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

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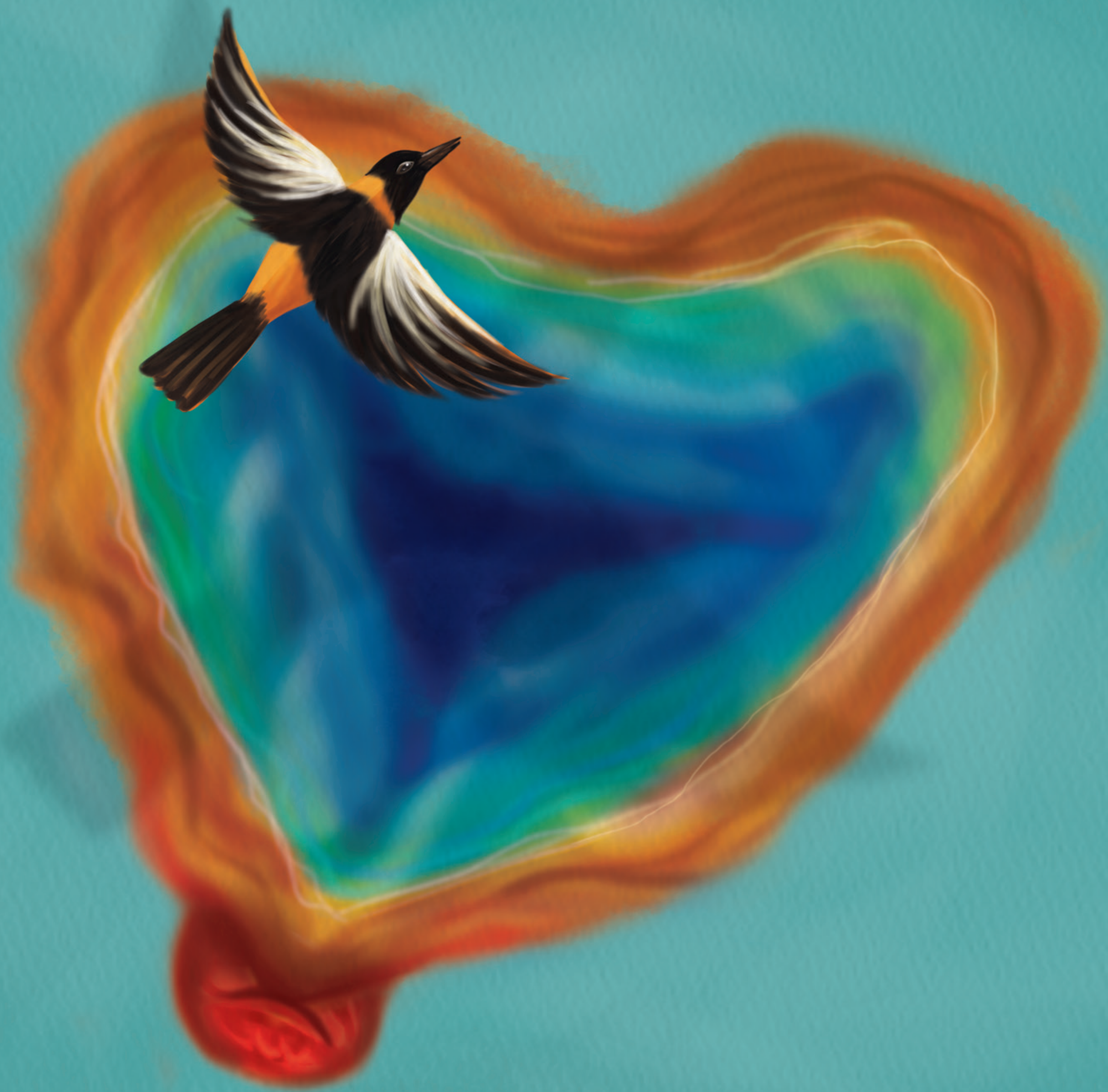

Part III

SUMMARY & APPENDICES

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SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

Summary

The general introduction of this thesis (Chapter 1) outlines the epidemiology of aortic valve disease in the developed countries and describes the differences in pathophysiology between aortic stenosis (AS) and aortic regurgitation (AR). In both valvular diseases, aortic valve intervention is indicated when patients are symptomatic or show signs of left ventricular (LV) dysfunction (defined as a LV ejection fraction [EF] <50%). Conventional two-dimensional and Doppler transthoracic echocardiography is the imaging modality of first choice for the correct assessment of severity of aortic stenosis or regurgitation, LV function and preprocedural risk stratification and is also the main imaging technique for the evaluation of therapy results. The additional value of multidetector row computed tomography (MDCT) in the evaluation of AS severity and subclinical leaflet thrombosis after transcatheter aortic valve implantation (TAVI) is introduced. The role of speckle tracking echocardiography for the assessment of LV global longitudinal strain (GLS), particularly in patients with aortic valve disease with preserved LVEF, is described. The current thesis aims at evaluating the role of multimodality imaging, in particular two-dimensional (speckle tracking) echocardiography and MDCT, in the risk stratification and evaluation of therapy in patients with aortic valve disease.

Part I: Risk stratification and timing of intervention

In the first part of this thesis, the role of conventional and speckle tracking echocardiography in risk stratification and timing of aortic valve intervention in severe AS patients is explored. Also, the role of MDCT for the assessment of aortic valve calcium load is introduced.

In severe AS patients, signs of extra-aortic valvular injury are often observed and can be classified according to a newly proposed staging classification. In Chapter 2, the prevalence of the different stages of extra-aortic valvular cardiac damage as assessed by echocardiography and its impact on prognosis are evaluated in a large real-world multicenter cohort of symptomatic severe AS patients. Patients were classified as Stage 0 (no cardiac damage), Stage 1 (LV damage), Stage 2 (mitral valve or left atrial damage), Stage 3 (tricuspid valve or pulmonary artery vasculature damage), or Stage 4 (right ventricular (RV) damage). On the basis of the proposed classification, 8% of patients were classified as Stage 0, 24% as Stage 1, 49% as Stage 2, 7% as Stage 3, and 12% as Stage 4. After correcting for clinically relevant variables (e.g., aortic valve replacement), cardiac damage was independently associated with all-cause mortality and the combined outcome (i.e., all-cause mortality, stroke, and cardiac-related hospitalization). However, this seemed to be predominantly driven by tricuspid valve or pulmonary artery vasculature damage (Stage 3) and RV dysfunction (Stage 4).

Cardiac damage as classified by a recently proposed staging classification has been shown to be strongly associated with prognosis in severe AS patients. LV GLS has also been demonstrated to be independently associated with outcome in severe AS patients with both preserved and impaired LVEF. In Chapter 3, the prognostic implications of the incorporation of LV GLS into this staging system are evaluated and the incremental prognostic value of LV GLS over the staging classification algorithm is investigated for a large population of symptomatic patients with severe AS. Patients were classified into five independent stages of cardiac damage and LV GLS was divided by quintiles and assigned to these different stages of cardiac damage. According to the original staging classification, 9% of patients had no signs of cardiac damage (Stage 0), 27% had LV damage (Stage 1), 45% had left atrial or mitral valve damage (Stage 2), 6% had pulmonary vasculature or tricuspid valve damage (Stage 3) and 13% had RV damage (Stage 4). Patients were reclassified by taking into account LV GLS: 4% of patients were categorized as Stage 0, 15% as Stage 1, 37% as Stage 2, 19% as Stage 3 and 25% as Stage 4. LV GLS was associated with all-cause mortality independent of stage of cardiac damage. After incorporation of LV GLS by quintiles into the staging classification, Stages 2 to 4 were independently associated with outcome. LV GLS showed incremental prognostic value over clinical characteristics and the originally proposed staging classification. Incorporation of LV GLS into a novel proposed staging classification resulted in refinement of risk stratification by identifying patients with more advanced cardiac damage.

In asymptomatic severe AS patients, aortic valve intervention is indicated if LV dysfunction (i.e., LVEF <50%) is present. In asymptomatic AS patients with preserved LVEF, the optimal timing to operate remains controversial. LV GLS has been proposed as a marker for subclinical myocardial dysfunction and may help to identify patients who might benefit from undergoing earlier aortic valve replacement. In Chapter 4, the prevalence of impaired LV GLS (defined as LV GLS >-18.2% based on the median value of the population), its natural course and the association of impaired LV GLS with symptom development and need for aortic valve intervention are assessed in a multicenter cohort of asymptomatic patients with severe AS with preserved LVEF. Despite comparable LVEF, LV GLS was significantly impaired in patients with asymptomatic severe AS compared with age- and sex-matched controls without AS. During follow-up, LV GLS significantly deteriorated while LVEF remained unchanged. Patients with impaired LV GLS at baseline (>-18.2%) showed a higher risk for developing symptoms and needing aortic valve intervention at follow-up compared with patients with more preserved LV GLS (≤-18.2%).

Renal dysfunction is a prevalent comorbidity in severe AS patients and has a negative influence on prognosis. However, the influence of renal dysfunction on the prognosis of patients with various grades of AS has not been extensively described. In Chapter 5, a large population of patients with aortic sclerosis and mild to severe AS is divided according to renal function by estimated glomerular filtration rate (eGFR) and the prognostic impact of renal dysfunction (i.e., eGFR <60 ml/min/1.73 m^2) is evaluated. In total, 28% of patients had aortic sclerosis, 7% had mild AS, 24% had moderate AS, and 41% had severe AS. Renal dysfunction was present in 37% of patients, and moderate to severe AS was observed more often in these patients compared to patients without renal dysfunction (70 vs. 62%, respectively). Severely impaired renal function (eGFR <30 ml/min/1.73 m^2) and aortic valve replacement (AVR) were independently associated with all-cause mortality after correcting for AS severity. Independent of renal function, AVR was associated with improved survival.

In the majority of patients with severe AS, a combination of high transvalvular gradients and a small aortic valve area is present. However, in up to 30% of patients with severe AS, a small aortic valve area is measured in the presence of low transvalvular gradients. In these low-gradient AS patients, discerning true severe AS (caused by degenerative calcification of the aortic valve) from pseudosevere AS (caused by a dysfunctional LV generating inadequate stroke volume) can be challenging. Assessment of the morphology and calcification burden of the aortic valve can help to identify the patients with true severe AS who may benefit from intervention. In Chapter 6, the role of computed tomography for the assessment of aortic valve calcium scoring as evaluated by a recent study is discussed and questioned.

Part II: Evaluation of therapy

The second part of this thesis focusses on the role of conventional and advanced echocardiography and MDCT in the evaluation of therapy in aortic valve disease, in particular follow-up after surgical aortic valve replacement or TAVI.

Echocardiography plays a crucial role in all steps of the TAVI procedure: proper selection of both patient and prosthesis, procedural guidance and follow-up of prosthesis performance. In Chapter 7, an overview of the clinical applications and current role of echocardiographic techniques in patient selection, prosthesis sizing, periprocedural guidance and post-procedural follow-up in TAVI is provided.

The presence of hypo-attenuated leaflet thickening (HALT) and/or reduced leaflet motion by MDCT has been proposed as a possible marker for early transcatheter aortic valve thrombosis. However, its association with abnormal valve hemodynamics on echocardiography (another potential marker of thrombosis) and clinical outcomes (i.e., stroke/transient ischemic attack [TIA]) remains unclear. In Chapter 8, the presence of HALT and/or reduced leaflet motion is assessed using MDCT and transcatheter valve hemodynamics are assessed by echocardiography in severe AS patients undergoing TAVI. On MDCT, 12.5% of patients showed HALT and/or reduced leaflet motion, whereas only one of these patients had abnormal valve hemodynamics on echocardiography. Neither HALT nor increased transvalvular gradient were associated with stroke or TIA.

Pressure overload in AS and both pressure and volume overload in AR induce concentric and eccentric LV hypertrophy, respectively. These structural changes influence LV mechanics, but little is known about the time course of LV remodelling and mechanics after aortic valve surgery and its differences in AS vs. AR. In Chapter 9, the time course of LV mass regression and changes in LV mechanics (by LV GLS) in patients with severe AS (63%) or severe AR (37%) undergoing aortic valve intervention are characterized and compared. LV mass regression and changes in LV GLS were similar despite different LV remodelling before aortic valve intervention. In AR, relief of volume overload led to reduction in LV mass and an initial decline in LV GLS. In contrast, relief of pressure overload in AS was characterized by a stable LV GLS and more sustained LV mass regression.

Conclusions and future perspectives

With the rising global health burden of aortic valve disease, growing awareness of the consequences of severe AS (mainly on LV myocardium and outcomes) and the need of intervention with current available interventions (surgical or transcatheter aortic valve replacement) at an earlier stage of the disease, the number of patients who will be referred for aortic valve replacement is expected to increase. The evidence of the efficacy of TAVI in lower risk and potentially even asymptomatic patients is currently being evaluated and multimodality imaging remains of paramount importance for proper patient selection for intervention, determining optimal timing of intervention and in the evaluation of therapy results.

For risk stratification and defining optimal timing of intervention, conventional and advanced echocardiography and computed tomography are crucial. Conventional echocardiography can be used to assess extra-aortic valvular cardiac damage in patients with severe AS. Especially the presence of tricuspid regurgitation or pulmonary hypertension and RV dysfunction showed a significant impact on prognosis. These components of advanced cardiac injury are generally not included in current risk prediction models, and therefore, prospective studies will need to evaluate whether incorporation of these aspects in future risk models will result in improved risk stratification. On top of conventional echocardiography, advanced echocardiography can provide additional insights. Left ventricular GLS by speckle tracking echocardiography has been suggested as a more sensitive marker of LV systolic dysfunction. In patients with asymptomatic severe AS and preserved LVEF, LV GLS declined over time while LVEF remained unchanged. Furthermore, impaired LV GLS was associated with symptom development and need for intervention. Therefore, LV GLS may be of help to define more optimal timing of intervention in asymptomatic patients with severe AS, before irreversible myocardial damage occurs. However, prospective studies are needed to determine the exact role of LV GLS in timing of intervention and to define potential cut-off values. In symptomatic severe AS patients, LV GLS had an incremental value on top of conventional echocardiographic parameters for the assessment of cardiac injury. Incorporation of LV GLS into a recently proposed staging classification for cardiac damage resulted in the identification of patients with more advanced cardiac damage compared to the original classification. Therefore, implementation of LV GLS in current risk prediction algorithms may provide better preprocedural risk assessment, although this needs to be confirmed in future studies. Computed tomography can be used for the quantification of aortic valve calcification (CT-AVC) in patients with low-gradient severe AS, identifying patients with true severe AS who might benefit from aortic valve intervention. Current and future randomized controlled trials will determine if CT-AVC may aid in decision making of these patients.

For the evaluation of prothesis function and durability after aortic valve implantation and detection of possible (late) complications, echocardiography is the mainstay imaging modality. Also, both conventional and advanced echocardiography can provide additional information on the effects of therapy on LV function and remodelling. Due to its high spatial resolution, computed tomography has emerged as a valuable modality to detect subclinical valve thrombosis after TAVI. HALT and/or reduced leaflet motion after TAVI was seen in 12.5% of patients. These patients showed slightly higher echocardiographic transvalvular gradients compared to patients without HALT, but this was not associated with stroke or TIA. However, the use of anticoagulation has been shown to restore the normal leaflet aspect and motion in patients who presented with HALT and it could be considered to perform computed tomography in these patients for early detection of these structural changes. Therefore, future clinical trials are needed to define specific recommendations for the use of computed tomography in post-TAVI follow-up and to determine optimal anticoagulation management in patients treated with TAVI.