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Chapter 1

General Introduction and Outline of the Thesis
Structural heart disease comprises a spectrum of non-coronary based cardiac pathologies, including valvular heart disease and primary hypertrophic cardiomyopathy (HCM). Valvular heart disease involves myopathy secondary to pressure loading (e.g. aortic stenosis) or volume loading (e.g. mitral regurgitation). In primary HCM the myocardium is primarily affected by mutation of sarcomeric protein encoding genes. Both forms of structural heart disease are characterized by structural and functional myocardial changes that ultimately impose a risk of arrhythmia, heart failure and (sudden) death, if left untreated.\textsuperscript{1, 2} Thorough risk stratification has therefore become mainstay for decision making concerning the need, timing, and type of therapeutic interventions. In addition adequate patient selection is crucial as these interventions tend to become less invasive, including transcatheter approaches. In this regard, the myriad of non-invasive cardiac imaging modalities and techniques, as well as clinical surrogates, provides unique opportunities for risk stratification and patient selection.

Due to its wide availability, versatility and non-invasive nature, echocardiography remains the first line modality for risk stratification and patient selection for transcatheter therapies. 3-Dimensional (3D) echocardiography offers superior valvular anatomical and structural information compared to 2-dimensional echocardiography and its accuracy to quantify left ventricular ejection fraction is superior to 2-dimensional echocardiography when compared to magnetic resonance imaging as reference standard.\textsuperscript{3, 4} Echocardiographic deformation imaging (strain, strain rate) can depict early and preclinical functional alterations of the myocardium.\textsuperscript{5} With the advent of advanced automatization, increasing measurement reproducibility, both advanced echocardiographic techniques may fuel further advances to establish their role in the clinical arena of structural heart disease management.\textsuperscript{6}

**PATIENT SELECTION FOR TRANSCATHETER VALVE THERAPIES: RISK SCORES AND 3-DIMENSIONAL ECHOCARDIOGRAPHY**

Significant valvular heart disease, mainly aortic stenosis and mitral regurgitation, affects 3% of the general population, and is associated with increased morbidity and mortality.\textsuperscript{7} The coincidence of population ageing with valvular heart disease prevalence raising over 8% in patients older than 65 years, makes that the global burden of valvular heart disease is expected to grow significantly.\textsuperscript{7} Due to inherent clustering of co-morbidities, however, many of these patients are at high or even prohibitive risk for conventional valve surgery, the gold standard treatment. Surveys have confirmed that such patients are often denied surgery, associated with dismal outcome.\textsuperscript{8, 9} Transcatheter valve therapies provide a valuable therapeutic
alternative for symptomatic patients with severe valvular heart disease that are at high or prohibitive surgical risk. Transcatheter aortic valve implantation (TAVI) comprises the insertion of a self or balloon-expandable bioprosthetic valve within the stenotic native aortic valve via percutaneous route. (Figure 1) Percutaneous mitral valve repair using Mitra-Clip involves placement of a cobalt-chromium clip to attach both mitral leaflets at the origin of the regurgitant jet. This procedure significantly reduces mitral regurgitation severity by creating a double orifice valve and is performed via transfemoral venous access. (Figure 2) Both therapies relieve symptoms and are associated with improved functional status, quality of life, reduced heart failure hospitalizations and, in case of TAVI, improved survival when compared to optimal medical therapy.\textsuperscript{10-12} Although an attractive option for many patients, the outcome of transcatheter therapies critically depends on adequate patient selection (including risk stratification and technical eligibility assessment) and procedural guidance. Clinical evaluation and 3D cardiac imaging have become key for this purpose.

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**Risk scores**

Surgical risk scores including EuroSCORE and Society of Thoracic Surgeons (STS) score have been widely adopted as a simple tool to calculate 30 day surgical mortality risk and categorize patients into high or prohibitive risk for conventional surgery.\textsuperscript{13, 14} Importantly, however, being at increased surgical risk does not imply beneficial outcome when transcatheter therapy is provided. In addition, these surgical risk scores have not been developed nor validated for patients undergoing percutaneous valvular interventions. Apart from procedural related factors, patient related factors including advanced age, renal dysfunction and frailty amongst others may independently relate to outcome after transcatheter therapies. Clinical risk scores, based on preprocedural patient related factors, to predict outcome in case of transcatheter valve therapy are an unmet clinical need that may represent a valuable additional tool for decision making and patient management.\textsuperscript{2}

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**Figure 1.2**

3-dimensional echocardiography

Tremendous advances have been made by the introduction of matrix-array transducers that allow for acquisition of a 3D pyramidal volume during one or more cardiac cycles while holding breath. Apart from more accurate and reliable semi-automated quantification of ventricular volumes, mass, and ejection fraction compared to conventional echocardiography, 3D-echocardiography has revolutionized cardiac valve assessment, in particular of the mitral valve. The technique permits simultaneous visualization of multiple transsections through a region of interest (multi-plane imaging), allows to cut and examine the 3D volume at any desired level or plane and, even more important, provides the surgical or en face view of the valve. These properties translate into unique, superior and reproducible morphological and structural evaluation of the diseased mitral valve, even for novice readers. (Figure 3) In addition quantification of valve area and (functional) regurgitation can be performed more reliably. Further software analysis also permits to create 3D models of the mitral valve complex to derive a multitude of geometric indices and measures, thereby providing unique pathophysiological insights into mitral valve disease. (Figure 3) Of note, acquisition quality of 3D datasets to avoid artifacts or low temporal resolution, subject to learning curve, is critical for reliable use.

Figure 1.3

In patients undergoing transcatheter valve therapies, including TAVI and Mitra-Clip, 3D-echocardiography is becoming mainstream for patient selection and procedural guiding. 3D-imaging by echocardiography or computed tomography shows the typical oval shape of the aortic annulus which critically determines the choice of adequate valve prosthesis size in patients undergoing TAVI. In addition 3D transesophageal echocardiography may be useful to assist in adequate positioning of the valve prosthesis during the procedure, an important outcome
3D-echocardiography is even more indispensable in patients undergoing Mitra-Clip therapy. Technical eligibility for Mitraclip includes a multitude of anatomic criteria that can easily be assessed by 3D-echocardiography: central (non-commissural) jet origin, mitral valve area > 3.5-4.0 cm², no calcification, cleft or significant leaflet thickening in the grasping area, non rheumatic disease, sufficient mobile leaflet length, minimal residual leaflet coaptation length and non extensive tethering (coaptation depth) for functional regurgitation and non extensive flail width and gap for organic regurgitation. Equally important 3D-echocardiography is the cornerstone during procedural guidance as, contrary to TAVI, fluoroscopic imaging has a very limited role to depict the mitral valve.

DEFORMATION IMAGING IN STRUCTURAL HEART DISEASE: ECG AND ECHOCARDIOGRAPHIC SURROGATES OF CARDIAC FIBROSIS

Myocardial Fibrosis
Myocardial fibrosis refers to increased collagen content in the myocardium. Focal fibrosis comprises myocardial cell loss replaced by collagen (replacement fibrosis, scar), while diffuse fibrosis represents increased interstitial collagen without notable cell loss (interstitial fibrosis). Diffuse fibrosis often precedes focal fibrosis and is predominantly found in non-ischemic mitral regurgitation patients. Focal fibrosis to a variable extent is found in 30-60% of patients with aortic stenosis and in 42-71% of primary HCM patients. Presence of fibrosis adversely affects myocardial diastolic and later systolic function due to reduced myocardial compliance and increased stiffness and relates to structural remodeling. Moreover, it provides a substrate for re-entry tachyarrhythmia. Fibrosis has been linked to clinical translates such as symptom and arrhythmia onset, heart failure and even (sudden) death. Identification of fibrosis therefore provides an attractive target that may hold the key for early risk stratification and hence decision-making in patients with structural heart disease.

ECG and fibrosis
Fragmentation of QRS complexes on surface ECG (comprising various RSR’ patterns) has been related to fibrosis in both ischemic and non-ischemic cardiomyopathy. Moreover its presence was shown to be associated with adverse outcome in a variety of cardiomyopathies such as ischemic cardiomyopathy, arrhythmogenic right ventricular dysplasia, Brugada syndrome and idiopathic dilated cardiomyopathy. Abnormal ECG findings are noted in 75 up to 95% of primary HCM patients, however, no such abnormalities have consistently shown a
relationship to poor outcome in these patients. The presence and potential clinical value of QRS fragmentation, as a surrogate marker of fibrosis, has been poorly explored in this patient population.

**Deformation imaging and fibrosis**

Speckle tracking echocardiography involves frame by frame tracking of natural acoustic markers present in B-mode images, so called 'speckles', during the cardiac cycle. This technique measures displacement of myocardial segments and allows semi-automated quantification of velocity, relative myocardial length changes (strain) and the speed of these changes (strain rate) in longitudinal, circumferential and radial direction, due to its angle independency. In addition the wringing motion of the left ventricle with clockwise rotation of the base and anticlockwise movement of the apex, due to the helical myocardial architecture, can be assessed as rotation and twist (net rotation difference between base and apex). It is a robust imaging technique, validated against sono-micrometry, that offers great opportunities to study the complex myocardial atrial and ventricular function, far more sensitive than ejection fraction. The average peak systolic strain value of all segments of the left ventricle is expressed as global longitudinal strain and often represented by a color-coded bull's eye plot. (Figure 4)

Longitudinal deformation is predominantly determined by endocardial fibers and explored most as the subendocardium is most vulnerable and early affected in the vast majority of cardiomyopathies. Longitudinal deformation is determined by intrinsic myocardial contractility, chamber structure, geometry, loading conditions and, importantly, fibrosis extent. Therefore it represents a valuable and sensitive marker yielding great potential as a biological signal related to multiple clinical endpoints in patients with structural heart disease, often regarded as a surrogate marker of fibrosis. As longitudinal dysfunction precedes overt left ventricular dysfunction in terms of reduced ejection fraction, it represents an ideal tool to detect subclinical dysfunction. Indeed, impaired left ventricular longitudinal deformation despite preserved left ventricular ejection has been consistently shown in patients with significant aortic stenosis, mitral regurgitation and hypertrophic cardiomyopathy. In valvular heart disease (early) impaired longitudinal deformation relates to symptom onset, heart failure, decreased survival and worse postoperative outcome. In primary HCM a relation with decreased survival and tachyarrhythmia has been shown. Although atrial remodeling is present in both mitral regurgitation and primary HCM, related to dismal outcome, the clinical value of left atrial function, assessed by deformation imaging, is far less elucidated. (Figure 4)
In this thesis we explore the risk stratification and management of patients with structural heart disease, focusing on valvular heart disease and primary HCM. In particular the potential clinical role of advanced echocardiography including 3D-echocardiography and deformation imaging (strain), as well as clinical surrogates are studied. Although risk often comprises a continuum rather than a dichotomous phenomenon, its assessment is a prerequisite for clinical decision making in daily practice.

Part I focuses on the potential role of 3-dimensional echocardiography. At first a clinical risk score model for prediction of outcome in patients undergoing TAVI is presented (Chapter 2). Second the role of 3D-echocardiography is explored in depth in patients with mitral valve disease. Different non-invasive cardiac imaging modalities to evaluate mitral valve function and anatomy are described and the use of 3D-echocardiography is put into perspective (Chapter 3). We then evaluate the role of the latter to gain insights in patients with functional mitral regurgitation (Chapter 4), to select patients and guide procedures regarding percutaneous mitral valve repair using Mitra-Clip (Chapter 5) and to assess the effect of Mitra-Clip on the mitral valve (Chapter 6).

In Part II we further elaborate the potential role of risk stratification by ECG and myocardial deformation imaging (strain), as surrogate markers of fibrosis. Surface ECG fragmentation in primary HCM is first evaluated (Chapter 7). The important future role of fibrosis imaging in valvular heart disease patients is then reviewed (Chapter 8). Finally the role of left atrial structure and function is evaluated in patients with mitral regurgitation (Chapter 9) and primary HCM (Chapter 10, 11).
REFERENCES


