Congenital diaphragmatic hernia: impact of prostanoids in the periparative period

A P Bos, D Tibboel, F W J Hazebroek, T Stijnen, J C Molemaar

Abstract
A prospective study of 10 neonates with congenital diaphragmatic hernia and five controls to determine the importance of prostanoid concentrations perioperatively and the relation with persistent pulmonary hypertension (PPH) is reported. In neonates with congenital diaphragmatic hernia postoperative concentrations of the vasoconstrictor thromboxane B2 rose significantly and were higher during episodes of PPH; this rise may provoke PPH and subsequent right to left shunting.

The outcome in patients with congenital diaphragmatic hernia depends either on the gravity of pulmonary hypoplasia or on the combination of pulmonary hypoplasia with persistent pulmonary hypertension (PPH). 

Degradation products of arachidonic acid such as the leukotrienes \(^2\) and the prostaglandins and thromboxanes (the so called prostanoids) have been associated with the generation of PPH in neonates. 

The purpose of this prospective study was to determine the importance of prostanoid concentrations and ventilatory variables in patients with congenital diaphragmatic hernia with and without PPH in the periparative period.

Patients and methods
During the study period, December 1987 to February 1989, 10 consecutive neonates with congenital diaphragmatic hernia (mean gestational age 37·6 weeks, birth weight 3050 g) were admitted to the paediatric surgical intensive care unit, because of severe respiratory insufficiency within six hours after birth.

During the same study period five patients with oesophageal atresia (mean gestational age 36 weeks, birth weight 2645 g) served as a control group and they followed the same protocol.

Registration of ventilatory variables was carried out on admission, one hour before surgery, and one and six hours after surgery. These variables included the alveolar arterial oxygen differences \((AaDO_2)\), mean airway pressure, oxygenation index, and ventilation index. 

Determination of thromboxane B2, a stable metabolite of the vasoconstrictor thromboxane A2, and 6-keto-prostaglandin F \(_1\alpha\) (PGF), a stable metabolite of the vasodilator prostacycline, were analysed by radioimmunoassay.

The diagnosis of PPH was confirmed with the following diagnostic procedures: (i) hyperoxic hyperventilation test in which the arterial oxygen pressure \((PaO_2)\) increased to >13·3 kPa after hyperventilation with 100% oxygen; (ii) pre- and postductal PaO\(_2\) differential of >2·7 kPa considered evidence of a transducal shunt; and (iii) positive contrast echocardiography showing right to left shunting.

As the distributions of most variables were highly skewed the median and range were used as descriptive statistics in the statistical analysis.

Results
Ten patients with congenital diaphragmatic hernia and five controls were examined. Two of the patients had a right sided defect and eight had a left sided defect, two had never had surgery because their condition deteriorated rapidly. These two patients died at 15 and 25 hours after admission and necropsy confirmed severe lung hypoplasia. A third patient did not undergo surgery because he had an isoelectric electroencephalogram after a prolonged period of hypoxia immediately after birth. One of the seven patients who underwent surgery had trisomy 18 and died. All five control patients were operated on. One prematurely born infant died after severe intracranial haemorrhage.

In patients with congenital diaphragmatic hernia median concentration of thromboxane B2 rose significantly from 250 (range 81–703) pmol/ml preoperatively to 740 (range 443–1030) pmol/ml postoperatively (signed rank test, \(p=0\cdot018\)). In the control group concentrations of thromboxane B2 were 376 (range 250–497) pmol/ml preoperatively and 185 (range 50–1010) pmol/ml postoperatively (\(p=0\cdot07\)). Plasma concentrations of PGF, increased from 260 (range 140–8835) to 2460 (range 1709–4150) pmol/ml in patients with congenital diaphragmatic hernia and from 455 (range 30–986) to 1145 (range 180–3682) pmol/ml in control patients; this was not significant. The increased concentrations of

\[\begin{align*}
\text{Thromboxane B2 (pmol/ml)} & \quad \text{Operative period} \\
\text{Time (hours)} & \\
-6 & \quad 0 \\
0 & \quad 4 \\
4 & \quad 8 \\
8 & \quad 12 \\
12 & \quad 16 \\
16 & \quad 20 \\
20 & \quad 24 \\
24 & \quad 28 \\
28 & \quad 32 \\
32 & \quad 36 \\
36 & \quad 40 \\
40 & \quad 44 \\
44 & \quad 48 \\
48 & \quad 52 \\
52 & \quad 56 \\
56 & \quad 60 \\
60 & \quad 64 \\
64 & \quad 68 \\
68 & \quad 72 \\
72 & \quad 76 \\
76 & \quad 80 \\
80 & \quad 84 \\
84 & \quad 88 \\
88 & \quad 92 \\
92 & \quad 96 \\
96 & \quad 100 \\
100 & \quad 104 \\
104 & \quad 108 \\
108 & \quad 112 \\
112 & \quad 116 \\
116 & \quad 120 \\
120 & \quad 124 \\
124 & \quad 128 \\
128 & \quad 132 \\
132 & \quad 136 \\
136 & \quad 140 \\
140 & \quad 144 \\
144 & \quad 148 \\
148 & \quad 152 \\
152 & \quad 156 \\
156 & \quad 160 \\
160 & \quad 164 \\
164 & \quad 168 \\
168 & \quad 172 \\
172 & \quad 176 \\
176 & \quad 180 \\
180 & \quad 184 \\
184 & \quad 188 \\
188 & \quad 192 \\
192 & \quad 196 \\
196 & \quad 200 \\
\end{align*}\]

Concentrations of thromboxane B2 before, immediately after, and six hours after surgery in seven patients with congenital diaphragmatic hernia. \(\dagger\) Patient died.
thromboxane B₂ at one hour postoperatively dropped to preoperative concentrations in all but two patients with congenital diaphragmatic hernia (figure). One of these patients died with high concentrations and the clinical picture of PPH.

In five patients with congenital diaphragmatic hernia at least one episode of PPH was diagnosed. The average values of the ventilatory variables and prostanoid concentrations are presented in the table, and compared with the values in patients without episodes of PPH. In patients with right to left shunting AaDO₂, oxygenation index, and thromboxane B₂ concentrations were significantly higher than in those without right to left shunting.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Congenital diaphragmatic hernia without PPH</th>
<th>Congenital diaphragmatic hernia with PPH</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AaDO₂</td>
<td>201 (127-385)</td>
<td>559 (318-623)</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean airway pressure</td>
<td>11 (6-13)</td>
<td>9 (8-15)</td>
<td>0.9</td>
</tr>
<tr>
<td>Oxygenation index</td>
<td>4 (2-10)</td>
<td>21 (8-30)</td>
<td>0.016</td>
</tr>
<tr>
<td>Ventilation index</td>
<td>630 (300-1296)</td>
<td>542 (497-1138)</td>
<td>0.4</td>
</tr>
<tr>
<td>Thromboxane B₂ (pmol/ml)</td>
<td>312 (262-456)</td>
<td>774 (477-3699)</td>
<td>0.03</td>
</tr>
<tr>
<td>PgF (pmol/ml)</td>
<td>726 (562-1056)</td>
<td>938 (55-2713)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Discussion
Oxygenation of neonates with congenital diaphragmatic hernia in the perioperative period remains a challenging problem because of the combination of pulmonary hypoplasia and PPH.

Recently Hammerman and coworkers correlated the presence of PPH in neonates to increased concentrations of thromboxane B₂. The pulmonary vascular system of the patient with congenital diaphragmatic hernia differs from that of normal newborns and may overreact to different stimuli.

In patients with congenital diaphragmatic hernia plasma concentrations of the vasoconstrictive metabolite thromboxane B₂ increased significantly during the surgical and anaesthetic procedure. If the pulmonary vascular system is still susceptible to vasoconstriction, it is obvious that in these cases pulmonary artery pressure may rise and right to left shunting may occur. In five out of seven patients thromboxane B₂ concentrations turned to baseline values at six hours postoperatively, showing that the rise of thromboxane B₂ is related to the operation.

In other words, the surgical procedure may provoke PPH in a ‘susceptible’ pulmonary vascular system.

Ventilatory variables have proved their use in prediction of survival in patients with congenital diaphragmatic hernia. The AaDO₂ and the oxygenation index values are significantly higher in patients who have PPH. In these patients, concentrations of thromboxane B₂ have increased and might reflect an imbalance between vasodilation and vasoconstriction, dipping to vasoconstriction.

In conclusion: we have shown that during surgery there is activation of the arachidonic prostanoid cascade leading to a rise in thromboxane B₂ concentrations in patients with congenital diaphragmatic hernia. This may be an additional risk factor for right to left shunting postoperatively and it may be an argument for delayed surgery till the moment when the pulmonary vascular system has become ‘stable’.

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