General introduction and outline of the thesis
GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Conventional echocardiography is the most commonly used imaging technique in clinical cardiology, due to its non-invasive approach and wide-availability. Diagnosis, therapeutic management and monitoring of patients with cardiovascular diseases are mostly based on echocardiographic assessments, including left ventricular (LV) volumes and ejection fraction (EF), LV thickness and wall motion abnormalities, LV diastolic function measurements, and valvular stenosis or regurgitation severity. However, conventional echocardiography is characterized by several important limitations: 1) for the quantification of LV volumes and EF, 2-dimensional (2D) echocardiography relies on significant geometric assumptions, it might be affected by oblique or “foreshortened” views and showed modest reproducibility; 2) LVEF and the conventional assessment of LV diastolic function have been shown to be not sensitive enough to detect subtle myocardial systolic and diastolic dysfunction that may occur in several cardiac conditions and should be the target for an early therapeutic approach; furthermore, these conventional measurements are not sophisticated enough to describe thoroughly the complex LV mechanics; 3) 2D echocardiography permits only limited cross-sectional views, which make in some cases the interpretation and diagnosis of cardiac pathologies, and in particular of valvular disease, extremely complex and achievable only by experienced operators; 4) image quality is often an important issue that may significantly affect the accuracy of this imaging modality.

Advances in echocardiography have more recently provided novel approaches, which may overcome the abovementioned limitations. Real-time 3D echocardiography (RT3DE), tissue Doppler imaging (TDI), 2D speckle tracking imaging and contrast-enhanced echocardiography have demonstrated their incremental value over conventional echocardiography for the assessment of global and regional LV function and for a better understanding of cardiac mechanics.

In addition, non-echocardiographic imaging modalities, such as multi-detector row computed tomography and magnetic resonance imaging (CMR) provide high-resolution images of the cardiac structures and therefore important additional information. In particular, CMR has emerged as the gold standard technique for the assessment of LV volumes and function and for the identification and quantification of myocardial scar/fibrotic tissue.

Therefore, advanced cardiac imaging modalities may play a crucial role to improve the diagnosis process and the clinical management of patients with different cardiac diseases, including heart failure, valvular heart disease, myocardial infarction and atrial fibrillation.
Real-time three-dimensional echocardiography

Thanks to significant technological developments, RT3DE is now readily available as a clinically applicable imaging technique and allows for the assessment of the whole heart in 3 dimensions, including all LV segments and unlimited image plane orientations. Therefore using this novel modality, quantification of LV size and function (but also of left atrium and of right ventricle) does not rely anymore on geometric assumptions and has been shown to be more accurate as compared to conventional echocardiographic measurements. Furthermore, regional LV function can be fully assessed based on the 3D endocardial motion of volumetric segments, giving the opportunity of having complete dynamic information on LV chamber contraction (Chapter 1, Figure 3). Therefore, accurate evaluation of LV regional motion can be performed in patients with ischemic cardiomyopathy. Furthermore, temporal sequence of regional myocardial contraction can be studied and measures of LV dyssynchrony can be derived and applied in patients with advanced heart failure referred for cardiac resynchronization therapy (CRT).

Finally, the 3D approach permits a direct visualization of the complex anatomy and the sophisticated functional mechanisms of the cardiac valves (in particular of the mitral valve), allowing for a unique evaluation of valve morphology and for an accurate assessment of valvular disease severity.

Assessment of myocardial velocity and deformation

Tissue Doppler imaging and more recently 2D speckle tracking imaging have been introduced for the quantification of myocardial velocity and deformation (strain). These techniques have been largely validated against sonomicrometry and are proposed as novel approaches for a more sensitive and accurate assessments of global and regional LV function.

In particular, TDI is an echocardiographic modality characterized by high frame rate (until 200 fps) and which is able to record myocardial velocities thanks to specific filter settings that exclude the blood flow high velocities. This modality can also be applied to a 3D dataset, displaying simultaneously 3 apical views (tri-plane modality) and therefore including all myocardial segments into account and avoiding potential problems of heart rate variability (Chapter 2, Figure 3). In clinical practice, TDI has been validated for the estimate of LV filling pressures, measuring the early diastolic relaxation (E') of the mitral annulus segments, and for the assessment of LV dyssynchrony, identifying the delay between myocardial peak systolic velocities of different LV segments. However, the measure of myocardial velocities does not reflect only the active contraction of the myocardium but is also strongly influenced by the tethering of the adjacent segments or translation motion. Therefore, in certain cases (especially of ischemic cardiomyopathy), it might not be an accurate measure.
of myocardial contractility. Conversely, myocardial deformation (strain) can be obtained as spatial derivative, integrated over time of myocardial velocity and reflects more closely the active component of myocardial contraction (Chapter 2, Figure 1). Therefore, it has been applied, together with strain rate (deformation velocity), as a promising direct measure of myocardial contractility. Being TDI a Doppler-based technique, however, makes these measures dependent on the insonation angle of the ultrasound beam and therefore limited in case of suboptimal alignment, such as in the evaluation of apical segments and of radial and circumferential deformation.

Two-dimensional speckle tracking imaging in turn, permits and angle-independent assessment of myocardial strain (and strain rate) in multiple directions (longitudinal, radial and circumferential), tracking over time in standard grey-scale 2D images the presence of natural acoustic markers (so-called speckles), equally distributed within the myocardial wall. Using this technique, regional and global LV contractility can be therefore accurately quantified and LV dyssynchrony can be assessed looking at the time sequence of LV segmental deformation. In addition, more complex cardiac mechanics can be studied. The human heart for example has a specific helical arrangement of the myofibers with a right-hand orientation from the base towards the apex in the endocardial layers and a left-hand orientation in the epicardial layers. This spiral architecture of the myofibers leads to the typical LV systolic wringing motion as a result of an opposite rotation of LV apex and base. The gradient between apex and base in the rotation angle along LV longitudinal axis is called twist and contributes significantly to LV systolic function, in addition to myocardial shortening and thickening. Speckle tracking imaging allows the quantification of LV twist as the net difference between apical (counterclockwise) and basal (clockwise) rotations and as a novel parameter of global LV performance (Chapter 22, Figure1).

Contrast-enhanced echocardiography

In patients with suboptimal acoustic windows, intravenous echocardiographic contrast is normally administered to improve endocardial border delineation, to increase accuracy and reproducibility of regional and global LV function assessment and to detect intracavitary thrombus. RT3DE image quality is highly dependent on the acoustic window, due to a lower spatial and temporal resolution as compared to 2D echocardiography. Accordingly, adequate endocardial border delineation may be difficult with this imaging modality, even in the presence of relatively good 2D image quality. Few studies explored the feasibility of RT3DE, in relation to the image quality, for the assessment of LV systolic function and reported a relative high prevalence of uninterpretable or poor quality RT3DE images. However, data regarding the use of contrast agents during RT3DE are scarce and only few studies evaluated the feasibility and accuracy of contrast-enhanced RT3DE.
Contrast-enhanced echocardiography may be particularly important in the management of patients presenting with acute myocardial infarction, in which urgent and repeated echocardiographic examinations are indeed crucial in order to evaluate LV global and regional function and to exclude infarction complications. Furthermore, this approach enables evaluation of myocardial perfusion and microvascular integrity, providing valuable information about myocardial viability, which is an important prognostic factor after infarction. Alternative diagnostic imaging techniques (i.e. transesophageal echocardiography, radionuclide ventriculography and cardiac magnetic resonance) are conversely more invasive or expensive.

Substantial safety data already exist for the use of echocardiographic contrast in stable patients with known or suspected cardiac disease. However, safety data on contrast-echo cardiography in critically ill patients and particularly in patients within 24 hours of acute myocardial infarction are lacking. As a consequence, the use of this echocardiographic approach in these patients is limited, although of potential great importance. Contrast-echo cardiography could in fact provide information on the extent of infarction, which is crucial, together with other parameters such as LV dyssynchrony and novel measurement of LV mechanics, to predict LV functional recovery or development of LV remodeling, and long-term morbidity and mortality.

**Magnetic resonance imaging**

CMR is currently considered the gold standard for the assessment of several cardiac measurements, providing highly accurate and reproducible data.

In particular, it was proven to be far superior to other techniques for quantification of LV volumes and EF, and for the assessment of LV regional wall motion and segmental thickness. Therefore, it has been used as a reference technique for the quantification of LV size and function in validation studies of different imaging modalities, including RT3DE.

In addition, CMR with delayed-gadolinium enhancement is considered the gold standard for the assessment of myocardial infarction extent. This technique in fact offers a direct visualization of scar/fibrotic tissue with high spatial resolution, enabling distinction between subendocardial and transmural myocardial involvement (Chapter 16, Figure 1). Therefore, it is widely applied for the assessment of myocardial viability and for treatment optimization and risk stratification of patients with ischemic LV dysfunction.

Velocity encoded CMR is also particularly suitable for determining trans-valvular blood flow, providing quantitative information on moving spins, and has been recently proposed as a reference method for the assessment of valvular heart disease. However, conventional single-slice one-directional velocity encoded CMR showed some limitations, mainly due to the fact that the acquisition plane can not be adapted to the systolic-diastolic motion of the valves. A more accurate approach is offered by the 3D 3-directional velocity encoded...
CMR with retrospective valve tracking. This technique is able to cover the complete velocity vector field of the blood flow and to correct for the through-plane myocardial motion in the apical-basal direction (Chapter 20, Figure 1). This approach can be therefore applied for the assessment of all 4 cardiac valves in one acquisition and to accurately evaluate potential flow abnormalities (valve stenosis or regurgitation) \(^8,\,31\).

When applied for myocardial wall motion measurement, velocity encoded CMR may obtain similar data to that provided by TDI, without the limitations of the acoustical window, and can be used for the assessment of myocardial velocities. As above-mentioned, potential clinical applications might be therefore in the assessment of LV diastolic function and for the measures of LV dyssynchrony \(^32,\,33\). More recently, CMR has also been proposed for the assessment of LV dyssynchrony looking at the changes in radial wall motion over time \(^34\). With this approach, which includes the identification of the endocardial and epicardial border of a series of short axis slices, the temporal sequence of LV segments contraction can be studied and measures of LV dyssynchrony can be derived.

CMR therefore provides unique detailed information about cardiac morphology and function, as well as assessment of myocardial viability, LV dyssynchrony and quantification of trans-valvular flows. This comprehensive approach is particularly useful in heart failure patients, especially as potential candidates to CRT.

**OBJECTIVES AND OUTLINE OF THE THESIS**

The objectives of this thesis were to investigate the incremental value of advanced cardiac imaging modalities for diagnosis and patient management in different cardiac disease. In **Part I**, current and future applications of RT3DE will be introduced. The use of this technique for the quantification of LV volumes and function and for the assessment of LV dyssynchrony is explored in heart failure patients before and after CRT implantation (Part IA). In particular, different 3D measures of LV dyssynchrony, based on the full volume approach (Chapter 2, 3 and 4) or on the tri-plane approach (Chapter 5, 6 and 7), are applied to improve candidate selection for CRT and to predict favorable response after implantation. In Part IB, RT3DE is applied in patients with atrial fibrillation or heart failure for the quantification of left atrium volume and for the assessment of different left atrial functions (conduit function, active contraction, reservoir function).

**Part II** will discuss the additional diagnostic and prognostic value of contrast-enhanced echocardiography, particularly in patients within 24 hours after acute myocardial infarction. Safety and accuracy (in combination with RT3DE) of this modality in this specific group are evaluated. In addition, the incremental value of myocardial infarction extension, as assessed with myocardial perfusion analysis, to predict LV remodeling after infarction is explored together with novel measures of LV performance (LV twist).
The use of CMR for a comprehensive assessment of patients with different cardiac disease will be the focus of Part III. Novel CMR approaches for an accurate and reproducible measure of LV dyssynchrony are proposed and applied in heart failure patients in order to predict significant LV reverse remodeling after CRT implantation (Part IIIA). In addition, the value of CMR for the assessment of myocardial viability is discussed in different groups of patients (heart failure, LV aneurysm, ischemic cardiomyopathy, Part IIIA). Part IIIB explores the values of CMR in valvular heart disease, and particularly as a reference technique for the assessment of mitral regurgitation severity.

Finally in Part IV, novel physiopathological aspects in CRT patients will be studied using advanced echocardiographic imaging modalities. In particular, this part of the thesis evaluates the effect of CRT on: 1) LV rotational mechanics, as assessed by speckle tracking strain analysis; 2) severity of mitral regurgitation, especially in patients with high operative risk; 3) cerebral blood flow, as measured by transcranial Doppler. Furthermore, whether the etiology of heart failure and biventricular pacemaker settings (when optimized) have a significant influence on response to CRT is further explored.
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