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General discussion and future perspectives
The number of patients with a congenital heart defect (CHD) surviving into adulthood is growing.\textsuperscript{1} Both improvements in surgical techniques, perioperative care and close postoperative follow-up have aided to this.\textsuperscript{2-4} Although long-term survival seems promising, a varying degree of impairment of ventricular performance was observed long-term after surgery.\textsuperscript{5,6} As mentioned in the introduction, this impairment may develop over time as a consequence of residua, sequelae and complications. Yet, preoperative and perioperative factors may also induce an impairment of ventricular performance shortly after surgical correction, which may persist over time. Only a limited number of studies describe longitudinal follow-up of ventricular performance after the immediate postoperative period. Accordingly, this thesis was aimed to shed more light on changes in ventricular performance after surgery for a CHD, with follow-up starting preoperatively and continuing to over one year after surgical correction.

Several techniques can be used to assess ventricular performance following CHD surgery. Especially in the immediate postoperative period, echocardiography is often used, as this technique is readily available, relatively inexpensive, and can be performed without sedation.\textsuperscript{7,8} In recent years a multitude of new echocardiographic techniques have been introduced. An overview of these techniques is given in chapter 2 of this thesis. As portrayed in this chapter the introduction of new echocardiographic techniques, including tissue Doppler imaging (TDI) and speckle tracking strain imaging, has boosted the ability of echocardiography to provide a comprehensive insight in both global and regional ventricular performance. Both TDI, speckle tracking strain imaging and 3-dimensional echocardiography have been suggested to detect more subtle changes in ventricular performance than conventional parameters (e.g. fractional shortening, FS).

These developments in echocardiographic techniques have been important for the evaluation of ventricular performance after surgery for a CHD. This suggestion is supported by the second part of chapter 2, which reviews existing literature on ventricular performance, as assessed using echocardiography, following correction of a CHD. Using a variety of echocardiographic techniques the cited studies describe a decrease in ventricular performance shortly after surgery. Both preoperative, perioperative and postoperative factors may add to this direct postoperative impairment. Studies describing ventricular performance more long-term after surgery of a CHD are often cross-sectional studies. These studies describe a varying degree of postoperative impairment of ventricular performance.

\textit{Healthy pediatric subjects}

To allow correct interpretation of echocardiographic measurements in pediatric CHD patients, knowledge of the characteristics of these techniques in healthy children is vital. In addition to
acquiring reference values, assessment of the reproducibility and feasibility of new measurements in children is important, as these may be different from adults.

In this thesis we focused on reference values and characteristics of two echocardiographic techniques in children, TDI and speckle tracking strain imaging. Prior to the start of this research project, our research group assessed TDI derived peak systolic velocity measurements and timing of peak systolic velocities in 123 healthy subjects (1 month to 18 years old). This analysis provided age-related reference values of peak systolic velocities. These results were in line with the few other studies evaluating TDI velocities in healthy pediatric subjects. However, knowledge of TDI velocities in specific subgroups of pediatric subjects, e.g. neonatal subjects, was limited.

Neonatal subjects constitute a specific subgroup of pediatric patients because especially in the first few months of life, hemodynamic and growth related changes occur. These changes may influence echocardiographic parameters, and thus careful evaluation of new echocardiographic techniques in neonatal subjects is desirable. Chapter 3.1 describes follow-up of TDI velocities and speckle tracking strain derived longitudinal, radial and circumferential peak strain as assessed in the LV of healthy neonates. Subjects were studied 1-3 days, 3 weeks and 6-7 weeks after birth. A significant increase in LV systolic and diastolic TDI parameters was observed up to 6-7 weeks after birth. These changes could be the result of an increase in LV performance or changes in translational movement of the heart. However, significant (cardiac) growth may also be a major determinant of changes in TDI velocities in neonates and infants. Previously a significant influence of growth on TDI parameters has been described in fetuses and children and Z-scores have been published for TDI parameters in children. Yet, in neonates this underlying cause for changes in TDI velocities has been underexposed thus far.

Furthermore, speckle tracking strain derived global peak strain parameters were assessed during echocardiographic follow-up in neonates. No significant changes were observed in these parameters during the entire follow-up period. This stability may render this technique particularly valuable in evaluation of LV systolic performance during periods of significant growth, such as the neonatal period.

In addition to evaluation of peak strain parameters, speckle tracking strain imaging can be used to assess intraventricular time-differences. Parameters describing intraventricular time-differences were introduced to detect disturbance of coordinate wall motion, mechanical dyssynchrony. Left ventricular (LV) dyssynchrony is believed to result in inefficient pump function, which could lead to depressed LV performance and heart failure. In addition, dyssynchrony was suggested to predict response to cardiac resynchronization therapy as therapy for heart failure. In chapter 3.2,
two types of speckle tracking strain derived parameters describing intraventricular time-differences were assessed in a sizable population of healthy subjects (n=183). Parameters describing intraventricular time-differences were calculated from longitudinal, radial and circumferential speckle tracking strain measurements. These parameters included the standard deviation of time to peak strain of several segments (SDt, ms) and the differences in time to peak strain between two specified segments (delay, ms). Both SDt-parameters and delay parameters had a relatively high feasibility in pediatric subjects and were age and heart rate independent; characteristics which could facilitate their possible use. However, the limited reproducibility of both SDt and delay parameters is worrisome. For delay parameters, the combination of limited reproducibility with a wide interquartile range may confine use of these parameters in clinical practice in children. Although not widely published, previous results of reproducibility analyses of delay parameters in adults show a similar trend.16

Besides parameters describing intraventricular time-differences chapter 3.2 describes reference values of LV global peak strain parameters. These parameters were age independent, and the reproducibility of longitudinal and circumferential global peak strain parameters was relatively good. Accordingly, these results in healthy children stimulate further study and use of global peak strain parameters in pediatric patients.

**CHD patients**

In the final part of this thesis, TDI velocities and speckle tracking strain derived peak strain parameters were used to describe follow-up of several subgroups of pediatric CHD patients after surgical correction.

In chapter 4.1 a mixed group of 141 CHD patients and 40 age-matched controls were included, who underwent echocardiographic follow-up after CHD correction. Patients underwent echocardiography preoperatively, one day postoperatively and at hospital discharge. A significant decrease in parameters describing LV and right ventricular (RV) systolic and diastolic performance was observed directly following surgery. This was followed by a recovery in most echocardiographic parameters in the following week. At discharge no significant differences were observed in conventional echocardiographic parameters in patients versus controls, while LV and RV TDI parameters remained significantly impaired. These results may imply that TDI parameters detect more subtle differences in ventricular performance than conventional parameters.

Furthermore, a possible association between various peri- and postoperative parameters and postoperative TDI parameters was evaluated in the mixed group of CHD patients. No association was observed between inotropic score and TDI parameters. However the presence of a negative association between aortic cross-clamp time and several TDI
measurements until discharge, suggests a prolonged influence of cardiopulmonary bypass (CPB) on biventricular performance.

In chapter 4.2 a longer follow-up, up to one year postoperatively, is described in ventricular septal defect (VSD) patients undergoing surgical correction. In this study, LV and RV systolic performance were assessed preoperatively, one day postoperatively, at discharge and at medium-term follow-up (3-20 months postoperatively) in 39 VSD patients and 22 age-matched controls. Similar to previous results in the mixed group of CHD patients, we observed an initial decrease in biventricular systolic performance directly following surgery. Subsequently LV and RV systolic performance parameters increased within the first year following repair. This resulted in LV systolic performance parameters which were comparable to controls after medium-term follow-up. Hence preoperative LV volume-loading, which is thought to induce preoperative LV remodeling in VSD patients, does not lead to persistent impairment of LV performance following surgery. In contrast, RV performance parameters remained impaired in patients versus controls up to 20 months after surgical correction.

A similar follow-up duration is described in Chapter 4.3 for a second subgroup of CHD patients undergoing surgical correction using CPB; patients with transposition of the great arteries (TGA) undergoing an arterial switch operation (ASO). Both LV and RV TDI velocities and speckle tracking strain derived LV peak strain parameters were used in this study to describe biventricular systolic and diastolic performance. After an initial decline in LV and RV systolic and diastolic performance, LV TDI velocities and speckle tracking strain derived peak strain parameters recovered to values comparable to controls within the first postoperative year. Hence, current results emphasize that if early surgical correction is performed, LV performance is not persistently impaired after ASO. In contrast, similar to previous results in VSD patients, parameters describing RV performance remained impaired in patients as compared to controls within the first postoperative year.

Although not previously observed in VSD and TGA patients, a persistent impairment of specifically RV performance was observed in both adults and children following a variety of other cardiac surgeries using CPB. Much has been speculated on the reason why specifically RV and not LV performance parameters remain impaired in patients after cardiac surgery. Possibly the thin-walled RV is more susceptible to local tissue damage than the LV or myocardial protection is less effective in the more anteriorly located RV than the LV. Alternatively, CPB associated ischemia and inflammatory cascades or preoperative pressure and volume overload could influence RV performance. Finally, pericardiectomy and pericardial adhesions have been suggested to play a role in RV dysfunction after surgery. Furthermore, in TGA patients
additional factors, including preoperative hypoxia and postoperative residua and complications of ASO may also affect postoperative ventricular performance.\textsuperscript{25}

In chapter 4.4 we describe follow-up of ventricular performance after surgical correction of an aortic coarctation up to one year postoperatively. Two distinct subgroups can be identified within the group of patients undergoing coarctation repair in the current era.\textsuperscript{26} These subgroups include neonatal patients presenting with a critical prostaglandin-dependent coarctation and non-neonatal coarctation patients, who usually present less symptomatic later in life. We hypothesized that follow-up of ventricular performance in patients who had to undergo a coarctectomy in the neonatal period, was characterized by a more persistent impairment of ventricular performance postoperatively, as compared to patients who underwent repair later in life. Hence, postoperative ventricular performance was analyzed separately in these subgroups.

In both subgroups of coarctation patients little change was observed in RV performance during follow-up and RV performance was not impaired in patients versus controls one year postoperatively. On the other hand, LV systolic and diastolic performance parameters were impaired in both subgroups of coarctation patients preoperatively. Although no change was observed in LV performance parameters one day postoperatively versus preoperatively, subsequent follow-up revealed a significant improvement in LV performance parameters within the first postoperative year. Nonetheless one year postoperatively LV diastolic performance parameters were still impaired in both subgroups of patients as compared to controls. In LV systolic performance parameters an important difference was observed between subgroups one year postoperatively; LV S’ recovered to normal values in non-neonatal patients while remaining impaired in neonatal patients. These results suggest a more persistent impairment in neonates. In addition to previously described differences in hemodynamic burden, prenatal development and residual stenosis at the previous coarctation site may add to this difference.

**Conclusions and future perspectives**

This thesis provides additive insights in characteristics of newly introduced echocardiographic parameters in healthy controls and their use in follow-up in patients with a CHD.

TDI derived velocity parameters are reproducible and feasible in children. Yet the use of age or growth-dependent reference values is recommended. This may be especially important in neonatal subjects, in whom we observed significant changes in (cardiac) growth simultaneously with significant changes in TDI parameters. Use of speckle tracking strain derived global peak strain parameters in children is encouraged based on current results. A good reproducibility, age-independent values and stability of global peak strain measurements in neonatal subjects support this. In contrast, the limited reproducibility of speckle tracking strain derived parameters
describing intraventricular time-differences is worrying. These observations underline the need for studies which critically validate newly introduced echocardiographic parameters in healthy children.

Introduction of TDI and speckle tracking strain imaging has enhanced the ability of echocardiography to objectively quantify ventricular performance. However, it is important to remain responsible in the use of the multitude of new echocardiographic parameters. Hence, in our opinion current trends of calculations of z-scores and standardization of echocardiographic measurements in pediatric patients should certainly be encouraged.

In addition to critical validation of newly introduced echocardiographic techniques in healthy children, validation in children with a cardiac disease remains imperative. Current results of characteristics and reference values in healthy children are an important first step. However, knowledge of the magnitude of deviations of normal values in patients with a cardiac disease for example is essential to place the observed characteristics in perspective. Accordingly, large studies in pediatric patients with a cardiac disease are important and needed to further evaluate the value of these parameters in pediatric patients.

In addition to echocardiographic parameters in healthy children, this thesis describes follow-up of ventricular performance in CHD patients. In brief, these studies describe a significant decrease in biventricular performance immediately postoperatively in patients undergoing surgery for a CHD using CPB. During subsequent follow-up LV performance recovered to control values, while RV performance remained impaired in both VSD and TGA patients up to one year postoperatively. Furthermore, a longer-lasting negative influence of CPB on myocardial performance was suggested.

Interestingly, follow-up in coarctation patients was very different from follow-up in VSD and TGA patients. No significant decrease was observed immediately after surgery, and LV in contrast to RV performance remained impaired up to one year postoperatively. These differences in follow-up patterns are remarkable. Coarctation patients were the only subgroup studied in this thesis that underwent surgery without use of CPB. In combination with the negative association of CPB and postoperative ventricular performance observed in chapter 4.1 and several previous studies, this observation suggests a role for CPB in postoperative impairment of ventricular performance. Yet, the absence of myocardial surgical scars and pericardiotomy in patients undergoing coarctectomy may also underlie this difference.

Based on current results, we can only speculate on the underlying cause for the observed difference in follow-up patterns. Yet, further understanding could provide valuable knowledge for development of therapeutic strategies. Hence, in our opinion, this is an important topic for future research.
Furthermore the observation of persistent impairment of RV systolic and diastolic performance in both VSD and TGA patients certainly deserves attention in future research. A significant decrease in biventricular performance immediately after surgery was described previously.\textsuperscript{30,31} However present studies in VSD and TGA patients are unique in their subsequent length of follow-up. Considering the persistent impairment of RV performance it is important to lengthen the follow-up duration further in future research. This will elucidate whether the impairment of RV performance is long-lasting but still transient or a life-long state.

In addition, the clinical relevance of the observed impairment of RV performance parameters was not established in current studies. Subtle changes in RV performance parameters have shown to be correlated to increased risk of cardiovascular events in adult heart failure patients.\textsuperscript{32,33} However, the prognostic value and clinical relevance of impaired RV performance parameters in children is less well established.

Both the persistence of RV impairment during long-term follow-up and its clinical relevance could be derived from a solid longitudinal follow-up study starting at surgery and continuing into adulthood. In practice, this may be best achieved by addition of a standardized protocol of TDI and speckle tracking strain imaging to current echocardiographic follow-up in CHD patients at a regular interval.
REFERENCES


