Dilatation of the Ductus Arteriosus by Prostaglandin E₁ in Aortic Arch Abnormalities

Michael A. Heymann, M.D., William Berman, Jr., M.D., Abraham M. Rudolph, M.D., and Victor Whitman, M.D.

SUMMARY Infants with aortic arch interruption or juxtaductal coarctation of the aorta may depend on patency of the ductus arteriosus to provide adequate lower body perfusion. In many such infants the ductus arteriosus constricts after birth, resulting in severe heart failure, poor systemic perfusion and acidemia. We infused prostaglandin E₁ (PGE₁) at a rate of 0.05–0.1 μg/kg/min into seven infants with aortic arch interruption and eight infants with coarctation. In one infant in each group the ductus arteriosus was already closed and did not reopen. In one infant with coarctation an adequate trial was not accomplished, and in another adequate pressure measurements were not obtained. Of the remaining 11, the ductus arteriosus was effectively dilated by PGE₁ in 10 infants. This was evidenced by an increase in descending aortic blood pressures and a reduction in the pressure difference between the main pulmonary artery and descending aorta in six infants with aortic arch interruption and between ascending and descending aorta in four infants with coarctation. Lower body perfusion improved and left ventricular failure was improved. The infant who did not respond was 5 months old. There were no complications.

THE DRAMATIC EFFECT of infusing prostaglandin (PG) E₁ or E₂ to improve the oxygenation of infants with cyanotic congenital heart lesions in which pulmonary blood flow dependent on patency of the ductus arteriosus has been reported.¹ ² ³ The clinical use of PGE₁ or PGF₂α was based on observations that isolated strips or rings of ductus arteriosus tissue were relaxed by these agents. Earlier studies suggested that relaxation of the ductus arteriosus by PGE₁ occurred predominantly in a low-oxygen environment and relaxation was limited in a high-oxygen environment.⁴ Recent studies in our laboratory, however, showed that PGE₁ is an effective relaxant of the ductus arteriosus in both high- and low-oxygen environments.⁵

In several congenital cardiac lesions, maintenance of systemic blood flow or provision of adequate blood flow to the descending aorta after birth depends on patency of the ductus arteriosus. When the aortic arch is interrupted, the ductus arteriosus is essential to permit blood flow into the descending aorta from the pulmonary artery. We have reported previously the role of the ductus arteriosus in precipitating development of aortic obstruction and left ventricular failure in infants with juxtaductal aortic coarctation.⁶ In infants with either of these lesions, arterial blood Po₂ is usually normal or only slightly reduced. We examined the effectiveness of a PGE₁ infusion in relieving symptoms in seven infants with aortic arch interruption and eight infants with juxtaductal aortic coarctation. The protocols for these studies were approved by the Human Research Committees at the University of California, San Francisco and the Milton S. Hershey Medical Center of the Pennsylvania State University.

Materials and Methods

The effects of infusion of PGE₁ were examined in 15 full-term infants at the time of diagnostic cardiac catheterization. Twelve infants were receiving digitalis and had received one or more doses of furosemide. Four infants received assisted ventilation during cardiac catheterization. The diagnosis of aortic arch interruption or juxtaductal coarctation was confirmed by cineangiography. The associated intracardiac abnormalities are listed in table 1. PGE₁ (U 10136 Upjohn) was infused initially into the main pulmonary artery in three infants, the descending thoracic aorta in 11, and a peripheral vein in one, in amounts of 0.025–0.1 μg/kg/min (table 1). In patients 1 and 4, a catheter was manipulated retrogradely from the umbilical artery into the main pulmonary artery. In patient 3, PGE₁ was infused into the main pulmonary artery only during the cardiac catheterization procedure and thereafter was infused into a peripheral vein. In patient 13, the infusion was given into a peripheral vein at the termination of the cardiac catheterization. In the other 11 infants, the catheter was advanced retrogradely from either the umbilical or femoral artery and the tip was positioned at the level of the ductus arteriosus.

In all infants in whom PGE₁ was infused into an arterial catheter, pressure was monitored continuously through the same catheter with a Sorenson Intraflo unit (Sorenson Research Co, Salt Lake City, Utah). The infusion was maintained for 30 minutes–20 hours (table 1). Both before and during PGE₁ infusion, patients 7 and 15 had no evidence of patency of a ductus arteriosus either by measurement of oxygen saturations or by cineangiography; the infusion was dis-
Table 1. Clinical and Infusion Data on the 15 Infants Who Received PGE1 Infusions

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (days)</th>
<th>Wt (g)</th>
<th>Diagnosis</th>
<th>Infusion site</th>
<th>Dose (µg/kg/min)</th>
<th>Duration of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>4</td>
<td>4000</td>
<td>Ao interruption between LCA and LS, PDA, Taussig-Bing anomaly</td>
<td>MPA</td>
<td>0.1</td>
<td>10 min</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>1</td>
<td>3050</td>
<td>Ao interruption between LCA and LS, PDA, VSD</td>
<td>TAO</td>
<td>0.05</td>
<td>8 hr</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>11</td>
<td>3350</td>
<td>Ao interruption beyond LS, PDA, A-P fenestration</td>
<td>MPA/Peripheral vein</td>
<td>0.05</td>
<td>10 hr</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>3</td>
<td>3400</td>
<td>Ao interruption beyond LS, PDA, VSD</td>
<td>MPA</td>
<td>0.05</td>
<td>20 min</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>2</td>
<td>3420</td>
<td>Ao interruption beyond LS, PDA, VSD</td>
<td>TAO</td>
<td>0.05</td>
<td>20 hr</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>10</td>
<td>2700</td>
<td>Ao interruption beyond LS, PDA, VSD</td>
<td>TAO</td>
<td>0.05</td>
<td>2.5 hr</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>8</td>
<td>3500</td>
<td>Ao interruption between LCA and LS, A-P fenestration, No PDA</td>
<td>TAO</td>
<td>0.05</td>
<td>1.5 hr</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>4</td>
<td>3600</td>
<td>Coarctation, PDA</td>
<td>TAO</td>
<td>0.1</td>
<td>6 hr</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>28</td>
<td>2980</td>
<td>Coarctation, PDA</td>
<td>TAO</td>
<td>0.1</td>
<td>3 hr</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>17</td>
<td>3300</td>
<td>Coarctation, PDA, VSD, ASD</td>
<td>TAO</td>
<td>0.1</td>
<td>4 hr</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>10</td>
<td>2800</td>
<td>Coarctation, PDA, ASD</td>
<td>TAO</td>
<td>0.1</td>
<td>8 hr</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>150</td>
<td>4700</td>
<td>Coarctation, PDA, VSD</td>
<td>TAO</td>
<td>0.1</td>
<td>1 hr</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>9</td>
<td>3360</td>
<td>Coarctation, PDA, ECD</td>
<td>Peripheral vein</td>
<td>0.05</td>
<td>3 hr</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>3</td>
<td>3000</td>
<td>Coarctation, PDA, VSD</td>
<td>TAO</td>
<td>0.05</td>
<td>1 hr</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>12</td>
<td>3000</td>
<td>Coarctation, no PDA</td>
<td>TAO</td>
<td>0.05</td>
<td>30 min</td>
</tr>
</tbody>
</table>

Abbreviations: Ao = aortic; LCA = left carotid artery; LS = left subclavian artery; PDA = patent ductus arteriosus; MPA = main pulmonary artery; VSD = ventricular septal defect; TAO = thoracic aorta; ECD = endocardial cushion defect; P = pulmonary; ASD = atrial septal defect.

continued after 90 minutes in patient 7 and after 30 minutes in patient 15. Because PGE1 did not reopen the ductus arteriosus in these two infants, they were excluded from the analysis of the effects of PGE1 on arterial pressure, perfusion, and blood gases. Patient 14 had had a cardiac arrest and several episodes of severe bradycardia and hypotension before the infusion. PGE1 infusion was discontinued after 60 minutes, when hypotension and bradycardia occurred again. This infant was also excluded from the pressure analyses, since we did not believe that an adequate therapeutic trial had been accomplished. In 11 of the other 12 infants, the infusion was continued until surgical repair was completed. In one infant (patient 12), despite patency of the ductus arteriosus, we noted no increase in descending aortic pressure and the infusion was discontinued after 60 minutes.

In each infant rectal temperature, respiratory rate, ECG, arterial blood pressure and heart rate were monitored throughout the infusion. The infant was observed closely for clinical evidence of distress. Descending aortic blood pH and blood gases were measured before and intermittently during the infusion.

The effectiveness of PGE1 in dilating the ductus arteriosus was assessed by measuring the pressure difference between the main pulmonary artery and the descending aorta in the infants with aortic arch interruption and between the left ventricle or ascending aorta and the descending aorta in the infants with jux-

Table 2. Descending Aortic pH and Blood Gases (torr) Before and During PGE1 Infusion in 13 Infants.

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Control pH</th>
<th>Control Po2</th>
<th>Control Pco2</th>
<th>30-45 min after starting PGE1 infusion pH</th>
<th>Po2</th>
<th>Pco2</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>7.39</td>
<td>46</td>
<td>26</td>
<td>7.40</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>7.41</td>
<td>70</td>
<td>21</td>
<td>7.48</td>
<td>143</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>7.42</td>
<td>56</td>
<td>27</td>
<td>7.36</td>
<td>60</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>7.40</td>
<td>34</td>
<td>30</td>
<td>7.36</td>
<td>40</td>
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<td>7.38</td>
<td>49</td>
<td>24</td>
<td>7.37</td>
<td>51</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>7.30</td>
<td>49</td>
<td>28</td>
<td>7.29</td>
<td>51</td>
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<td>8</td>
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<td>32</td>
<td>7.33</td>
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<td>7.33</td>
<td>57</td>
<td>35</td>
<td>7.30</td>
<td>66</td>
<td>42</td>
</tr>
<tr>
<td>10</td>
<td>7.26</td>
<td>57</td>
<td>32</td>
<td>7.31</td>
<td>68</td>
<td>39</td>
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<td>11</td>
<td>7.29</td>
<td>54</td>
<td>36</td>
<td>7.32</td>
<td>71</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>7.41</td>
<td>76</td>
<td>31</td>
<td>7.43</td>
<td>84</td>
<td>31</td>
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<td>13</td>
<td>7.31</td>
<td>69</td>
<td>26</td>
<td>7.30</td>
<td>61</td>
<td>25</td>
</tr>
<tr>
<td>14</td>
<td>7.05</td>
<td>44</td>
<td>43</td>
<td>7.16</td>
<td>71</td>
<td>34</td>
</tr>
</tbody>
</table>
Infants

Juxtaductal coarcta- tion in all infants

tention occurred, the
descending, while systolic,
diastolic, was
obtained in patient 13; the effects of PGE$_1$, therefore,
were documented satisfactorily in only 11 infants, six
with aortic arch interruption and patent ductus arte-
riosus and five with juxtaductal coarctation and pa-
tent ductus arteriosus. In consideration of the small
number of infants involved and the wide variations
of pressures between patients, statistical analyses were
not performed.

Results

The sex, age, and weight at the time of catheteri-
ization in all infants are shown in table 1.

Descending aortic blood gases and pH before and
30–45 minutes after starting the PGE$_1$ infusion are
shown in table 2. With few exceptions, no major
change occurred, and the general trend was an in-
tcrease in pH, PO$_2$, and PCO$_2$.

During PGE$_1$ infusion in the six infants with aortic
arch interruption and patent ductus arteriosus, there
was no change in main pulmonary arterial pressures,
while systolic, diastolic, and mean blood pressures in
the descending aorta increased (table 3). The systolic,
diastolic, and mean pressures difference between the
main pulmonary artery and the descending aorta de-
creased in all instances (table 3). An example of pres-
sure recordings obtained from one of these infants is
shown in figure 1.

In the five infants with juxtaductal coarctation and
patent ductus arteriosus, ascending aortic systolic,
diastolic, and mean pressures fell (table 3). In four of
the five infants, descending aortic systolic, diastolic,
and mean pressures rose; in one infant (patient 12),
however, there was no change in the descending aortic
pressures. For the group, the systolic, diastolic, and
mean pressure difference between the ascending aorta
and the descending aorta fell markedly during in-
fusion (table 3). An example of simultaneously re-
corded left ventricular and descending aortic pres-
sures in one of these infants is shown in figure 2; in this
infant there was no systolic pressure difference
between the left ventricle and the ascending aorta.
Left ventricular end-diastolic pressure in the five
infants with coarctation fell from an average of 21 mm
Hg to 16 mm Hg during PGE$_1$ infusion.

Apart from the episode of bradycardia and hypo-
tension in one infant (patient 14), no adverse effects
of PGE$_1$ infusion were noted.

TABLE 3. Systolic (s), Diastolic (d), and Mean (m) Blood Pressures (mm Hg), Range and Average, in the Main Pulmonary Artery (MPA), Descending Aorta (DAo), and Ascending Aorta (AAo) and the Difference between MPA and DAo or AAo and DAo in 11 Infants Treated with Infusion of Prostaglandin E$_1$.

<table>
<thead>
<tr>
<th></th>
<th>Systolic (s)</th>
<th>Diastolic (d)</th>
<th>Mean (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>During PGE$_1$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>s</td>
<td>d</td>
<td>m</td>
</tr>
<tr>
<td></td>
<td>s</td>
<td>d</td>
<td>m</td>
</tr>
<tr>
<td></td>
<td>m</td>
<td>m</td>
<td>m</td>
</tr>
<tr>
<td>Aortic interruption (n = 6)</td>
<td>72–100 (86)</td>
<td>35–55 (43)</td>
<td>50–65 (59)</td>
</tr>
<tr>
<td></td>
<td>70–95 (85)</td>
<td>35–60 (46)</td>
<td>47–75 (60)</td>
</tr>
<tr>
<td></td>
<td>61–80 (70)</td>
<td>38–60 (47)</td>
<td>52–65 (58)</td>
</tr>
<tr>
<td></td>
<td>3–25 (15)</td>
<td>0</td>
<td>0–10 (2)</td>
</tr>
<tr>
<td>Juxtaductal coarctation (n = 5)</td>
<td>105–170 (133)</td>
<td>70–90 (81)</td>
<td>85–110 (98)</td>
</tr>
<tr>
<td></td>
<td>100–115 (108)</td>
<td>60–80 (69)</td>
<td>74–92 (83)</td>
</tr>
<tr>
<td></td>
<td>75–110 (93)</td>
<td>40–75 (59)</td>
<td>53–87 (72)</td>
</tr>
<tr>
<td></td>
<td>0–20 (10)</td>
<td>0</td>
<td>0–24 (11)</td>
</tr>
</tbody>
</table>

Figure 1. Pressure recordings during withdrawal of the catheter from the main pulmonary artery (MPA) across the ductus arteriosus into the descending aorta (DAo) before and during prostaglandin E$_1$ (PGE$_1$) infusion in an infant with aortic arch interruption.
Discussion

These studies have confirmed the recent experimental observations that the ability of PGE₁ to relax the ductus arteriosus is independent of PO₂ and that relaxation occurs at both high and low oxygen concentrations.⁶ In the infants with aortic arch interruption, the pressure differences between the main pulmonary artery and the descending aorta were reduced markedly, but were not completely abolished in any instance. This could be explained by anatomical changes within the ductus arteriosus or perhaps by lack of complete relaxation of the ductus arteriosus by the concentration of PGE₁ achieved. Higher doses may be effective; however, the degree of clinical and hemodynamic improvement did not justify increasing the infusion rate. In those infants with juxtaductal coarctation of the aorta, the pressure difference between the ascending and descending aorta was abolished completely in two infants and reduced markedly in two infants. This further confirms the role of constriction of the ductus arteriosus in precipitating hemodynamic obstruction of the aorta in infants with symptomatic coarctation.⁶, ⁷

In two infants, we could not produce reopening of the ductus arteriosus after it had already closed. Possibly, anatomic closure had occurred in these infants, thereby preventing dilatation. In one infant (patient 14), an adequate trial of PGE₁ was not accomplished, because the infant was gravely ill before and during the procedure and the hypotensive episode could have been related to the PGE₁. In patient 12, who was 5 months old, descending aortic pressure did not increase, although ascending aortic systolic pressure fell. This suggested that the ductus arteriosus did not dilate and that peripheral vasodilatation was responsible for the pressure fall. In the other infants not only was there a marked increase in descending aortic blood pressure and a reduction in the pressure gradient either across the coarctation or across the ductus arteriosus in those infants with aortic interruption, but an improvement in pH and PO₂ and also noticeable clinical improvement as well.

In most instances the infant had not voided for many hours before study, and all passed urine after the PGE₁ infusion. This may have been related to improved renal perfusion or to a direct effect of PGE₁ on renal function. Clinical improvement in peripheral circulatory perfusion with improved capillary filling was evident in all of the infants. In addition, improvement in myocardial function resulting from afterload reduction may have occurred, as evidenced by the reduced left ventricular end-diastolic pressure in infants with juxtaductal coarctation. The tendency for PCO₂ to increase also might have been related to improved left ventricular function, improvement in congestive heart failure and a reduction in respiratory rate.

We have shown that infusion of PGE₁ has no deleterious effects on these infants, and it would therefore seem appropriate to continue the infusion until a surgical procedure, used to establish adequate systemic flow, has been completed. In those infants in whom the ductus arteriosus already is closed, it is unlikely that PGE₁ will reopen the ductus arteriosus; however, a short trial infusion is probably indicated. Although one of the infants in whom a response was obtained was 28 days old, it is unlikely that PGE₁ will be as effective in children out of the immediate newborn period, as evidenced by the lack of response in the 5-month-old infant. The site of infusion does not appear to be critical, as similar responses were obtained with infusion into the aorta, main pulmonary artery or a peripheral vein.

PGE₁ infusion is an effective and safe method to improve systemic blood flow in infants with congenital heart disease who depend on the ductus arteriosus to supply part or all of systemic blood flow. In severely ill infants in whom the diagnosis of coarctation or interruption of the aorta is clinically suspected, it might be
appropriate, and perhaps even life-saving, to start a PGE₁ infusion before transfer of an infant to a center for definitive diagnostic evaluation by echocardiography and cardiac catheterization. However, systemic output also may be improved in infants with hypoplastic left heart syndrome; this has been our experience. Since clinical differentiation between hypoplastic left heart syndrome and other forms of left ventricular outflow obstruction is often difficult, it may be preferable to improve systemic blood flow temporarily in an occasional infant with the hypoplastic left heart syndrome than delay this in infants with surgically correctable lesions such as coarctation or interruption of the aorta.

Acknowledgment

Prostaglandin E₁ (U 10136) was supplied by the Upjohn Co, Kalamazoo, Michigan.

References


Anatomy of Aortic Atresia

Cases Presenting with a Ventricular Septal Defect

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SUMMARY The anatomy of 58 specimens of aortic outflow tract atresia was studied. All cases had situs solitus and levocardia, 37 had atrioventricular (AV) concordance, two had common inlet to a right ventricle and 19 had mitral atresia. The great arteries were normally interrelated in all cases. Fifty-one cases had an intact ventricular septum, while seven presented with a ventricular septal defect (VSD). Of the seven with VSD, in two it was associated with a common AV orifice draining exclusively into the right ventricle in the presence of a rudimentary left ventricular chamber. In one case a small VSD accompanied combined mitral and aortic atresia. In the other four cases the left ventricles and mitral valves were fairly normal in size; the VSD was subpulmonary in three cases, due to infundibuloventricular malalignment, and perimembranous in one. These last four cases are of particular interest since they could be amenable to surgical correction. Possible approaches to surgical treatment and morphologic features pertinent to them are described and discussed.

MANY INVESTIGATORS have studied aortic atresia and have revealed a high degree of uniformity in morphology.¹⁻⁴ Recently, variations of morphology have been described; aortic atresia was found in hearts with ventricular septal defects (VSD) and normally developed left ventricles.⁵⁻¹² This reported variation in morphology, some of it of potential surgical significance, prompted us to review the anatomy of hearts with aortic atresia, with special reference to cases with VSD.

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Address for reprints: Dr. Gaetano Thiene, Department of Pathology, Via Gabelli 61, 35100 Padova, Italy.


Materials

Fifty-eight hearts with aortic atresia were obtained from the Department of Pathology at the University of Padova, Italy; the Thoracic Unit, The Hospital for Sick Children, London, England; and the Department of Pediatrics, Cardiothoracic Institute, Brompton Hospital, London, England.

All hearts were from persons with viscero-atrial situs solitus and levocardia. In 37 hearts, we observed atrioventricular (AV) concordance, with the left atrium and the left ventricle connecting through a hypoplastic mitral valve. In 19 hearts, there was absence of the left AV connection (mitral atresia). In the remaining two hearts, both atria drained through a common AV orifice to a right ventricle,¹³ a rudimentary chamber of left ventricular type being identified in both. In all hearts the hypoplastic ascending aorta was posterior and to the right of the pulmonary trunk.
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