Does endothelin-1 reduce superior mesenteric artery blood flow velocity in preterm neonates?

Fiona J Weir, Arne Ohlsson, Katherine Fong, Kofi Amankwah, Flavio Coceani

Abstract

**Aim**—To compare plasma endothelin-1 (ET-1) concentrations in preterm neonates from pre-eclamptic and normal mothers; and to evaluate whether ET-1 has a role in altered arterial blood flow velocity.

**Methods**—Umbilical arterial blood and neonatal arterial blood were sampled on days 1 and 3 for gas analysis and measurement of plasma ET-1. Doppler ultrasonography of the middle cerebral, renal, and superior mesenteric arteries (SMA) was performed.

**Results**—Neonates in the pre-eclampsia (n=18) and control (n=18) groups had mean (SD) gestational ages of 31.1 (2.5) weeks and 30.4 (2.1) weeks; their birth-weights were 1432 (SD 676) g and 1692 (SD 500) g, respectively. In the pre-eclampsia group mean umbilical arterial PO2 was lower—1.88 (0.75) kPa compared with 3.27 (1.41) kPa (p < 0.01)—and mean plasma ET-1 concentration was higher in the umbilical artery—40.6 (SD 15.0) compared with 30.5 (SD 13.8) pg/ml (p=0.04) and day 1 blood—54.9 (35.0) pg/ml compared with 33.6 (14.6) pg/ml (p=0.03). Middle cerebral artery peak systolic velocity was higher and SMA time averaged, peak systolic, and mean peak velocities were lower in the pre-eclampsia group. SMA time averaged velocity was inversely related to plasma ET-1 concentration.

**Conclusion**—The association between increased production of ET-1 and reduction in SMA time averaged velocity suggests a possible mechanism for hypoperfusion of the intestinal wall in neonates.

(Arch Dis Child Fetal Neonatal Ed 1999;80:F123–F127)

Keywords: eclampsia; hypoxia; vasoconstriction; endothelin-1

Endothelins are a family of peptides synthesised by many tissues. Among them, endothelin-1 (ET-1) is produced in the vessel wall by both endothelial and smooth muscle cells. ET-1 is a powerful vasoconstrictor, which acts through specific ETa receptors on smooth muscle cells. On endothelial cells, ETa receptor stimulation causes the release of nitric oxide. Stimuli for ET-1 include hypoxia and shear stress. Hypoxia directly stimulates ET-1 secretion by rat mesenteric artery in vitro. Infusion of ET-1 causes an increase in peripheral vascular resistance predominantly in the gastrointestinal, renal, and skeletal muscle vascular beds. ET-1 may therefore have a pathophysiological role in hypoxia–ischaemia, specifically as a precipitating factor in the development of necrotising enterocolitis.

We have shown that fetal blood vessels have a functioning ET-1 system in lambs, which, depending on the site, may be activated by an increase (ductus arteriosus) or decrease (pulmonary vasculature) in oxygen tension. In humans umbilical cord blood ET-1 concentrations are raised at birth in asphyxia, pre-eclampsia, and intrauterine growth retardation. Increasing circulating concentrations of ET-1 in neonates with persistent pulmonary hypertension of the newborn or respiratory distress syndrome, and increased urinary concentrations of ET-1 in neonates with post-hypoxic renal failure have been described.

In pre-eclampsia reduced placental transport of oxygen and nutrients results in fetal hypoxia and often growth retardation. Clinical and animal studies suggest that an hypoxic fetus attempts to preserve cerebral perfusion at the expense of visceral perfusion. Studies of fetuses and neonates with growth retardation or abnormal umbilical arterial blood flow velocity have shown an association between fetal hypoxia and perinatal asphyxia, hyperviscosity, necrotising enterocolitis, renal failure and haemorrhage. Nevertheless, studies have not simultaneously measured ET-1 and organ blood flow velocities.

We hypothesised that in pre-eclampsia fetal hypoxia upregulates the ET-1 system in blood vessels. This in turn would lead to vasocostriction and impaired regional blood flow in the neonate. This study aimed to determine the effect of fetal hypoxia caused by pre-eclampsia on ET-1 production and organ blood flow velocity in preterm infants.

**Methods**

Mothers at risk of preterm delivery between 26 and 34 weeks of gestation, admitted to Women’s College Hospital, were eligible for study. The pre-eclampsia group comprised mothers with pregnancy induced hypertension and proteinuria, and the control group comprised mothers with normal blood pressure, in spontaneous preterm labour. Mothers were excluded if they developed chorioamnionitis, antepartum haemorrhage, or if a congenital anomaly was recognised in the infant before or after birth. Written, informed consent was obtained from mothers before delivery for participation in the study.

Venous blood from the mother was drawn before delivery. Umbilical arterial samples were obtained after double clamping the cord at birth. Arterial blood was obtained through indwelling arterial, central, or peripheral cath-

Accepted 16 October 1998


Table 1 Characteristics (means and standard deviations) of neonates in pre-eclampsia and control groups

<table>
<thead>
<tr>
<th></th>
<th>Pre-eclampsia group (n=18)</th>
<th>Control group (n=18)</th>
<th>( p ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestation (weeks)</strong></td>
<td>31.1 (2.5)</td>
<td>30.4 (2.1)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Birthweight (g)</strong></td>
<td>1412 (115)</td>
<td>1692 (500)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>7.42 (0.06)</td>
<td>7.40 (0.06)</td>
<td>0.26</td>
</tr>
<tr>
<td>Day 3</td>
<td>7.40 (0.06)</td>
<td>7.39 (0.05)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Arterial PO(_2) (kPa)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>43 (9)</td>
<td>43 (5)</td>
<td>0.13</td>
</tr>
<tr>
<td>Day 3</td>
<td>42 (6)</td>
<td>43 (5)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Arterial PCO(_2) (kPa)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>0.46 (0.08)</td>
<td>0.46 (0.08)</td>
<td>0.62</td>
</tr>
<tr>
<td>Day 3</td>
<td>0.48 (0.09)</td>
<td>0.46 (0.08)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>0.51 (0.06)</td>
<td>0.51 (0.06)</td>
<td>0.57</td>
</tr>
<tr>
<td>Day 3</td>
<td>0.48 (0.09)</td>
<td>0.46 (0.08)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Mean arterial blood pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>38 (6)</td>
<td>37 (5)</td>
<td>0.83</td>
</tr>
<tr>
<td>Day 3</td>
<td>43 (9)</td>
<td>43 (5)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Level of significance determined by unpaired \( t \) test.
between the groups at the time of study in respiratory support (ventilator rate, pressures, and inspired oxygen concentration).

The plasma ET-1 concentrations were significantly higher in the pre-eclampsia group, specifically in maternal venous blood (p=0.012), the umbilical artery (p=0.044) and in day 1 neonatal arterial blood (p=0.027). The results are shown in fig 1.

Sonographic studies were discontinued before completion in a few neonates either because they were disturbed or because it was impossible to visualise adequately the RA or SMA due to breathing movements or intestinal gas shadows. Doppler studies of the MCA were completed in 16 neonates from each group, while RA and SMA were completed in matched groups of, respectively, 12 and 9 neonates. The differences in blood flow velocity measurements in the MCA, SMA, and RA between both groups are shown in table 2. The MCA PS was significantly higher in the pre-eclampsia group compared with the control group. The TAV, PS, and MV were significantly lower in the pre-eclampsia group compared with the control group. There were no differences between the groups in RA blood flow velocity measurements.

Subsequent analysis showed that mean SMA TAV was inversely related to mean plasma ET-1 concentration.

**Table 2** Middle cerebral artery, superior mesenteric artery, and renal artery blood flow velocity (mean and SD) (cm/s) in pre-eclampsia and control groups

<table>
<thead>
<tr>
<th></th>
<th>Pre-eclampsia group (N=16)</th>
<th>Control group (N=16)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA TAV (cm/s)</td>
<td>9.5 (6.6)</td>
<td>8.6 (6.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>PS (cm/s)</td>
<td>38.0 (9.9)</td>
<td>31.6 (11.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>ED (cm/s)</td>
<td>8.5 (3.2)</td>
<td>7.8 (3.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>MV (cm/s)</td>
<td>19.5 (6.4)</td>
<td>16.9 (6.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>SMA TAV (cm/s)</td>
<td>12.5 (6.1)</td>
<td>17.4 (8.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>PS (cm/s)</td>
<td>52.3 (19.8)</td>
<td>80.2 (40.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>ED (cm/s)</td>
<td>9.2 (7.5)</td>
<td>10.5 (11.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>MV (cm/s)</td>
<td>15.9 (10.5)</td>
<td>33.8 (17.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RA TAV (cm/s)</td>
<td>N=9</td>
<td>N=9</td>
<td></td>
</tr>
<tr>
<td>PS (cm/s)</td>
<td>8.1 (6.1)</td>
<td>3.0 (3.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>ED (cm/s)</td>
<td>39.6 (15.2)</td>
<td>40.6 (21.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>MV (cm/s)</td>
<td>17.3 (8.0)</td>
<td>17.5 (6.8)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

MCA = middle cerebral artery; SMA = superior mesenteric artery; RA = renal artery; TAV = time averaged velocity; PS = peak systolic velocity; ED = end diastolic velocity; MV = mean velocity.

ET-1 concentration (means of complete data from day 1 and day 3 from 17 infants) (fig 2).

**Discussion**

This prospective cohort study has shown that preterm neonates with pre-eclampsia had fetal hypoxia, increased circulating ET-1, reduced SMA blood flow velocity and an inverse correlation between ET-1 and SMA blood flow velocity. ET-1 acts primarily in blood vessels and only under certain conditions does the compound appear in the circulation. ET-1 concentrations in arterial blood reflect primarily production by the arterial wall. The relation between blood and vascular wall concentrations is not known. Descriptive studies of plasma concentrations in human neonates have not shown an association with gestational age nor with birthweight. In experimental studies the observed response to ET-1 seems to depend on the vascular bed and the experimental conditions. Mothers with pre-eclampsia have higher circulating ET-1 than mothers of a similar gestational age who present with preterm labour. Both low and high oxygen and shear stress may stimulate ET-1 synthesis. We found relative fetal hypoxia in the pre-eclampsia group, which may have stimulated the higher ET-1 concentrations observed in the fetuses and neonates. Although high plasma ET-1 concentrations have been described in sick neonates, there were no differences between the groups in the current study with regard to severity of respiratory disease, blood pressure, or incidence of PDA, to account for the high ET-1 concentrations in the pre-eclampsia group.

Blood flow velocity measurements correlated well with actual blood flow, the best measurement being the TAV. We have shown that neonatal SMA blood flow velocity is reduced in a group of neonates with antenatal hypoxia. The PS, MV, and TAV were all reduced in the SMA of the pre-eclampsia group and therefore these neonates are likely to have reduced intestinal blood flow after birth. We reported measurements of blood flow velocities, as they are more reliable than the resistive or pulsatility indices. Studies of neonates with risk factors...
We thank Mary Lou Ryan and Lois Kelsey for their excellent technical help in performing this study.

8 Wang Y, Coo Y, Toyoda O, Coceni F. Involvement of endothelin-1 in hypoxic pulmonary vasoconstriction in the lamb. J Physiol (Lond) 1995;482:421-34.


