Chapter 8

General discussion and future perspectives
GENERAL DISCUSSION

Congenital heart disease (CHD) is the most common birth defect and affects 6 to 8 per 1000 newborns. The detection rate of CHD has increased over time to about 60% in screening centers. In third-level centers, the accuracy of the prenatal diagnosis of CHD is around 87%—9. Real time two-dimensional ultrasound (2DUS) is the conventionally used tool in fetal echocardiography. Continuous improvements in the hardware of ultrasound equipment and post-processing software have resulted in a good image quality nowadays; however, 2DUS still has its limitations. A well-known difficulty in echocardiography is capturing and identification of the outflow tracts by 2DUS, especially when there is a cardiac malformation with stenosis or atresia of one of the outflow tracts. The interpretation of the images must be done in real-time, making it operator dependent and time consuming. Furthermore, specific views of the heart like the surface of the ventricular septum and the anteroposterior view of the atroioventricular annuli (mitral and tricuspid valves) are difficult to visualize in detail using 2DUS.

Four-dimensional ultrasound has advantages over the conventional 2DUS. Volumetric scanning is less dependent on the angle of acquisition, and thus less dependent on fetal position or operator expertise. Spatiotemporal image correlation (STIC) is a software modality used to analyze a cine sequence of a moving fetal heart. With STIC the heart can be examined offline in every desired plane while maintaining the synchronized cardiac loop. With several post-processing rendering capabilities, an unlimited number of 'virtual planes' of the fetal heart can be obtained. Therefore, four-dimensional ultrasound (4DUS) using STIC could help to increase the detection rate of cardiac defects.

Value of 4DUS in fetal echocardiography

Morphology of the valves of the fetal heart

STIC could be useful to visualize the morphology of the atroioventricular and semilunar valves, which is difficult using 2DUS. In this thesis the assessment of the morphology of the fetal heart valves was studied in a prospective systematical manner using STIC. In chapter 2 and 3 we showed that it is feasible to visualize the morphology (shape, number of leaflets) of the atroioventricular and semilunar valves in normal and abnormal fetuses. Only one other study developed reference ranges for the area of the valves. However, in this study by Rolo et al., the examiners did not take into account that the mitral and tricuspid valves insert to the septum at a different angle. In chapter 2 different insonation angles were used to measure each atroioventricular valve area to avoid oblique projection, which can lead to underestimation of the valve area. In cases with an atroioventricular septal defect (AVSD) the common valve was visualized successfully. We concluded that STIC may be beneficial in the differentiation between complete and partial AVSDs, as this is difficult in 2DUS. However, a pitfall was acknowledged...
using the render mode for visualization of the atrioventricular valves. In an AVSD case with a small sized ventricular septal defect, the top of the septum mimicked the separation between the right and left valve as in normal atrioventricular valves. Awareness of this pitfall is important if this technique is used more frequently. If there is suspicion of a septal defect based on 2DUS, STIC can be used to view the heart from different angles to exclude artifacts. Furthermore, the knowledge that an atrioventricular valve opening shows a round as well as a square opening might help to interpret the conflicting results in cardiac output measurements with Doppler studies, which use formulas based on a round opening of the valves.

Our studies showed a relatively low success rate of visualization of the leaflets of the semilunar valves (52.6% in normal hearts). The success rate was highest (72.1% in normal hearts) at 19 to 24 weeks. Scanning difficulties attributed to the lower success rates in the first and third trimester. Unfortunately the overall success rate is too low to be clinically relevant at this moment. With further development of ultrasound machines, which may lead to higher resolution, visualization of the leaflets will probably be easier. STIC could be helpful in the detection of bicuspid valves and coarctation of the aorta, which was the primary goal of our morphology study of the valves in chapter 3. We hypothesize that the visualization of bicuspid valves in the second trimester might help to predict which heart will develop in a hypoplastic left heart syndrome and which heart will only develop a coarctation of the aorta or even remain without any further CHD, in cases that present with an asymmetrical four-chamber view. A prospective trial should be performed to analyze the additional value of STIC to 2DUS in visualization of the valve morphology in comparison to 2DUS only.

**Training and research**

Manipulation of STIC volumes could help sonographers to gain experience in fetal echocardiography without the actual presence of a patient. It helps inexperienced examiners to understand the spatial relationships between the cardiac structures and how to navigate in the heart to visualize the anatomy. Practicing with STIC volumes of cases with CHD could help to gain insight in the diagnoses of different defects in daily practice. Furthermore, offline analysis offers a wealth of research opportunities. Comparison of fetal specimens to STIC volumes helps to correlate ultrasound abnormalities with postpartum or postmortem findings. In chapter 5 and 6 we showed that STIC was helpful to examine the morphology of the atrioventricular valves in normal hearts and hearts with Down syndrome with and without an AVSD. STIC facilitated in the understanding of the exact plane that is needed for an accurate measurement of the differential insertion of the atrioventricular valves. Without 4DUS we would not have discovered that the size of the differential insertion becomes smaller when scrolling through the heart caudally. Abnormal values of the DIAVV are encountered in AVSDs as well as in conotruncal abnormalities. The conotruncal abnormalities double outlet right ventricle, truncus arteriosus and tetralogy of Fallot all showed a decreased DIAVV, except for transposition of
the great arteries. We hypothesize that abnormal embryologic development of the cushion tissue relates to a defect in the membranous part of the septum in AVSDs as well as in the septal defects in conotruncal abnormalities which could result in a smaller size of the DIAVV. This might explain the decreased DIAVV in all conotruncal abnormalities except for transposition of the great arteries, which can be an interesting focus for future developmental research.

Furthermore, the sliding scale of a fetal heart with Down syndrome without an AVSD towards a complete AVSD (chapter 6) is a new finding. As people with Down syndrome grow older nowadays, knowledge of the subtle changes in their cardiac anatomy could be beneficial for their cardiac follow-up. The clinical importance is, however, not known at the moment, and future follow-up studies on older individuals with Down syndrome will show if this finding is clinically relevant.

**Accuracy of 4DUS in prenatal diagnosis**

Spatiotemporal image correlation has been introduced more than ten years ago. In the initial period of 4DUS, one of the main goals of STIC was to depict a heart in three dimensions to view additional details. In the existence of fetal cardiac malformations, counseling regarding management options is of high importance for the parents. An accurate prenatal diagnosis of CHD is indispensable in the care of these fetuses. Offline analysis provides the possibility to diagnose cardiac defects at a distance. Our telemedicine study (chapter 7) is the first to explore if detailed diagnosis of the cardiac defect is possible in such a setting. Through a comprehensive scoring system we were able to analyze if, besides a general diagnosis, all details of the defect were detected, which are important for adequate counseling and correct planning of the neonatal care. As shown in other studies, the results are operator dependent. Even though all three examiners were experienced in fetal echocardiography, not all examiners reached high concordance using STIC. We showed that details required for planning of postnatal care were missed, even by the most experienced examiner. For example, in the case of tetralogy of Fallot premature closure of the ductus arteriosus was not diagnosed. Furthermore, the confident score of the examiners was rather low which implies that examiners were not willing to rely fully on STIC for their diagnosis of CHD. Two large studies addressed the accuracy of 4DUS in the prenatal diagnosis of cardiac defects in third-level centers. Bennasar et al. reported a high accuracy (91.6%) and absolute concordance in 80.1% in normal fetuses and 74.3% in CHD using STIC, while 2DUS showed 94.2, 84.8 and 81.7% respectively. Recording of the volumes as well as analysis of the volumes was performed by the same examiner, while in our study the examiner of the volumes was blinded to exclude recall bias. The COFEHD study presented a high sensitivity (93%) and specificity (96%) of 4DUS for the diagnosis of CHDs and a good inter-center agreement in diagnosis (k = 0.97) between seven centers. However, this study included STIC volumes with a single heart defect. Our telemedicine study (chapter 7) included complex diagnoses as well, which is important for implementation of this method in daily practice.
The additional clinical value of STIC is still topic of current debate\textsuperscript{19-21}. Numerous reports showed that interesting details were detected by STIC, which remained undiscovered with conventional echocardiography\textsuperscript{22-31}. For example, in a case of tetralogy of Fallot with absent pulmonary valve syndrome, appropriate rendering of the spatial relationships of the enlarged pulmonary trunk and its branches using STIC was helpful, because the prognosis is related to the size of the pulmonary arteries and the possible bronchial obstruction\textsuperscript{25}. Only one study of Yagel et al. focused on the added value of various 4DUS ultrasound modalities to diagnose CHD. This study showed an added value in 6.6\% (12/181) of the cases\textsuperscript{21}. However, the sensitivity using 2DUS was 93\%, so this is only a relatively small increase in sensitivity. Furthermore, the STIC volumes were compared to 2DUS cine-loops, which are dependent on the examiners experience at the time of recording. Probably real-time 2DUS would lead to an even higher sensitivity in this center.

Combining all the evidence, STIC has not proven its promised additional value, which justifies incorporation into clinical practice. Visualization of the morphology of the atrioventricular and semilunar valves using 4DUS is feasible. The added value is relatively small in the diagnosis of CHD. STIC is a promising modality to diagnose cardiac defects at a distance, however, examiners should be aware of possible pitfalls of STIC in a telemedicine setting.

**Value of 4DUS in screening setting**

For incorporation of STIC in a screening setting, inexperienced sonographers need to be able to acquire a STIC volume and to detect if the heart is normal or abnormal. STIC acquisition by sonographers without experience in 4DUS is feasible\textsuperscript{15,32,33}. However, the success rate of inexperienced sonographers is lower compared to experienced sonographers\textsuperscript{15}. Only one study evaluated the accuracy of 4DUS in a screening setting and revealed also operator dependency with the individual diagnostic accuracy ranging from 66 to 100\% (median 85.5\%).

To increase the detection rate of CHD we developed reference values for the differential insertion of the atrioventricular valves (DIAVV) in normal fetuses using 4DUS with STIC in chapter 4. A new strict measurement protocol for measurement of the DIAVV is presented using STIC. With STIC the exact moment of the cardiac cycle and the precise plane could be acquired by manipulation of the volume around the three axes, which is more difficult using 2DUS. In chapter 4 we showed a decreased size of the DIAVV in conotruncal abnormalities, which are frequently missed in routine screening programs. Theoretically measurement of the DIAVV could help to increase the detection rate of these defects. However, 4DUS visualization of the DIAVV has contributed to the awareness that using the DIAVV as a screening tool is not realistic. Four-dimensional ultrasound revealed the information that the size of the DIAVV can vary in images that are all called ‘four-chamber view’. This will make this measurement unsuitable to use as a screening tool in routine obstetric practice. Only a small deviation could lead to a misinterpretation of the DIAVV. For incorporation of the DIAVV measurement in an ultrasound screening program,
extensive training should be provided. The costs of such a training program could probably be invested more efficiently in other, more simple, visualization techniques like hands-on training for the routine views of the outflow tracts.

To our knowledge, STIC is not widely used in ultrasound screening settings. Probably the operator dependency is the main problem concerning analysis of a STIC volume. Several techniques have the aim to simplify the evaluation of the cardiac anatomy using 4DUS. The SPIN, STAR, FAST and FINE algorithms are examples to help less experienced sonographers to identify the normal echocardiographic planes. The SPIN technique helps to rotate the heart around the x- and y-axes to visualize the outflow tracts and septum more easily. With the STAR technique visualization of the outflow tracts is facilitated by tracing three lines into a four-chamber view of a STIC volume. The FAST technique shows standard fetal echocardiographic planes by drawing dissecting lines through the longitudinal view of the ductal arch. For an automatical analysis of the heart with a STIC volume the FINE technique is developed. The standard echocardiographic planes are automatically generated from the volume. These techniques help to examine the fetal heart using STIC; however, they have not been analyzed in a prospective manner to determine if they are really helpful in a screening setting. Furthermore, the sonographer needs to recognize and to determine the correct ultrasound plane to start the acquisition and the analysis of the fetal heart. Therefore these modalities are still operator dependent like we showed with measurement of the DIAVV. Another reason that these modalities are probably not yet widely in use, is the fact that 3D/4D is time consuming. Therefore, on balance, implementation of 4DUS in a screening setting in its current form is not recommended.

**FUTURE PERSPECTIVES**

Four-dimensional ultrasound is useful for examiners with experience in fetal echocardiography in a diagnostic setting. STIC provides the possibility to examine ultrasound planes, which are difficult to visualize using 2DUS. Volume measurement using 4DUS is a promising tool for analysis of the cardiac function. Furthermore, offline analysis provides multidisciplinary consultation, facilitates understanding of the fetal anatomy and can be extremely useful for education. Despite these hopeful possibilities, STIC is not incorporated into the daily practice as was expected. Fetal echocardiography using STIC requires extra time and effort when the patient is not present. In the diagnostic setting 3D/4D has additional value, however, a detailed diagnosis of cardiac defects in this setting is already very high. This raises the question if 4DUS is worth the effort, while 2DUS leads to a good diagnosis in most third-level centers. In my opinion the additional time and effort makes STIC less attractive for an experienced sonographer. Perhaps in the near future these disadvantages are resolved with new technologies which make real-time 4D ultrasonography available. Fast acquisition of the volume could minimize the risk of movement artifacts, which
are common in current practice. Recently a new electronic 4D curved matrix array probe has been introduced which enables a simultaneous display of two perpendicular sectional planes in real-time. Plane adjustment and a narrow ultrasound beam will enhance the contrast, which helps in visualization of subtle abnormalities. These new technologies overcome some of the disadvantages and may be the start of a future in which 4DUS might be integrated more easily. With the expected incorporation of real-time 4D probes, together with the help of navigation techniques, interpretation and understanding of rendered ultrasound images, like we provided in this thesis, are important for the implementation of these new technologies. New techniques are introduced easily without proven to be beneficial. New technologies require good quality research before the introduction. A blinded trial with randomization to either 2DUS or 4DUS would not be possible due to ethical issues. Instead, 4DUS should be tested as an additional tool to 2DUS. A future study could be a large trial that analyzes if the addition of 4DUS to 2DUS increases the detection rate of cardiac defects. A patient should be randomized to one of the procedures (2DUS and 4DUS together or solely 2DUS) and should be examined within a strict time frame to secure clinical relevance for the daily practice. I would propose to include 2-3 volumes, each from a different angle, to minimize the risk of artifacts. This type of trial could be conducted in a third-level ultrasound center as well as in a screening setting. However, in screening centers a more extensive training of the sonographers should precede examination of the volumes. Although this might require more time and effort, screening centers could benefit most from additional screening methods due to a low prenatal detection rate of CHD. Furthermore, automatic retrieval of a 3D volume is more helpful for inexperienced examiners, who have more difficulty in transforming multiple 2DUS images into a 3D image in their mind than experienced examiners.

With increasing technology, 4DUS may also be useful for intra-uterine interventions. Crucial information normally only achieved in neonatal echocardiography can then be extended to the prenatal period, for example when fetuses present with aortic or pulmonary valve stenosis in early pregnancy. Aortic valvuloplasty might prevent the heart from evolution to hypoplastic left heart syndrome. Biventricular repair can be achieved in some cases if treatment is started in early pregnancy. Four-dimensional ultrasound could help to select the cases or equipment for fetal aortic balloon valvuloplasty by providing detailed information regarding the valve annulus and mobility of the leaflets of the aortic and mitral valve. These parameters are predictors of technical success and postnatal biventricular outcome.

Furthermore, the combination of 4DUS with the upcoming 3D printing could lead to a new era of imaging in the prenatal period. A 3D printed heart could be beneficial for detailed examination of complicated cardiac defects. For example, subtle details in specific cases of double outlet right ventricle can determine a bi- or univentricular repair. This can help to predict and prepare the optimal surgery. Furthermore 3D printing may be helpful in medical education.
This thesis provides an up-to-date overview of 4DUS and its clinical applications, especially with regards to the morphology of the valves of the fetal heart. Currently, the additional value of 4DUS is limited in a screening setting. The additional value of STIC in prenatal diagnosis has only been reported in third-level ultrasound centers with experienced sonographers. STIC proofed its usefulness by giving insight in fetal anatomy. Furthermore, STIC can be extremely useful for education. Training inexperienced sonographers to examine the fetal heart using STIC gives them the opportunity to get familiar with the anatomy of the fetal heart, the rendered views and the spatial relationships of the heart structures. With increasing technology and training of the sonographers 4DUS could be incorporated in daily practice in the future.
REFERENCES


