Thromboxane A2 and Prostacyclin Biosynthesis in Children and Adolescents With Pulmonary Vascular Disease

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**Background.** The pathogenesis of pulmonary vascular disease in children with congenital heart disease is incompletely understood. Thromboxane (TX) A2 and prostacyclin (PGI2) have opposing effects on platelet aggregation and pulmonary vascular smooth muscle. An imbalance in their biosynthesis could contribute to the progressive increase in pulmonary vascular resistance seen in older untreated patients with pulmonary hypertensive congenital heart disease and the thrombotic complications they may develop.

**Methods and Results.** We investigated TXA2 and PGI2 biosynthesis in 15 young children (0.2 to 2.25 years old) with congenital heart disease with increased pulmonary blood flow and potentially reversible pulmonary vascular disease by measuring urinary excretion of 2,3-dinor-TXB2 and 2,3-dinor-6-oxo-prostaglandin (PG) F1alpha, and compared the findings with those in 16 healthy children (0.5 to 2.8 years old). 2,3-Dinor-TXB2 excretion was greater in the patients than in control subjects (1252±161 versus 592±122 ng/g creatinine; P<.001). Excretion of 2,3-dinor-6-oxo-PGF1alpha was 452±54 compared with 589±95 ng/g creatinine in control subjects. In 5 patients who underwent successful cardiac surgery ≥1 year later excretion of 2,3-dinor-TXB2 decreased from 1100±298 to 609±131 ng/g creatinine (P<.05), a value comparable to those in 5 healthy children of similar age (749±226 ng/g creatinine). We also compared 15 patients (11 to 23 years old) with advanced irreversible pulmonary vascular disease with 19 healthy control subjects (10 to 23 years old). The ratio of TX to PGI2 metabolite excretion was greater in the patients than in control subjects (3.5±0.6 versus 2.0±0.3; P<.05).

**Conclusions.** There is increased 2,3-dinor-TXB2 excretion in children with congenital heart disease and a high pulmonary blood flow that may reflect an imbalance in biosynthesis of TXA2 and PGI2 in the pulmonary vascular bed. The imbalance may contribute to the progressive development of increased pulmonary vascular resistance and persists in older patients whose heart defects are uncorrected.

**Key Words** • heart defects, congenital • pulmonary heart disease • hypertension

In children with a high pulmonary blood flow caused by congenital heart disease, the pulmonary arterial endothelial cells are exposed to an increased shear stress from birth and develop marked structural abnormalities if the pulmonary arterial pressure remains elevated.1 Nevertheless, functional abnormalities are thought to precede morphological damage,2 raising the possibility that vasoactive mediators produced by or acting on the abnormal endothelium may contribute to the evolution of pulmonary vascular disease.

Thromboxane (TX) A2 is synthesized by activated platelets and to a lesser extent by endothelial cells.3 It is vasoconstrictive and proaggregatory.4,5 Prostacyclin (prostaglandin [PG] I2) is synthesized by endothelial cells, including pulmonary arterial endothelial cells,6 and acts as a physiological antagonist of TXA2, inhibiting platelet aggregation and relaxing vascular smooth muscle, including fetal pulmonary vascular smooth muscle.7,9 Abnormal biosynthesis of these eicosanoids has been implicated in several systemic vascular disorders10,11 and in both primary pulmonary hypertension and some forms of secondary pulmonary hypertension.12-14 Clinical studies have shown that prolonged infusion of PGI2 leads to a marked improvement in young adults with primary pulmonary hypertension.15,16 The purpose of the present study was to investigate whether there is abnormal eicosanoid biosynthesis in young children with potentially reversible pulmonary vascular disease and in adolescents with advanced irreversible pulmonary vascular disease caused by congenital heart defects and, when possible, to determine whether any abnormalities in eicosanoid biosynthesis are reversed after successful surgical repair.

PGI2 and TXA2 both have short half-lives in the circulation, and accurate measurements in vivo are possible only by measuring their stable breakdown products or metabolites. Since stimulation of the endo-
The table below shows the clinical features and eicosanoid excretion rates in young children with congenital heart disease:

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>Diagnosis</th>
<th>Medication</th>
<th>Systemic Arterial Pressure, S/D (m), mm Hg</th>
<th>Pulmonary Artery Pressure, S/D (m), mm Hg</th>
<th>Aortic Saturation, %</th>
<th>Pulmonary vascular resistance, TXB_{2} ng/g creatinine</th>
<th>2,3-Dinor-TXB_{2} ng/g creatinine</th>
<th>2,3-Dinor-6-oxo-PGF_{1α} ng/g creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>AVSD</td>
<td>Digoxin, furosemide</td>
<td>90/45 (60)</td>
<td>33/10 (18)</td>
<td>95</td>
<td>2:1</td>
<td>4</td>
<td>1315</td>
</tr>
<tr>
<td>4</td>
<td>PDA</td>
<td>Digoxin, furosemide</td>
<td>80/40 (53)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>666</td>
</tr>
<tr>
<td>5</td>
<td>DORV</td>
<td>Digoxin, furosemide</td>
<td>85/50 (62)</td>
<td>30/15 (20)</td>
<td>92</td>
<td>3:1</td>
<td>1.8</td>
<td>1219</td>
</tr>
<tr>
<td>6</td>
<td>VSD</td>
<td>Digoxin</td>
<td>90/60 (70)</td>
<td>65/29 (41)</td>
<td>91</td>
<td>3:1</td>
<td>5</td>
<td>474</td>
</tr>
<tr>
<td>7</td>
<td>VSD</td>
<td>Furosemide, spironolactone</td>
<td>100/50 (67)</td>
<td>105/50 (68)</td>
<td>99</td>
<td>3:1</td>
<td>1.3</td>
<td>2213</td>
</tr>
<tr>
<td>8</td>
<td>VSD, PDA</td>
<td>Digoxin, furosemide</td>
<td>100/60 (73)</td>
<td>41/13 (22)</td>
<td>97</td>
<td>2:1</td>
<td>1.6</td>
<td>1719</td>
</tr>
<tr>
<td>9</td>
<td>VSD</td>
<td>Furosemide, spironolactone</td>
<td>95/60 (72)</td>
<td>100/70 (80)</td>
<td>97</td>
<td>3:1</td>
<td>1 . . .</td>
<td>1401</td>
</tr>
<tr>
<td>10</td>
<td>VSD</td>
<td>Digoxin, furosemide</td>
<td>85/55 (65)</td>
<td>30/14 (19)</td>
<td>99</td>
<td>3:1</td>
<td>1.3</td>
<td>2213</td>
</tr>
<tr>
<td>11</td>
<td>ASD</td>
<td>Digoxin</td>
<td>110/70 (63)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>1780</td>
</tr>
<tr>
<td>12</td>
<td>ASD,</td>
<td>Digoxin, spironolactone</td>
<td>95/60 (72)</td>
<td>65/28 (40)</td>
<td>96</td>
<td>2:1</td>
<td>3.2</td>
<td>2294</td>
</tr>
<tr>
<td>13</td>
<td>VSD, ASD</td>
<td>Digoxin, furosemide</td>
<td>105/50 (68)</td>
<td>25/13 (17)</td>
<td>99</td>
<td>2:1</td>
<td>0.8</td>
<td>1247</td>
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<tr>
<td>14</td>
<td>Truncus</td>
<td>None</td>
<td>100/60 (73)</td>
<td>80/38 (52)</td>
<td>89</td>
<td>2:1</td>
<td>5.5</td>
<td>336</td>
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<tr>
<td>15</td>
<td>PDA/</td>
<td>None</td>
<td>90/40 (57)</td>
<td>35/10 (18)</td>
<td>100</td>
<td>3:1</td>
<td>0.6</td>
<td>608</td>
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<td>16</td>
<td>TR121</td>
<td>None</td>
<td>100/60 (73)</td>
<td>47/9 (22)</td>
<td>97</td>
<td>3:1</td>
<td>1.3</td>
<td>615</td>
</tr>
<tr>
<td>17</td>
<td>VSD</td>
<td>None</td>
<td>95/54 (68)</td>
<td>50/22 (31)</td>
<td>96</td>
<td>2.5:1</td>
<td>2.4</td>
<td>1253</td>
</tr>
<tr>
<td>18</td>
<td>Mean</td>
<td></td>
<td>8/8 (8)</td>
<td>22/17 (18)</td>
<td>3</td>
<td>0.5</td>
<td>1.6</td>
<td>604</td>
</tr>
</tbody>
</table>

*S indicates systolic; D, diastolic; m, mean; Qp, pulmonary blood flow; Qs, systemic blood flow; TX, thromboxane; PG, prostaglandin; AVSD, atrioventricular septal defect; PDA, patent ductus arteriosus; DORV, double outflow right ventricle; VSD, ventricular septal defect; ASD, atrial septal defect; TR121, trisomy 21; Truncus, truncus arteriosus; and . . ., no cardiac catheterization.

*Oxygen consumption assumed in calculations.

Methods

We investigated 15 children (10 boys and 5 girls, 0.2 to 2.25 years old; median, 0.7 years) with congenital heart disease who had increased pulmonary blood flow. Their clinical features are shown in Table 1. A healthy control group of 16 children (9 boys and 7 girls, 0.5 to 2.8 years old; median, 2.0 years) attending the Great Ormond Street Hospital staff crèche was also studied. In all children, systemic arterial blood pressure was normal for age. In the patients, an overnight 12-hour bagged urine collection using silicone adhesive was taken in hospital on the night before cardiac catheterization or cardiac operation. In the control subjects, an overnight 12-hour bagged urine sample was collected at home. One year or more after surgery, a second overnight 12-hour urine sample was collected from 5 of the patients whose heart defects were successfully repaired. At the same time, a second overnight 12-hour urine sample was collected from 5 appropriately aged children from the original control group.

The second patient group consisted of 15 nonsmoking adolescents and young adults (9 males and 6 females, 11 to 23 years old; median, 18 years) with advanced pulmonary hypertension secondary to untreated or unsuccessfully palliated congenital heart disease (Table 2). All patients had unequivocal evidence of pulmonary vascular disease with a right-to-left shunt in 13, and all had normal systemic arterial pressure. A control group of 19 healthy nonsmoking normotensive subjects (11 males and 8 females, 10 to 23 years old; median, 17 years) was studied. Twenty-four-hour urine samples were collected by these patients and control subjects as they carried out their normal daily activities.

None of the patients or control subjects took aspirin or other nonsteroidal anti-inflammatory drugs for at least 2 weeks before study. All patients and control subjects and/or their parent or guardian gave informed consent to participate in the study.

Urinalysis

In each case, a well-mixed sample of 30 to 50 mL urine was stored at -20°C. Urine samples were assayed for creatinine with routine clinical chemistry techniques and for 2,3-dinor-TXB_{2} and 2,3-dinor-6-oxo-PGF_{1α}.
TABLE 2. Clinical Features and Eicosanoid Excretion Rates in Adolescents and Young Adults With Congenital Heart Disease

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Diagnosis</th>
<th>Medication</th>
<th>Age, y</th>
<th>Pulmonary Artery Pressure, S/D (m), mm Hg</th>
<th>Aortic Saturation, %</th>
<th>Pulmonary Vascular Resistance, units/m²</th>
<th>Present Systemic Arterial Pressure, S/D (m), mm Hg</th>
<th>2,3-Dinor-TXB₂, ng/g creatinine</th>
<th>2,3-Dinor-6-oxo-PGF₁α, ng/g creatinine</th>
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<tbody>
<tr>
<td>11</td>
<td>DILV</td>
<td>None</td>
<td>3</td>
<td>90/60 (70)</td>
<td>61</td>
<td>25</td>
<td>120/75 (90)</td>
<td>410</td>
<td>165</td>
</tr>
<tr>
<td>13</td>
<td>PDA-ligated</td>
<td>Digoxin</td>
<td>5</td>
<td>100/40 (60)</td>
<td>97</td>
<td>10</td>
<td>115/80 (92)</td>
<td>1308</td>
<td>129</td>
</tr>
<tr>
<td>16</td>
<td>PDA-ligated</td>
<td>None</td>
<td>16</td>
<td>86/20 (42)</td>
<td>96</td>
<td>14</td>
<td>115/65 (82)</td>
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<td>60</td>
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<tr>
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<td>DILV</td>
<td>Digoxin</td>
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<td>100/50 (67)</td>
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<td>11</td>
<td>120/80 (93)</td>
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<td>18</td>
<td>VSD</td>
<td>None</td>
<td>9</td>
<td>90/40 (57)</td>
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<td>9</td>
<td>100/70 (80)</td>
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<td>142</td>
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<tr>
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<td>17</td>
<td>147/61 (90)</td>
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<td>115/70 (85)</td>
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<td>Digoxin</td>
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<td>85/40 (55)</td>
<td>96</td>
<td>5</td>
<td>115/85 (95)</td>
<td>91</td>
<td>39</td>
</tr>
<tr>
<td>18</td>
<td>VSD</td>
<td>Sodium valproate</td>
<td>5</td>
<td>58/30 (39)</td>
<td>84</td>
<td>8</td>
<td>110/80 (90)</td>
<td>1052</td>
<td>194</td>
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<tr>
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<td>Digoxin</td>
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<td>80/50 (60)</td>
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<td>3</td>
<td>105/80 (88)</td>
<td>403</td>
<td>104</td>
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<td>90/70 (77)</td>
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<td>22</td>
<td>120/85 (97)</td>
<td>373</td>
<td>62</td>
</tr>
<tr>
<td>20</td>
<td>TGA, VSD</td>
<td>Digoxin, furosemide</td>
<td>20</td>
<td>139/80 (100)</td>
<td>76</td>
<td>36</td>
<td>120/80 (93)</td>
<td>600</td>
<td>310</td>
</tr>
<tr>
<td>20</td>
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<td>8</td>
<td>90/50 (83)</td>
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<td>23</td>
<td>115/90 (98)</td>
<td>347</td>
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</tr>
<tr>
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<td>105/80 (88)</td>
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<tr>
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<td>105/68 (80)</td>
<td>90</td>
<td>16</td>
<td>112/82 (92)</td>
<td>326</td>
<td>129</td>
</tr>
<tr>
<td>23</td>
<td>TGA, VSD</td>
<td>Digoxin</td>
<td>18</td>
<td>110/48 (69)</td>
<td>75</td>
<td>11</td>
<td>112/90 (97)</td>
<td>292</td>
<td>126</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>9</td>
<td>97/50 (66)</td>
<td>83</td>
<td>15</td>
<td>113/79 (91)</td>
<td>462</td>
<td>148</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td>6</td>
<td>22/16 (16)</td>
<td>12</td>
<td>10</td>
<td>67/5 (5)</td>
<td>320</td>
<td>89</td>
</tr>
</tbody>
</table>

S indicates systolic; D, diastolic; m, mean; TX, thromboxane; PG, prostaglandin; DILV, double inlet left ventricle; PDA, patent ductus arteriosus; VSD, ventricular septal defect; TGA, transposition of the great arteries; TA, tricuspid atresia; and DORV, double outlet right ventricle.

*Oxygen consumption assumed in calculations.

with immunoaffinity chromatography and gas chromatography/mass spectrometry as described previously. Briefly, urine samples (10 mL) were diluted 1:1 by volume with Tris buffer at pH 8.0, and [3H]2,3-dinor-TXB₂ and [3H]2,3-dinor-6-oxo-PGF₁α (5 ng each) were added. Eicosanoids were extracted with cyanogen bromide-activated Sepharose columns containing immobilized antibodies that had been raised against TXB₂ and 6-oxo-PGF₁α and that cross-reacted with their respective 2,3-dinor metabolite. Urine samples were applied under vacuum to the columns, which were washed with water (10 mL). Eicosanoids were eluted by addition of 0.5 mL acetone:water (95:5) and rotation of the columns for 15 minutes. Samples were taken to dryness (N₂ stream) and were derivatized as 3,5-bis-trifluoromethylbenzyl esters, trimethylsilyl ethers. They were analyzed with a VG 70-SEQ gas chromatograph/mass spectrometer in the electron capture mode with methane as reagent gas. Carboxylate anions at mass/charge (m/z) ratio 557 were monitored for 2,3-dinor-TXB₂ and 2,3-dinor-6-oxo-PGF₁α and at m/z 561 for the deuterated internal standards. The detection limit for each eicosanoid was 5 pg/mL. Eicosanoid excretion rates of 2,3-dinor-TXB₂ and 2,3-dinor-6-oxo-PGF₁α are expressed as nanograms per gram creatinine. Since aspirin inhibits eicosanoid biosynthesis, is widely available, and may be consumed unknowingly, all urine samples were screened for salicyluric acid (a metabolite of aspirin) by the method of Rumsby et al. No salicyluric acid was detected in any sample.

**Statistical Analysis**

Results are summarized as mean±SEM. Differences in eicosanoid excretion rates were sought by ANOVA followed by Fisher’s test. Eicosanoid excretion rates were transformed logarithmically to obtain normally distributed data before analysis. Differences were considered significant when P<.05.

**Results**

Excretion rates of 2,3-dinor-TXB₂ and 2,3-dinor-6-oxo-PGF₁α in patients with pulmonary vascular disease and in healthy control subjects are summarized in Fig 1. Excretion of both eicosanoid metabolites was greater in the younger control group than in the older control group (P<.01 and P<.001, respectively). The younger patients with a high pulmonary blood flow excreted more 2,3-dinor-TXB₂ than did the healthy control group of similar age (1253±161 versus 592±122 ng/g creatinine; P<.001 [Table 1]). Excretion of 2,3-dinor-6-oxo-PGF₁α was 452±54 in the patients compared with 589±95 ng/g creatinine in control subjects. In the older patients with advanced pulmonary vascular disease, excretion of 2,3-dinor-TXB₂ was 462±76 compared with...
311±28 ng/g creatinine in the healthy older control group. Excretion of 2,3-dinor-6-oxo-PGF\(_{1\alpha}\) in the older patients was 148±21 compared with 199±28 ng/g creatinine in the older control group (Table 2). The ratio between 2,3-dinor-TXB\(_2\) and 2,3-dinor-6-oxo-PGF\(_{1\alpha}\) was significantly greater than respective control values in both the young patients with potentially reversible disease (3.9±1.2 versus 1.3±0.2; \(P<.001\)) and the older patients with irreversible disease (3.5±0.54 versus 2.0±0.3; \(P<.05\)).

After successful cardiac surgery, excretion of 2,3-dinor-TXB\(_2\), decreased in all five of the younger patients studied, from 1100±298 before to 609±131 ng/g creatinine 1 year or more after surgery (\(P<.05\); Fig 2), the latter rate being similar to that of five of the control subjects of similar age who were restudied at the same time (749±226 ng/g creatinine). Excretion of 2,3-dinor-6-oxo-PGF\(_{1\alpha}\) was 369±92 before and 498±93 ng/g creatinine after surgery. The ratio of 2,3-dinor-TXB\(_2\) to 2,3-dinor-6-oxo-PGF\(_{1\alpha}\) decreased from 5.8±3.4 to 1.3±0.2 after surgery (\(P<.05\)), which was similar to the ratio in five healthy subjects of similar age (0.9±0.1).

**Discussion**

The excretion rates of both 2,3-dinor-TXB\(_2\) and 2,3-dinor-6-oxo-PGF\(_{1\alpha}\) in the healthy adolescents and young adults in the present study were similar to those previously reported in 36 healthy nonsmoking men (17 to 40 years old; median, 22 years) studied by the same techniques.\(^{21}\) We found higher urinary excretion rates of both TXA\(_2\) and PGI\(_1\) metabolites in the younger healthy children. High rates have been documented in
normal neonates by other investigators.23-26 Fischer et al24 showed that excretion of both 2,3-dinor-TXB2 and 2,3-dinor-6-oxo-PGF1α falls over the first week of life, and at 3 years of age approximates adult values. However, Kühle et al27 suggested that in very low birth weight babies, 2,3-dinor-6-oxo-PGF1α excretion is similar to that of adults by day 10 of life, but 2,3-dinor-TXB2 excretion remains elevated on day 10. Our results suggest that excretion of these metabolites remains elevated during the first 3 years of life, and this emphasizes the importance of using control subjects of appropriate age when studying the immature vasculature. The main conclusion from the present study is that there is increased excretion of 2,3-dinor-TXB2 in young children with congenital heart disease and high pulmonary blood flow. This falls to normal after successful repair of heart defects. This increase may reflect an imbalance in biosynthesis of TXA2 and PGI2 within the pulmonary vasculature resulting from an abnormally high blood flow, damaged endothelium, and abnormal platelet/endothelium interactions that precede the development of irreversible structural abnormalities. In adolescents and young adults whose heart defects remain uncorrected and who have developed irreversible pulmonary vascular disease, an increase in excretion of 2,3-dinor-TXB2 relative to 2,3-dinor-6-oxo-PGF1α persists. Moncada and Vane28 were the first to suggest that the balance between TXA2 and PGI2 may be more important than their absolute concentrations in maintaining vascular homeostasis. A chronic imbalance in eicosanoid biosynthesis could contribute to the progressive development of thrombotic complications and the irreversible structural changes within the pulmonary vasculature that can occur in these patients. 

These results confirm and extend the findings of Barst et al, who reported elevated plasma TXB2 levels in 4 of 16 children with idiopathic pulmonary hypertension or pulmonary hypertension secondary to congenital heart disease13 and in a 17-month-old child who benefited from infusion with PGI2.12 Our results are also consistent with a recent study of adults with primary pulmonary hypertension and secondary pulmonary hypertension.14

Our results do not allow us to demonstrate a direct association between abnormal eicosanoid biosynthesis and the abnormalities within the pulmonary vascular bed, although the reduction in 2,3-dinor-TXB2 excretion that occurs in young children who have undergone successful cardiac repair favors the pulmonary vasculature as the site of abnormal eicosanoid biosynthesis. An attractive proposition is to measure plasma concentrations of eicosanoids in the pulmonary circulation.13 However, catheters themselves can stimulate eicosanoid biosynthesis by endothelium and platelets and can confound results obtained by this means.17,18

The cellular origin of the increased TXA2 biosynthesis found in our patients is uncertain. There is evidence of chronic platelet activation in children with primary pulmonary hypertension and pulmonary hypertensive congenital heart disease.29 Advanced obliterator pulmonary vascular disease can be accompanied by microemboli,30 and cyanotic pulmonary hypertensive patients can develop consumptive thrombocytopenia.31,32 Despite the evidence for platelet dysfunction, however, other cell types could be contributing to an increase in TXA2 biosynthesis, including endothelium33 and macrophages.34 The atherosclerotic human aorta synthesizes an excessive amount of TXA2 in vitro,35 and it is possible that an excessive amount of TXA2 is generated by the diseased pulmonary vasculature of patients with pulmonary hypertension. The findings in the present study suggest that the pulmonary hypertensive vasculature may synthesize excessive amounts of TXA2 in the early phase of the disease but that TXA2 biosynthesis may decrease with time. In the older patients with irreversible disease, the ratio of the excretion rates of the TXA2 and PGI2 metabolites was significantly abnormal, although the excretion rate of TXA2 was not. The influence of the endothelium on the evolution of pulmonary vascular disease may thus become "burned out" with time.

In addition to predisposing to thrombotic complications, it is conceivable that an increase in TXA2 biosynthesis in the pulmonary vascular bed could contribute to the progression of pulmonary vascular disease as a result of pulmonary arterial medial hypertrophy and pulmonary vasoconstriction. Intravenous infusion of U46619, a thromboxane mimetic, produces pulmonary hypertension in animals,36,37 and treatment with OKY-046, a thromboxane synthase inhibitor, reverses the acute pulmonary hypertension induced by endotoxin in sheep.38 Stimulation of TXA2 receptors stimulates PGI2 biosynthesis by vascular tissue in vitro,39 and thus, one might have anticipated that an increase in TXA2 biosynthesis in vivo would be accompanied by an increase in PGI2 production, resulting in a self-limiting process. This did not occur in our patients, and it is possible that the resulting imbalance in eicosanoid biosynthesis might exacerbate the disease process. Some experimental data support this possibility. Rats are partially protected from the pulmonary hypertensive effect of chronic hypoxia by the ingestion of fish oil, which reduces TXA2 biosynthesis and increases production of biologically active prostacyclins.40 These rats show less pulmonary arterial medial hypertrophy and right ventricular hypertrophy and have lower mortality than do hypoxic rats fed a normal diet. In humans with essential hypertension, unpalatable large doses of fish oil are required to reduce systemic arterial blood pressure, and the increase in total prostacyclin biosynthesis is transient.41 However, thromboxane synthase inhibitor and/or receptor antagonists offer a potential therapeutic approach in patients with pulmonary hypertension secondary to congenital heart disease.

In conclusion, in children and young adults with pulmonary vascular disease associated with congenital heart defects, there is an imbalance in eicosanoid biosynthesis that favors TXA2 production. The imbalance may contribute to changes that occur within the pulmonary circulation and is abolished in young children after successful corrective heart surgery. A better understanding of the mediators that influence the pulmonary circulation may provide the basis for a rationale for more specific pharmacological intervention that not only could influence acute changes but also may prevent the progressive development of irreversible structural damage that can occur in these patients.

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