GENERAL INTRODUCTION
AND OUTLINE OF THE THESIS

Novel cardiac imaging technologies in current clinical practice

Current guidelines for the management of patients with cardiovascular diseases base the therapeutic approach on several echocardiographic parameters, such as left ventricular dimensions or ejection fraction.\(^1\)\(^-\)\(^4\) However, the assessment of the cardiac substrate may provide more insightful information than conventional echocardiographic measures to properly guide the clinical decision-making.

In the last years, several novel echocardiographic imaging tools have been developed to evaluate the properties of the myocardial tissue. For example, tissue Doppler imaging and 2-dimensional speckle tracking imaging permit quantification of myocardial motion and deformation in a region-by-region basis. These methodologies have been extensively validated against sonomicrometry and magnetic resonance imaging and have demonstrated their usefulness in the management of heart failure, evaluation of ischemia and viability, detection of subclinical left ventricular dysfunction and evaluation of contractile reserve in valvular heart disease.\(^5\)\(^-\)\(^11\)

In addition, integrated backscatter imaging is an echocardiographic imaging tool developed few decades ago that permits evaluation of the ultrasound reflectivity properties of the myocardium.\(^12\),\(^13\) The myocardial ultrasound reflectivity can be corrected by the ultrasound reflectivity of the pericardium, the cardiac structure containing fibrotic tissue, providing an estimate of the myocardial fibrosis content. Large myocardial fibrosis content may have a detrimental effect on myocardial motion and deformation that can be detected with tissue Doppler and 2-dimensional speckle tracking imaging techniques before a decrease in cardiac function can be identified with conventional echocardiographic techniques.

Finally, the advent of novel echocardiographic contrast agents has allowed evaluation of cardiac hydrodynamics, closely related to myocardial motion and deformation.\(^14\)\(^-\)\(^16\) The study of the vortex formation in the left ventricle provides novel insight into the relation between left ventricular mechanics and fluid dynamics. The left ventricular vortex redirects the blood flow from left ventricular base to left ventricular apex during isovolumic relaxation and toward the left ventricular outflow tract and aorta during isovolumic contraction. An abnormal left ventricular vortex formation timing indicates the presence of an increased myofiber cardiac work and oxygen demand.\(^17\)

Therefore, beyond the assessment of cardiac dimensions or function, the assessment of myocardial tissue properties and cardiac mechanics may refine the risk stratification and clinical decision-making of patients with cardiovascular risk factors or overt cardiac diseases.
In addition, recent advances in catheter-based interventions have provided effective alternative treatments to surgery for several structural heart diseases. Particularly, the advent of transcatheter valve implantation/repair techniques constitutes one of the main breakthroughs of the last decades offering an effective alternative to patients with symptomatic valvular heart disease and high mortality operative risk.\textsuperscript{18-20} Accurate assessment of the cardiac valvular structures and their spatial relationships with the surrounding structures is key to achieve the highest procedural success rate with the lowest frequency of complications. Real-time 3-dimensional echocardiography, multi-detector row computed tomography and magnetic resonance imaging have provided superb image quality to evaluate the patients who are candidates to these novel therapies.

Therefore, advances in cardiac multimodality imaging may be crucial to improve the clinical management of patients with cardiac diseases and to achieve a more widespread use of novel treatments.

\textbf{Figure 1. Tissue Doppler imaging.}
From color-coded tissue Doppler imaging several parameters can be measured: myocardial velocity, displacement, strain and strain rate.
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Tissue Doppler imaging and the recently introduced 2-dimensional speckle tracking imaging have allowed a more detailed characterization of ventricular function. With the use of these imaging techniques myocardial velocities, displacement, strain and strain rate can be evaluated providing comprehensive information on myocardial function in a region-by-region and global basis. With tissue Doppler imaging, instrumentation filters are set to exclude the high velocities of the blood flow and to record only the low velocities of the myocardium. The fundamental parameter obtained with tissue Doppler imaging is myocardial velocity. By integrating the velocity over time, myocardial displacement can be calculated (Figure 1).

Either velocity or displacement can overestimate or underestimate the active component of myocardial function, since these parameters are strongly influenced by tethering or translational motion. Strain and strain rate, more complex derivatives of velocity, evaluate the active deformation of the myocardium, reflecting more closely the myocardial contractility. Strain is calculated as the percentage change in length during myocardial contraction or relaxation and strain rate is calculated as the

Figure 2. Two-dimensional speckle tracking imaging.

Two-dimensional speckle tracking enables comprehensive assessment of left ventricular mechanics and yields information on multidirectional myocardial deformation, left ventricular mechanical dyssynchrony and left ventricular twist.
difference between two velocities, normalized to the distance between them. The measurement of Doppler derived strain or strain rate is affected by the insonation angle of the ultrasound beam and therefore, data acquisition requires proper alignment of the ultrasound beam with the direction of the myocardial motion.

In contrast, 2-dimensional speckle tracking permits angle-independent assessment of myocardial deformation in multiple directions (radial, circumferential and longitudinal). On conventional gray-scale 2-dimensional images, this methodology identifies natural acoustic markers (so-called speckles), equally distributed within the myocardial wall. Tracking the speckles throughout the cardiac cycle, myocardial motion can be evaluated and strain can be derived (Figure 2).

In addition, the time sequence of left ventricular segmental deformation can be evaluated characterizing the synchronicity of the left ventricular contraction. As previously described, the assessment of left ventricular mechanical dyssynchrony is one of the determinants of the response to cardiac resynchronization therapy. Furthermore, in the normal heart, the myofiber geometry of the left ventricle changes gradually from a right-handed helix in the subendocardium to a left handed helix in the subepicardium. This geometry determines the characteristic wringing motion of the left ventricle with a counterclockwise rotation of the apical level changing to a clockwise rotation in the base. The net difference between the apical and the basal rotations yields the left ventricular twist, a novel parameter of left ventricular global performance. Two-dimensional speckle tracking permits also the assessment of left ventricular twist.

These novel imaging analyses can be coupled to the analysis of left ventricular hydrodynamics with the use of novel echocardiographic contrast media. During early left ventricular filling, the blood flow forms an intraventricular rotational body of fluid (so-called vortex) which is considered to be critical in optimizing the blood flow during left ventricular ejection. A novel echocardiographic dimensionless index (vortex formation time) has recently been introduced to quantitatively characterize the optimal conditions leading to vortex formation (Figure 3).

Knowledge of abnormalities involving intraventricular fluid dynamics in this clinical setting may indeed be useful, since it would provide direct information regarding the ultimate goal of left ventricular performance, i.e. optimal blood flow.

**Novel imaging modalities to characterize left atrial myocardium in patients with atrial fibrillation**

Atrial fibrillation is the most frequent arrhythmia with a prevalence around 1-2% of the population. The associated high morbidity and mortality have promoted extensive research to better understand the pathophysiological aspects of the atrial fibrillation and to achieve a successful mechanism-based treatment. One of these pathophysiological aspects is the left atrial remodeling. Several clinical conditions, such as structural heart disease, hypertension or simply ageing, increase the atrial pressure and volume and induce structural changes that may predispose to atrial fibrillation. These structural changes consist of activation of fibroblasts and increased deposition of collagen, resulting in electrical dissociation between the muscle bundles and conduction heterogeneities that initiate
and perpetuate atrial fibrillation.

Cardiac imaging permits to characterize the atrial remodeling and provides invaluable information to estimate the efficacy of the different therapeutical approaches. Beyond the left atrial dimensions and function evaluated with conventional 2-dimensional echocardiography, novel imaging modalities enable the assessment of the atrial fibrosis and the electro-mechanical properties of the myocardial tissue. As previously described, integrated backscatter may constitute a valuable tool to evaluate the fibrosis content of the left atrial wall. A larger amount of fibrosis may predict a poor response to radiofrequency catheter ablation procedures and a high atrial fibrillation recurrence rate. In addition, this high fibrosis content may determine a low compliance of the left atrium that can be identified by reduced myocardial deformation. Doppler-derived strain and 2-dimensional speckle tracking strain permit the evaluation of these myocardial functions. Finally, the electromechanical properties of the atrial wall can be evaluated by tissue Doppler imaging techniques calculating the time from P-wave onset (on the surface electrocardiogram) to the peak velocity of the A’ wave. A large time delay may reflect a more electrical dissociation of the myocardial wall and may predict a high atrial fibrillation recurrence rate after radiofrequency catheter ablation procedures.

**Novel imaging modalities to assess valvular heart disease: implications for emerging transcatheter based therapies**

Degenerative aortic stenosis and mitral regurgitation are the most common valvular heart diseases in the western countries. Aortic valve replacement is the only effective treatment for symptomatic, severe aortic stenosis. However, the operative risk of some patients outweighs the benefits of aortic valve replacement and, consequently, up to 30% of these patients are denied for surgery. In addition, surgical mitral valve repair, combining leaflet repair techniques and restrictive ring annuloplasty, remain the treatment of choice for symptomatic severe mitral regurgitation. In the last decade, elderly patients have benefited most of recent advances in surgical repair techniques. However, the presence of depressed left ventricular systolic function or associated co-morbidities increase the mortality operative risk and, consequently, the denial of surgery in this subgroup of patients rises up to 50%.

The advent of novel transcatheter valve implantation/repair procedures has provided feasible and less invasive alternative treatments for patients with high operative risk. These novel therapies demand high resolution visualization of the valvular structures and characterization of the anatomi-
cal relationships with the surrounding structures. Advances in real-time 3-dimensional echocardiography, multi-detector row computed tomography and magnetic resonance imaging have provided superb image quality to evaluate the patients who are candidates to these novel therapies.

The assessment of the procedural feasibility is key to achieve the highest success rate with the lowest complication rate. The combination of conventional 2-dimensional and 3-dimensional imaging modalities may improve the accuracy of this pre-procedural screening. Furthermore, peri-procedural assistance with multimodality imaging may help to optimize position and deployment of the transcatheter prosthesis while minimizing the fluoroscopy timings. Finally, the post-procedural results may be accurately evaluated 3-dimensional imaging techniques, enabling visualization of the implanted prosthesis from several angles, previously limited to the surgical field.

**Objectives and outline of the thesis**

The objectives of this thesis were to investigate the role of novel cardiac imaging technologies in the current clinical daily practice with the advent of novel therapies.

In **Part I**, the role of novel imaging modalities to assess left ventricular mechanics will be discussed, focusing on 1) the incremental value of novel myocardial deformation indices over conventional echocardiographic parameters to characterize left ventricular performance in several cardiac conditions (Part IA); 2) the relationship between left ventricular synchronicity and mechanics (Part IB); and the effect of different therapies on left ventricular mechanics (Part IC). The value of two-dimensional speckle tracking imaging to characterize all these left ventricular electromechanical aspects will be thoroughly described and the additional value of integrated backscatter imaging and the study of left ventricular vortex formation will be introduced.

The evaluation of left atrial myocardial tissue properties in patients with atrial fibrillation undergoing radiofrequency catheter ablation procedure will be the focus of **Part II**. Integrated backscatter imaging was used to evaluate the fibrosis content of the left atrial wall and related to atrial fibrillation recurrence rate after radiofrequency catheter ablation (Chapter 18). As previously discussed, the fibrosis content of the left atrial wall may determine the deformation properties of the myocardium and the reverse remodeling of the left atrium after ablation (Chapter 19). Therefore, tissue Doppler derived strain may predict the occurrence of left atrial reverse remodeling after radiofrequency catheter ablation. In addition, tissue Doppler imaging may be useful to evaluate the electromechanical properties of the left atrial wall, in close relation with the occurrence of new atrial fibrillation onset and perpetuation of the arrhythmia (Chapter 20).

Finally, the role of novel cardiac imaging modalities in the emerging transcatheter valve therapies will be discussed in **Part III**. Part IIIA will outline the prevalence of valvular heart disease in relation to several clinical conditions (post-Streptococcal reactive arthritis and use of dopamine agonist therapy) and ageing. Particularly, in elderly patients who show an increased operative morbidity and mortality, the advent of transcatheter valve repair/replacement techniques has provided alternative therapies to surgery. Part IIIB will discuss the role of 3-dimensional imaging techniques (real-time 3-dimensional echocardiography and multi-detector row computed tomography) in the pre-procedural screening and to guide the procedure.
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