4.1. Tissue Tracking (TT) in Fetal Echocardiography

4.1.1. A Comparison of Previous Studies, Their Results and Our Findings

First studies utilized TT in fetal echocardiography came from two research groups Younoszai et al. (19) and Ta-Shma et al. (67). Younoszai et al. evaluated with VVI software myocardial mechanics in preselected regions along the endocardial border (Figure 42).

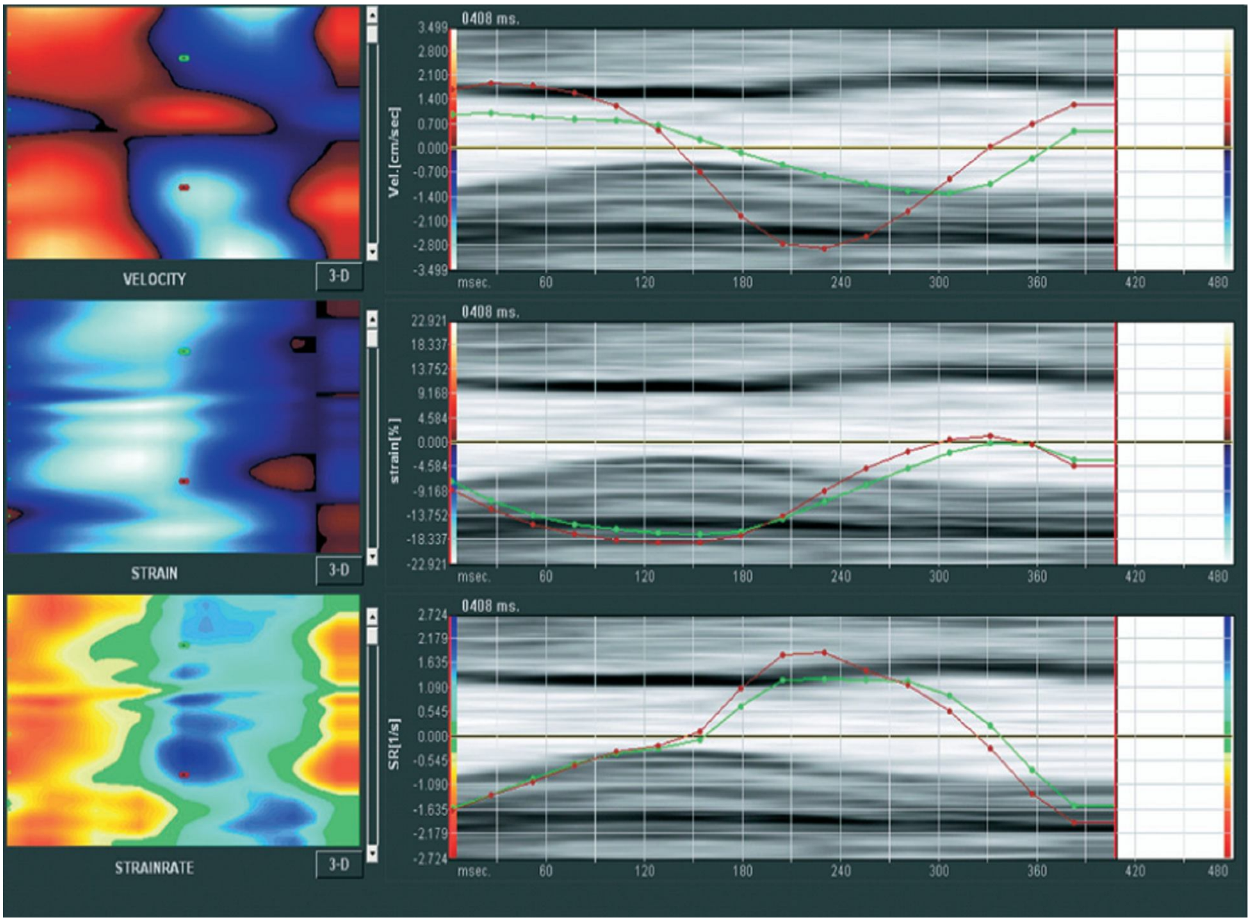

Fig. 42. Two random points in the mid portion of myocardium are selected to investigate S and SR. Regions evaluated for V measurements are not shown. On the left side the so called “Island Maps” for V, S and SR for very detailed analysis of myocardial motion and deformation especially in adult cardiology where the timing of certain short-living events are not a major problem. On the right side of the figure V, S and SR graphs.

According to their study design they measured longitudinal velocity (V) at right ventricular (RV) free wall, septum and left ventricular (LV) free wall at the level of the atrioventricular (AV) valves, and longitudinal systolic strain (S) and strain rate (SR) were measured in the midportion of the myocardium of the same 3 walls. They found that systolic and diastolic V increase with gestational age, a finding which is in accordance with our results. They additionally reported that S and SR were not found to have significant correlation with gestational age (GA) in any of the wall segments. This findings are not in accordance with our results since our findings speak for a gradual decrease in deformation parameters throughout the gestation. This discrepancy may have been resulted from the fact that Younoszai et al. investigated this features locally whereas we measured all parameters in segments and averaged the values to have a global picture of a ventricle. It is important to note that in this study the frame rate was relatively low for regular fetal imaging (30 frames per second). Although it is possible that septal values in different ventricles have similar figures and may represent each other it is not reported in this study whether this has been elucidated since they gave single values for septal parameters.

Younoszai et al. also evaluated the relationship between V, systolic SR, S and heart rate (HR). They concluded that there are no significant correlation between V and HR and S and HR. Our findings are only partly in conjunction with these findings since we determined a slight decrease in systolic RV V with increasing HR and marked increase in LV S with increasing HR. They stated that RV and septal SR increase with HR whereas on LV this was only a trend. Based on our collective we can say that both systolic and diastolic SR in both ventricles have significant correlation with HR and they increase with increasing HR. These discrepancies can be attributed to the relatively low number of evaluated fetuses (24 successfully evaluated cases from 27 recorded 4 Ch-view loops), relatively low frame rate used in this study and differences in sampling areas between the two studies.

Ta-Shma et al. analyzed 28 fetuses with Automatic Functional Imaging® (AFI) a similar software package from General Electric Medical Systems, Milwaukee, WI, USA. They chose an approach where the ventricular septum is not incorporated into the assessment process as shown on figure 43.

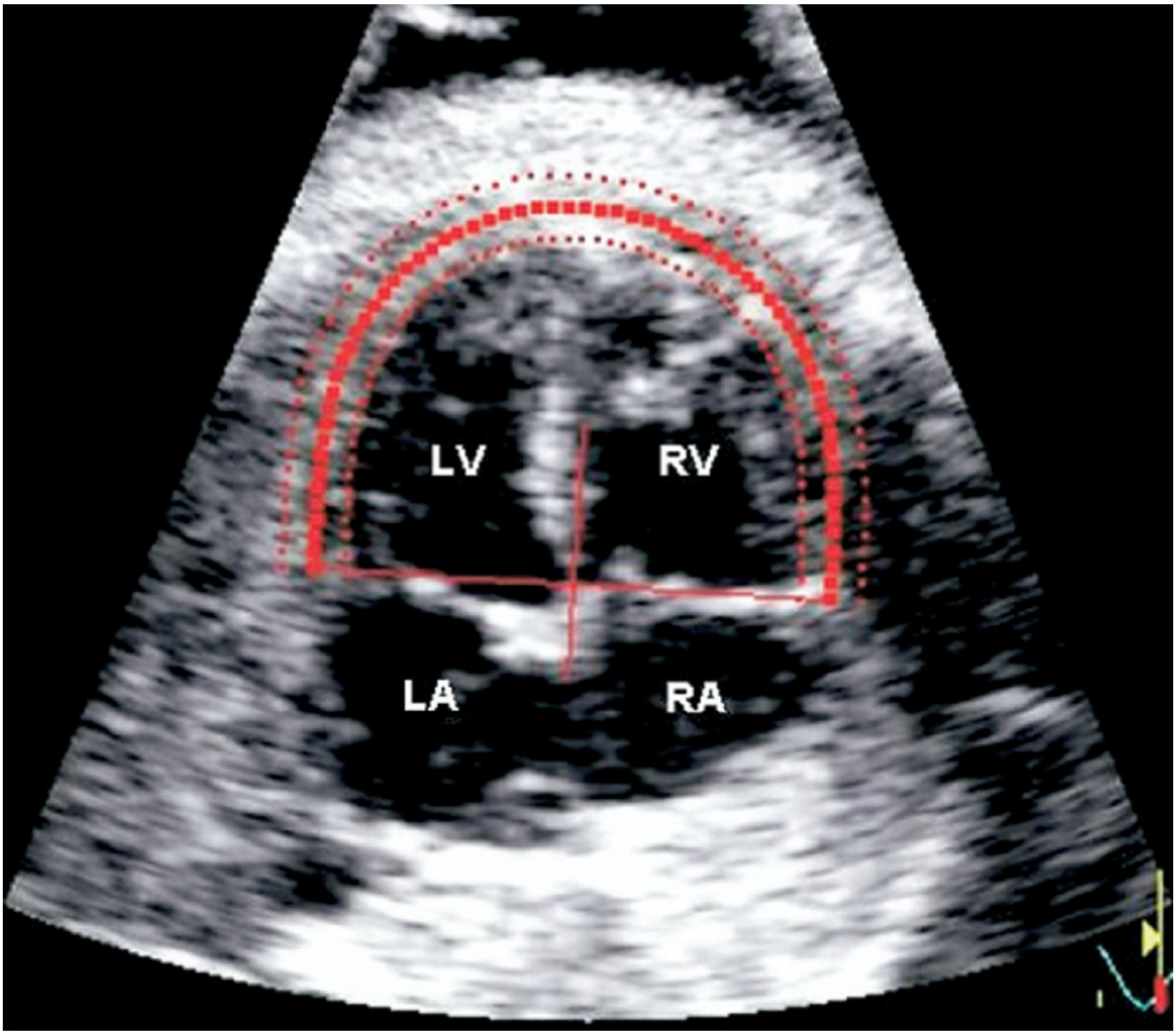

Fig. 43. Fetal 4 Ch-view. Both lateral walls and apex of the heart are assessed as a single unit. Notice that interventricular septum is not analyzed.

They obtained an U-shaped endocardial line stretches from one lateral wall to the other lateral wall of the fetal heart. They derived V, S and SR data at the level of the AV annulus. Additionally they combined both lateral LV and RV S and SR and so indicated a "Global Strain" and "Global Strain Rate". They concluded that RV V and S were higher and the LV V and S and that no difference in SR was shown when both sides compared. Their correlation revealed that segmental V increases on both sides and S does not change although there was a tendency in global S towards decrease with gestational age. They found that segmental SR and global SR decrease significantly during gestation. Despite different sampling regions our data are in large part in agreement with the data of Ta-Shma et al. Our data indicate, too, that both systolic and diastolic SR in both ventricles decrease as pregnancy advances. Our data indicate also that there is a significant relationship between S and gestational age which is more pronounced in RV than in LV. Global S in either ventricle shows a slight but statistically significant decrease as gestation proceeds.

Further studies were conducted by Barker et al. (20) and Di Salvo et al. (68) which recruited more cases to investigate with TT algorithms. Barker et al. used VVI to evaluate 33 normal and 15 fetuses with heart disease. Their strategy was the same used in our study. After definition of the cardiac cycle, the endocardium of one ventricle was traced manually from a single frame of the digital loop that provided the clearest stillframe endocardial border definition (Figure 44).

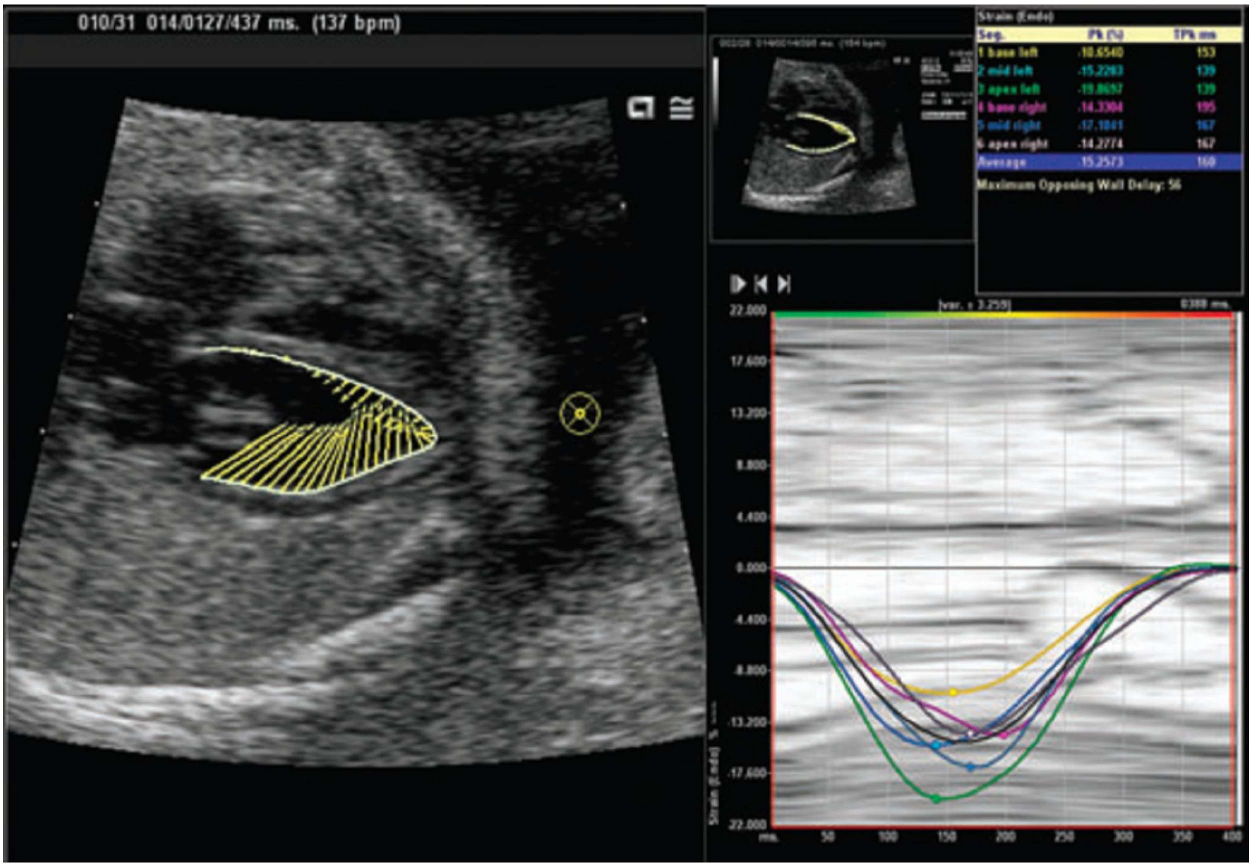

Fig. 44. After R-wave gating the endocardial border traced manually by the operator and a white continuous line establishes along the border. Yellow velocity vectors are seen radiating from the endocardial border, indicating that lateral velocities are higher than the medial ones.

The data were collected for either ventricles separately. Barker et. al observed systolic myocardial function only and presented the first results for systolic V, SR and S in a segmental and global fashion. They came to the conclusion that global values can be representative for all systolic parameters except basal velocities which differed significantly from the global velocities values. They reported that from 33 normal fetuses only in 22 cases V and SR could be analyzed. This may be a result of the fact that this research group analyzed only one single cardiac cycle in their study. According to our experience the beat to beat variability in fetuses are relatively high which makes a thorough assessment of any curve with TT very difficult if only one cardiac cycle is defined by the user. Since the V and SR data are sensitive to timing, for adequate temporal distribution of cardiac events more than one cardiac cycle is needed to get valid curves. This is one of the features of VVI which incorporates speckle periodicity to create more accurate “feature” tracking over several beats. When we compare our values with those values of Barker et al. we encounter similar results for mean and median V and S values but the ranges in S and SR were different then our ranges. Moreover there is a statistically significant difference between our systolic global SR and these from Barker study. We determined a lower mean and a narrower range for systolic SR for LV. RV global SR values were similar except a wider range in the study of Barker et al. We have no solid explanation why there are some discrepancies in ranges.

Di Salvo et al. recruited 100 normal fetuses. They investigated S only and postulated that S was homogeneously distributed in LV free wall, septum and RV free wall. Although they worked with AFI and hence traced the ventricles separately there is no indication in their paper whether they compared the septal values for statistical difference which might have justified the fact that they gave single value for the septum. Di Salvo et al. chose a transmural approach by selecting a different region of interest its outer border being adjusted to the epicardial border. They found that S values increase with gestational age but did not specify which S values were meant. There are various inconsistencies within the paper regarding what was being assessed and what the actual values are so it is necessary to review this work carefully. Our data indicate that global S in both ventricles decreases with gestational age.

The last paper on feature tracking is from Peng et al. who examined 151 normal fetuses (74). They investigated the V, S and SR gradient inside the LV free wall and septum and correlated their results with GA. They stated that systolic and diastolic V decreased from the basal to the apical segment but there was no difference in S and SR. The systolic and diastolic V was dependent on GA whereas S and SR were stable throughout gestation. As seen in Figure 45 they selected three arbitrary points along the endocardial border which can hardly be standardized since there is no measurement tool to verify the exact same place in every fetal ventricle.

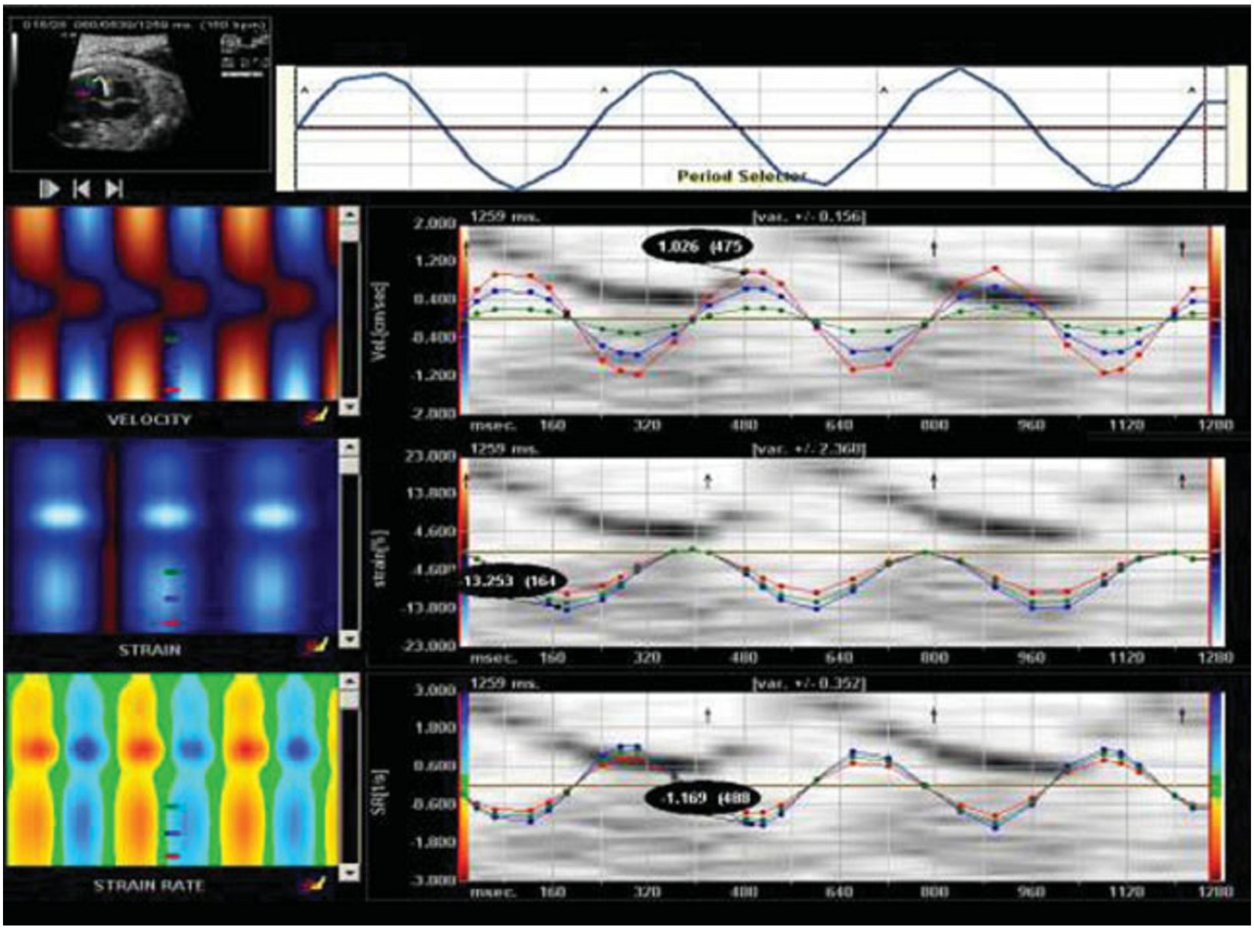

Fig. 45. Three points along the lateral wall of LV. It is difficult to place the points to the very same location in every analysis. Representative V, S and SR curves are shown to illustrate the progression in these parameters during heart cycle.

Peng et al. worked with a maximum frame rate of 40 frames per second (fps), which may be relatively low to depict peak values and slope changes in a fast beating fetal heart, and our results are only partly in conjunction with the data of this study. Both data have similar S values and systolic SR but we found statistically significantly higher systolic and diastolic V and diastolic SR values compared to the data of Peng et al.

Moreover our data suggest a slight decrease in S and relatively marked decrease in both systolic and diastolic SR in contrast to the data from this study group. These can be a manifestation of sampling site differences and relatively low frame rate used by Peng et al.

4.1.2. Our Feature Tracking Echocardiography Results

4.1.2.1. Motion Parameters

As the fetus develops and ages in the uterus there are clear changes in fetal heart mechanics. Both LV and RV become larger and the cavity size increases. The speed cardiac muscle moves with towards the apex and back to its first position increases as gestation proceeds since the length of myocardium and endocardium increases, respectively. Agreeable to the cardiac growth it is not surprising that there is moderately strong relationship between V and GA and Displacement (D) and GA. The relationships between RV diastolic V and HR and D in both ventricles and HR can be a result of the fact that higher heart frequencies are encountered in the beginning of the pregnancy where the cavity size is smaller and there is a well-known decrease in HR towards the end of gestation where the length of myocardium is maximum. One can hypothesize that there is a mutual effect on D both from GA and HR. It is important to note that the relationship between RV diastolic V and HR was relatively weak and is subject to further verification by studies with larger case numbers. The most striking feature of the cardiac motion is that the RV global diastolic V is higher than the LV global diastolic V. We lack a reasonable explanation for this result.

4.1.2.2. Deformation Parameters

The relationship between systolic and diastolic SR in both LV and RV and GA is statistically significant and is more pronounced in RV. While the effect of GA on LV SR is weaker, the link between HR and LV SR is stronger. This suggests that both ventricles have differing contractile properties and respond to the cardiac growth and HR changes varyingly strong. The finding that RV and LV S have similar relationships with GA but in different degrees, indicates, too, that both ventricles might possess varied contractility. This hypothesis is substantiated by the outcome that there is no significant relationship between RV S and HR and a weak but positive correlation exists between LV S and HR. The difference between RV and LV deformation becomes more clear when we compare LV and RV global diastolic SR, RV global diastolic SR being greater then the LV global diastolic SR. It is hard to interpret this difference between RV and LV diastolic SR. It is interesting to note that the diastolic V is higher in RV, too. These findings obviously indicate that RV myocardium needs to recover quicker than LV to be ready for the next cycle. It should be underlined here that V and SR are different concepts. V is a marker of the rapidity of a myocardial segment and SR is an indicator of the rapidity of the contraction which takes place within this myocardial segment. In the light of these two findings it can be said that RV owns a different relaxation pattern than LV. This could be attributable to the distinct myocardial architecture of the RV. For solid propositions these observations need to be verified by other research groups. Both parameters V and SR have great connection with the time, and it is rather difficult to interpret such findings since we lack exact determination methods for timing cardiac events in fetal echocardiography.

4.1.2.3. Strain as a Sign of Pump Function

As the myocardium contracts more pronounced the ejected blood ratio to the general circulation from either ventricle increases. The relationship between EF and S is stronger in RV which suggests that RV has a more deformation-dependent ejection function than LV ejection, which indicates that RV exhibits different contractile properties than LV has.

4.2. Critical Analysis of Our Study

4.2.1. Global Perspective Versus Regional Perspective

Ventricular function can be interpreted either from a global perspective as overall relaxation-contraction performance or from a regional perspective where the contributions of individual wall segments are taken into account. In this study we chose to evaluate the global systolic and diastolic cardiac function since we believe that changes appear significantly in the global assessment have the possibility to alter our consideration of fetal heart more soundly than finding out many parameters which change in a statistically relevant way.

4.2.2. Is every heart the same?

The contractile performance and relaxation capacity of a heart depend on many properties such as tissue composition, elasticity, fiber structure and global geometry (different morphology of RV and LV), which determine the local segmental interactions and the resulting wall stress (69). The interaction between the heart and peripheral circulation also plays a considerably important role in establishing of ventricular contraction and filling. In this study we worked under the assumption that the myocardial properties among subjects are uniform, homogenous and there are no differences between pressure and loading conditions in fetal circulations. This simplification may or may not play a crucial role in studying cardiac status with the feature tracking algorithm, since the measured indices derive from the speckle pattern of the scanned tissue not from the actual tissue. Although the studied subjects did not present any Doppler flow abnormalities, still this should be mentioned as a potential bias.

4.2.3. No Comparison with Another Method

Although it was not one of the study aims, the estimation of internal pressure changes and ejected blood volume of respective ventricle via pulsed Doppler could have provided a method to verify the values generated by means of 2D grey-scale images. Blood flow readings and their derivatives for pressure and cardiac output could be a way to assess the agreement of Doppler and TT studies. Furthermore EF values could be verified by STIC volumes in 4 Ch-view. However this would exceed the level of competence of the examiner.

4.2.4. Other Limitations of Our Study

Limitations to our study were mostly software and algorithm related, related to the fact that the analysis is based on 2D video clips and that myocardial motion and deformation are complex.

4.2.4.1. The Nature of Fetal Echocardiographic Examination

Any 2D based system that relies on Tissue Tracking (TT) needs good quality images. However, in daily practice it is difficult to obtain good quality images every time and as a consequence the feasibility ratio goes down. In favor of high frame rate acquisition we sacrificed image quality. Fetal motion including respiratory excursion and body constitution and abdominal breathing movements of the participants were limiting in gaining good quality and stable images. Since analysis is affected by the quality of the gray scale image, and artifacts such as shadowing could have led to erroneous strain rates, we excluded many video clips (42 due to excessive fetal motion, 5 unfavorable fetal lie, 24 due to no tracking [adequate images in high frame rates] and technical error [not captured as video clips], 16 poor image quality (includes improper visualization of first trimester fetal hearts and shadowing), 3 pronounced translational motion of the fetal heart, 3 wrong positioning of cardiac chambers due to inexperience of the examiner)

4.2.4.2. Issues Related to Software and Algorithm

- It has been investigated that the accuracy of the strain component which is perpendicular to axial axis was poor in the long axis cardiac imaging and in imaging the chambers at an angle. In fetal cardiac imaging, in case of a lateral 4Ch-view or an oblique presentation (when ultrasound wave is perpendicular to or hit the ventricular septum at an angle), there could be variability between consequent measurements (75). This article tested another algorithm which is not utilized in this study, but a similar phenomenon in Feature Tracking could be accounted for the variability we observed in our data. Same opinion has been issued by Yue et al. (76). The variation within estimations might have been caused by system noise, tissue deformation and speckle decorrelation. Speckle decorrelation has the most profund effect on texture variation. All types of spatial motion can result in speckle decorrelation. Speckle decorrelation along the longitudinal (axial) motion is usually solved by relying on the similarity between speckle patterns, whereas speckle decorrelation due to elevational (perpendicular to the image plane) and lateral motion may be generally difficult to track, since pixels observed in one frame may move out of the scanning plane in the next frame. This possible interruption of speckle pattern between frames may have resulted in different calculations therefore in different results and can be accounted for excluded cases despite adequate image quality.

- That the intrinsic spatial resolution of the images in TTE are limited and that the lateral resolution of ultrasound images intrinsically less than in the axial direction is, were unknown to us prior to and during this study (77). In order to maximize the frame rate we adjusted the scanning field as narrow as possible. Since we were close to the outer contour of the fetal heart we encountered poor tracking results since the lateral resolution worsened as we were too close to the lateral attachments of atrioventricular valves.
- Algorithm with which we worked in this study employs at one of its calculation steps cross-correlation approach for estimating the shift in the speckle patterns, which is of limited usefulness both when the deformations are either very small (stiffer, less compliant tissue) or very large (fast moving, relatively greatly deforming tissue) between frames (78). For example, when the speckle motion between successive frames is only a fraction of a pixel, cross-correlation approaches lack the resolution to robustly track the shift. Such a case would dictate high enough sample rates to ensure that speckles remain correlated at least through several image acquisitions. At the other extreme, relatively large tissue movement rapidly decorrelates the speckle pattern from one frame to the other frame, limiting the large-motion applicability of correlation based approaches. In this work we aimed to obtain the highest frame rate one can obtain within the scope of fetal echocardiography to minimize these limitations. Our average Interframe Time (IFT, the time between two frames) speaks for this effort but the question still remains to be answered why we were not able to depict the separation of diastolic information into early and late phases in every curve.
- In a few cases there has been a shift of the beginning of Velocity curve to the diastole where we observed the E and A wave in the systole. In this cases the

Displacement data were distorted, too, so we reversed the peak values accordingly. Figure 46 represents an example of the shift.

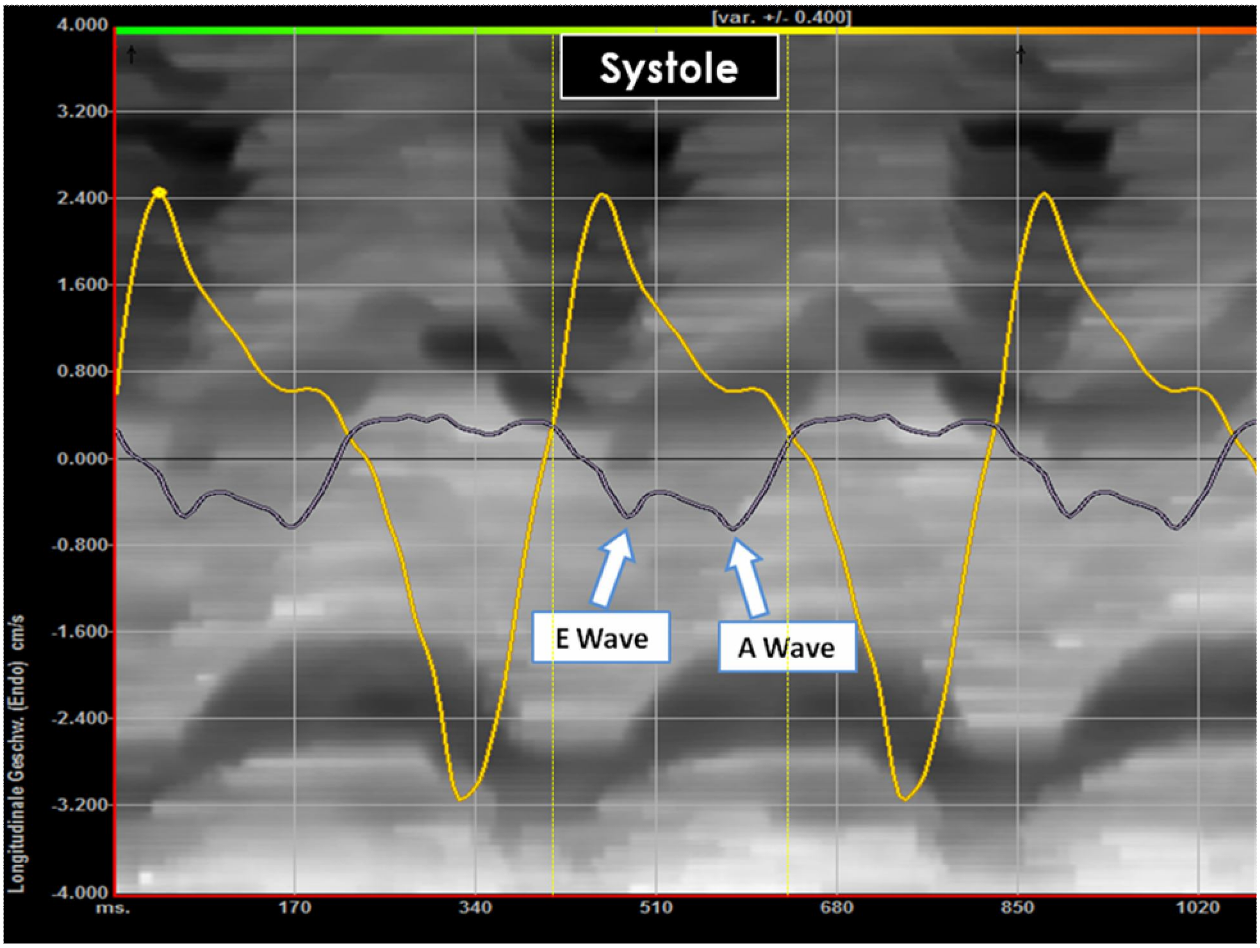

Fig. 46. The shift of reference point in Velocity curves. Yellow curve follows a regular pattern whereas grey curve exhibits a reversed course during systole and diastole. According to the shift the displacement showed an up-side-down fashion.

- During our study it was noticeable that Strain values in the basal regions of either ventricle tend to vary greatly. We regard this as a major handicap of the algorithm. When there was considerably amount of inconsistency within two consecutive Strain measurements in basal regions we repeated the trace until similar values were achieved to not to underestimate the deformation. An example is shown in the figure 47.

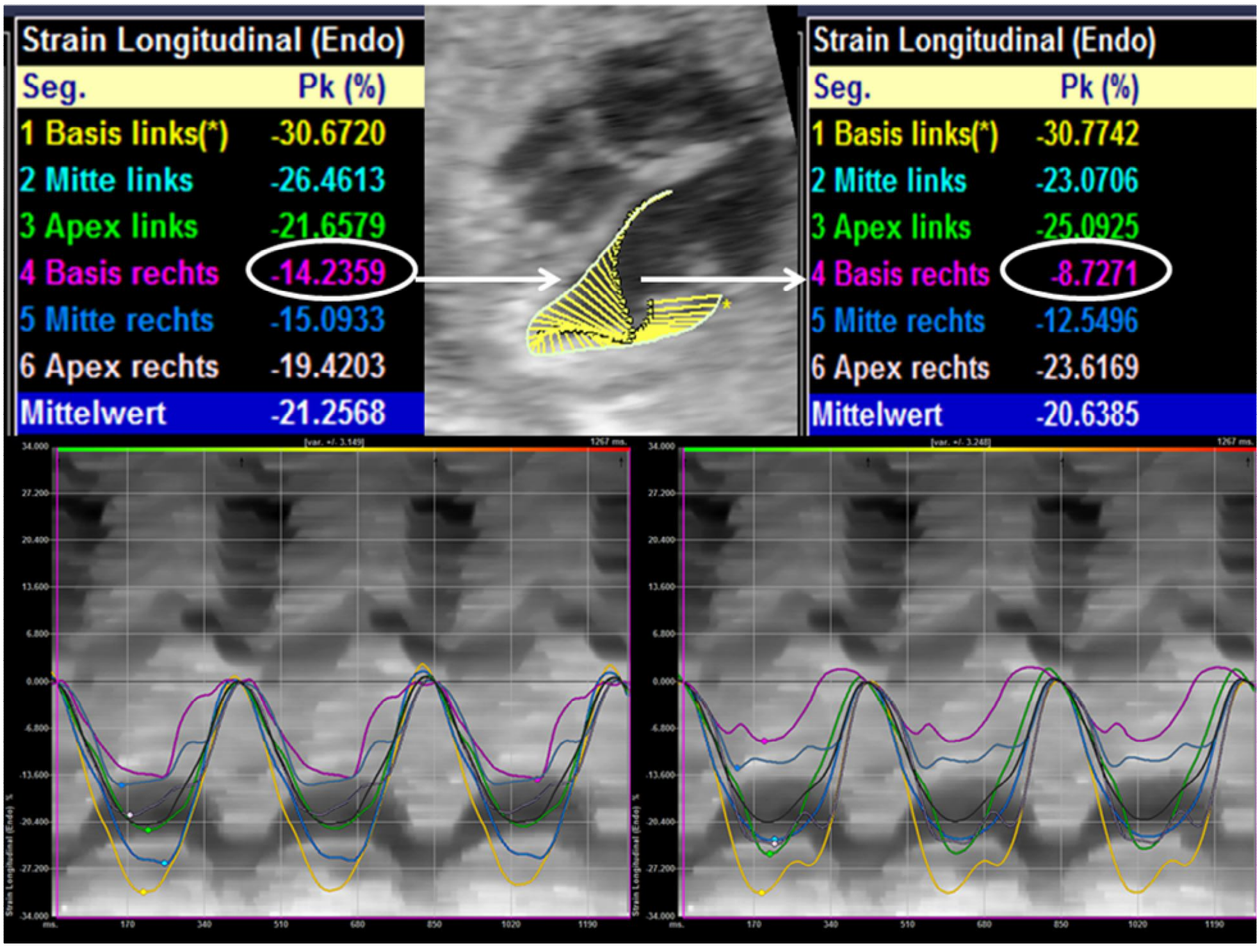

Fig. 47. Striking variation between basal S estimation at the septum at the atrioventricular (AV) valve level. To prevent any inaccuracy between the dataset we rerun the trace until we achieved valid values. This error was common to the AV level Strain estimation only and indicates strongly a need of fetal ventricular model for VVI.

- Tissue motion and deformation of both ventricles were evaluated by a technique which is originally developed for the analysis of the left ventricle. RV strain and strain rate were calculated using a LV-derived six-segment model, which may not accurately reflect the more complex geometry of the right ventricle. Moreover the chamber size, the magnitude of velocities and the variability in heart rate distinguish fetal heart from pediatric and adult heart. There is no profound previous knowledge acquired under these unique circumstances in utero.

- We showed that the method was practically not feasible in every case in the sense of robust estimation.
- The technique is highly computionally intensive and time-consuming, which makes its current application to 2D images impractical.

4.3. Future Directions

- Both acquisition and storage of image clips were relatively time consuming, and off-line strain analysis usually took more than 15 minutes or longer per fetus. As with all echocardiographic measurements, the measurement of strain and strain rate was limited by image and signal quality. The profile signal of the curves tends to be noisy with current technology, and determination of peak values is difficult and variable. A possible clinical application of strain analysis by feature tracking technique will depend on the parallel development of faster acquisition and analysis programs. Improving the signal quality will enable reliable and reproducible measurements during fetal heart imaging. In order to investigate regional cardiac mechanical activity both temporal and spatial accuracy need to be improved significantly.
- Since the calculation occurs over speckle pattern changes, interruption of the pattern over frames might influence the calculation algorithm and its effect on value generation needs further investigation, especially in instances where the alignment is not parallel to the ultrasound beam.
- The study includes a low number of subjects. We must consider enrolling and evaluation of larger numbers of cases to establish the possible role of the Tissue Tracking (TT) in Fetal Echocardiography. Despite the low number of analyzed digital loops in this investigation, the data obtained are indicative of a future role of TT if the tracking performance and calculation algorithm will be improved and the time of case processing will be lowered for clinical application. This will facilitate the research on fetuses in disadvantageous intrauterine environment and fetuses with cardiovascular abnormalities. In this stage of development TT in fetal echocardiography will remain as a research tool.

- The optimal data set which to analyse myocardial function with would be the one that defines wall deformation characteristics in three dimensions and in real time. Combination of 4D ultrasound and more robust and less error-prone tracking techniques could reveal an exact cardiac state in utero.
- Future efforts should focus on the possibility of higher frame rate acquisition since it is not possible to determine short-living occurrences with the current software. This approach would open the door to the fetal rhythmology in the absence of electrical correlate of the heart activity and may simultaneously provide most reliable data on myocardial mechanics both globally and regionally.