CHAPTER 1
General Introduction
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Advances in clinical, surgical and peri-operative knowledge have led to an increased survival of patients with congenital heart disease (CHD). As a result, the population with CHD has doubled over the last decades, and a growing extent of patients are surviving into late adulthood.(1) However, despite the improvements in clinical and surgical care, progressive heart failure remains a major cause of death during late follow-up of patients with complex CHD.(2) In adult (non-CHD) patients with heart failure, the recent advent of cardiac resynchronization therapy (CRT) has improved the clinical outcome of heart failure in patients with poor left ventricular (LV) ejection fraction and a wide QRS complex. CRT typically involves atrial-synchronized biventricular pacing, and improves LV function by inducing a more synchronous contraction pattern. Consequently, CRT has resulted in improvements in heart failure symptoms (New York Heart Association [NYHA] functional class, exercise capacity or quality of life) and all-cause mortality of heart failure patients.(3-7) Currently, CRT is a class I indication for adult non-CHD patients with NYHA functional class III or IV despite optimized pharmacological therapy, LV ejection fraction <35% and QRS duration >120 ms.(8,9)

The excellent outcomes obtained with CRT in adult non-CHD patients have raised interest to apply this therapy in CHD patients with heart failure. However, the etologies of heart failure differ substantially between ‘acquired’ heart disease and CHD. An important subgroup of CHD patients with heart failure during follow-up are those with failure of the RV, of which the majority are patients with corrected Tetralogy of Fallot (cToF).(10) RV dysfunction is an important predictor of poor clinical outcome in these patients.(11) The RV differs importantly from the LV from an anatomical, embryological and functional point of view. The RV shape has a complex geometry, with a crescent shape when viewed in cross-section and a more triangular shape when viewed from the side. Embryologically, the RV can be divided into three sections: the sinus (inlet), the apical trabecular part, and the infundibulum (outlet).(12,13) Functionally, the RV is coupled to the pulmonary circulation which is highly distensible and has a low resistance.

Accordingly, the mechanical activation of the RV and its relation with myocardial performance, and hence the appropriate therapeutic strategies in RV failure may be different from the LV. Various advanced echocardiographic and cardiac magnetic resonance (CMR) imaging techniques have recently been developed, allowing comprehensive assessment of global and regional myocardial performance, motion and deformation. With the use of these imaging techniques, the mechanical activation pattern of the RV can be characterized in detail. Comprehensive knowledge on RV mechanics and performance may guide clinical decision-making with regard to therapeutic strategies in patients with RV failure, including the application of CRT.

Right ventricular imaging: echocardiography

Echocardiography is a readily available, non-invasive imaging tool that is routinely used in clinical practice for repeated cardiac imaging during follow-up of CHD patients. Various advanced echocardiographic imaging modalities allow a detailed characterization of myocardial performance, motion and deformation of the RV. Tissue Doppler imaging (TDI) enables the assessment of RV mechanics by measuring myocardial velocities and the temporal occurrence of myocardial motion with high temporal resolution. With the use of TDI, the velocity of the myocardium with respect to the transducer is measured. The assessment of peak systolic velocities at the basal RV free wall with TDI has shown to be of incremental value to conventional echocardiography to assess global and regional ventricular performance in various clinical conditions.(14,15) Furthermore, with TDI, the temporal occurrence of mechanical events can be measured, by calculating the time of the events relative to the onset of the QRS complex on the electrocardiogram. The assessment of timings of peak systolic velocities provides insight into electromechanical coupling and possible mechanical dyssynchrony.(16)

Another advanced echocardiographic technique is two-dimensional strain imaging or speckle-tracking strain imaging. Speckle-tracking strain imaging permits multidirectional and angle-independent assessment of myocardial deformation. With this echocardiographic technique, the so-called speckles (natural acoustic markers equally distributed within the myocardium in 2-dimensional gray-scale echocardiographic images) are tracked frame-by-frame throughout the cardiac cycle. The change of their position relative to their original position is used to calculate myocardial strain. The assessment of myocardial strain has demonstrated to be useful to detect subclinical cardiac dysfunction in several clinical conditions.(17,18) Similar to TDI, with speckle-tracking strain imaging, the timing of peak systolic strain may be assessed, providing insight into possible dyssynchrony. Furthermore, speckle-tracking strain imaging permits imaging of torsional mechanics. LV twist takes into account the complex helical disposition of the myofibers and is a sensitive index of LV performance. By evaluating RV and LV strain, LV apical and basal rotation and LV twist, the ventricular-ventricular interaction between the LV and RV may be assessed at a regional level. Finally, reliable assessment of volumes and ejection fraction of the RV is of clinical importance in CHD patients with RV failure. Quantification of RV volumes by two-dimensional echocardiography is hampered by the complex ventricular geometry. Real-time three-dimensional echocardiography of the RV overcomes this problem by imaging the entire RV in a three-dimensional volume. Furthermore, real-time three-dimensional echocardiography enables computation of regional volumes and function of the various RV segments: RV inlet, apical trabecular part and RV outlet.

Right ventricular imaging: cardiac magnetic resonance

CMR is a versatile non-invasive imaging technique during clinical follow-up of post-operative CHD patients.(19) With echocardiography, imaging of the RV is hampered by its complex geometry and its anterior position within the chest. CMR is independent of geometrical assumptions and of the acoustic window. Currently, CMR is the reference standard to quantify RV volumes and function, as well for the quantification of flow over the cardiac valves.(19) In addition, various advanced CMR techniques have enabled insight into ventricular mechanics. With the use of Tissue-velocity magnetic resonance imaging (TV-MRI), myocardial velocities can be assessed. TV-MRI has been validated against TDI for the assessment of myocardial velocities and timings of peak systolic velocities in the LV.(20-23) In CHD patients undergoing routine CMR evaluation, the validation of TV-MRI to assess myocardial velocities of the RV would permit a comprehensive assessment of ventricular volumes, function and myocardial velocities during a single integrated MRI examination. The evaluation of systolic velocities provides insight into ventricular performance.
and possible dyssynchrony. In addition, the evaluation of diastolic velocities with TV-MRI or TDI yields a detailed quantitative assessment of RV diastolic function at a regional level, which can provide insight into the pathophysiological mechanism leading to RV dysfunction in CHD patients. In cToF patients, pulmonary regurgitation is a common hemodynamic lesion. Pulmonary regurgitation is an important cause of RV dilatation and RV failure. Therefore, reliable assessment of pulmonary flow has important clinical implications. Furthermore, comprehensive quantification of pulmonary regurgitation with CMR provides the opportunity to investigate the complex relationship among chronic volume overload, RV mechanics, and RV failure. Two-dimensional velocity-encoded CMR, the current reference standard for assessing PV flow, is hampered by cardiac motion, because the acquisition plane is fixed throughout the cardiac cycle. Three-dimensional three-directional velocity-encoded flow imaging (3D flow) has recently been introduced for the assessment of transvalvar flow. The use of 3D velocity-encoded MR imaging resolves the problem of valvar annulus motion owing to retrospective valve tracking and velocity-encoding in three orthogonal directions. Furthermore, 3D flow imaging allows simultaneous assessment of flow over all four cardiac valves. This simultaneous assessment enables evaluation of global RV diastolic function of in cToF patients with pulmonary regurgitation. In the presence of pulmonary regurgitation, the flow pattern over the tricuspid valve does not reflect RV relaxation, since RV filling occurs also from the pulmonary regurgitation. Summation of the 3D time-resolved diastolic flow curves of the pulmonary valve and tricuspid valve permits the reconstruction of RV time-volume curves. From the time-volume curve of the RV, global RV diastolic function can be comprehensively appreciated.

Prediction of outcome of CHD patients with echocardiography
In current clinical practice, echocardiography plays a central role to routinely assess cardiac anatomy and function during follow-up of CHD patients. The advent of new echocardiographic imaging modalities provides novel anatomical, functional or electromechanical parameters, which may improve clinical-decision making by predicting outcome in the individual patient. Hence, novel imaging techniques may refine risk stratifications in known clinical protocols. Conversely, when new therapeutic strategies emerge (such as CRT for heart failure or pulmonary valve replacement for pulmonary regurgitation), conventional as well as novel imaging techniques may aid the selection of patients that are most likely to benefit from these new interventions. Accordingly, an important goal of clinical research on cardiac imaging techniques is to ultimately gain insight into the clinical implications with respect to patient outcome and to refine therapeutic and interventional protocols.

Objectives and outline of this thesis
The objective of this thesis was to obtain insight into the electromechanical activation of the RV in CHD patients as well as in healthy subjects. Furthermore, the relation between global RV performance and electromechanical activation was investigated with various non-invasive echocardiographic and CMR imaging techniques. Finally, the clinical role of echocardiography to predict outcome in CHD patients was explored.
REFERENCE LIST