Assessment of myocardial function in preterm infants with patent ductus arteriosus using tissue Doppler imaging

Ravikumar Parikh,1 Robert J. S. Negrine,1 Ashish Chikermane,2 Shree Vishna Rasiah,1 Andrew K. Ewer,1,3

1Department of Neonatology, Birmingham Women’s Hospital NHS Trust, Birmingham, B15 2TG, United Kingdom; 2Department of Paediatric Cardiology, Birmingham Children’s Hospital NHS Trust, Birmingham, B4 6NH, United Kingdom; 3School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, B15 2TT, United Kingdom

Abstract Objective: To assess myocardial function in preterm infants with different degrees of ductal patency in the first week of life using tissue Doppler imaging. Study design: Infants <30 weeks of gestation underwent echocardiography on day 3. A total of 72 infants were recruited into the study and categorised into three groups (i) haemodynamically significant ductus arteriosus, (ii) patent ductus arteriosus and (iii) no patent ductus arteriosus. Those with haemodynamically significant ductus arteriosus were treated with indometacin and echocardiography was repeated after 48–72 hours following treatment. Peak systolic and diastolic myocardial velocities were obtained using tissue Doppler imaging, and myocardial performance index was calculated.

Results: Initial myocardial velocities were significantly lower and myocardial performance index significantly higher in the haemodynamically significant ductus arteriosus group compared with other groups. For the haemodynamically significant ductus arteriosus group, post-treatment myocardial velocities were higher and myocardial performance index lower than pre-treatment.

Conclusion: Preterm infants with haemodynamically significant ductus arteriosus had lower myocardial velocities and higher myocardial performance index, suggesting relative systolic and diastolic myocardial dysfunction. Babies whose patent ductus arteriosus remained open despite indometacin had lower pre-treatment myocardial velocities and higher myocardial performance index than those babies whose patent ductus arteriosus closed, suggesting worse myocardial function in this group. Measurement of myocardial function using tissue Doppler imaging in preterm infants is feasible and may prove to be helpful in the management of babies with patent ductus arteriosus.

Keywords: Premature infants; neonate; tissue Doppler imaging; myocardial performance index; patent ductus arteriosus; very low birth weight infants

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PATENT DUCTUS ARTERIOSUS IS A COMMON PROBLEM in preterm infants, with rates of 40–55% in those born <1000 g.1,2 Haemodynamically significant ductus arteriosus in preterm infants can have important clinical consequences, particularly during the period of recovery from respiratory distress syndrome.3 As pulmonary vascular resistance decreases, the increase in pulmonary blood flow can lead to pulmonary oedema and pulmonary haemorrhage. In addition, ductal steal can cause hypoperfusion of the kidneys, brain, intestines and other organs. The major effects of patent ductus arteriosus tend to occur in the first week of life and are associated with neonatal morbidities including chronic lung disease,4 pulmonary haemorrhage,3 intraventricular haemorrhage6,7 and necrotising enterocolitis.8

Generally, combinations of clinical and echocardiographic assessments are used to assign haemodynamic
significance to a ductus.\textsuperscript{9} Echocardiographic assessment of patent ductus arteriosus in preterm infants is traditionally performed by measuring ductal size and assessing the degree of pulmonary and systemic perfusion related to the transductal shunt using Doppler studies of ductal flow and calculation of the left atrium to aortic (LA:Ao) ratio. These methods give useful information about the effect of patent ductus arteriosus on pulmonary circulation but little about the effect on the myocardium. Monitoring left ventricular diastolic function using pulse wave Doppler has been shown to add significant information in preterm infants with a patent ductus arteriosus.\textsuperscript{10}

The additional assessment of myocardial function using tissue Doppler imaging may give further information about the effect of haemodynamically significant ductus arteriosus on the myocardium. Myocardial velocity waveforms acquired using tissue Doppler imaging allow measurement of peak velocities and calculation of myocardial performance index, allowing assessment of myocardial function. Myocardial velocities are measured in systole (S'), early diastole (E') and late diastole (A'). In general, the higher the myocardial velocities and lower the myocardial performance index, the better the myocardial function.

Our group has recently published the first study examining the role of biventricular tissue Doppler imaging assessment in preterm infants.\textsuperscript{11} This study demonstrated the normal range of myocardial peak velocity values using tissue Doppler imaging and highlighted the potential application of tissue Doppler imaging as an additional tool in the assessment of neonatal cardiac function.\textsuperscript{11} Tissue Doppler imaging may complement the previously described assessments of a patent ductus arteriosus, with myocardial velocities and myocardial performance index providing important information relating directly to myocardial function. Tissue Doppler imaging is also thought to be less preload dependent than blood pool pulse wave Doppler-derived data. This is the first study to investigate biventricular myocardial velocities and myocardial performance index in preterm infants with varying degrees of ductal patency.

**Methods**

Ethical approval was obtained by the West Midlands Research Ethics Committee and infants <30 weeks of gestation were recruited prospectively following written consent. Babies with congenital abnormalities were excluded. A total of 72 infants were recruited in the study. The recruited infants underwent echocardiography by one investigator (R.P.), on day 3 of life using a Philips HD11xe system (S12-4 Hz transducer) (Philips healthcare, Best, The Netherlands). Babies were then categorised into three groups depending on the degree of ductal patency (measured at the narrowest dimension), which was determined using a previously published classification system.\textsuperscript{9} The groups were defined as follows: (i) haemodynamically significant ductus arteriosus (ductal diameter $\geq 2.5$ mm and left atrium to aortic (LA:Ao) ratio $\geq 1.5$, (ii) patent ductus arteriosus (ductal diameter $< 2.5$ mm or LA:Ao ratio $< 1.5$ and (iii) no patent ductus arteriosus. Babies with haemodynamically significant ductus arteriosus were treated with indomethacin according to local unit guidelines (0.2 mg/kg 12 hourly for three doses). All babies underwent standard and tissue Doppler imaging echocardiography. Echocardiography was repeated between 48–72 hours after completion of the indomethacin therapy. Tissue Doppler myocardial velocities were acquired from an apical four-chamber view. A pulse-wave Doppler sample gate of 0.12 cm was positioned at the lateral tricuspid and mitral annuli. Peak velocities in systole (S'), early diastole (E') and late diastole (A') were obtained from each site. An angle of $< 20$ degrees was maintained using two-dimensional hold and the Doppler signal was not corrected. Average readings were taken from three to five cardiac cycles during off-line analysis. Left and right myocardial performance index was calculated. Mitral and tricuspid inflow was obtained from the standard apical four-chamber view analysing the flow of blood through the mitral valve and tricuspid valve, respectively. The myocardial performance index was also calculated. The myocardial performance index is a ratio of time intervals derived from the tissue Doppler waveform (Fig 1). The myocardial performance index evaluates both the systolic and diastolic function of a ventricle and provides a non-invasive, quantitative assessment of ventricular function. The myocardial
performance index is a ratio in which the numerator is the sum of isovolumetric contraction and relaxation times and denominator is the ejection time with all the parameters measured from the same ventricle (Fig 1).

In the haemodynamically significant ductus arteriosus group, a further analysis was undertaken following indometacin treatment to examine the following: (i) whether myocardial function improved following closure of haemodynamically significant ductus arteriosus (ii) whether differences in myocardial function could be used to predict success or failure of treatment. Statistical analysis was by GraphPad Instat v 3.05. For data comparison, one-way analysis of variance and t-test were used. Reproducibility of this method has been studied previously and has demonstrated acceptable interobserver and intraobserver bias.11

Table 1. Demographic data.

<table>
<thead>
<tr>
<th></th>
<th>HSDA group (n = 20)</th>
<th>PDA group (n = 22)</th>
<th>No PDA group (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation (weeks)</td>
<td>26.4</td>
<td>26.7</td>
<td>27.1</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>860</td>
<td>830</td>
<td>940</td>
</tr>
<tr>
<td>Duration of ventilation (days)</td>
<td>12.5</td>
<td>7.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Heart rate (bpm)*</td>
<td>166</td>
<td>161</td>
<td>148</td>
</tr>
<tr>
<td>SpO2*</td>
<td>95</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>Blood pressure* (mmHg)</td>
<td>28</td>
<td>29</td>
<td>32</td>
</tr>
</tbody>
</table>

HSDA = haemodynamically significant ductus arteriosus; PDA = patent ductus arteriosus
All data expressed as mean
*At the time of initial echocardiogram

Results

A total of 72 preterm infants born <30 weeks of gestation were recruited and a total of 64 babies were investigated – four babies died before day 3, one baby had coarctation of the aorta and three babies were considered clinically too unstable to undergo further echocardiography. In all, 20 babies were recruited into the haemodynamically significant ductus arteriosus group and 22 babies into each of the patent ductus arteriosus and no patent ductus arteriosus groups. The demographic details of the three groups are shown in Table 1. Table 2 shows mean myocardial velocities in each group.

There were significantly lower velocities in the haemodynamically significant ductus arteriosus group compared with the two other groups (p < 0.0001). There was a trend to lower velocities in the patent ductus arteriosus group compared with the no patent ductus arteriosus group, but this did not reach statistical significance. Myocardial performance index was higher in the haemodynamically significant ductus arteriosus group compared with the other two groups reaching statistical significance for the right ventricle (p = 0.013) (Table 2). Biventricular myocardial performance index was significantly higher in the patent ductus arteriosus group compared with the no patent ductus arteriosus group (p < 0.0001).

In the haemodynamically significant ductus arteriosus group, a further comparison was undertaken following indometacin therapy to examine the effect of treatment on myocardial function and to identify whether tissue Doppler imaging could be used to predict likelihood of treatment success. In the haemodynamically significant ductus arteriosus group, all received treatment with indometacin, with successful closure of patent ductus arteriosus in eight out of 20 babies. For the haemodynamically significant ductus arteriosus group, post-treatment myocardial velocities were significantly higher and myocardial performance index significantly lower than pre-treatment except right ventricular early and late diastolic and left ventricular late diastolic myocardial velocities. (Table 3)

On further analysis, the pre-treatment myocardial velocities were significantly lower (p < 0.001) and myocardial performance index was higher in babies whose patent ductus arteriosus remained open (n = 12) compared with babies whose patent ductus arteriosus closed (n = 8) with indometacin (Tables 3 and 4). These myocardial performance index differences were statistically significant for the left ventricle (p = 0.014).

Table 2. Myocardial peak velocities and myocardial performance index.

<table>
<thead>
<tr>
<th></th>
<th>HSDA group</th>
<th>PDA group</th>
<th>No PDA group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tri</td>
<td>Mit</td>
<td>Tri</td>
</tr>
<tr>
<td>Peak velocity systole (S')</td>
<td>4.94 (0.4)</td>
<td>3.47 (0.3)</td>
<td>5.29 (0.3)</td>
</tr>
<tr>
<td>Peak velocity early diastole (E')</td>
<td>4.70 (0.5)</td>
<td>4.38 (0.6)</td>
<td>4.90 (0.4)</td>
</tr>
<tr>
<td>Peak velocity late diastole (A')</td>
<td>6.96 (1.1)</td>
<td>5.31 (0.8)</td>
<td>7.48 (1.4)</td>
</tr>
<tr>
<td>MPI</td>
<td>0.47 (0.037)</td>
<td>0.50 (0.031)</td>
<td>0.44 (0.022)</td>
</tr>
</tbody>
</table>

Mit = mitral; MPI = myocardial performance index; Tri = tricuspid
Values are mean (SD)
Discussion

This study has demonstrated significantly lower biventricular myocardial velocities and higher right ventricular myocardial performance index in babies with haemodynamically significant ductus arteriosus compared with those with smaller or absent ducts, suggesting relative myocardial dysfunction in these babies. In babies with non-significant patent ductus arteriosus, there was a trend to higher myocardial velocities and significantly lower myocardial performance index compared with babies with no patent ductus arteriosus. These results correlate with data from studies utilising pulse wave Doppler to measure left myocardial ventricular function.10

Table 3. Pre-treatment to post-treatment changes to velocities and myocardial performance index.

<table>
<thead>
<tr>
<th>Pre- and post-treatment MPI and velocities</th>
<th>Pre</th>
<th>Post</th>
<th>p-values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV MPI open</td>
<td>0.47</td>
<td>0.42</td>
<td>0.0036</td>
</tr>
<tr>
<td>RV MPI closed</td>
<td>0.48</td>
<td>0.36</td>
<td>0.0011</td>
</tr>
<tr>
<td>LV MPI open</td>
<td>0.52</td>
<td>0.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV MPI closed</td>
<td>0.49</td>
<td>0.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV S′ open</td>
<td>4.80</td>
<td>5.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV S′ closed</td>
<td>4.96</td>
<td>5.89</td>
<td>0.0005</td>
</tr>
<tr>
<td>RV E′ open</td>
<td>4.61</td>
<td>4.7</td>
<td>0.8213</td>
</tr>
<tr>
<td>RV E′ closed</td>
<td>4.67</td>
<td>5.16</td>
<td>0.0019</td>
</tr>
<tr>
<td>RV A′ open</td>
<td>6.49</td>
<td>7.07</td>
<td>0.1548</td>
</tr>
<tr>
<td>RV A′ closed</td>
<td>7.28</td>
<td>7.67</td>
<td>0.0462</td>
</tr>
<tr>
<td>LV S′ open</td>
<td>3.28</td>
<td>4.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV S′ closed</td>
<td>3.62</td>
<td>4.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV E′ open</td>
<td>4.25</td>
<td>4.60</td>
<td>0.0017</td>
</tr>
<tr>
<td>LV E′ closed</td>
<td>4.42</td>
<td>4.94</td>
<td>0.001</td>
</tr>
<tr>
<td>LVA′ open</td>
<td>5.21</td>
<td>5.32</td>
<td>0.066</td>
</tr>
<tr>
<td>LV A′ closed</td>
<td>5.31</td>
<td>5.73</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

A′ = peak late diastolic velocity; E′ = peak early diastolic velocity; LV = left ventricle; MPI = myocardial performance index; RV = right ventricle; S′ = peak systolic velocity
*p-values are mean (paired t-test)

Table 4. Pre- and post-treatment myocardial peak velocities and MPI.

<table>
<thead>
<tr>
<th></th>
<th>PDA closed (n = 8)</th>
<th>PDA open (n = 12)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tricuspid</td>
<td>Mitral</td>
<td>Tricuspid</td>
</tr>
<tr>
<td>Pre systole (S′)</td>
<td>5.13 (0.11)</td>
<td>3.64 (0.05)</td>
<td>4.81 (0.1)</td>
</tr>
<tr>
<td>Pre early diastole (E′)</td>
<td>4.76 (0.1)</td>
<td>4.51 (0.08)</td>
<td>4.65 (0.12)</td>
</tr>
<tr>
<td>Pre late diastole (A′)</td>
<td>7.15 (0.14)</td>
<td>5.44 (0.06)</td>
<td>6.83 (0.12)</td>
</tr>
<tr>
<td>Post systole (S′)</td>
<td>5.88 (0.1)</td>
<td>4.51 (0.11)</td>
<td>5.37 (0.1)</td>
</tr>
<tr>
<td>Post early diastole (E′)</td>
<td>5.16 (0.05)</td>
<td>4.94 (0.12)</td>
<td>4.68 (0.09)</td>
</tr>
<tr>
<td>Post late diastole (A′)</td>
<td>7.66 (0.12)</td>
<td>5.73 (0.08)</td>
<td>7.07 (0.13)</td>
</tr>
<tr>
<td>Pre MPI</td>
<td>0.45 (0.042)</td>
<td>0.48 (0.025)</td>
<td>0.47 (0.034)</td>
</tr>
<tr>
<td>Post MPI</td>
<td>0.37 (0.016)</td>
<td>0.35 (0.05)</td>
<td>0.42 (0.027)</td>
</tr>
</tbody>
</table>

MPI = myocardial performance index
Values are mean (SD)
before and after indomethacitin therapy. Although the
numbers studied were small, comparison of pre- and
post-treatment myocardial function of babies whose
patent ductus arteriosus closed (successful treatment)
with those babies whose patent ductus arteriosus
remained open (unsuccessful treatment) demonstrated
higher pre-treatment myocardial velocities and lower
myocardial performance index in the successful treat-
ment group. This observation suggests that myocardial
function is impaired by haemodynamically significant
ductus arteriosus and improves significantly if the
patent ductus arteriosus closes following treatment.
In our study, treatment failures had worse pre-treat-
ment biventricular myocardial function and persist-
ing relative biventricular diastolic dysfunction after
indometacin compared with treatment successes. Our
data suggest that tissue Doppler imaging assessment
of myocardial function in babies with haemodyna-
mically significant ductus arteriosus may be useful in
predicting those ducts that may be more resistant to
medical intervention but further research is necessary.
The persistence of the patent ductus arteriosus
despite indometacin is associated with continuing
biventricular diastolic dysfunction.

Our study has shown that tissue Doppler imaging
can be used to measure myocardial velocities and
myocardial performance index in preterm infants
with different degrees of ductal patency. These data
may help to improve our understanding of the effect
of patent ductus arteriosus on myocardial function
and the likelihood of response to pharmacological
treatment.

There are limitations to our study. Intrinsic myo-
cardial immaturity and hypoxia can cause myocardial
dysfunction in premature babies. In all three groups,
the mean gestational age was comparable. Birth
weight was slightly higher in the no patent ductus
arteriosus group, whereas mean ventilation days were
higher in the haemodynamically significant ductus
arteriosus group as might be expected. However,
we have clearly demonstrated that ductal closure in
this group was associated with improvement in
myocardial function.

Conclusion

Preterm infants with haemodynamically significant
ductus arteriosus had lower myocardial velocities and
higher myocardial performance index, suggesting
relative systolic and diastolic myocardial dysfunction
in this group. Babies whose patent ductus arteriosus
remained open despite indomethacin had lower pre-
treatment myocardial velocities and higher myocardial
performance index than those babies whose patent
ductus arteriosus closed successfully with treatment,
suggesting relatively worse myocardial function in
this group. Post-treatment myocardial velocities
improved in babies whose patent ductus arteriosus
remained open, but were still lower and myocardial
performance index higher suggesting a persistence of
relative biventricular diastolic dysfunction. Our study
demonstrates that measurement of myocardial function
in premature babies with patent ductus arteriosus is
feasible and may be a helpful adjunct in the manage-
ment of these babies, although larger studies are
required to define the precise role of tissue Doppler
imaging in this respect.

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funding agency, commercial or not-for-profit sectors.

Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to
this work comply with ethical standards of National
Research Ethics Standards (NRES), UK on human
experimentation and with the Helsinki Declaration
of 1975, as revised in 2008, and has been approved by
the West Midlands Research and Ethics Committee.

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