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Prostacyclin Treatment for Persistent Pulmonary Hypertension of the Newborn

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Abstract. To study the effect of prostacyclin treatment on pulmonary arterial pressure (PAP), systolic pressure (BP), and systemic oxygenation, eight infants with persistent pulmonary hypertension of the newborn (PPHN) born between 34 and 42 weeks' gestation and having a birth weight of 2540–4130 g were studied using Doppler echocardiography. At a mean age of 19 hours (range 3–32 hours), despite maximal ventilator therapy and an FiO_2 of 1.0, the mean PaO_2/PAO_2 was 0.07 (range 0.04–0.09) and the $AaDO_2$ was 616 mmHg (range 521–654 mmHg). After volume correction and during inotropic medication with dopamine and dobutamine, the mean PAP by echocardiography was 68.6 ± 6.5 mmHg and the mean BP 59.8 ± 4.8 mmHg. Prostacyclin infusion was then started at a dose of 20 ng/kg/min and increased stepwise to a mean dose of 60 ng/kg/min (range 30–120 ng/kg/min) over 4–12 hours, at which time PAP decreased to 49.2 ± 3.5 mmHg ($p = 0.0005$) and BP to 53.2 ± 9.1 mmHg ($p = 0.17$); the PAP thereafter remained below the BP. After 72 hours of prostacyclin infusion, PAP was 49.6 ± 18 mmHg, BP 66.1 ± 5.4 mmHg, PaO_2/PAO_2 0.14 ± 0.12, and $AaDO_2$ 428 ± 189 mmHg at FiO_2 0.65. The median duration of prostacyclin infusion was 3.6 days and of respirator treatment 7.0 days. All patients survived without extracorporeal membrane oxygenation. At 6–12 months, none of the patients had severe central nervous system complications, but two had bronchopulmonary dysplasia. These findings indicate that prostacyclin is able to reverse the right-to-left shunt in PPHN by decreasing PAP, and that systemic hypotension can be prevented with adequate volume correction and inotropic medication.

Key words: Prostacyclin — Primary pulmonary hypertension — Neonate — Doppler ultrasonography

Persistent pulmonary hypertension of the newborn (PPHN) continues to be associated with serious morbidity and mortality [7, 10]. Treatment using hyperventilation can lead to barotrauma, increasing the danger of pneumothorax [11] and bronchopulmonary dysplasia [22]. In addition, hypocapnia can cause cerebrovascular vasoconstriction with a subsequent reduction in cerebral blood flow [22]. Pulmonary vasodilators either have been ineffective or have induced systemic hypotension [14]. Extracorporeal membrane oxygenation (ECMO) represents invasive care at its most demanding level [4, 9] and is not available in every neonatal intensive care unit. Nitric oxide administration by inhalation is a promising but still experimental approach for treatment of PPHN [20].

Although pulmonary vasodilators are commonly used in older infants as well as in neonates [2, 5, 23], no studies documenting (BP) pulmonary arterial pressure (PAP) and the systolic blood pressure measurements during treatment have been reported. Measurement of cardiac hemodynamics in neonates has been particularly difficult. Recent advances in Doppler ultrasonography have made it possible to evaluate PAP noninvasively by measuring either regurgitant tricuspid jet velocity or ductal velocities [16]. This study was designed to investigate the effects of prostacyclin infusion on PAP and BP and on systemic oxygenation in infants with PPHN.

Patients and Methods

The study was conducted at the Children's Hospital, University of Helsinki. The patient population consisted of eight consecutive severely hypoxemic infants with a clinical diagnosis of PPHN. The clinical characteristics of the patients are shown in Table 1. The inclusion criteria were as follows: birth weight > 2500 g; age < 48 hours; oxygen saturation < 70% at an FiO_2 > 0.9; absence of congenital structural heart disease, sepsis, and diaphragmatic hernia. All the patients fulfilled the usual criteria for ECMO [3, 17]. The study was approved by the hospital ethics committee.

Each infant was treated with conventional mechanical ventilation

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Table 1. Clinical characteristics of the patients

Patient no.	Birth weight (g)	Gestational age (weeks)	Sex	Etiology	Apgar score	Prostacyclin treatment		Outcome
						Age at onset (hours)	Duration (hours)	
1	2540	34	Male	RDS	9	30	96	BPD
2	3100	37	Male	Meconium aspiration	4/5	8	72	Normal
3	3350	36	Male	RDS	5/8	24	72	Normal
4	3630	41	Male	Meconium aspiration	5/8	3	168	BPD
5	3670	42	Female	Meconium aspiration	9/9	12	252	Normal
6	3760	39	Male	Pulmonary hemorrhage	9/9	23	101	Normal
7	4020	38	Female	Blood aspiration	6/5	18	72	Normal
8	4130	39	Female	Primary PPHN	9	32	192	Normal
Mean	3525	38.5				19	128	

RDS, respiratory distress syndrome; PPHN, primary pulmonary hypertension of the newborn; BPD, bronchopulmonary dysplasia.

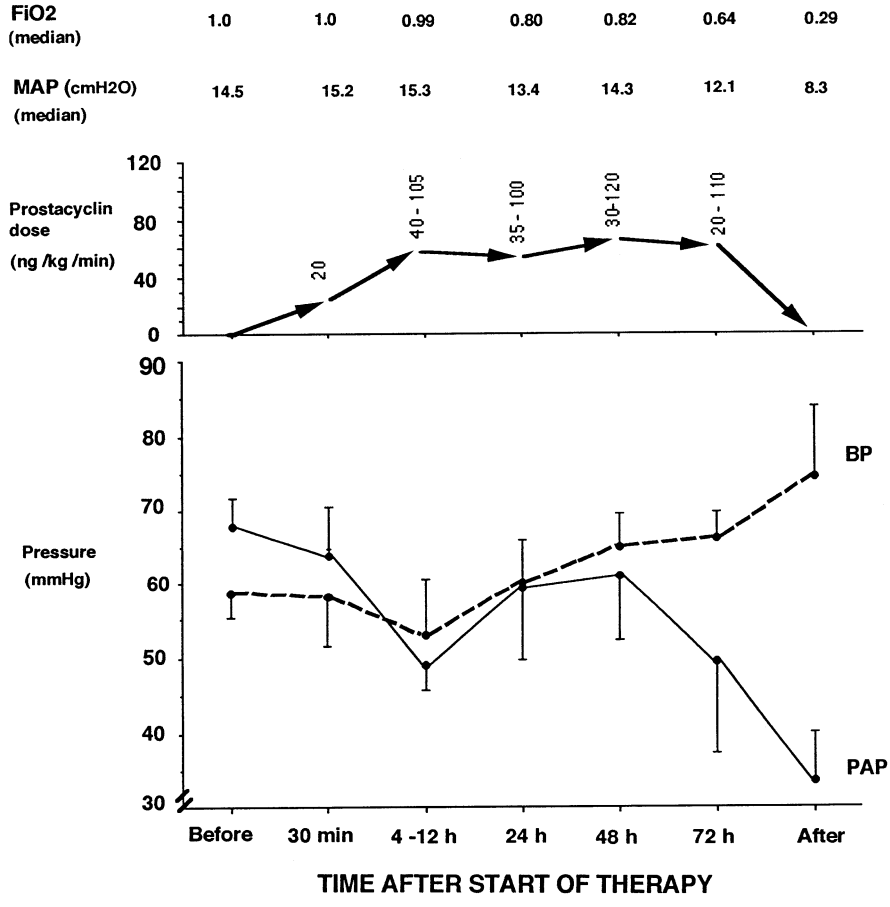

Fig. 1. Respirator settings [FiO_2 and mean airway pressure (MAP)], doses of prostacyclin infusion (median and range), and PAP and BP values (mean ± SD) at baseline and during the first 3 days of prostacyclin treatment in eight patients.

using a Baby Bird respirator. None of the patients received surfactant therapy. The aim was to achieve normal ventilation at as low airway pressures as possible without producing alkalosis. The settings of the respirator before starting prostacyclin (Fig. 1) illustrate the severity of the respiratory failure in our patients. Inotropic agents—dopamine at a median dose of 4.5 μg/kg/min (range 2.0–9.2 μg/kg/min) and dobutamide at a median dose of 4.7 μg/kg/min (range 0–9.2 μg/kg/min)—were given to maintain the mean BP at 45 mmHg or above. Before and during the first hours of prostacyclin administration the infants required a mean of 31 ml/kg (range 17–83 ml/kg) additional intravenous fluids (colloids and packed erythrocytes) to maintain adequate blood pressure. Each infant received morphine (0.4–0.6 mg/kg/day). All the infants had repeated ultrasound scans of the brain to detect ischemic lesions or cerebral hemorrhages.

When the criteria for impaired oxygenation were met and elevated PAP was demonstrated by echocardiography, prostacyclin treat-

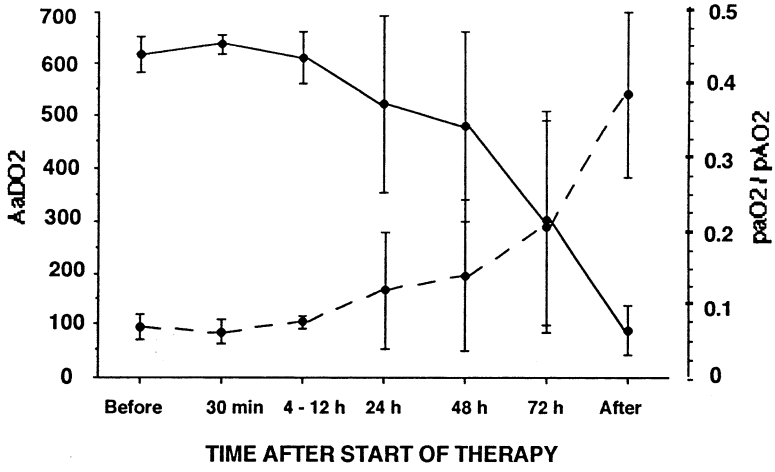

Fig. 2. $AaDO_2$ values (continuous line) and PaO_2/PAO_2 values (broken line) before, during, and after prostacyclin infusion. Values are the mean ± SD.

ment (Flolan 10 μg/ml; Wellcome, London, UK) through a peripheral venous catheter was started at a dose of 20 ng/kg/min and increased at 30-minute intervals up to 120 ng/kg/min until a response, in terms of improved oxygenation, was obtained (Fig. 1). Oxygenation was monitored continuously with a pulse oximeter (Ohmeda, Louisville, CO, USA) and with intermittent arterial samples drawn from an indwelling radial or umbilical artery catheter, which was also used for monitoring the BP.

The infant heart was studied with two-dimensionally guided, pulsed-wave and continuous-wave Doppler equipment (Acuson 128, Mountain View, CA, USA) before and 30 minutes after the start of prostacyclin infusion and then 4–12, 24, 48, and 72 hours later. In addition, an examination was performed 24 hours after discontinuation of prostacyclin therapy. At the first examination normal intracardiac anatomy was confirmed by cross-sectional echocardiography and pulsed-wave Doppler studies. PAP was estimated by measuring either regurgitant tricuspid jet velocity or ductal Doppler velocity if the ductus was open [16]. The presence and maximal Doppler velocity of tricuspid regurgitation were evaluated using color flow guidance to direct nonimaging continuous-wave interrogation from the parasternal short-axis view and apical four-chamber view to allow assessment of PAP. The estimation of PAP was based on the Bernoulli equation ($P = 4V^2$), where V = velocity [24]. An assumed right atrial pressure of 10 mmHg was added to the tricuspid regurgitant Doppler velocity value to represent PAP. Ductal flow was assessed by continuous- and pulsed-wave Doppler [16]. The pulmonary artery and ductus were visualized on cross-sectional echocardiography and with a continuous-wave sample placed at the pulmonary end of the arterial ductus. PAP was defined according to Musewe et al. [16]. If there was bidirectional ductal shunting, the ductal Doppler velocity gradient was added to the BP. If unidirectional shunting was present, the ductal velocity gradient was subtracted from the BP. All the Doppler measurements were made by the same investigator (M.E.).

Data are expressed as the mean (SD) or median and range. Analysis of variance with repeated measures was used. p Values ≤ 0.05 were regarded as significant.

Results

Before the start of therapy, the mean alveolar/arterial oxygen gradient ($AaDO_2$) was 616 mmHg (range 521–654 mmHg) and the lowest PaO_2/PAO_2 was 0.067 (range 0.04–0.09). Altogether 50 Doppler studies were performed to assess PAP. In five studies the pressure could not be calculated because of unmeasurable tricuspid regurgitant jet accompanied by closed ductus. In the study patients, ductal closure was observed at an average age of 78 hours (range 6–192 hours). One patient (no. 1) underwent indomethacin treatment for ductal closure after prostacyclin infusion.

The PAP and BP measurements are shown in Figure 1. Before the start of prostacyclin infusion, the mean PAP was 68.6 ± 6.5 (± SD) and the mean BP 59.8 ± 4.8 mmHg. Prostacyclin infusion at the starting dose of 20 ng/kg/min failed to reduce either PAP or BP ($p > 0.4$). However, when the dose was increased to a mean of 60 ng/kg/min 4–12 hours after the start of therapy, PAP decreased significantly to a mean of 49.2 ± 3.5 mmHg ($p = 0.0005$). BP decreased less, to a mean of 53.2 ± 9.1 mmHg ($p = 0.17$); and the ductal shunt was reversed. Prostacyclin at a mean dose of 65 ng/kg/min (range 30–120 ng/kg/min) maintained PAP at a lower level than the BP. After 72 hours of prostacyclin infusion, the PAP was 49.6 ± 18 mmHg, BP 66.1 ± 5.4 mmHg, PaO_2/PAO_2 0.14 ± 0.12, and the median $AaDO_2$ 428 ± 189 mmHg at an FIO_2 of 0.65 (range 0.21–1.00). To achieve stable oxygenation, a median time of 87 hours (range 47–224 hours) of prostacyclin infusion at the maintenance dose was needed. Weaning was started after stabilization of oxygenation by first decreasing the FIO_2 to 0.40 and then the peak airway pressure to 25 cm H_2O, and finally tapering the prostacyclin infusion.

The FIO_2, mean airway pressure (MAP), and indices of oxygenation ($AaDO_2$ and PaO_2/PAO_2) before, during, and after prostacyclin treatment are summarized in Figures 1 and 2. Oxygenation improved significantly when a maintenance dose of prostacyclin of 65 ng/kg/min was attained. The change was significant for both $AaDO_2$ ($p = 0.0075$) and PaO_2/PAO_2 ($p = 0.029$). Because of ventilator adjustments, there were no significant changes

in blood gas measurements. The ventilatory support level, as indicated by the FIO_2 and MAP, decreased during the first 3 days of treatment was oxygenation improved. The median duration of respirator treatment was 7 days (range 4–13 days).

All eight infants subsequently recovered without a need for ECMO. The outcome of the patients is shown in Table 1. At the age of 28 days, two infants fulfilled the criteria of for bronchopulmonary dysplasia (BPD) according to Bancalari et al. [1], but none required oxygen treatment at 6 months. One patient had muscular hypotonia at the age of 1 year. None of the patients had significant neurologic or developmental impairment after a mean follow-up of 18 months (range 14–29 months).

Discussion

There is no consensus about the optimal management of PPHN. No randomized, controlled trial on any of the therapeutic modalities has been carried out, perhaps because PPHN is too rarely encountered at any individual institution for a controlled trial to be feasible.

Recent trends, moving from hyperventilation, which is associated with significant complications, toward a more conservative use of respirators, have necessitated a search for new methods for treating PPHN. Tolazoline is still widely used in newborns, although its efficacy is questionable and the overall complication rate approaches 50% [18]. ECMO offers a high-technologic approach to treating infants who appear destined to die of respiratory failure, the treatment criteria usually based on a predicted 80% mortality rate. Survival with ECMO has been reported as ranging from 58% to 100% when using the treatment criteria applied in the present study [13, 17], but several serious complications, such as chronic lung disease and neurodevelopmental handicap, have been reported [3, 13, 17].

Prostacyclin is an endogenous arachidonic acid metabolite that causes vasodilatation in the systemic and pulmonary circulations and inhibits platelet aggregation [6]. Evidence of improved oxygenation when using prostacyclin has been documented in a small series of patients with PPHN [5, 12]. In previous studies the responsiveness to prostacyclin has been individually tested by monitoring oxygenation and systemic blood pressure. In the present study, cardiac ultrasonography was used to estimate pulmonary arterial pressure. In earlier studies on adults, doses up to 35 ng/kg/min were used [19] and a maximum dose of 40 ng/kg/min was suggested for children [2]. However, in this study prostacyclin at a starting dose of 20 ng/kg/min failed to reduce either PAP or BP, and when the dose was increased to 60 ng/kg/min a significant decrease in PAP was detected. A median maintenance dose of 65 ng/kg/min was needed to maintain stable oxygenation. Systemic arterial hypotension during prostacyclin treatment is a serious complication [8, 12]. In this study, systemic BP could be maintained using plasma expanders and vasopressor medication.

Considering the fact that all infants in our study fulfilled ECMO criteria at the start of prostacyclin treatment, the outcome was good. All survived, but two infants had transient symptoms of BPD. In follow-up studies, chronic lung disease seems surprisingly common in ECMO survivors [21], and many children have neurologic abnormalities associated with changes in cranial ultrasonography or computed tomography [15]. To compare the outcome of the infants on prostacyclin treatment with those on ECMO therapy, more neonates should be studied in a comparative trial.

This study was designed to document PAP, in relation to systemic BP, using Doppler ultrasonography during prostacyclin infusion in infants with PPHN. We have demonstrated improvement of oxygenation and a more significant decrease in PAP than in BP when we used prostacyclin at higher doses than previously recommended. Systemic hypotension was prevented by using plasma expanders and vasopressor medication. Additional studies are under way to compare the effects of prostacyclin therapy with inhaled nitric oxide on pulmonary arterial pressure and perinatal outcome for treatment of PPHN.

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The Bazett Square Root Formula

Bazett pioneered the concept of QT interval correction to variable heart rates. In 1920, he studied the QT interval of 39 healthy subjects, and noted that the QT interval shortens as the heart rate increases [1]. Bazett concluded that the QT interval could be corrected to the square root of the R–R interval. His formula was initially expressed as $QT = k \times \sqrt{R–R}$. The constant k was determined by Bazett to be 0.37 in men and 0.40 in women. Shipley and Hallaran studied 200 normal subjects in the mid 1930s [3]. Based on their measurements, they modified the constant values (k) in Bazett's formula to 0.397 in men and 0.415 in women. Bazett's formula is now expressed as $QTc = QT/\sqrt{R–R}$.

In the adult population, Bazett's equation tends to overcorrect QT interval at high heart rates and undercorrect it at low heart rates [2]. Despite this deficiency, it continues to be widely utilized. This is largely due to its relative simplicity as well as the shortcomings associated with many of the formulas introduced since Bazett published his findings.

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