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Title: Tissue Doppler and speckle tracking strain echocardiography: from evaluation in healthy children to follow-up after surgery for a congenital heart defect
Issue Date: 2014-01-09
Longitudinal follow-up of ventricular performance in healthy neonates

Early Hum Dev 2013

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ABSTRACT

Background  Specific follow-up of newly introduced echocardiographic parameters in healthy neonates and infants is limited.

Aim  To prospectively describe follow-up of left ventricular (LV) tissue Doppler imaging (TDI) and speckle tracking strain parameters in healthy subjects up to two months after birth.

Design  This is a longitudinal follow-up study.

Subjects  Twenty-eight (10 male) healthy newborns were included and underwent transthoracic echocardiography 1-3 days, 3 weeks and 6-7 weeks after birth.

Outcome measures  In each echocardiogram, parameters describing cardiac growth, including LV mass (LVM), were assessed. Additionally, TDI derived peak systolic velocity (S’) and peak early (E’) and late (A’) diastolic velocities were assessed in the basal LV free wall and interventricular septum (IVS). Finally LV longitudinal, radial and circumferential global peak strain parameters were assessed using speckle tracking strain imaging.

Results  LVM significantly increased during follow-up (7.6±2.4 versus 12.4±3.2g, p=0.002). Similarly at 1-3 days versus 6-7 weeks after birth, an increase in LV and IVS systolic (LV S’ 4.1±1.5 versus 6.3±1.5cm/s, p=0.001; IVS S’ 3.6±0.9 versus 6.4±1.3cm/s, p<0.001) and diastolic (LV E’ 6.1±2.2 versus 9.7±2.9cm/s, p=0.002; IVS E’ 5.1±1.4 versus 10.7±3.3cm/s, p<0.001) TDI parameters was observed. In contrast, global peak longitudinal, radial and circumferential strain parameters did not significantly change during follow-up.

Conclusions  A significant increase in LV systolic and diastolic TDI parameters was observed up to two months after birth. Yet this increase may be (cardiac) growth-dependent. No significant changes were observed in speckle tracking strain derived global peak strain parameters; this may render the technique particularly valuable in evaluation of LV systolic performance during periods of significant growth, such as the neonatal period.
INTRODUCTION
Patients with a congenital heart defect frequently undergo surgery in the first weeks to months of life. Preoperative monitoring and postoperative monitoring of biventricular performance in these patients is important and is often assessed using echocardiography. Yet especially in these first few weeks of life hemodynamic and growth related changes occur, which may influence echocardiographic parameters. Accordingly, follow-up of echocardiographic parameters in healthy neonates and infants is important to allow correct interpretation of echocardiographic parameters in patients born with cardiac disease.

Speckle tracking strain imaging and tissue Doppler imaging (TDI) are relatively new echocardiographic techniques which have been shown to detect subtle alterations of left ventricular (LV) performance in both adults and children. The few previous follow-up studies in healthy neonates and infants using TDI have suggested that LV systolic performance and diastolic performance increase up to one year after birth. A prospective follow-up study of LV performance in the first months of life using speckle tracking strain imaging has not been performed. Accordingly, we aimed to prospectively describe follow-up of LV TDI and speckle tracking strain parameters in healthy subjects up to two months after birth.

METHODS
In this prospective follow-up study, healthy newborns who were born in the Leiden University Medical Center were enrolled. Subjects were eligible for inclusion if they were born term (37-42 weeks) and echocardiographic evaluation showed structurally normal hearts with a normal cardiac function. Exclusion criteria were factors influencing neonatal cardiac function (e.g. maternal diabetes mellitus or maternal use of cardiovascular medication). If present, the neonate was not eligible for inclusion in the study. The institutional review board approved this study and written informed consent was obtained from the parents.

Demographic parameters including gestational age and sex were documented at study inclusion. All subjects underwent transthoracic echocardiography at several time points, namely at the ages of 1-3 days, 3 weeks and 6-7 weeks.

Echocardiography
Echocardiography was performed using a commercially available system (Vivid-7.0.0, General Electric Vingmed Ultrasound, Horten, Norway) and included recordings of M-Mode, Doppler flow, TDI and grayscale images. Images were stored in digital format to allow off-line analyses using EchoPac version 11.1.8 (General Electric Vingmed). All subjects were in sinus rhythm at the time of echocardiographic investigation.
**M-mode and Doppler flow**

In M-mode recordings of the LV long axis LV internal diameter at end-diastole (LVIDd) and at end-systole (LVIDs), as well as ventricular septal wall thickness (VSTd) and LV posterior wall thickness (PWTd) at end-diastole, were assessed in centimeters (cm). Subsequently LV mass (LVM) was calculated using LVIDd, VSTd, and PWTd, as previously described.

Furthermore, to conventionally assess LV systolic performance, LVIDd and LVIDs were combined to calculate fractional shortening (FS, %) as follows: \((\text{LVIDd}-\text{LVIDs})/\text{LVIDd} \times 100\%\). To conventionally assess LV diastolic performance, peak mitral early wave velocity (E, m/s) was measured in spectral Doppler tracings recorded in the apical four-chamber view at the tip of the mitral valve.

**TDI**

In addition to conventional parameters, LV systolic performance and diastolic performance were assessed using pulsed wave TDI. TDI images were obtained in two-dimensional images of the four-chamber view throughout three consecutive cardiac cycles. The angle of insonation was adjusted to align the ultrasound beam along the direction of myocardial motion. Subsequently, myocardial velocity curves were acquired by placing the cursor at the basal part of the LV lateral wall and interventricular septum (IVS). In each myocardial velocity curve peak systolic velocities (S'), peak early diastolic velocities (E') and peak late diastolic velocities (A') were assessed. In addition, LV E/E', a diastolic parameter strongly correlated with ventricular filling pressure, was calculated for further assessment of LV performance.

**Speckle tracking strain imaging**

Finally, speckle tracking strain analysis was used to assess LV systolic performance. Speckle tracking strain analysis was performed in grayscale images of the apical four-chamber view (longitudinal analysis) and the LV parasternal short-axis view at the level of the papillary muscle (radial and circumferential analyses). In these images, manual endocardial border tracing at end-systole was used to set the region of interest. The region of interest was automatically divided into six segments for further analysis. In the four-chamber view this included the basal, mid and apical segments of the LV lateral wall and of the IVS. The short-axis image was divided into septal, anteroseptal, anterior, lateral, posterior and inferior segments to evaluate both radial and circumferential strain.

Data obtained by speckle tracking were displayed in longitudinal time-strain curves for each segment in the four-chamber view and radial and circumferential time-strain curves for each segment in the short-axis view. From these time-strain curves segmental peak strain was obtained. Peak radial strain was defined as the most positive strain value and peak longitudinal
and circumferential strain as the most negative strain value at any time point during one cardiac cycle. The mean strain of the six segments in one view was calculated and constituted the global peak strain. Intra- and interobserver variability of speckle tracking strain parameters in children have been previously published by our group.\textsuperscript{12}

**Statistics**

Normally distributed data are expressed as mean ± standard deviation. Non-normally distributed data are expressed as median (interquartile range). At first, the Friedman test was used to assess whether differences were present in echocardiographic parameters between the three measurement occasions. If the Friedman test indicated a significant difference, the Wilcoxon signed rank test was used to more specifically assess this difference, by comparing echocardiographic parameters at the ages of 1-3 days versus 3 weeks, 3 weeks versus 6-7 weeks and 1-3 days versus 6-7 weeks. Finally, the percentile change in LVM, weight, LV S’ and IVS S’ 1-3 days versus 6-7 weeks after birth was calculated. These parameters were subsequently used to assess the correlation between changes in LVM and weight versus changes in LV systolic TDI parameters using scatter plots and Spearman’s rank tests. Data analysis was performed using SPSS 20. A p-value <0.05 was considered statistically significant.

**RESULTS**

A total of 28 (10 male, 36 %) healthy newborns were included in this prospective follow-up study. The mean gestational age at birth in the study population was 40+0 weeks. Transthoracic echocardiograms were performed at a median age of 2 (2-3) days (N=28), 23 (19-30) days (N=19) and 48 (44-53) days (N=23).

A significant increase in weight was observed in healthy subjects 1-3 days versus 6-7 weeks after birth (3.5 ± 0.5 versus 4.9 ± 0.7, p<0.001). Similarly parameters describing cardiac growth, including LVIDs and LVM, significantly increased during follow-up (1-3 days versus 6-7 weeks after birth: LVIDs 1.1 ± 0.2 versus 1.4 ± 0.2 cm, p=0.001; LVM 7.6 ± 2.4 versus 12.4 ± 3.2 g, p=0.002).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>1-3 days</th>
<th>3 weeks</th>
<th>6-7 weeks</th>
<th>Friedman test</th>
<th>P-Value 1-3 days versus 3 weeks</th>
<th>P-Value 3 weeks versus 6-7 weeks</th>
<th>P-Value 1-3 days versus 6-7 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>100'04</td>
<td>100'04</td>
<td>100'04</td>
<td>0.09</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.39</td>
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<td>LVIDd (cm)</td>
<td>0'90</td>
<td>1'02</td>
<td>1'04</td>
<td>0.03</td>
<td>4.1 ± 1.5</td>
<td>6.3 ± 1.5</td>
<td>0.002</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>0'10</td>
<td>0'04</td>
<td>0'04</td>
<td>0.002</td>
<td>5.2 ± 1.5</td>
<td>6.3 ± 1.5</td>
<td>0.004</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>0'09</td>
<td>0'22</td>
<td>0'25</td>
<td>0.03</td>
<td>7.6 ± 2.4</td>
<td>10.2 ± 3.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0'04</td>
<td>0'04</td>
<td>0'04</td>
<td>0.004</td>
<td>3.5 ± 0.5</td>
<td>1.9 ± 0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Global peak longitudinal strain (%)</td>
<td>0'04</td>
<td>0'04</td>
<td>0'04</td>
<td>0.06</td>
<td>4.9 ± 1.7</td>
<td>6.4 ± 1.3</td>
<td>0.09</td>
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<tr>
<td>Global peak radial strain (%)</td>
<td>0'04</td>
<td>0'04</td>
<td>0'04</td>
<td>0.03</td>
<td>3.6 ± 1.6</td>
<td>5.5 ± 1.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Global peak circumferential strain (%)</td>
<td>0'04</td>
<td>0'04</td>
<td>0'04</td>
<td>0.002</td>
<td>4.1 ± 1.5</td>
<td>6.3 ± 1.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

FS, Fractional shortening; IVS, Interventricular septum; LV, Left ventricle; LVIDd, Left ventricular internal diameter at end-diastole; LVIDs, Left ventricular internal diameter at end-systole; LVM, Left ventricular mass.
Systolic performance

An increase was observed in LV S’ and IVS S’ during our follow-up (1-3 days versus 6-7 weeks after birth LV S’ 4.1 ± 1.5 cm/s versus 6.3 ± 1.5, p=0.001; IVS S’ 3.6 ± 0.9 versus 6.4 ± 1.3 cm/s, p<0.001; Table 1, Figure 1). No significant associations were observed between the percentile changes in weight and LVM versus the percentile change in LV S’ during our follow-up. However, a larger percentile change in weight 1-3 days versus 6-7 weeks after birth was associated with a larger percentile increase in IVS S’ (p<0.001, R²=0.63; Figure 2). A similar association was observed between the percentile change in LVM and the percentile change in IVS S’ (p=0.02, R²=0.33).

In contrast to TDI parameters, neither FS nor global peak longitudinal, radial or circumferential strain parameters significantly changed during our follow-up period (1-3 days versus 3 weeks versus 6-7 weeks after birth: FS 38 ± 5 versus 34 ± 5 versus 34 ± 6, p=0.06; global peak longitudinal strain -18.8 ± 3.5 versus -18.6 ± 2.5 versus -19.4 ± 2.3 %, P=0.09; global peak radial strain 29.4 ± 12.2 versus 31.1 ± 15.2 versus 32.3 ± 12.0%, p=0.92; global peak circumferential strain -19.7 ± 4.3 versus -20.5 ± 4.5 versus -19.6 ± 4.9 %, p=0.78).

Diastolic performance

A significant increase was observed in MV E during our follow-up (1-3 days versus 6-7 weeks after birth 0.6 ± 0.1 versus 1.0 ± 0.2 m/s, p<0.001). Similarly, LV diastolic TDI parameters, including LV E’, IVS E’, and IVS A’, significantly increased during the first 6-7 weeks of life (1-3 days versus 6-7 weeks after birth LV E’ 6.1 ± 2.2 versus 9.7 ± 2.9 cm/s, p=0.002; IVS E’ 5.1 ± 1.4 versus 10.7 ± 3.3 cm/s, p<0.001; Table 2). No significant differences were observed in LV E/E’ during follow-up (Table 2).

Figure 1. Follow-up of echocardiographic parameters in healthy neonates and infants

Box plots depicting mean and 95% confidence interval of the mean of LV tissue Doppler imaging and speckle tracking strain parameters during follow-up.

IVS, interventricular septum; LV, left ventricular; S’, peak systolic tissue Doppler imaging velocity.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>1-3 days</th>
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<th>P-value 3 weeks versus 6-7 weeks</th>
<th>P-value 1-3 days versus 6-7 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV E' (cm/s)</td>
<td>0.6 ± 0.1</td>
<td>0.9 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>0.03</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>LV E' (cm/s)</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.3</td>
<td>0.7 ± 0.3</td>
<td>0.03</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>IVS E' (cm/s)</td>
<td>5.1 ± 1.4</td>
<td>9.3 ± 3.3</td>
<td>10.7 ± 3.9</td>
<td>0.06</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>A' (cm/s)</td>
<td>0.1 ± 0.2</td>
<td>0.4 ± 0.8</td>
<td>0.7 ± 0.4</td>
<td>0.03</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>MV E/E'</td>
<td>1.2 ± 0.9</td>
<td>1.2 ± 0.9</td>
<td>1.0 ± 0.6</td>
<td>0.58</td>
<td>0.14</td>
<td>0.04</td>
</tr>
<tr>
<td>IVS E/E'</td>
<td>1.2 ± 0.9</td>
<td>1.2 ± 0.9</td>
<td>1.0 ± 0.6</td>
<td>0.58</td>
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<td>0.14</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Notes
- MV: mitral valve.
- LV: left ventricle.
- IVS: interventricular septum.
- MV E/E': mitral E to E' ratio.
- LV E/E': left ventricular E to E' ratio.
- IVS E/E': interventricular septum E to E' ratio.
- A': peak late diastolic tissue Doppler imaging velocity.
- E': peak early diastolic tissue Doppler imaging velocity.
DISCUSSION

Current results describe a significant increase in parameters describing (cardiac) growth and LV systolic and diastolic TDI parameters two months after birth compared with 1-3 days after birth. In contrast, no significant changes were observed in speckle tracking strain parameters within the first two months after birth.

Systolic performance

TDI

The observed increase in LV systolic TDI parameters during our follow-up is in line with the few previous studies in healthy neonates and infants using TDI.\cite{6,7,13} In these studies LV S’ was described to increase up to three months after birth.\cite{6,7} Furthermore, significantly higher LV systolic TDI velocities have been described in children (mean age of 9.0 years) as compared to neonates.\cite{13} This significant increase in LV systolic TDI parameters during the first 7 weeks of life could reflect an increase in LV systolic performance. Furthermore, changes in translational movement of the heart and loading alterations could influence TDI parameters in the early postnatal period, as previously suggested.\cite{6,7} However, changes in (cardiac) growth may also be a major determinant of TDI velocities in neonates and infants.

![Figure 2. Correlation between percentile changes in weight and IVS S’ 1-3 days versus 6-7 weeks after birth.](image)

Previously in fetuses and children a significant influence of (cardiac) growth on TDI parameters has been described.\cite{14,15} These studies have resulted in the publication of Z-scores of TDI-parameters in children.\cite{16} However, in neonates and infants the influence of (cardiac) growth on TDI parameters has been under-exposed thus far. Especially in the first few months of life significant (cardiac) growth is observed,\cite{17} as supported by the significant changes in parameters describing (cardiac) growth in our study. Hence, current results encourage a more specific study in healthy neonates and infants to check the validity of previously published Z-scores, considering the rapid changes observed in parameters describing cardiac growth in this population.
Studies describing reference values of echocardiographic parameters and influence of (cardiac) growth in healthy children are important to remain responsible in the use of the multitude of new echocardiographic parameters in children. An underlying influence of (cardiac) growth-related alterations on the changes in TDI parameters during longitudinal follow-up in pediatric subjects is an important consideration when evaluating results. Therefore knowledge of these characteristics in healthy children is vital before ‘abnormal’ observations in children with a cardiac disease can be distinguished.

Furthermore, if (cardiac) growth is indeed a major determinant of changes in TDI parameters in healthy subjects in the first few months of life, this may also be the underlying reason for the observed significant differences in LV S’ between term and preterm neonates\textsuperscript{18} and between small and appropriate for gestational age neonates.\textsuperscript{19,20} Similar to our results, significant differences in TDI parameters and parameters describing cardiac growth were described between subgroups in these studies.\textsuperscript{18,19}

**Speckle tracking strain imaging**

In contrast to TDI parameters, no changes were observed in speckle tracking strain derived parameters during our follow-up. These results are in line with the only previous study using speckle tracking strain imaging in healthy neonates and infants. In this study, no significant difference was observed in LV longitudinal or circumferential strain measurements in 1-3 day old neonates compared to one or three month old subjects.\textsuperscript{21} Yet, our study is the first to describe the lack of change in speckle tracking strain parameters using a prospective study design. Furthermore, radial strain was assessed, in addition to longitudinal and circumferential strain, in our study.

LV peak systolic longitudinal strain has been previously assessed in neonates using TDI derived strain parameters.\textsuperscript{22} In contrast to our study, a significant decrease was observed in LV peak systolic longitudinal strain within the first month after birth in this study.\textsuperscript{22} These contrasting results may be explained by the use of TDI derived peak strain measurements, instead of speckle tracking strain derived parameters, in the study by Pena et al.\textsuperscript{22} Considering previously described growth-dependence of TDI parameters, the TDI derived strain parameters may also be influenced by (cardiac) growth. Furthermore, echocardiograms were obtained within the first 24 hours after birth in these subjects, a period in which hemodynamic changes are more prominent than 1-3 days postnatally, as elaborately discussed below.

Considering previously described significant changes in parameters describing (cardiac) growth during follow-up, the absence of changes in global peak strain parameters in our study suggests no relation between these parameters and age. A lack of relation between parameters describing
cardiac growth and strain parameters is in line with most previous studies in children and fetuses. While Marcus et al.\textsuperscript{23} described a significant correlation between age and strain in healthy children, no significant correlation was observed in two other studies in the pediatric age group.\textsuperscript{12,24} Furthermore LV strain parameters have been described to be stable during gestation.\textsuperscript{25,26} The stability of LV speckle tracking strain parameters during the first few weeks to months of life may render this technique particularly valuable in evaluation of LV systolic performance during periods of significant growth, such as the fetal and neonatal period.

**Diastolic performance**

Current results revealed significant changes in LV diastolic TDI parameters 1-3 days compared to 6-7 weeks after birth. These results are in line with previous studies in healthy neonates and infants, which described an increase in LV E’ and decrease in LV E/E’ up to six months after birth.\textsuperscript{6,7}

Similar to changes in LV systolic performance parameters, changes in diastolic TDI parameters may in part be caused by (cardiac) growth. However, an additional influence of alterations in LV diastolic performance on the observed changes in diastolic TDI parameters is also probable. This hypothesis is supported by the observed increase in MV E during follow-up in our study, and in several previous studies in healthy neonates and infants using Doppler flow imaging to describe LV diastolic performance.\textsuperscript{3,27} In these studies, the changes in Doppler flow parameters were suggested to be the result of an increase in LV diastolic performance up to 6 months after birth. Decreasing pulmonary vascular resistance and adjustments of the collagen content of the myocardium were proposed to be the cause of this ongoing increase in LV diastolic performance.\textsuperscript{3,28}

**Study limitations**

The sample size of this prospective follow-up study was relatively small. This limits the power of our analyses of the correlation between the percentile change in TDI parameters and the percentile change in parameters describing (cardiac) growth. Accordingly, a study with a larger sample size, which specifically focuses on this association, is necessary to check our suggestion of a significant influence of (cardiac) growth on changes observed in TDI parameters in neonates and young infants.

As the heart transfers from the fetal to neonatal circulation important hemodynamic alterations occur, which may influence echocardiographic parameters. The direction of shunting through the ductus arteriosus changes and the ductus arteriosus closes.\textsuperscript{22} In addition, the pulmonary vascular resistance decreases, stimulating pulmonary blood flow, and the systemic vascular resistance increases.\textsuperscript{22} These changes lead to alterations in loading conditions, including
an increase in LV preload and afterload. As both TDI parameters and speckle tracking strain parameters may be affected by acute loading alterations, this may cloud correct interpretation of echocardiographic results. Furthermore, the functional capacity of the LV may be transiently affected by occult myocardial injury during the transition period, as suggested by a recent study comparing fetal and neonatal TDI parameters. Yet, the most prominent hemodynamic changes take place within the first 24 hours after birth. Accordingly, to minimize the influence of postnatal hemodynamic changes the first echocardiogram was performed more than 24 hours after birth.

In the present study we focused solely on the left ventricle. However, right ventricular (RV) TDI parameters have also been described in neonates and infants. An increase in RV S’ was observed within the first week after birth. Furthermore, RV S’, E’ and A’ parameters significantly increased in time within the first year after birth. Hence, these results suggest that RV TDI parameters also increase after birth, which may be the result of (cardiac) growth as well. Yet, this conclusion remains highly speculative and future studies should be conducted to check this suggestion.

CONCLUSIONS
A significant increase was observed in LV systolic and diastolic TDI parameters in healthy subjects 1-3 days versus 6-7 weeks after birth. This could be caused by an ongoing increase in LV performance. Yet the possible (cardiac) growth-dependence of TDI parameters in combination with the significant changes observed in parameters describing cardiac growth in neonates and infants suggests that the observed changes may in part be growth-related. In contrast to TDI parameters, no significant changes were observed in speckle tracking strain derived global peak strain parameters during our follow-up. This stability may render this technique particularly valuable in evaluation of LV systolic performance during periods of significant growth, such as the fetal and neonatal period.
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