CHAPTER 5
Summary and conclusions
Nederlandse samenvatting
5.1

Summary and conclusions

RIGHT VENTRICULAR IMAGING: ECHOCARDIOGRAPHY

The first part of this thesis aimed to characterize ventricular mechanics and performance with advanced echocardiographic imaging techniques in patients with congenital heart disease (CHD), with particular focus on the right ventricle (RV). In chapter 2.1, an overview was provided on the current role of cardiac resynchronization therapy (CRT) in CHD and pediatric patients with heart failure. CRT is a novel therapy and typically involves atrio-biventricular pacing. CRT has demonstrated to improve left ventricular (LV) function and outcome of adult patients with LV failure by inducing a more synchronous contraction pattern. Based on the current clinical evidence, CRT is a promising therapy to improve cardiac performance and clinical outcome of CHD and pediatric patients with heart failure, in particular in those with LV failure as a result of chronic RV pacing. However, trials reporting on the long-term effects of CRT in CHD and pediatric patients are warranted. Furthermore, no trials have been performed to assess the adult selection criteria for CRT (New York Heart Association functional class III or IV despite optimized pharmacological therapy, left ventricular ejection fraction [LVEF] <35% and QRS duration >120 ms) in CHD and pediatric patients. The various anatomical substrates in CHD patients (systemic LV, systemic RV, single ventricle) may result in patterns of cardiac dyssynchrony that are not accurately characterized by the adult criteria. Future trials are needed to establish appropriate guidelines for CHD patient selection for CRT, taking into account the different anatomical subgroups.

Subsequently, the role of conventional and advanced echocardiographic techniques to response to CRT in CHD and pediatric patients was discussed in detail in chapter 2.1. In adult trials, the assessment of dyssynchrony with echocardiography has been shown to predict a favorable response to CRT. At present, few studies are available on cardiac mechanics and dyssynchrony parameters that predict CRT response in CHD and pediatric patients. Therefore, studying LV and RV mechanics with various (advanced) imaging modalities can provide a definition of cardiac dyssynchrony in CHD and pediatric patients.

Accordingly, the promising results of CRT have encouraged the research on LV and RV mechanics in pediatric and CHD patients, which was the focus of the subsequent chapters of this thesis. First, understanding ventricular mechanics in healthy children can help optimize the benefits of pacing strategies such as CRT in pediatric and CHD patients with heart failure. Chapter 2.2 aimed to provide reference values of peak systolic velocities and timings of peak systolic velocities of the LV and RV, as assessed with tissue Doppler imaging (TDI) in healthy children. Peak systolic velocities increased significantly with age at both ventricles, reflecting cardiac maturation. Within the LV, no relevant intra-ventricular time differences were observed at any age. This observation of a synchronous contraction of the LV is in agreement with adult studies, and provides an empirical basis for the application of CRT in pediatric candidates with LV failure.

In contrast, within the RV of healthy children, a significant mechanical time delay was observed between the peak systolic velocity at the RV free wall (RVFW) and the intra-ventricular septum (IVS) and between the RVOT and the RV free wall (RVFW). In a subsequent study, this phenomenon of a mechanical time delay between the outlet and inlet regions of the RV was also observed with speckle tracking strain imaging, as described in chapter 2.3. In this study, the longitudinal deformation pattern of the RVFW and RVOT was evaluated in healthy children and in patients with corrected tetralogy of Fallot (cToF). As assessed with speckle tracking strain imaging, longitudinal deformation of the RVOT preceded longitudinal deformation of the RVFW in children with a structurally normal RV. In cToF patients, this mechanical activation sequence was also observed. However, in the cToF patients, the RVOT deformation was significantly delayed, causing a reduction of the mechanical time delay within the RV. Furthermore, the reduced time delay was related to impairment in RV performance. The observed mechanical activation pattern of the healthy RV, with longitudinal motion and deformation of the RVFW preceding that of the RVFW, seems to conflict with the theory of a peristalsis-like contraction pattern of the RV segments. This peristalsis theory postulates that the RV body contracts prior to the RVOT and was mainly derived from experimental animal studies. However, data from these experiments did not uniformly point towards a peristalsis-like pattern of RV contraction. Importantly, two directions of motion of the RVFW have been explored in these studies: transversal and longitudinal. In individuals with a structurally normal RV, a peristalsis-like pattern of RV contraction was only observed in the transversal direction. However, in the longitudinal direction, the peristalsis-like pattern was not observed, which is in agreement with our data. The presence of a mechanical delay during contraction of the structurally normal RV has important clinical implications for the treatment of RV dysfunction with CRT. The pathophysiological basis of CRT is the restoration of electromechanical dyssynchrony. With the observed mechanical delay within the healthy RV, this concept of resynchronization may not be applicable to the RV. Additional studies to confirm this model of RV sequential contraction are warranted prior to the application of CRT in patients with RV failure.

In chapter 2.4, ventricular-ventricular interaction was studied with speckle tracking strain imaging by assessing the relationship between longitudinal RV and LV strain and LV rotation in cToF patients and in healthy subjects. Despite a normal LV ejection fraction [as assessed with cardiac magnetic resonance (CMR)], subclinical dysfunction of both the RV and LV was observed with speckle tracking strain imaging in the cToF patients. At a regional level, analysis with two-dimensional speckle tracking revealed a homogeneous reduction of longitudinal RV strain in cToF patients in all segments, whereas at the LV, impairment in longitudinal strain and rotational mechanics was only observed at the mid and apical levels. Furthermore, a close relationship was observed between global RV and LV mechanics. This close relationship was most pronounced at the apical levels of the RV and LV, indicating that the observed adverse ventricular-ventricular interactions may start at the apical level in cToF patients.
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These conclusions were endorsed by a subsequent study in chapter 2.5 that showed pronounced volume increase in cToF patients with chronic volume overload at the apical level of the RV. In this study, a segmental analysis of the RV was performed with real-time three-dimensional echocardiography (RT3DE). In healthy subjects as well as in cToF patients, RV volumes and ejection fraction were analysed at a global and regional (inlet, apical trabecular and outlet) level. Global RV volumes were significantly increased in cToF patients. The segmental analysis pointed out that the volume increase in cToF patients was most pronounced at the apical trabecular segment. According to these results and the results of chapter 2.4, the apical trabecular part plays a central role in the adaptive response of the RV to volume overload in cToF patients. Furthermore, regional volume increase at the apex of the RV may account for the observed adverse ventricular-ventricular interaction at the apex. As a result of the volume increase at the apex, altered apical geometry of the RV may distort regional fiber orientation, which could have a deleterious effect on systolic biventricular performance. Future studies in cToF and other CHD patients with RV dilatation may need to focus on the apical trabecular segment of the RV to determine criteria for therapeutic intervention.

RIGHT VENTRICULAR IMAGING: CARDIAC MAGNETIC RESONANCE

The second part of this thesis aimed to investigate the role of advanced cardiac magnetic resonance (CMR) techniques to characterize RV mechanics in CHD patients. CMR plays an increasing role during clinical follow-up of CHD patients, especially in those with complex CHD. Chapter 3.1 provided an overview of the current clinical applications of CMR in various subgroups of post-operative CHD patients. Furthermore, an overview of advanced CMR techniques in CHD patients and their clinical value was presented in this chapter. One of these advanced CMR techniques is the assessment of myocardial velocities and timings with tissue-velocity magnetic resonance imaging (TV-MRI). In chapter 3.2 a direct comparison between TV-MRI and TDI was performed to assess peak systolic velocities and timings of peak systolic velocities within the RV in cToF patients and in healthy subjects. The results demonstrated that TV-MRI and TDI can be used interchangeably for the clinical evaluation of RV mechanics in healthy subjects and in cToF patients. Furthermore, with both TV-MRI and TDI, the peak systolic velocity at the RVOT occurred prior to the peak systolic velocity at the RVFW in cToF patients as well as in healthy subjects. These results underpin the observations on the temporal activation pattern of the RV as described in chapters 2.2 and 2.3.

Chapter 3.3 extended the validation of TV-MRI to assess RV mechanics by comparing diastolic velocities between TV-MRI and TDI in cToF patients and healthy subjects. The assessment of diastolic function is relevant in cToF patients, since RV end-diastolic volume and pulmonary regurgitation (two parameters strongly related to adverse outcome in cToF patients) are diastolic parameters. Conflicting results have been published on the clinical implications of global diastolic dysfunction in cToF patients. However, TV-MRI enables the assessment of diastolic performance of the RV at a regional level. Diastolic velocities of the RVOT had not been investigated previously. During surgical correction of tetralogy of Fallot, manipulation of the RVOT is almost invariably needed to relieve the pulmonary stenosis. As a result, regional scar tissue may lead to functional abnormalities of the RVOT. In chapter 3.3, regional diastolic velocities (early diastolic velocity: E', late diastolic velocity: A') were measured at the RVFW and at the RVOT with TV-MRI and with TDI in cToF patients and in controls. It was demonstrated that TV-MRI and TDI can be used interchangeably for the assessment of regional diastolic velocities and performance of the RV. Furthermore, the regional diastolic velocities and diastolic performance at the RVFW and RVOT were impaired in cToF patients. At the RVOT, the observed impaired diastolic performance was independently related to RV dilatation. This observation was in accordance with previous studies that pointed out the independent role of RVOT integrity to prevent RV dilatation in cToF patients. Accordingly, the assessment of regional RV diastolic performance with TV-MRI yielded insight into the pathophysiological mechanism leading to RV dilatation in cToF patients. More trials are needed to further investigate the observed relation between diastolic performance of the RVOT and RV dilatation.

In chapter 3.4, novel three-dimensional three-directional velocity-encoded flow imaging with retrospective valve tracking (3D flow) was validated for the assessment of RV flow volumes. 3D flow was compared with conventional two-dimensional velocity-encoded flow imaging (2D flow) for the assessment of flow volumes over the pulmonary valve and the tricuspid valve in cToF patients and in healthy subjects. Planimetry was used as the reference standard. The study demonstrated that 3D flow is more accurate than 2D flow for the assessment of both pulmonary valve flow volumes as well as for tricuspid valve flow volumes. An important advantage of 3D flow is the retrospective valve tracking, enabling angulation of the imaging plane according to the position and the direction of the flow jet. Adjusting of the imaging plane is especially important for the assessment of flow at the tricuspid valve, since this valve may move up to 24 mm during image acquisition. Furthermore, during 3D flow assessment, the pulmonary and tricuspid valve flow is acquired simultaneously. The simultaneous assessment of various valves during 3D flow acquisition reduces scan time. Furthermore, with the use of 3D flow, global diastolic function of the RV in cToF patients with pulmonary regurgitation can be evaluated. The assessment of diastolic function of the RV in patients with pulmonary regurgitation is complicated, since diastolic filling occurs from two sources, the tricuspid valve and the pulmonary valve. The simultaneous assessment of flow over both valves during 3D flow enables accurate summation of both flow volume curves during diastole. Summation of the tricuspid and pulmonary flow volumes during diastole provides time-volume curves, reflecting the diastolic filling pattern of the RV. Hence, 3D flow-derived RV time-volume curves permit the evaluation of global diastolic function of the RV in patients with pulmonary regurgitation. It was shown in chapter 3.4 that diastolic assessment with 3D flow was able to discriminate between patients and controls. Furthermore, 3D flow assessment of diastolic function discriminated cToF patients with a restrictive RV filling pattern from those without RV restriction. In conclusion, the advanced MRI applications of 3D flow and TV-MRI provide novel parameters for the assessment of RV diastolic function at a global and regional level, respectively. The evaluation of global and regional RV diastolic function with these advanced CMR techniques can facilitate ongoing research on the clinical implications of RV diastolic dysfunction during long-term follow-up in CHD patients.
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PREDICTION OF OUTCOME

The prediction of clinical outcome is an important goal of clinical studies on cardiac imaging techniques. The last part of this thesis focused on the prediction of clinical outcome of CHD patients with the use of conventional and advanced echocardiographic techniques. Chapter 4.1 investigated clinical predictors for the need for pulmonary valve replacement. In particular the relation between residual pulmonary stenosis, as assessed with conventional Doppler echocardiography, and the need for pulmonary valve replacement during long-term follow-up of cToF patients was investigated. Current surgical strategies to relieve pulmonary stenosis in cToF patients aim to limit the amount of patch use whenever possible, since patch use is related to pulmonary regurgitation. However, this ‘restrictive approach’ may result into a (mild) degree of residual pulmonary stenosis in post-operative cToF patients. A mild residual pulmonary stenosis may reduce the amount of pulmonary regurgitation and consequently, may reduce the need for pulmonary valve replacement during follow-up of cToF patients. Indeed, the results of our study indicated that a mild gradient over the pulmonary artery is independently associated with a reduced risk of pulmonary valve replacement. These findings underscore the importance of the current surgical strategies in cToF patients that advocate a restrictive surgical relief of the pulmonary stenosis in ToF patients. Furthermore, knowledge on the clinical implications of a mild residual pulmonary stenosis improves patient-based counseling during clinical follow-up of cToF patients.

Finally, in chapter 4.2, the advanced echocardiographic application of TDI was used for the prediction of atrial arrhythmias in a cohort of adult CHD patients. With TDI of the atria, the time interval from the onset of the P-wave on the electrocardiogram to the peak of the A-wave on the TDI tracings of the lateral atrial wall can be measured (PA-TDI duration). In CHD patients, the principal pathophysiological substrate for atrial arrhythmias is provided by electrical re-entry through atrial areas with delayed electrical conduction. These sites of delayed electrical conduction prolong the time required for atrial electrical activation. Prolonged total atrial conduction time is a reliable predictor of atrial arrhythmias. The PA-TDI duration reflects the total atrial conduction time, and has been shown to be a predictor of atrial arrhythmias in adult patients with ‘acquired’ heart disease. In our study, the PA-TDI duration was independently associated with the occurrence of atrial arrhythmia in adult CHD patients. Therefore, the PA-TDI duration can be a useful tool for the identification of CHD patients at risk for atrial arrhythmias during clinical follow-up.

Conclusions

In this thesis, important new insights were gained in the electromechanical activation and deformation pattern of the RV with the use of advanced echocardiographic and MRI techniques. The obtained insights have clinical implications for future treatment strategies in CHD patients with RV failure. The population of patients with CHD is growing, and RV failure is frequently observed in this population. Nevertheless, the pathophysiology of RV failure remains incompletely understood. In current clinical practice, the application of CRT has recently gained ground in the treatment of patients with LV failure. The beneficial results of CRT in adult patients with LV failure have encouraged studies on RV mechanics and performance, as presented in this thesis. With the use of three different noninvasive advanced imaging techniques (TDI, speckle tracking strain imaging, TV-MRI) it was demonstrated in this thesis that a considerable mechanical delay during longitudinal systolic contraction is present in the healthy RV. In addition, this mechanical delay was related to the performance of the RV. Accordingly, the concept of resynchronization by the application of CRT seems not directly applicable in patients with RV failure, and this should be an important starting point for future studies on pacing strategies in patients with RV failure.

Additional insight into RV mechanics and performance in the presence of volume overload was obtained by studying the RV of cToF patients at a regional level. It was demonstrated that adverse RV remodeling after chronic volume overload in cToF patients starts at the apical level. Furthermore, adverse ventricular-ventricular interaction, leading to subclinical LV dysfunction, was also most apparent at the apical level. At present, there is ongoing debate on the optimal cut-off values for pulmonary valve replacement in cToF patients. The results of this thesis indicate that future trials on cut-off values may need to focus specifically on the apical trabecular part of the RV. Finally, novel insight was obtained on the role of the (surgically remodeled) RVOT in the pathophysiological pathway leading to RV dilatation in cToF patients. Both the study on regional diastolic velocities as well as the report on the clinical predictors of the need for pulmonary valve replacement pointed out that in cToF patients, the integrity and function of the RVOT is important in the pathophysiological mechanism leading to RV dilatation. Accordingly, a targeted intervention on the RVOT in cToF patients undergoing pulmonary valve replacement could lead to improved outcomes.