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

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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 in-
 fused prostaglandin E₁ (PGE₁) at a rate of 0.05−0.1 µg/kg/min into seven infants with aortic arch interrup-
tion 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 ade-
quate pressure measurements were not obtained. Of the remaining 11, the ductus arteriosus was effectively di-
lated 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 prosta-
glandin (PG) E₁ or E₂ to improve the oxygenation of
infants with cyanotic congenital heart lesions in which
pulmonary blood flow depended on patency of the
ductus arteriosus has been reported.¹ ² The clinical use
of PGE₁ or PGE₂ was based on observations that iso-
lated strips or rings of ductus arteriosus tissue were re-
lexical 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 environ-
ment.⁴ Recent studies in our laboratory, however,
showed that PGE₁ is an effective relaxant of the
ductus arteriosus in both high- and low-oxygen environ-
ments.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 per-
mit blood flow into the descending aorta from the pul-
monary 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.⁸ In infants
with either of these lesions, arterial blood Po₂ is usu-
ally normal or only slightly reduced. We examined the
effectiveness of a PGE₁ infusion in relieving symp-
toms in seven infants with aortic arch interruption and
eight infants with juxtaductal aortic coarctation. The
protocols for these studies were approved by the Hu-
man Research Committees at the University of Cali-
fornia, 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 dig-
talis and had received one or more doses of furose-
mide. Four infants received assisted ventilation dur-
ing cardiac catheterization. The diagnosis of aortic
arch interruption or juxtaductal coarctation was con-
firmed by cineangiography. The associated intra-
cardiac abnormalities are listed in table 1. PGE₁ (U
10136 Upjohn) was infused initially into the main pul-
monary 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 pa-
tients 1 and 4, a catheter was manipulated retro-
gradely from the umbilical artery into the main pul-
monary 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 ar-
teral catheter, pressure was monitored continuously
through the same catheter with a Sorenson Intrafo-
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, pa-
tients 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>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 0.05</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>T Ao</td>
<td>0.05 0.025</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 0.05</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 0.025</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>2</td>
<td>3420</td>
<td>Ao interruption beyond LS, PDA, VSD</td>
<td>T Ao</td>
<td>0.05 0.025</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>10</td>
<td>2700</td>
<td>Ao interruption beyond LS, PDA, VSD</td>
<td>T Ao</td>
<td>0.05 0.025</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>T Ao</td>
<td>0.05 0.025</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>4</td>
<td>3600</td>
<td>Coarctation, PDA</td>
<td>T Ao</td>
<td>0.1 0.1</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>28</td>
<td>2980</td>
<td>Coarctation, PDA</td>
<td>T Ao</td>
<td>0.1 0.1</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>17</td>
<td>3300</td>
<td>Coarctation, PDA, VSD, ASD</td>
<td>T Ao</td>
<td>0.1 0.1</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>10</td>
<td>2800</td>
<td>Coarctation, PDA, ASD</td>
<td>T Ao</td>
<td>0.1 0.1</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>150</td>
<td>4700</td>
<td>Coarctation, PDA, VSD</td>
<td>T Ao</td>
<td>0.1 0.1</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 0.05</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>3</td>
<td>3000</td>
<td>Coarctation, PDA, VSD</td>
<td>T Ao</td>
<td>0.05 0.025</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>12</td>
<td>3000</td>
<td>Coarctation, no PDA</td>
<td>T Ao</td>
<td>0.05 0.025</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; T Ao = 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 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 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 in 11 Infants Treated with Infusion of Prostaglandin E1.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>During PGE1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>s</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>s</td>
<td>d</td>
</tr>
<tr>
<td>Aortic interruption (n = 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPA</td>
<td>72–100 (88)</td>
<td>35–55 (43)</td>
</tr>
<tr>
<td>DAo</td>
<td>49–55 (51)</td>
<td>30–45 (39)</td>
</tr>
<tr>
<td>MPA-DAo</td>
<td>22–48 (35)</td>
<td>0–15 (4)</td>
</tr>
<tr>
<td>Juxtaductal coarctation (n = 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAo</td>
<td>105–170 (133)</td>
<td>70–90 (81)</td>
</tr>
<tr>
<td>DAo</td>
<td>50–75 (61)</td>
<td>35–55 (47)</td>
</tr>
<tr>
<td>AAo-DAo</td>
<td>42–95 (71)</td>
<td>20–55 (34)</td>
</tr>
</tbody>
</table>

Results

The sex, age, and weight at the time of catheterization in all infants are shown in table 1. Descending aortic blood gases and pH before and 30–45 minutes after starting the PGE1 infusion are shown in table 2. With few exceptions, no major change occurred, and the general trend was an increase in pH, PO2, and PCO2.

During PGE1 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 decreased in all instances (table 3). An example of pressure 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 infusion (table 3). An example of simultaneously recorded left ventricular and descending aortic pressures 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 PGE1 infusion.

Apart from the episode of bradycardia and hypotension in one infant (patient 14), no adverse effects of PGE1 infusion were noted.

![Figure 1](https://example.com/figure1.png)

**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 E1 (PGE1) 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. 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.

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
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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

GAETANO THIENE, M.D., VINCENZO GALLUCCI, M.D., FERGUS J. MACARTNEY, M.D., STEFANO DEL TORSO, M.D., PIERO A. PELLEGRINO, M.D., AND ROBERT H. ANDERSON, M.D.

SUMMARY The anatomy of 58 specimens of aortic outflow tract atresia was studied. All cases had situs solitus and levocardia, 37 had atriointerventricular (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 infundibulovenous 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.

From the Departments of Pathology, Pediatrics and Cardiovascular Surgery, University of Padova, Medical School, Padova, Italy, and from the Department of Pediatrics, Cardiothoracic Institute, Brompton Hospital and the Thoracic Unit, The Hospital for Sick Children, London, England.

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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 atriointerventricular (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.
Dilatation of the ductus arteriosus by prostaglandin E1 in aortic arch abnormalities.
M A Heymann, W Berman, Jr, A M Rudolph and V Whitman

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