

# Prostacyclin concentrations and transitional circulation in preterm infants requiring mechanical ventilation

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## Abstract

**Aim**—To describe the association between early postnatal prostacyclin concentrations in preterm infants; echocardiographic measurements of ductal diameter and ventricular output and clinical outcomes of intraventricular haemorrhage (IVH) and patent ductus arteriosus (PDA).

**Methods**—Forty nine preterm infants born before 30 weeks of gestational age (median birthweight 980 g, median gestational age 27 weeks) underwent echocardiographic studies at 5, 12, 24 and 48 hours of postnatal age. Measurements included ventricular outputs and the ductal shunt diameter as a measure of the shunt size. Simultaneous measurements of blood pressures, mean airway pressure and inspired fraction of oxygen (FIO<sub>2</sub>) were recorded. A blood sample for the prostacyclin metabolite 6-ketoprostaglandin F1- $\alpha$  (6KPGF<sub>1 $\alpha$</sub> ) was taken at the 5 and 24 hour echocardiogram.

**Results**—The mean 6KPGF<sub>1 $\alpha$</sub>  concentrations were higher than adult concentrations at 5 (515 pg/ml) and 24 (255 pg/ml) hours. There was no association with gestational age. Raised 6KPGF<sub>1 $\alpha$</sub>  concentrations were related to increased need for mechanical ventilation and severity of respiratory disease. At 5 hours, increased 6KPGF<sub>1 $\alpha$</sub>  concentrations were associated with larger PDA and at 24 hours with larger PDA and higher left ventricular output. Infants with higher 6KPGF<sub>1 $\alpha$</sub>  concentrations were more likely to develop clinically significant PDA. There was no association between early measurements of 6KPGF<sub>1 $\alpha$</sub>  and IVH.

**Conclusions**—Early postnatal prostacyclin concentrations are markedly raised in preterm infants, particularly in those with more severe lung disease. Raised 6KPGF<sub>1 $\alpha$</sub>  concentrations were associated with an increased ductal diameter and subsequent PDA, but not IVH.

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**Keywords:** prostacyclin; ductal diameter; ventricular output; intraventricular haemorrhage; patent ductus arteriosus

Prostacyclin (or its stable metabolite, 6-ketoprostaglandin F<sub>1 $\alpha$</sub> ) is present in high concentrations in the plasma of preterm infants, particularly those with hyaline membrane disease.<sup>1-4</sup>

Prostacyclin is a vasodilatory prostaglandin that is present in high concentrations in the fetal ductus<sup>5</sup> and the preterm transitional circulation.<sup>4</sup> Prostacyclin is also likely to have a role in cerebral blood flow control.<sup>6</sup> We have shown before that there is a strong correlation between the size of the ductus arteriosus on colour Doppler echocardiography in the first 24 hours of life and intraventricular haemorrhage.<sup>7</sup>

Intraventricular haemorrhage (IVH) in premature infants is related to both respiratory distress syndrome and the presence of a patent ductus arteriosus.<sup>8</sup> We postulated that prostacyclin may be an important link between the size of the ductus arteriosus and intraventricular haemorrhage in preterm infants.

Although several investigators have examined the role of prostacyclin, most of these have comprised small numbers and were measured after the first 24 hours of life when the greatest risk period for intraventricular haemorrhage has passed. These studies did not examine the other complex haemodynamic changes that occur at the same time as hormonal measures are being made, including changes in ductal diameter and ventricular outputs.<sup>9</sup>

Our aim was to examine the association between the size of the PDA in the first 24 hours, the occurrence of IVH and the concentrations of prostacyclin, as measured by its stable metabolite, 6KPGF<sub>1 $\alpha$</sub> . A secondary aim was to confirm the previously documented relation with respiratory diagnosis and examine the association between all of these variables and the invasively measured blood pressure.

## Methods

Forty nine preterm infants born before 30 weeks gestation and requiring mechanical ventilation underwent serial echocardiographic studies at 5, 12, 24 and 48 hours of life. Information collected included demographic details, use of antenatal steroids, and exogenous surfactant. Oxygen requirements, ventilatory settings, and intra-arterial blood pressures were recorded at the time of each scan. All blood gases with the associated ventilator settings were recorded. Blood pressures were downloaded every 5 minutes from Hewlett Packard Merlin monitors to a central database in all but seven of the 49 infants. These infants had hourly recordings taken from the nursing charts as the download facility was not available for technical reasons.

An Acuson 128/XP10 (Acuson Corporation, Mountain Drive, California) ultrasound machine incorporating colour flow, pulsed wave,

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Table 1 Relation between clinical and demographic variables and 6KPGF<sub>1α</sub> concentration at 5 and 24 hours

	5 hours correlation coefficient R (p value)	24 hours correlation coefficient R (p value)
Gestational age (weeks)	0.04 (0.82)	0.08 (0.60)
MAP at scan (cm H <sub>2</sub> O)	0.26 (0.08)	0.13 (0.39)
MAP following scan (cm H <sub>2</sub> O)	0.35 (0.02)	0.24 (0.10)
Ductal diameter (mm)	0.33 (0.03)	0.31 (0.03)
Mean blood pressure at scan (mm Hg)	0.20 (0.18)	0.04 (0.81)
LV output (ml/kg/minute)	0.07 (0.64)	0.34 (0.02)
RV output (ml/kg/minute)	0.04 (0.80)	0.006 (0.97)

and continuous wave Doppler was used. Structural normality of the heart was established during the course of the scan. All studies were recorded on video tape for later review and performance of measurements. At each study the following measurements were taken using protocols described in detail in previous publications<sup>10</sup>: Doppler volumetric measurement of right and left ventricular output; colour Doppler diameter of the ductus arteriosus shunt as an index of the shunt size.

Subsequent echocardiograms (usually because of a clinically suspected PDA) were performed only if requested by a clinician. A symptomatic PDA in our unit is defined by clinical signs such as an increased precordial impulse and pulses, a heart murmur, difficulty maintaining blood pressure or worsening ventilatory status, together with echocardiographic evidence of a clinically significant PDA.<sup>11</sup>

With each echocardiogram, 2D imaging of the brain was performed in the coronal and sagittal planes to look for evidence of haemorrhage or ischaemic injury. Further cerebral scans were routinely done on these infants at the end of the first week and at 28 days and reported by a paediatric radiologist masked to the clinical status of the baby. Any haemorrhage was noted and classified according to the Papile grading.

Blood (1 ml) anticoagulated with heparin was taken from an indwelling arterial line routinely (placed for monitoring of ventilation) at 5 and 24 hours of life at the same time as the echocardiogram was performed. The sample was collected into a pre-chilled polypropylene tube coated with a solution of EDTA and indomethacin (10 µg/ml), immediately centrifuged, the plasma fraction retrieved and then stored at -70°C. Assays were performed within three months of collection. The samples were diluted (3 in 10) in assay buffer to minimise interference by plasma components. They were then assayed in duplicate for 6KPGF<sub>1α</sub> concentrations using a standard radioimmunoassay (NEN Research Products, Boston MA, USA, [125I] radioimmunoassay kit: sensitivity equivalent to 30 pg/ml plasma).

Table 2 Respiratory diagnosis and relation to median 6KPGF<sub>1α</sub> concentrations at 5 hours

Respiratory diagnosis	Normal (n=6)	Immature (n=7)	HMD (n=30)	Pneumonia (n=3)	p Value
6KPGF <sub>1α</sub> (pg/ml)	231	343	529	657	0.01
Gestational age (weeks)	29	27	25	27	0.02
Blood pressure (mm Hg)	34	29	31	29	0.11
FIO <sub>2</sub> (%)	21	21	28	100	<0.001
MAP (cm H <sub>2</sub> O)	6	7	9	17	0.006

This study was approved by the Royal Prince Alfred Hospital Ethics Committee and informed parental consent was obtained for each participant.

Correlations were examined using Spearman's correlation coefficient. Group data were analysed using Mann Whitney U and Kruskal-Wallis ANOVA tests for non-parametric data distribution. Multivariate analysis using linear regression was performed to control for factors important during univariate analysis. The SPSS-PC computer statistical package was used.

## Results

Forty nine infants with a median gestational age of 27 weeks (range 23 to 29) and a median birthweight of 980 g (range 466–1492 g) were enrolled into the study. Forty four infants (90%) had received some antenatal corticosteroid. Thirty five (71%) were delivered by caesarean section. All of the infants were mechanically ventilated initially and 30 infants (64%) received exogenous surfactant.

Of the 49 infants enrolled in the study, 46 had blood samples for 6KPGF<sub>1α</sub> taken at 5 hours and 47 had blood samples taken at 24 hours of age. The mean 6KPGF<sub>1α</sub> concentration at 5 hours of age was 515 (SE 48 pg/ml) and at 24 hours 255 (20 pg/ml). There was a much greater range of values at 5 hours than at 24 hours. The mean 6KPGF<sub>1α</sub> concentrations decreased between 5 and 24 hours (mean decrease 249 pg/ml, range -1598 pg/ml to +160 pg/ml, SD 284 pg/ml) and individual infants' measurements almost all decreased. There was no correlation between 6KPGF<sub>1α</sub> concentrations and gestational age at either 5 or 24 hours of age.

The association between clinical and echocardiographic parameters and the 6KPGF<sub>1α</sub> concentrations at 5 and 24 hours is summarised in table 1.

Of the 49 enrolled infants, six had normal lungs (ventilated for less than 24 hours), 30 had hyaline membrane disease (ventilated for more than 24 hours with radiological evidence of hyaline membrane disease; all of these infants received surfactant with the first dose before the first blood sample), 10 had pulmonary immaturity (ventilated for greater than 24 hours but no evidence of hyaline membrane disease), and three had pneumonia.

At 5 hours, increased 6KPGF<sub>1α</sub> concentrations were associated with a higher mean airway pressure (MAP) over the following 6 hours (table 1). There was also a strong positive correlation with the respiratory diagnosis, with babies with abnormal lungs and requiring mechanical ventilation having higher concentrations of 6KPGF<sub>1α</sub> (median 529 vs 231; p<0.001).

Infants were grouped according to their respiratory diagnosis, and the association between gestation, condition at birth, respiratory and blood pressure parameters and 6KPGF<sub>1α</sub> concentrations at 5 and 24 hours is shown in tables 2 and 3. Infants with more severe respiratory disease, as defined by diagnosis, MAP,

Table 3 Respiratory diagnosis and relation to median 6KPGF<sub>1α</sub> concentrations at 24 hours

Respiratory diagnosis	Normal (n=6)	Immature (n=10)	HMD (n=30)	Pneumonia (n=3)	p Value
6KPGF <sub>1α</sub> (p/ml)	108	281	279	129	0.003
Gestational age (weeks)	29	27	26	26	0.03
Blood pressure (mm Hg)	41	35	34	35	0.34
FIO <sub>2</sub> (%)	24	23	28	42	0.03
MAP (cm H <sub>2</sub> O)	5	6	7	7	0.02

and FIO<sub>2</sub>, had significantly higher values of 6KPGF<sub>1α</sub> at both 5 and 24 hours of age.

Seventeen (35%) of the infants developed a clinically significant patent ductus arteriosus which required treatment with indomethacin or ligation. At 5 hours, the median 6KPGF<sub>1α</sub> concentrations for those who developed a clinically significant PDA was 539 pg/ml *vs* 372 pg/ml (p=0.03) in those who did not. There was a significant correlation between higher median 6KPGF<sub>1α</sub> concentrations and larger ductal diameter, as measured by colour Doppler mapping as a continuous variable (R=0.33, p=0.03). At 24 hours, the median 6KPGF<sub>1α</sub> concentrations for those who developed a significant PDA was 263 pg/ml *vs* 196 pg/ml (p=0.04) in those who did not. There was a significant correlation between median 6KPGF<sub>1α</sub> concentrations and the ductal diameter, as measured by colour Doppler mapping as continuous variables (R=0.31, p=0.03).

Of the 49 infants, 11 had evidence of intraventricular haemorrhage. Three infants had a grade 1, two had a grade 2, one had a grade 3 and five had a grade 4 haemorrhage using the Papile classification. Two infants died before having a definitive cranial ultrasound scan; the remaining 36 infants had no intraventricular haemorrhage. Four of the 11 infants had early IVH with evidence of the haemorrhage on the first scan at 5 hours of age. One of these extended to a grade 3 haemorrhage at the 24 hour scan. We excluded those with early IVH from further analysis as these haemorrhages were likely to have been related to antenatal or intrapartum factors more than to postnatal factors. There were seven late haemorrhages of which two were grade 2 and five grade 4. The median 6KPGF<sub>1α</sub> concentrations in infants with late IVH, as opposed to those with no IVH, were not significantly different either at 5 or 24 hours (514 *vs* 656 pg/ml and 268 *vs* 250 pg/ml, respectively). The median 6KPGF<sub>1α</sub> concentrations of infants with early IVH was 279 pg/ml at the 5 hour scan and 220 pg/ml at the 24 hour scan.

The median 6KPGF<sub>1α</sub> concentrations were not related to the blood pressure at the time of the scan or the average blood pressure in the 6 hours before or after the scan at either 5 or 24 hours. At 24 hours there was a strong positive relation between median 6KPGF<sub>1α</sub> concentrations and the left ventricular output (r= 0.45, p= 0.001). There was no association between these parameters at 5 hours, nor was there a significant correlation between median 6KPGF<sub>1α</sub> concentrations and right ventricular output at either 5 or 24 hours.

Linear regression analysis of factors that may have contributed to prostacyclin concentra-

tions was then performed. We included the gestational age, mean airway pressure as a measure of respiratory severity, left and right ventricular outputs, and the ductal diameter. At 5 hours mean airway pressure and left ventricular output were included in the model while at 24 hours only left ventricular output was independently associated with the 6KPGF<sub>1α</sub> concentrations.

## Discussion

The results of this study suggest that prostacyclin has an important role in the transitional circulation of mechanically ventilated preterm infants. Previously identified problems relating to the haemodynamic state of this group of infants include hypotension,<sup>12</sup> low ventricular outputs,<sup>9</sup> and ductal shunting. Varying peripheral resistance may also be important. Many of these factors are also related to subsequent cerebral injury in preterm infants. Prostacyclin is one of several hormonal substances that may be involved in the transitional circulation changes of preterm infants. These include endothelial active compounds such as nitric oxide and endothelin,<sup>13</sup> other prostaglandins, catecholamines and atrial natriuretic peptide.<sup>14</sup> This study is the first to our knowledge to examine the 6KPGF<sub>1α</sub> concentrations in relation to accurate measures of ductal diameter and patency.

This study has shown that 6KPGF<sub>1α</sub> concentrations are markedly raised in preterm infants compared with older children and adults.<sup>15</sup> There is a rapid reduction in these high values by 24 hours of age, thereby suggesting a role for this vasodilatory prostaglandin in the transitional circulation of the preterm infant. The highest concentrations of 6KPGF<sub>1α</sub> were seen in those infants who were mechanically ventilated, with lung parenchymal pathology such as respiratory distress syndrome or pneumonia. There was a strong positive association between mechanical ventilation and prostacyclin concentration. Infants who were receiving mechanical ventilation, but with normal lungs, had relatively lower 6KPGF<sub>1α</sub> values. One of the main sources of prostacyclin is the lung and it is not metabolised in the pulmonary circulation unlike other prostaglandins.<sup>16</sup> Mechanical ventilation in both humans and animals has been shown to release prostacyclin.<sup>17</sup> Other groups have also found that persistent high concentrations of 6KPGF<sub>1α</sub> are present in infants with respiratory distress syndrome.<sup>3</sup> This association may also explain our previous observations that large and/or clinically significant PDAs are less common in infants with normal lungs.<sup>9</sup>

One of the more important aspects of prostaglandins in preterm infants is the effect on the ductus arteriosus. The major product of ductus homogenate is 6KPGF<sub>1α</sub>, suggesting that prostacyclin is an important factor in ductus physiology.<sup>5</sup> This study used a direct measure of the ductal diameter on colour Doppler flow mapping, a measurement that we have previously correlated with clinically significant PDA,<sup>11</sup> and compared it with prostacyclin concentrations to attempt to assess the direct effect

of prostacyclin on ductal diameter. There was a direct correlation between ductal diameter and prostacyclin concentration at both 5 and 24 hours. We also found a positive association between the prostacyclin concentration at both 5 and 24 hours and the subsequent need for clinical treatment of a ductus. Prostaglandin concentrations have been studied several times in small numbers of premature neonates, mainly by Hammerman's group in Chicago.<sup>1 18 19</sup> They determined PGE<sub>2</sub> and 6KPGF<sub>1α</sub> concentrations. They found that in infants with a "silent" or asymptomatic echocardiographically detected ductus on day 2 or 3 the concentrations of 6KPGF<sub>1α</sub> were raised significantly compared with infants without a PDA. PGE<sub>2</sub> values were also raised in infants with silent PDA compared with those without, but this failed to reach significance.<sup>1</sup> This group also correlated 6KPGF<sub>1α</sub> concentrations with indomethacin responsiveness in 16 infants,<sup>18</sup> and found that those infants whose PDA closed in response to indomethacin had significantly higher 6KPGF<sub>1α</sub> concentrations. These studies were performed after 2 days of age and no attempt was made to relate 6KPGF<sub>1α</sub> concentrations to the size of the PDA as only the presence or absence of ductal shunting on contrast echocardiography was recorded. A further study related 6-KPGF1 concentrations to the severity of PDA, as suggested by left ventricular systolic time intervals<sup>19</sup> which is again an indirect method of assessing ductal size.

Our study found no associations between these early measures of 6KPGF<sub>1α</sub> and subsequent intraventricular haemorrhage. Rennie *et al* showed that in infants who subsequently developed intraventricular haemorrhage, there were raised 6KPGF<sub>1α</sub> concentrations which persisted over the first 3 days of life compared with infants who did not develop intraventricular haemorrhage.<sup>20</sup> They did, however, find that the differences were not significant on day 1, which is consistent with our findings. It may be that IVH itself causes an increase or persistence of high 6KPGF<sub>1α</sub> concentrations in preterm infants. There was a trend to more IVH in infants with a silent PDA and raised 6KPGF<sub>1α</sub> concentrations, but this was not significant.<sup>1</sup>

Blood pressure is related to both the cardiac output and systemic vascular resistance. In preterm infants the cardiac output may be influenced by myocardial dysfunction, high pulmonary vascular resistance, positive pressure ventilation and ductal shunting. Systemic vascular resistance will also be affected by a patent ductus and may be affected by vasodilatory hormonal influences such as prostacyclin. We found no correlation between blood pressure and the 6KPGF<sub>1α</sub> concentration. There was a strong positive correlation between 6KPGF<sub>1α</sub>

concentrations and left ventricular output at 24 hours. This was not seen at 5 hours or reflected in the right ventricular output. We speculate that this is likely to have been secondary to an increasing left to right shunt through a PDA, resulting in the increased left ventricular output, rather than a primary factor.

We conclude that prostacyclin is likely to have an important role in the transitional circulation and postnatal adaptation of mechanically ventilated preterm infants. The high concentrations in the first 24 hours of life, particularly in those with severe respiratory disease, are related to subsequent clinically significant PDA but not intraventricular haemorrhage or systemic blood pressure.

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