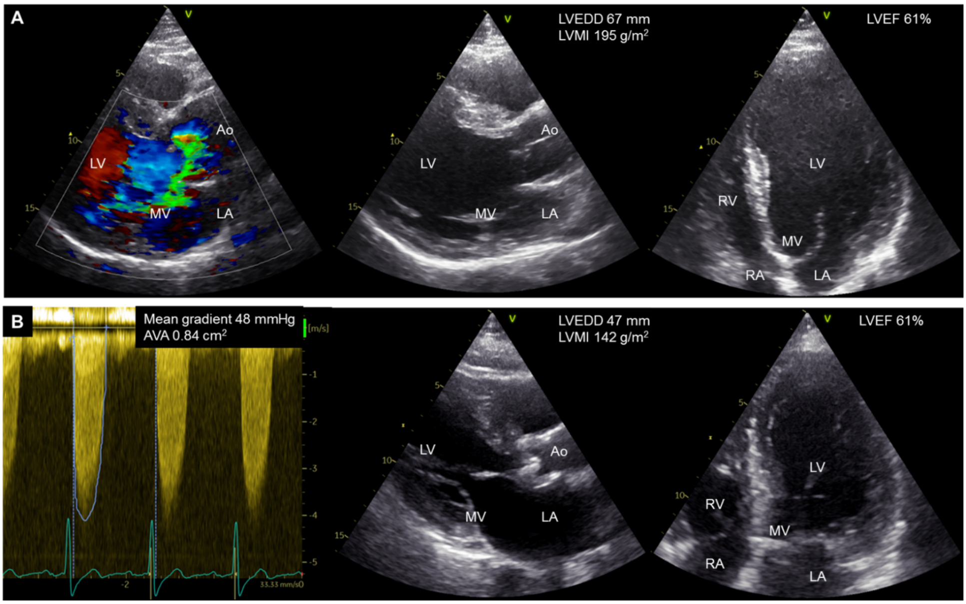

Figure 1: Examples of the differences in left ventricular (LV) remodelling in AR vs. AS. In this patient with severe AR (*panel A*), an eccentric aortic regurgitant jet towards the mitral valve is observed. Due to the volume overload by AR, eccentric remodelling with LV dilatation occurs. In this patient with severe AS (*panel B*), the pressure and volume overload imposed by the stenotic aortic valve results in concentric hypertrophy. Ao, aorta; AR, aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MV, mitral valve; RA, right atrium; RV, right ventricle.

dial fibrosis which may result in LV dysfunction [4, 5].

Aortic valve intervention is the only effective treatment for severe AS and severe AR and is indicated in patients presenting with symptoms due to the valvular disease or when LV dysfunction is present [6]. In addition, in AR, the presence of severe dilation (i.e., aneurysm) of the aortic root and/or ascending aorta may be the underlying pathophysiological mechanism of AR and may form the primary indication for aortic valve intervention. For AS, surgical aortic valve replacement (AVR) is recommended for patient with low surgical risk and absence of surgical risk factors (e.g., frailty). In patients unsuitable for surgical AVR, transcatheter aortic valve implantation (TAVI) may be considered after assessment by the Heart Team [6]. In AR, aortic valve repair may be a feasible alternative for AVR in selected patients [6]. Significant mortality has been reported in severe AS and severe AR patients who remain untreated. For AS, a recent study reported a 5-year mortality of 67% in these patients [7]. Similarly, a recent study of severe chronic AR patients with preserved LV ejection fraction observed a 10-year mortality of 29% for patients who remained untreated vs. 13% for patients undergoing aortic valve surgery ($P<0.001$) [8].

Correct assessment of AS and AR severity and careful risk evaluation are crucial for the proper selection of patients and timing of AVR. Multimodality imaging, particularly echocardiography and multi-detector row computed tomography, is of paramount importance herein.

Multimodality imaging in risk stratification and timing of intervention

For the assessment of AS and AR severity and aortic valve morphology (i.e., tricuspid vs. bicuspid), two-dimensional and Doppler transthoracic echocardiography is the imaging technique of first choice. It also provides information on LV dimensions and function and associated conditions such as pulmonary hypertension.

Severity of AS is determined by several hemodynamic parameters using the continuity equation: peak aortic jet velocity, (indexed) aortic valve area (AVA) and transvalvular pressure gradient (Table 1) [9]. Low-gradient severe AS, defined by an AVA <1.0 m^2 and a mean gradient <40 mmHg, is seen in approximately one third of patients with severe AS and more frequently in those with low flow due to LV dysfunction. Low-dose dobutamine stress echocardiography can be utilized to discern true severe AS from pseudosevere AS in these patients. Alternatively, the presence of a high aortic valve calcification burden as detected by aortic valve calcium scoring using computed tomography may be of ad-

Table 1: Diagnostic criteria for severity of aortic stenosis.

	Aortic sclerosis	Mild AS	Moderate AS	Severe AS
Peak velocity (m/s)	≤2.5	2.6-2.9	3.0-4.0	≥4.0
Mean gradient (mmHg)	-	<20	20-40	≥40
AVA (cm^2)	-	>1.5	1.0-1.5	<1.0
Indexed AVA (cm^2/m^2)	-	>0.85	0.60-0.85	<0.6

AS, aortic stenosis; AVA, aortic valve area.

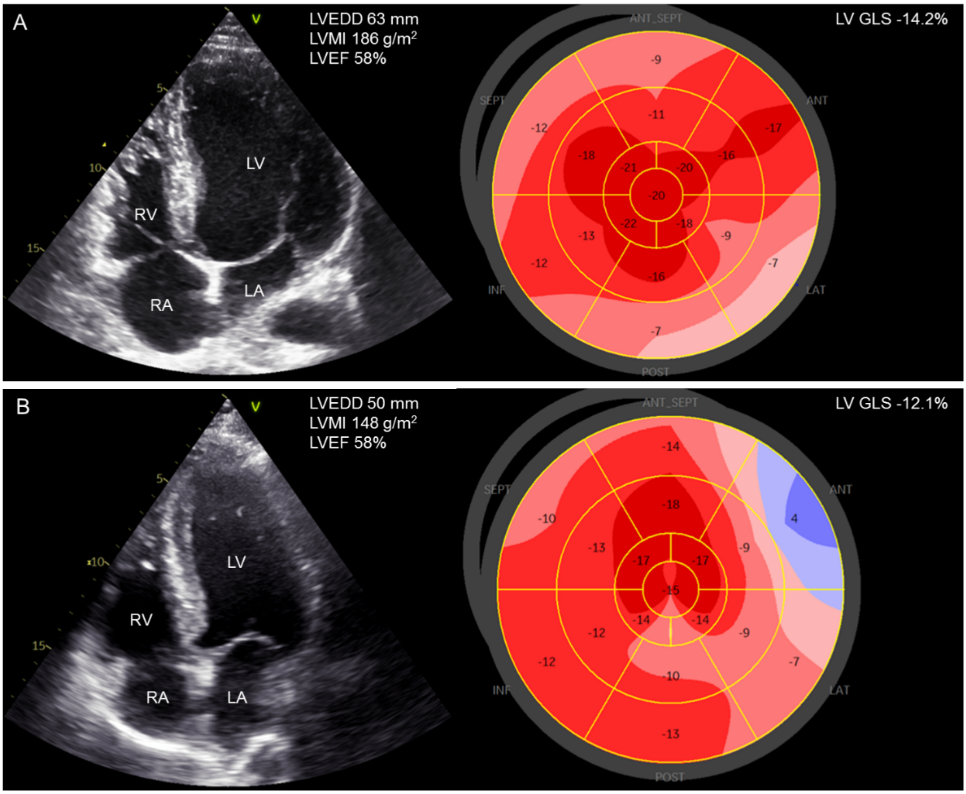

Figure 2: Examples of a patient with severe AR (*panel A*) and of a patient with severe AS (*panel B*) with preserved LVEF but impaired LV GLS, suggesting the presence of subclinical myocardial dysfunction. AR, aortic regurgitation; AS, aortic stenosis; GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MV, mitral valve; RA, right atrium; RV, right ventricle.

ditional value in the identification of true severe AS (as compared to moderate AS) in low-gradient AS patients [10–12]. For AR, severity is assessed using a multi-parametric approach including qualitative and (semi-)quantitative parameters (Table 2) [13].

Assessment of LV function is paramount in the selection of patients for AVR and timing of intervention, as LV dysfunction (defined as LV ejection fraction [EF] <50%) is a class I indication for aortic valve intervention in both AS and AR [6]. However, subclinical myocardial dysfunction may be present in patients with preserved LVEF and can be detected by the assessment of LV global longitudinal strain (GLS) using speckle tracking echocardiography (Figure 2) [14]. Impaired LV GLS in patients with preserved LVEF has been associated with worse prognosis in both AS [15] and AR [16]. The role of LV GLS in asymptomatic severe AS and its implications for timing of intervention has not yet been elucidated.

Recent studies have shown a high prevalence of mitral and tricuspid regurgitation (13 to 20% and 11 to 27%, respectively) [17–19], pulmonary hypertension (10 to 36%)

Table 2: Diagnostic criteria for severity of aortic regurgitation.

Parameters	**Severity of paravalvular regurgitation**		
	Mild	**Moderate**	**Severe**
Qualitative			
Aortic valve morphology	Normal/abnormal	Normal/abnormal	Abnormal/flail/ large coaptation defect
Colour flow AR jet width	Small in central jets	Intermediate	Large in central jet, variable in eccentric jets
CW signal of AR jet	Incomplete/faint	Dense	Dense
Diastolic flow reversal in descending aorta	Brief, protodiastolic flow reversal	Intermediate	Holodiastolic flow reversal (end-diastolic velocity >20 cm/s)
Diastolic flow reversal in abdominal aorta	Absent	Absent	Present
Semi-quantitative			
VC width (mm)	<3	Intermediate	≥6
Pressure half-time (ms)	>500	Intermediate	<200
Quantitative			
EROA (mm^2)	<10	10-19; 20-29*	≥30
Regurgitant volume (ml)	<30	30-44; 45-59*	≥60

AR, aortic regurgitation; CW, continuous wave; EROA, effective regurgitant orifice area; VC, vena contracta.
*Subclassification of moderate AR in “mild-to-moderate” (EROA of 10-19 mm^2 or regurgitant volume of 30-44 ml) and “moderate-to-severe” (EROA of 20-29 mm^2 or regurgitant volume of 45-59 ml).

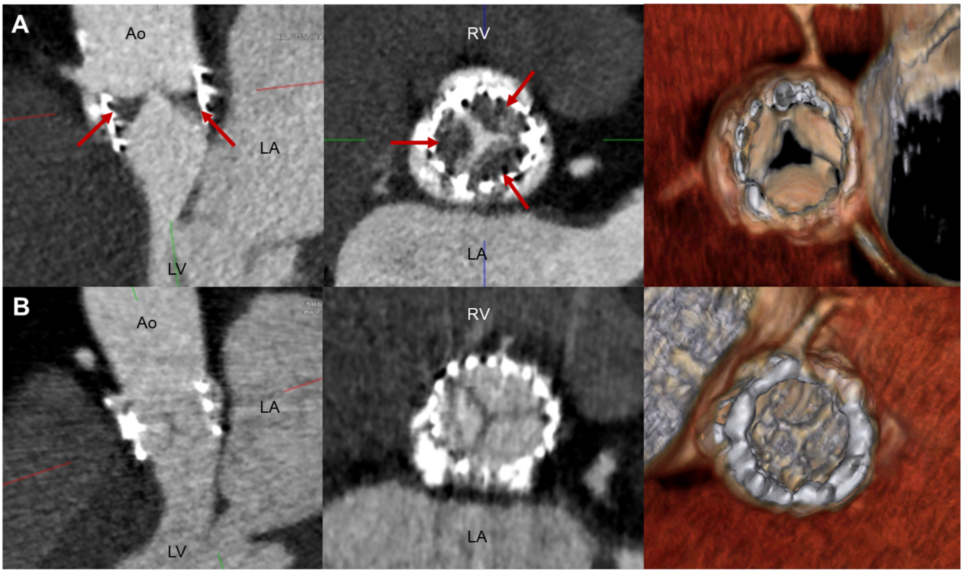

Figure 3: Four-dimensional multidetector row computed tomography reconstructions after TAVI of a patient with hypo-attenuated leaflet thickening (HALT) with reduced leaflet mobility (*panel A*) and of a patient without HALT (*panel B*). The red arrows depict the hypo-attenuated lesions suggestive of the presence of subclinical leaflet thrombosis. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle; TAVI, transcatheter aortic valve implantation.

[20, 21] and RV dysfunction (24 to 29%) [22, 23] in severe AS patients. The presence of these markers of cardiac injury, as categorized in a novel proposed staging classification, have been reported to have a significant prognostic impact in this patient population [24]. Therefore, echocardiography can provide important information for further risk stratification by identification of these markers of cardiac damage. Improvement of this staging classification by incorporation of advanced imaging parameters, e.g., LV GLS, may provide further refinement of risk stratification in severe AS patients.

MULTIMODALITY IMAGING IN THE EVALUATION OF THERAPY

For the evaluation of therapy, multi-modality imaging plays a pivotal role. Echocardiography is the mainstay imaging modality for the evaluation of prosthesis function and durability after surgical AVR or TAVI and for the detection of potential late complications. It may also be used to evaluate LV function (i.e., using LVEF or LV GLS) and regression of LV hypertrophy after intervention.

Recently, multi-detector row computed tomography has been used to detect hypo-attenuated leaflet thickening (HALT) with or without reduced leaflet motion after TAVI, which may suggest subclinical leaflet thrombosis in the absence of symptoms and increased transprosthetic gradients (Figure 3) [25–27]. The prevalence of HALT and its clinical implications remain unclear.

Outline of the thesis

The objective of this thesis was to evaluate the role of multimodality imaging, in particular two-dimensional (speckle tracking) echocardiography and multi-detector row computed tomography, in risk stratification and evaluation of therapy in patients with aortic valve disease, specifically AS.

In **Part I**, the role of conventional echocardiography and LV GLS measured by speckle tracking echocardiography is evaluated for patient selection and risk stratification in AS. In Chapter 2, the prevalence and prognostic impact of the presence of extra-aortic valvular cardiac injury assessed by conventional echocardiography and categorized according to a newly proposed staging classification is investigated in symptomatic severe AS patients. Chapter 3 evaluates the incremental prognostic value of LV GLS over proposed stages of cardiac damage in symptomatic severe AS patients. Chapter 4 describes the prevalence of impaired LV GLS, the time course of LV GLS and its prognostic implications in asymptomatic severe AS with preserved LV ejection fraction. In Chapter 5, the prevalence and prognostic impact of renal dysfunction in patients with aortic sclerosis and patients with mild to severe AS is assessed. Chapter 6 discusses the role of multi-detector row computed tomography in the evaluation of aortic valve calcification for the identification of patients with true severe AS among those with low-gradient AS.

Part II focusses on the role of echocardiography and multi-detector row computed tomography in the evaluation of therapy, particularly follow-up after surgical and transcatheter AVR. Chapter 7 provides an overview of the clinical applications and current role of echocardiography in the patient selection, prosthesis sizing, periprocedural guidance and post-procedural follow-up in TAVR. In Chapter 8, the prevalence of hypo-attenuated leaflet thickening after TAVR is evaluated using multi-detector row computed tomography and its association with abnormal valve hemodynamics on echocardiography and occurrence of ischemic stroke and/or transient ischemic attack is studied. Chapter 9 characterizes and compares the time course of LV mass index and LV mechanics as assessed by LV GLS in patients with AS vs. patients with AR after aortic valve surgery.

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