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Summary and conclusions

SUMMARY AND CONCLUSIONS

The general introduction of this thesis (Chapter 1) outlines the epidemiology and the impact of aortic valve (AV) disease in the western world. The thesis further discuss the current and future role of advanced cardiac imaging modalities, using 3-dimensional (3D) echocardiography and speckle tracking echocardiography (STE) strain imaging in the diagnostic and clinical management of patients with aortic regurgitation (AR). In addition, the clinical applications of multimodality cardiac imaging in transcatheter aortic valve implantation (TAVI) for the treatment of severe aortic stenosis (AS) will be discussed: from pre-procedural patient evaluation, to the understanding of complications post-TAVI such as paravalvular regurgitation (PVR), and the assessment and monitoring of patients after TAVI.

Part I: Novel imaging to assess aortic valve regurgitation – incremental role in diagnosis

The first part of the thesis evaluates the incremental value of 3D echocardiography over the conventional 2-dimensional (2D) echocardiographic method to quantify AR, using 3D 3-directional velocity encoded magnetic resonance imaging (MRI) as the reference method (which has been proposed as an accurate method to assess transvalvular flow, after correcting for throughplane motion). Regurgitant volume obtained by 3D echocardiography showed excellent agreement with MRI, better than when comparing 2D echocardiography and MRI. When these two echocardiographic modalities are applied in the assessment of eccentric jets, 3D echocardiography showed a far better correlation with MRI ($r=0.95$), whereas the correlation with 2D echocardiography and MRI was weak ($r=0.66$). Therefore, quantification of AR using 3D echocardiography has shown to be superior to 2D echocardiography, particularly in patients with eccentric jets (**Chapter 2**). These observations are related to the fact that 3D echocardiography has the advantage of unlimited plane orientation, allowing the exact shape and size of the true cross-sectional view of the regurgitant orifice

area to be planimeted, without any geometric or flow assumptions or multiple computation steps.

Chapter 3 evaluated the usefulness of myocardial strain imaging using 2D STE, in patients with chronic AR and baseline preserved left ventricular (LV) systolic function, and its predictive value of myocardial strain for future need of AV surgery was also assessed. In this evaluation, the extent of global longitudinal strain (GLS), circumferential strain and radial strain was calculated in each patient. Despite preserved LV ejection fraction (EF), multidirectional LV strain was more impaired in patients with chronic AR with symptoms than those without symptoms. In chronic AR, the LV adapts in the early course of the disease, normalizing wall stress and permitting normal filling pressures despite a substantial increase in LV volume overload. Hence, LVEF is normally preserved during the compensated phase, and many patients may remain asymptomatic for years. With time, the progressive LV enlargement and the increase in LV pressure will result in an increase in LV wall stress, and marks the onset of impairment in LV performance. New parameters such as myocardial strain, is more sensitive technique than LVEF to detect the subtle change in LV performance.

In the same chapter, in asymptomatic patients who were followed-up conservatively, GLS provided a significant incremental value over clinical and established echocardiographic predictors of poor outcome (including LV volume, parameters of AR severity) to predict those who are at risk of requiring AV surgery. Accordingly, GLS may serve as a potential screening tool in clinical risk stratification of asymptomatic patients with chronic AR and preserved LV ejection, in whom more aggressive follow-up and early intervention should be considered in patients with more impaired GLS.

PART II: ROLE OF MULTIMODALITY IMAGING IN TRANSCATHETER AORTIC VALVE IMPLANTATION – FROM SCREENING TO OUTCOMES

The second part of the thesis focuses on the clinical applications of multimodality cardiac imaging in TAVI for the treatment of severe AS. First and foremost, as opposed to conventional surgical aortic valve replacement (SAVR), direct visualization of the AV is lacking during the TAVI procedure. As a result, imaging becomes mandatory before the procedure, to ensure appropriate sizing of the valve prosthesis. Moreover, the best possible access to reach the valve, either via the transfemoral (TF), transapical (TA), transaortic or transsubclavian approach, needs to be evaluated carefully. Multidetector row computed tomography (MDCT), which has superior spatial resolution and 3D volumetric data sets, is capable of allowing unlimited plane reconstructions and thus, is a highly valuable screening modality in the pre-procedural work up of patients who are being considered for TAVI. **Chapter 4** summarizes the evolving role of MDCT in the patient selection and strategy planning of transcatheter valve intervention. Although transcatheter technology and its delivery and valve systems have improved over the years, and recent randomized studies have shown encouraging results with TAVI, there is still a high early risk of death and complications such as vascular complications, stroke, conduction block, coronary injury and PVR following the intervention. Some of these areas of concern can be minimized by careful patient selection, valve sizing and planning of the procedure. Therefore, the clinical application of multimodality imaging is proposed in the pre-TAVI evaluation algorithm (in **Chapter 5**), highlighting the important factors that need to be considered before the intervention.

Despite the combined effort of learning curve, advances in device technology and the better understanding of aortic root anatomy, AR remains frequent after TAVI. Accurate assessment of AR post-TAVI is clinically relevant since moderate to

severe AR have been associated with poor clinical outcomes. In this respect, supra-aortic angiography and transesophageal echocardiography (particularly 3D echocardiography), is the preferred cardiac imaging technique to assess and to provide an evaluation of the mechanisms underlying AR immediately after valve deployment during the TAVI procedure (**Chapter 6**). This assessment step is crucial to decide whether additional maneuvers such as re-ballooning or valve-in-valve are needed to reduce the AR grade.

Severe AV calcification has been associated with PVR after TAVI due to bulky calcification that may prevent complete annular sealing by the deployed prosthesis, leaving gaps where the regurgitations jets may arise. **Chapter 7** highlighted that both the amount of AV calcification and its location (which can be visualized and quantified on pre-procedural MDCT) are important in determining PVR after TAVI. In particular, the amount of calcium at the valvular commissure and at the aortic wall could predict the occurrence of PVR, whereas the calcium at the valvular body or edge could not. The likely mechanism for this is that when there is significant amount of calcium present at the circumference of the native valve, it may prevent perfect apposition between the new transcatheter valve and the aortic wall, resulting in PVR at these sites.

Although many studies have reported worse clinical outcomes with significant AR immediately post-TAVI, there is limited data on how post-TAVI AR evolve over time. **Chapter 8** reported that significant AR (grade ≥ 2) appeared to improve over time, particularly within the first 6 months. Interestingly, significant PVR (grade ≥ 2) followed similar course with improvement over time, whereas intravalvular AR (AR within the prosthesis) remained unchanged over time. Importantly, patients who remained with significant AR (grade ≥ 2) at 6 months, continued to have negative impact on survival, when compared to those with AR grade < 2 .

Prosthesis-patient mismatch (PPM) occurs when the effective orifice area of a normally functioning prosthetic valve is too small in relation to the patient's body size. This phenomenon is not uncommon

mon in SAVR, particularly in patients with large body size and small aortic annulus. The incidence of at least moderate PPM (indexed effective orifice area $\leq 0.85\text{cm}^2/\text{m}^2$) is 18% in our TAVI experience, and larger body size is a risk factor (**Chapter 9**). Similar to the experience of SAVR, PPM is also associated with less improvement in clinical functional status and less LV mass regression, together with persistent elevated LV filling pressure (as measured on serial echocardiography), when compared to patients without PPM after TAVI.

Finally, whether patients with depressed or preserved LVEF derive similar benefits from TAVI are explored in **Chapter 10**. Although higher perioperative and midterm mortality have been associated with patients with depressed LVEF undergoing SAVR, our experience showed that TAVI could be safely performed with similar procedural success in patients with LVEF $<50\%$ or $\geq 50\%$ after careful pre-procedural patient selection and screening. In fact, patients with baseline LVEF $<50\%$ showed marked LV reverse remodeling, with marked improvement in LVEF after TAVI. In the last **Chapter 11** of the thesis, the clinical outcomes and changes in cardiac performance on echocardiographic evaluations were compared between patients undergoing TAVI through a TF or TA approach. Not surprisingly, patients who underwent TF approach had more vascular complications, although the early, and midterm survival rates were comparable. Both groups achieved similar improvements in transvalvular hemodynamics and LV mass regression. Interestingly, patients with TA approach had significantly shorter fluoroscopy time and less use of contrast volume, when compared to patient with TF approach. A likely explanation for this observation is that less time is required for valve implantation via the TA approach due to better control of the device with a shorter distance between the AV and the apical access site.

CONCLUSIONS

Advanced cardiac imaging modalities play a central role in the diagnostic process and clinical management of patients with AV disease and in patients undergoing transcatheter AV therapy. In particular, 3D echocardiography is a very useful addition to cardiac imaging modality, which has demonstrated several advantages over the conventional 2D echocardiography, such as a more accurate assessment of valvular regurgitation, and the possibility of presenting real-time visualization of 3D cardiac structures with unlimited imaging plane, which is integral for guiding transcatheter valve intervention. Therefore, 3D echocardiography will be part of routine echocardiographic assessment of valvular heart disease. Myocardial strain imaging has also undergone tremendous development. With STE, it has become relatively easy to perform and is reproducible. In fact, GLS is now considered an established marker of global LV systolic function, which is far more sensitive and superior as compared to LVEF, and has prognostic value in patients valvular heart disease.

Finally, advanced multimodality imaging (combining echocardiography, MDCT and MRI) has provided superior anatomic and physiologic information that is crucial in the evaluation of patients with severe AS referred for transcatheter valve therapy. Post-procedural results and its impact on outcomes can also be accurately evaluated and monitored using advanced cardiac imaging over time, providing insights into the understanding of this relatively new therapy, which is regarded as an alternative to SAVR in high-risk patients.

