

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/39145> holds various files of this Leiden University dissertation.

Author: Debonnaire, Philippe Jean Marc Rita

Title: Advanced echocardiography and clinical surrogates to risk stratify and manage patients with structural heart disease

Issue Date: 2016-04-28

Summary, conclusions
and future perspectives

SUMMARY

In this thesis we explored risk stratification and management of patients with structural heart disease, focusing on valvular heart disease and primary hypertrophic cardiomyopathy. In particular the potential clinical role of advanced echocardiography, including 3D-echocardiography and deformation imaging (strain), as well as clinical surrogates, were evaluated. The introduction of this thesis summarizes the rationale and background of our study.

The global burden of valvular heart disease such as aortic stenosis or mitral regurgitation is significant, and it is expected to increase due to Western population ageing. Left untreated, valvular heart disease is associated with poor prognosis. As older patients often present with several co-morbidities, interventional treatment tailored to their inherent high or prohibitive surgical risk is key and can nowadays be provided by less invasive percutaneous valve replacement or repair techniques, as indicated in the introduction of this thesis. Primary hypertrophic cardiomyopathy due to sarcomeric mutation(s), affecting about 1 out of 500 people, is associated with increased risk of sudden cardiac death, heart failure, arrhythmia and thrombo-embolism. Although the absolute sudden cardiac death risk is rather low, its impact is substantial as it tends to occur in young patients and gains significant media attention when it affects young athletes during sports, fueling debates about preventive sport participation screening. Risk stratification and adequate patient selection for interventions in patients with structural heart disease such as valvular heart disease or primary hypertrophic cardiomyopathy are critical to assess the need, timing and type of therapeutic intervention and assure beneficial outcomes. We elaborated how clinical risk scores or surrogates as well as advanced echocardiography techniques including 3-dimensional echocardiography and deformation imaging (strain) may be ideally suited for this purpose in patients with valvular heart disease and primary hypertrophic cardiomyopathy. In particular, the search for techniques or clinical surrogates that relate to the presence of fibrosis, a critical determinant of disease course in both forms of structural heart disease, is explained.

Part I: 3-Dimensional echocardiography

In the first part we explored the value of a novel clinical risk score to predict outcome after transcatheter aortic valve implantation and studied the potential role of non-invasive cardiac imaging in mitral valve disease, focusing on 3-dimensional echocardiography.

In Chapter 2 we present a clinical risk score, the '*TAVI₂-SCORE*', that we developed to predict one year mortality after transcatheter aortic valve implantation

(TAVI), based on preprocedural clinical and echocardiographic characteristics of 511 patients that underwent this procedure. Porcelain Thoracic aorta, Anemia, left Ventricular dysfunction, recent myocardial Infarction, male Sex, Critical aortic valve stenosis, Old age and Renal dysfunction, were independently related to 1 year mortality after TAVI and comprised the constituents of the 'TAVI2-SCORE'. Proportional to the hazard ratio, each constituent was assigned 1 point and 2 points for recent myocardial infarction. We indicated better discrimination and calibration performance of this novel risk score compared to conventional surgical risk scores to predict the endpoint. The 'TAVI₂-SCORE' is an accurate, simple and bed-side available score that might assist to select those patients at high surgical risk that may ultimately benefit from TAVI treatment.

In Chapter 3 we provided an overview of contemporary non-invasive cardiac imaging techniques that can be applied to study mitral valve anatomy and function, in perspective to potential clinical applications. In particular we highlighted the role of 3-dimensional echocardiography for superior mitral valve morphological evaluation compared to 2-dimensional echocardiography, its potential for valve geometry assessment and its additive value to assess valve function comprising mitral stenosis or regurgitation. Multidetector row computed tomography offers mitral valve morphology and geometry evaluation with high spatial resolution in addition to providing anatomical imaging of the relationship of the valve with surrounding structures such as coronary sinus or circumflex artery. Such information may be critical when evaluating technical feasibility for indirect percutaneous annuloplasty techniques. The strength of cardiac magnetic resonance imaging in mitral valve disease involves being an accurate alternative for mitral regurgitation assessment, particularly in patients with poor acoustic window or contra-indication for transesophageal echocardiography.

Evidence is accumulating that mitral valve leaflets in patients with heart failure undergo active ultrastructural and structural remodeling, including larger leaflet area compared to normal controls. In Chapter 4 we showed, using advanced 3-dimensional echocardiography, that patients with functional mitral regurgitation indeed show larger leaflet area compared to normal subjects. More important, less leaflet remodeling was noted in patients with $\geq$ grade 3 versus $<$ grade 3 functional mitral regurgitation, despite similar tethering degree. Lack of coaptation reserve (coaptation area $\leq$ 24% of the overall mitral valve leaflet area) was independently related to more severe mitral regurgitation. In addition we indicated that left ventricular function and sphericity as well as tenting volume and annulus dilatation are determinants of mitral leaflet remodeling. Such findings imply that the mitral valve leaflets are no innocent bystanders in functional mitral valve disease as larger leaflets for similar tethering degree might protect from significant mitral

regurgitation. Therefore the mitral leaflets in functional mitral valve disease might represent a biological or interventional therapeutic target.

In Chapter 5 we described the use of 3-dimensional transesophageal echocardiography (3D-TOE) for selecting and guiding in percutaneous mitral valve repair treatment using MitraClip. Evaluating technical feasibility for MitraClip therapy is a critical determinant of postprocedural success. 3D-TOE offers superior morphological characterization of the mitral valve and displays the presence and extent of morphological lesions. In addition it offers unique possibilities for evaluating coaptation length and depth in functional regurgitation as well as flail width and gap in organic disease. Furthermore, characterization of the origin and number of regurgitant jets as well as accurate quantification of regurgitation severity and leaflet area can be accomplished. During the percutaneous MitraClip procedure, 3D-TOE is indispensable for guiding transseptal puncture, steering of the guiding catheter in the left atrium, positioning and perpendicular alignment of the clip, mitral leaflet grasping and postprocedural evaluation, including regurgitation reduction and residual valve area. Finally, 3D-TOE provides a common and comprehensible communication platform between imagers, interventionalists and cardiac surgeons.

In Chapter 6 we aimed to assess the effect on mitral valve geometry in 42 patients that underwent percutaneous MitraClip therapy for functional mitral regurgitation. We showed that the mitral annulus becomes more elliptical with a tendency towards antero-posterior dimension reduction. Importantly, the coaptation area significantly increases after MitraClip by including mainly a larger part of the anterior mitral valve leaflet into the coaptation, bringing the coaptation point more anteriorly. These beneficial effects are noted, despite no increased leaflet stress as no change occurred in tenting volume or annular height to intercommissural width ratio. Therefore MitraClip therapy seems to affect mitral coaptation geometry similarly to surgical mitral annuloplasty, however, through a different mechanism. These geometric insights might fuel further design iterations and help understanding therapeutic efficacy and ultimately durability of percutaneous repair using MitraClip.

Part II: Echocardiographic deformation imaging

In the second part of this thesis we explored the role of risk stratification by ECG and myocardial deformation imaging (strain), as surrogate markers of fibrosis.

Chapter 7 comprises an evaluation of QRS fragmentation, a surrogate marker of fibrosis, and QTc duration on surface ECG in 195 primary hypertrophic cardiomyopathy patients without (in)complete bundle branch block. We showed that the presence of extensive QRS fragmentation in ≥ 3 territories (inferior, lateral,

septal and/or anterior) and/or QTc $\geq$ 460 ms independently related to malignant ventricular tachyarrhythmia and sudden cardiac death in these patients. Importantly, we indicated that both surface ECG markers provide incremental value on top of conventional sudden cardiac death risk factors to predict the combined endpoint, each yielding a positive predictive value of about 30%, which is higher than the usually reported 10 to 20% for conventional sudden death risk factors. These findings implicate that QRS fragmentation and QTc duration may serve as additional sudden death risk markers that might optimize selection of appropriate candidates for implantation of automated implantable cardioverter defibrillators (ICD).

In Chapter 8 we documented the potential role of imaging fibrosis in patients with severe left-sided valvular heart disease, focusing on aortic stenosis and mitral regurgitation. Focal and/or diffuse fibrosis formation is inherent to the natural disease course of severe valvular heart disease and relates to symptoms and dismal outcome. This renders imaging markers or surrogates of fibrosis a valuable potential tool to assist in risk stratification and decision making for the need and timing of valvular interventions. Delayed contrast-enhanced cardiac magnetic resonance imaging, T1 weighted cardiac magnetic resonance imaging, calibrated integrated backscatter echocardiography and several molecular nuclear imaging techniques provide direct fibrosis assessment. Indirect evaluation of ventricular fibrosis is offered by strain (rate) imaging using echocardiography or cardiac magnetic resonance as well as perfusable tissue fraction and index using positron emission tomography. Evidence for the use of imaging markers of fibrosis in left-sided valvular heart disease is rapidly accumulating as they hold great promise for early risk stratification in asymptomatic patients with severe left-sided valvular heart disease. Whether such an approach outperforms conventional risk factors in valvular heart disease and ultimately can improve outcome after valve intervention needs to be proven.

Volume overload in mitral regurgitation primarily affects the left atrium, making it an attractive potential subject for risk stratification. In Chapter 9 we explored the value of left atrial function assessment using 2-dimensional speckle tracking echocardiography in 121 patients with severe organic mitral regurgitation compared to 70 control subjects. We indicated that significant left atrial reservoir and contractile dysfunction was present in mitral regurgitation patients, particularly in those subjects with indication for mitral valve surgery based on current recommendations. Left atrial reservoir function (strain) independently predicted presence of surgical indication and proved to be more sensitive than left atrial diameter or volume. Left atrial strain $\leq$ 24% identified those patients with worse survival after mitral valve surgery, regardless the symptomatic status prior to

intervention. Impaired left atrial reservoir strain provided incremental value to predict mortality after surgery over current guidelines-based indications for mitral surgery. Therefore left atrial reservoir strain might be a valuable marker for follow-up and decision-making in patients with severe organic mitral regurgitation.

ICD device therapy improves outcome in selected primary hypertrophic cardiomyopathy patients, but accurate predictors of appropriate ICD therapy are poorly documented in this subgroup of patients. In Chapter 10, global longitudinal left ventricular strain (GLS) and left atrial volume index (LAVI) were evaluated in 92 primary hypertrophic cardiomyopathy patients that underwent ICD implantation. Both imaging markers related to appropriate ICD therapy, a combined endpoint of antitachycardia-pacing and/or shock for ventricular arrhythmia, independently of and incremental to conventional sudden cardiac death risk factors. Importantly, the combined presence of $\text{LAVI} < 34 \text{ mL/m}^2$ and $\text{GLS} < -14\%$ adequately ruled out likelihood of appropriate ICD therapy, reflected by a 100% negative predictive value. Therefore both LAVI and GLS assessment on top of conventional sudden cardiac death risk factors might be helpful to optimize referral criteria and timing of ICD implantation in hypertrophic cardiomyopathy patients.

Hypertrophic cardiomyopathy patients with left atrial diameter $\geq 45 \text{ mm}$ are considered to be at high risk for atrial fibrillation and are recommended to undergo at least 6-monthly arrhythmia surveillance using 24 hour Holter registration. In the final Chapter 11 of this thesis, we assessed left atrial diameter, volume and function (reservoir strain by 2-dimensional speckle tracking echocardiography) in relation to new onset atrial fibrillation in 243 primary hypertrophic cardiomyopathy patients. Although all 3 left atrial parameters were independent correlates of atrial fibrillation, 58% of atrial fibrillation events occurred despite left atrial diameter $< 45 \text{ mm}$. In those patients, we showed high negative predictive values of 93% and 94% for left atrial volume $< 36 \text{ mL/m}^2$ and strain $> 23.4\%$, respectively. In this group of patients, left atrial volume provided incremental predictive value over left atrial diameter, even further increased by left atrial strain. In primary hypertrophic cardiomyopathy patients with preserved left atrial diameter but increased left atrial volume ($\geq 36 \text{ mL/m}^2$) or impaired strain ($\leq 23.4\%$), intensification of follow-up to detect subsequent atrial fibrillation might be warranted, in addition to current recommendations.

CONCLUSIONS AND FUTURE PERSPECTIVES

As risk is a continuum rather than a dichotomous event, risk stratification will not be perfect. Nevertheless risk stratification is key for optimal management of

patients with structural heart disease in daily clinical practice, including those with valvular heart disease or primary hypertrophic cardiomyopathy. Advanced echocardiographic techniques such as deformation imaging (strain) provide a very sensitive tool to assess early subclinical atrial or ventricular dysfunction, related to fibrosis, loading conditions, contractility and geometry in patients with valvular heart disease or primary hypertrophic cardiomyopathy, and offer a strong biological correlate to prognosis. In addition clinical markers, including surface ECG markers such as fragmented QRS, may yield prognostic clinical value. Whether early fibrosis imaging represents a hallmark for risk stratification needs to be proven, but ongoing research and scientific efforts in search for optimized risk stratification using advanced echocardiography and clinical surrogates will guarantee optimal outcome for patients with structural heart disease.

A clear tendency towards less invasive and more percutaneous therapies for valvular heart disease, including direct or indirect repair and valve replacement, is present and fueled by tremendous efforts of clinicians, scientists, engineers and medical industry. Non invasive cardiac imaging, including 3-dimensional echocardiography, offers unique pathophysiological insights as well as accurate anatomical, morphological and functional imaging of patients with valvular heart disease that aids in the optimal selection of candidates and procedural guiding of patients undergoing such percutaneous interventions. As we are just at the beginning of this intriguing era of percutaneous therapies for structural heart disease, it is crucial to confirm and further explore the indispensable role of 3-dimensional echocardiography and other imaging techniques for the management of these patients.

