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Effects of Prostacyclin and Milrinone on Pulmonary Hemodynamics in Newborn Lambs With Persistent Pulmonary Hypertension Induced by Ductal Ligation

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ABSTRACT: Prostacyclin (PGI_2) stimulates adenyl cyclase to synthesize cAMP within the vascular smooth muscle resulting in vasodilatation. Milrinone inhibits cAMP clearance by phosphodiesterase type III. We studied the dose response of pulmonary and systemic hemodynamics to intratracheal (IT) PGI_2 in newborn lambs with pulmonary hypertension (PH) and whether intravenous milrinone potentiate these effects. IT-PGI_2 at varying doses was administered to lambs with PH induced by prenatal ductal ligation. IT-PGI_2 doses were repeated in the presence of intravenous milrinone (bolus—100 μg/kg followed by infusion at 1 μg/kg/min). Increasing doses of IT-PGI_2 significantly decreased mean pulmonary arterial pressures (PAP) and pulmonary vascular resistance (PVR) and increased pulmonary blood flow (PBF). Intravenous milrinone by itself produced a significant reduction in PVR and a significant increase in PBF. Intravenous milrinone significantly shortened the onset, prolonged the duration and degree of pulmonary vasodilation produced by PGI_2. We conclude that intravenous milrinone potentiates the pulmonary vasodilator effects of PGI_2 at lower doses. **(*Pediatr Res* 60: 624–629, 2006)**

PPHN is a disorder of term and near term infants with significant morbidity and mortality. PPHN results from disruption of the normal decrease in PVR at birth. PGI_2, the main cyclo-oxygenase product of arachidonic acid in the vascular tissue, is a potent vasodilator and its actions are mediated by cAMP (1,2). It is one of the important mediators of the decrease in PVR at birth (3,4). PGI_2 has been used widely in the treatment of adults with PH. Although there are reports of PGI_2 being used anecdotally in human infants (5,6), systematic studies on the dose response effects of PGI_2 in PPHN are lacking. Milrinone selectively inhibits PDE3, resulting in accumulation of cAMP in myocardium and vascular smooth muscle, improving myocardial performance and producing vasodilation. Milrinone has been used in patients to improve pulmonary hemodynamics in association with systemic hemodynamic dysfunction (7,8). Studies on the use of milrinone in neonates are lacking. Figure 1 shows the PGI_2–cAMP signal transduction pathway in the vascular smooth muscle. PGI_2 and milrinone in combination can act synergistically in increasing cAMP levels and hence enhance the relaxation of the vascular smooth muscle.

The newborn pulmonary circulation is different from the adult pulmonary circulation in its anatomy and physiology (9,10). The response of the infant with PPHN to NO is closer to that of newborn lambs with persistent pulmonary hypertension induced by ligation of the ductus arteriosus (11) than it is to the response of adult humans with PH. Examination of the responses to manipulating cAMP with PGI_2 and milrinone in such lambs seemed warranted in advance of clinical trials. Thus we studied the dose response to IT PGI_2, the response to intravenous milrinone and enhancement of the effect of PGI_2 by milrinone in newborn lambs with PH induced by ligation of the ductus arteriosus.

METHODS

The study was performed at the Center for Developmental Lung Biology at the State University of New York (SUNY) at Buffalo. In a well-established lamb model of PPHN, ligation of the ductus arteriosus 9 d before delivery causes PPHN (12–14). These studies were approved by the Institutional Animal Care and Use Committee (IACUC) at SUNY, Buffalo.

Fetal ductal ligation was performed *via* thoracotomy at 129 d of gestation (term = 146 d) as previously described (13). Time dated pregnant ewes (n = 6) were brought to the laboratory animal facility 24–72 h before surgery. The ewe was intubated after intravenous pentothal (750 mg) and ventilated with 0.5–1% isoflurane in oxygen. A left lateral thoracotomy was performed in the fourth intercostal space of the fetus, and the ductus arteriosus ligated. The fetal was then returned to the uterus and the abdominal wall was closed. The ewe was allowed to recover for 9 d. At 138 d gestation, the ewe was anesthetized and the fetus was partially exteriorized *via* hysterotomy, the carotid artery and jugular vein were exposed, and polyvinyl catheters were inserted and advanced into the aorta and right atrium, respectively. A left thoracotomy was performed and polyvinyl catheters placed in the main pulmonary artery (PA) and left atrium (LA). An ultrasonic flow transducer (Transonics Systems Inc., Ithaca, NY) was placed around the main PA. The lamb was then intubated by direct visualization and the endotracheal tube secured. The lambs were delivered and placed under an infant warmer to maintain temperature at 39°C. Lambs were covered in a plastic bag to prevent heat loss. Ventilation was initiated with a time cycled pressure controlled

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Abbreviations: IT, intratracheal; **PAP,** pulmonary arterial pressure; **PDE 3,** phosphodiesterase type 3; **PGI_2,** prostacyclin; **PH,** pulmonary hypertension; **PPHN,** persistent pulmonary hypertension of the newborn; **PVR,** pulmonary vascular resistance

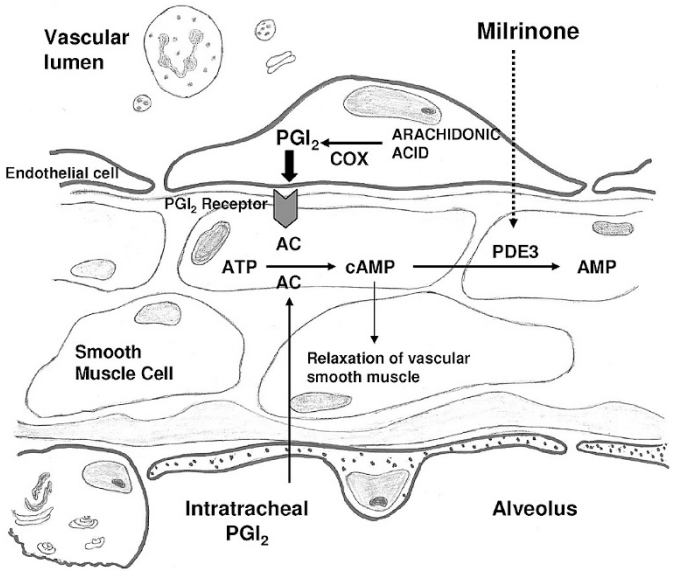

Figure 1. Signal transduction pathway of PGI_2–cAMP system. PGI_2 and milrinone increase cAMP by different mechanisms and hence combination of these two therapies will greatly increase cAMP levels enhancing the relaxation of the vascular smooth muscle. *COX*, cyclo-oxygenase; *AC*, adenylate cyclase.

Sechrist ventilator (Sechrist Industries Inc., Anaheim, CA) at a rate of 60, positive inspiratory pressure (PIP) of 24–26 cm of H_20, positive end-expiratory pressure (PEEP) of 4–5 cm of H_20, Inspiratory time (I-time) of 33%, and fraction of inspired oxygen (Fio_2) of 1.0. Initial stabilization included IV fluids at 100 mL/kg/d, monitoring blood pressure, heart rate, temperature, oxygen saturation, arterial blood gases (ABG), glucose, and electrolytes. The lambs were sedated with fentanyl infusion (3 μg/kg/h) and also received fentanyl bolus of 5 μg/kg i.v. when needed. The lambs were paralyzed with pancuronium (0.1 mg/kg q 3–4 prn] at birth and prn. Lambs received normal saline or whole cord blood for low mean systemic blood pressure (SBP) of <35 mm Hg and bicarbonate for base deficit of ≥8 mEq/L. Whenever the lambs received supportive therapy such as blood products, bicarbonate and volume, we deferred initiation of PGI_2 protocols for at least 30 min, to minimize the effects of these therapies on hemodynamic variables. ABG were done frequently during stabilization to maintain $PaCO_2$ between 35 and 55 mm Hg and pH between 7.35 and 7.45. Fio_2 was kept at 1.0 during the study. All catheters were connected to a physiologic recorder (Gould Instrument Systems, Inc., Valley View, OH) for monitoring of SBP, PAP and left atrial pressure (LAP). The flow probe was connected to the flow meter (Transonic Systems Inc., Ithaca, NY) for monitoring of pulmonary blood flow (PBF). PVR was calculated using the standard formula: PVR = (PAP – LAP)/PBF.

Delivery of prostacyclin and milrinone. PGI_2 (Sigma Chemical Co., St. Louis, MO) was prepared fresh immediately before the start of the experiment using glycine buffer. PGI_2 was delivered as a bolus dose directly into the trachea. The doses of PGI_2 studied were 200, 500, 1000, 2000, 4000, and 8000 ng/kg given in random order. Glycine buffer (vehicle) was used as a control. All IT doses were prepared to a final volume of 2.5 mL. The doses were delivered by the feeding tube, cut to exact length, so that the doses are delivered 0.5–1 cm beyond the tip of the endotracheal (ET) tube. Autopsy studies show that the ET tube tip is generally 4 cm above the carina. Hemodynamic changes were recorded before and after administration of each dose. A 30-min interval was maintained between doses to allow for the PAP to come back to the baseline (pre-dose values). On completion of all of the doses of PGI_2, milrinone (Baxter Healthcare Corporation, Deerfield, IL) was administered as a bolus dose of 100 μg/kg i.v. over 5 min followed by an infusion at 1 μg/kg/min. Baseline hemodynamic measurements were recorded before and for an hour after administration of milrinone. PGI_2 was then repeated randomly by IT route at the same doses while on intravenous milrinone infusion. Hemodynamic measurements and ABG were done before and after the IT bolus dose. These measurements were made continuously to determine the onset and duration of action of PGI_2. Onset of action was defined as the time for any decrease in PAP after administration of PGI_2. Duration of action was defined as the time elapsed since administration of PGI_2 for the PAP to decrease and then come back to its original baseline. Experiments were done in six newborn lambs with PPHN. Data are expressed as mean ± SEM, with n representing the number of animals. Statistical comparisons of the curves were performed with one way or repeated measures ANOVA as appropriate. Fisher's post hoc test was used as needed to compare among groups. All statistical analysis was performed with StatView software (Abacus Concepts, Berkley, CA). Significance was accepted at $p < 0.05$.

RESULTS

Tables 1 and 2 summarize the data of PVR, PAP, PBF, and SBP after randomly administered IT PGI_2 and intravenous milrinone when given separately (Table 1) and in combination (Table 2). The baseline PAP before administration of PGI_2 doses was between 60 and 65 mm Hg (Table 1). Percent changes in pulmonary hemodynamics are presented in Figure 2. PGI_2 significantly decreased PAP at all doses but the vehicle did not (Fig. 2*A*). There was a significant increase in PBF with increasing doses of IT PGI_2 (Fig. 2*B*). IT PGI_2 decreases PVR from predose baseline values in a dose dependent manner (Fig. 2*C*). Vehicle did not affect hemodynamics and PGI_2 did not affect SBP.

Table 1. *Hemodynamic variables following randomly administered IT PGI_2 or intravenous milrinone in newborn lambs with pulmonary hypertension induced by antenatal ductal ligation*

		Hemodynamic variable							
		Mean PAP (mm Hg)		PBF (mL/kg/min)		PVR (mm Hg/mL/kg/min)		Mean SBP (mm Hg)	
Drug	Dose	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Vehicle	2.5 mL	63.6 (3)	64.6 (4)	89 (4)	98 (9)	0.552 (0.1)	0.52 (0.01)	57 (5)	57 (7)
IT PGI_2 (ng/kg in 2.5 mL of buffer)	200	60.5 (5)	57.8 (5)	95 (11)	103 (11)	0.545 (0.1)	0.482 (0.09)	56 (1)	56 (2)
	500	62.3 (5)	58.6 (6)	93 (12)	100 (10)	0.584 (0.07)	0.517 (0.07)	60 (3)	59 (4)
	1000	64.6 (3)	55.6 (1)*	83 (8)	104 (3)*	0.669 (0.07)	0.485 (0.06)*	57 (4)	56 (3)
	2000	62.6 (3)	53.8 (1)*	96 (8)	116 (15)	0.519 (0.01)	0.363 (0.02)*	51 (3)	48 (4)
	4000	64.3 (5)	55.6 (6)	92 (8)	122 (15)	0.62 (0.08)	0.393 (0.07)*	56 (5)	53 (5)
	8000	63 (3)	55.5 (4)	97 (16)	133 (14)	0.617 (0.07)	0.376 (0.01)*	54 (3)	49 (4)
Intravenous milrinone (μg/kg/min)	Bolus = 100 μg/kg and infusion of 1 μg/kg/min	57.8 (2)	54 (5)	110 (15)	130 (16)	0.503 (0.06)	0.383 (0.03)*	54 (3)	51 (4)

Data represents mean (SEM) from 6 newborn lambs. *SBP*, systemic blood pressure
* $p < 0.05$ compared with pre-dose value by Fisher's post hoc test.

Table 2. *Hemodynamic variables following combination of IT PGI_2 and intravenous milrinone in newborn lambs with pulmonary hypertension induced by antenatal ductal ligation*

		Hemodynamic variable							
		Mean PAP (mm Hg)		PBF (mL/kg/min)		PVR(mm Hg/mL/kg/min)		Mean SBP (mm Hg)	
Drug	Dose	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Vehicle(glycine buffer)	2.5 mL	53.3 (3)	49.6 (2)	136 (19)	129 (24)	0.373 (0.08)	0.382 (0.09)	40 (1)	41 (1)
IT PGI_2 (ng/kg in 2.5 mL of buffer)	200	52.2 (4)	48.4 (2)	98 (12)	105 (10)	0.5 (0.01)	0.423 (0.03)	43 (2)	43 (1)
	500	52.8 (3)	46.4 (2)	116 (15)	124 (16)	0.453 (0.04)	0.329 (0.03)*	46 (3)	46 (3)
	1000	51.8 (3)	39.8 (2)*	98 (14)	111 (13)	0.543 (0.13)	0.334 (0.06)*	43 (6)	44 (4)
	2000	52.4 (2)	41.6 (1)*	119 (12)	131 (9)	0.413 (0.05)	0.282 (0.03)*	48 (3)	44 (4)
	4000	54.2 (3)	42.4 (2)*	116 (12)	132 (17)	0.437 (0.06)	0.292 (0.03)*	46 (3)	44 (5)
	8000	43.6 (1)	37.3 (2)	75 (20)	93 (15)	0.591 (0.18)	0.344 (0.03)	41 (3)	35 (3)

Data represents mean (SEM) from six newborn lambs. SBP, systemic blood pressure.
* $p < 0.05$ compared with pre-dose value by Fisher's post hoc test.

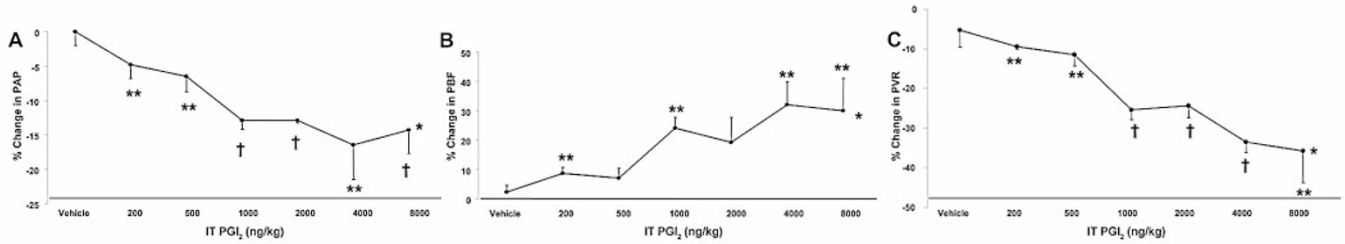

Figure 2. Dose response effects of randomly administered IT PGI_2 on percentage change in mean PAP (*A*), PBF (*B*), and PVR (*C*) in newborn lambs with fetal ductal ligation induced pulmonary hypertension. Data represent mean ± SEM of six newborn lambs. *$p < 0.05$, ANOVA repeated measures; **$p < 0.01$; †$p < 0.001$ compared with predose values, Fisher's Post hoc test.

Intravenous milrinone by itself decreased PVR by 22% (Fig. 3). Intravenous milrinone increased pulmonary blood flow by 18% (Fig. 3). The effect of intravenous milrinone on mean PAP and mean SBP were not significant. IT PGI_2 decreased mean PAP and PVR in the presence of intravenous milrinone in a dose-dependent manner (Fig. 4, *A* and *C*). Intravenous milrinone enhanced the response to PGI_2. At doses of 500 and 1000 ng/kg PGI_2 reduced mean PAP to a greater extent in the presence of intravenous milrinone than it did alone (Fig. 5*A*). Similarly, PGI_2 produced a greater decrease in PVR in the presence of intravenous milrinone at doses of 200 ng/kg and 500 ng/kg than it did alone (Fig. 5*B*). Milrinone facilitates the response to PGI_2 at lower doses.

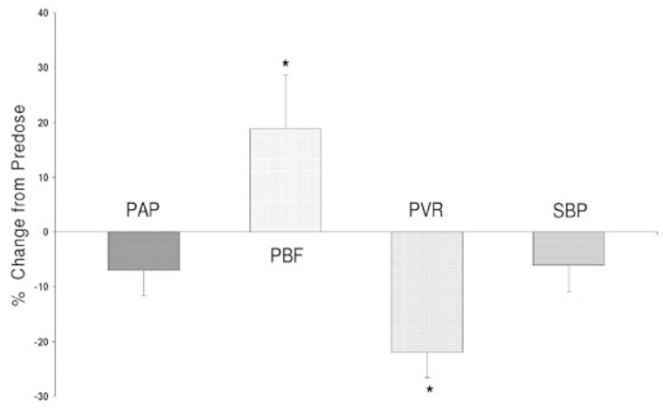

Figure 3. Percentage change in PVR, mean PAP, mean systemic blood pressure, and pulmonary blood flow after intravenous milrinone (100 μg/kg bolus followed by infusion of 1 μg/kg/min for 60 min) in newborn lambs with fetal ductal ligation induced pulmonary hypertension. Data represent mean ± SEM in six lambs. *$p < 0.05$ compared with predose values, Fisher's post hoc test.

The onset of action of IT PGI_2 on PAP was seen within 60 s of administration of the drug. The range of onset of action varied from 39–60 s (49.7 ± 10.1 s) for PGI_2 alone compared with 10–20 s (15.4 ± 4.1 s) for PGI_2 in the presence of intravenous milrinone (Fig. 6*A*). The onset of action of PGI_2 was significantly shorter in the presence of milrinone. The duration of action of PGI_2 was significantly prolonged in the presence of intravenous milrinone compared with PGI_2 alone (Fig. 6*B*). The range of duration of action was 5–7 min (6.13 ± 1.01 min) for PGI_2 alone compared with 8–11 min (9.36 ± 1.18 min) for PGI_2 in the presence of intravenous milrinone.

No significant difference in mean SBP was noted before and after IT PGI_2 at all doses studied. Similarly, there was no difference in mean SBP before and after IT PGI_2 in the presence of milrinone. Lower doses of PGI_2 produced only minimal change (0% to 2%) in mean SBP compared with a 6–12% decrease at higher doses (doses >2000 ng/kg) both in the absence and presence of intravenous milrinone. The data on mean PAP to mean SBP ratio is shown in Figure 7. PAP to SBP ratio was significantly lower following IT PGI_2 compared with predose (Fig. 7*A*). Similarly, IT PGI_2 in the presence of milrinone had a significantly lower PAP/SBP ratio compared with predose (Fig. 7*B*). This effect was more pronounced at lower doses (<2000 ng/kg of PGI_2). IT PGI_2 alone or with intravenous milrinone did not produce any significant difference in arterial blood gas parameters including Pa_{O_2}, pH, and Pa_{CO_2} before and after various doses of PGI_2.

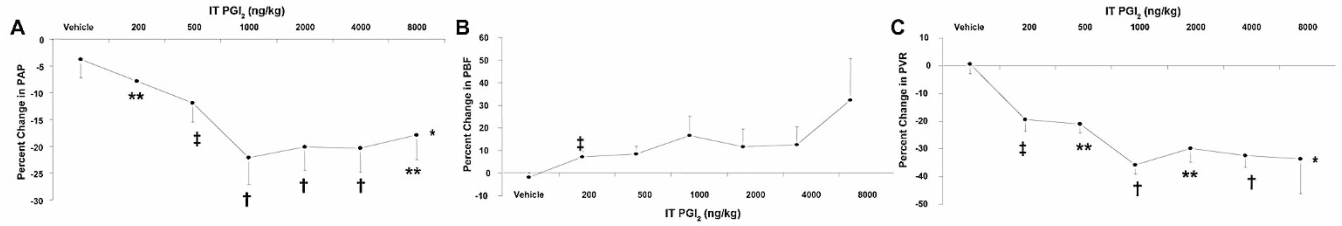

Figure 4. Percent change in PAP (*A*), pulmonary blood flow (*B*), and PVR (*C*) of randomly administered IT PGI_2 in the presence of intravenous milrinone (bolus = 100 μg/kg; infusion = 1 μg/kg/min) in newborn lambs with fetal ductal ligation induced pulmonary hypertension. Data represent mean ± SEM of six newborn lambs. $*p < 0.05$, ANOVA repeated measures; $‡p < 0.05$, $**p < 0.01$; $†p < 0.001$ compared with predose values, Fisher's post hoc test.

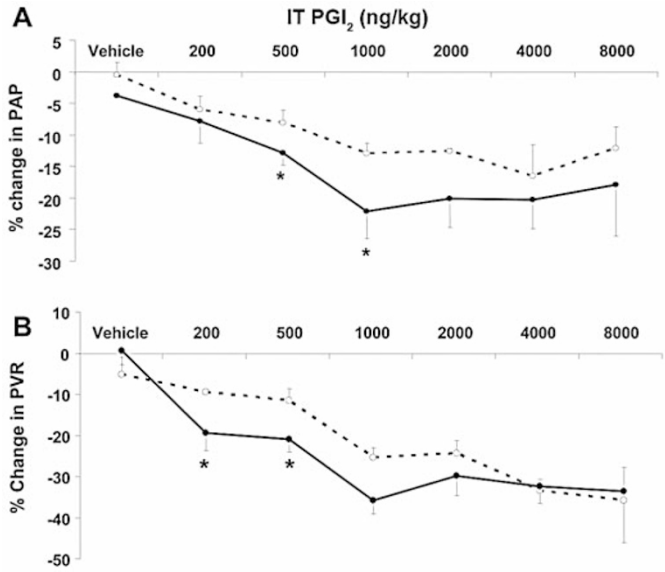

Figure 5. Comparison of percent change in PAP (*A*) and PVR (*B*) of IT PGI_2 alone (*dashed line*) with IT PGI_2 plus intravenous milrinone (*solid line*) in newborn lambs with fetal ductal ligation–induced PH. Data represent mean ± SEM of six newborn lambs. IT PGI_2 doses of 500 and 1000 ng/kg significantly reduced PAP in the presence of intravenous milrinone compared with IT PGI_2 alone. Similarly IT PGI_2 doses of 200 and 500 ng/kg reduced PVR in the presence of milrinone. $*p < 0.05$ compared with similar dose of IT PGI_2; Fisher's post hoc test.

DISCUSSION

Closure of ductus arteriosus of the fetal lamb 7–10 d before delivery causes persistent PH after birth (13). In our experiments, mean PAP soon after birth before start of the study were between 60–65 mm Hg. Ductal ligation also induces an increase in the proportion of partially and fully muscularized pulmonary arteries at the level of the terminal bronchiole and within the acinus (14). Thus, the anatomic and physiologic changes in the ductal ligation model of PPHN are similar to alterations reported in human neonates dying with idiopathic PPHN (14). This model of PH of the newborn has been used extensively in the preclinical studies of inhaled nitric oxide (iNO) on pulmonary hemodynamics and survival (12,15,16).

The effects of aerosolized PGI_2 in PH in adults are well studied. Aerosolized PGI_2 has been shown to be at least as effective as inhaled nitric oxide in decreasing PH in both animals and humans (17,18). Aerosolized PGI_2 selectively dilates the pulmonary circulation and redistributes PBF away from nonventilated lung regions (19) and has been shown to improve oxygenation in patients with ARDS or acute lung injury (19–21). Aerosolized PGI_2 reduced pulmonary pressures and improved right ventricular stroke volume in patients with PH undergoing cardiac surgery (22). The data on the effects in the neonate are anecdotal (5,23,24). IT instillation of PGI_2 at 50 ng/kg when injected as a bolus dose in four preterm infants with documented PH resulted in a significantly improved oxygenation index without systemic hypotension (23). Neither human nor animal studies have addressed the role of PGI_2 as a first line therapy in the management of PPHN soon after birth nor has there been determination of the pulmonary hemodynamic response to various doses of PGI_2 in neonates.

Most of the studies in adults with PH have delivered PGI_2 by intravenous or aerosolized route. As noted above, PGI_2 was given by IT instillation in a pilot study of neonates with apparent success. Each of these methods of drug delivery to the lung has drawbacks in distribution, deposition with aerosols or systemic delivery with intravenous administration. As

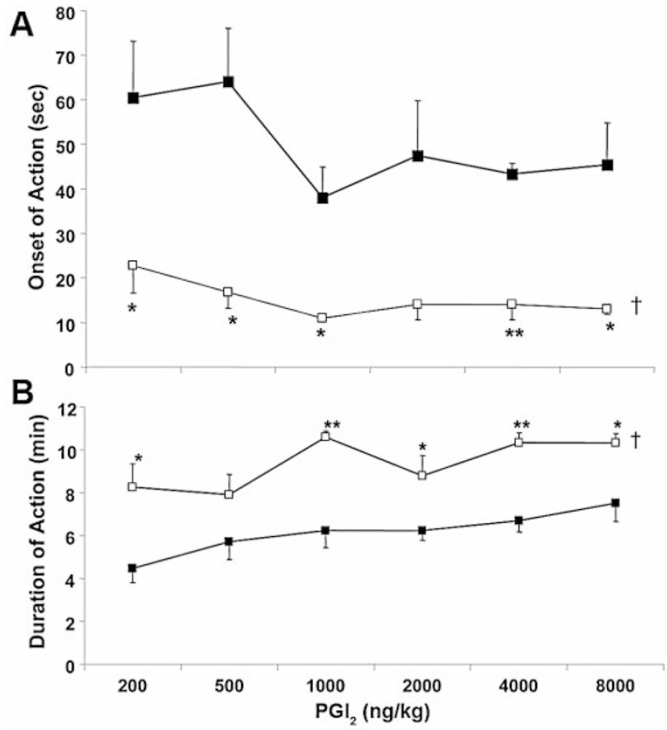

Figure 6. Onset (*A*) and duration (*B*) of action of PGI_2 alone (*open squares*) and in the presence of intravenous milrinone (*shaded triangles*). The onset of action was significantly shorter and the duration of action was significantly longer in the presence of milrinone. $†p < 0.05$ by ANOVA repeated measures *vs* PGI_2 alone. $*p < 0.05$ and $**p < 0.01$ by Fisher's post hoc test *vs* corresponding PGI_2 doses.

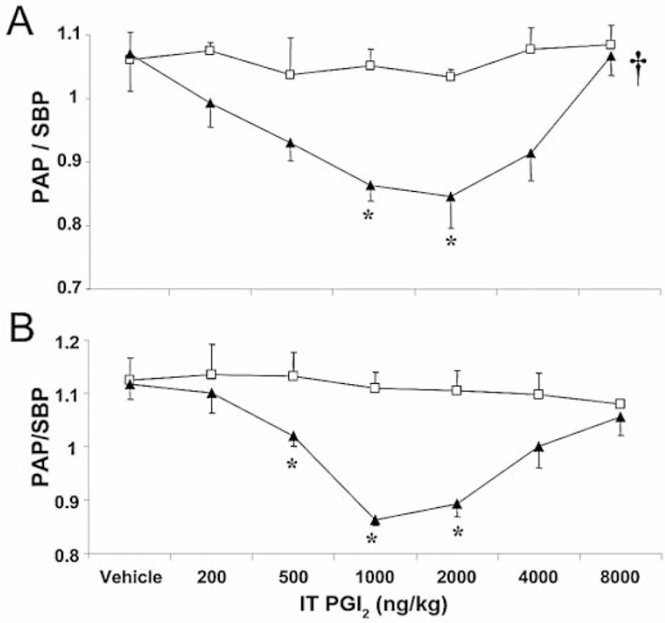

Figure 7. Changes in PAP/SBP ratio following IT PGI_2 with and without intravenous milrinone. (*A*) Represents PAP/SBP ratio before and after IT PGI_2. (*B*) Represents PAP/SBP ratio before and after IT PGI_2 in the presence of intravenous milrinone. Mean values are given and error bars represent SE. □ (*open squares*) represents the ratio before PGI_2 and ▲ represents data post IT bolus of PGI_2. *$p < 0.05$ by Fisher's post hoc test; †$p < 0.05$ by ANOVA repeated measures.

we were doing the first dose response studies in this very labor-intensive model of fetal ductal ligation induced PPHN, we chose the IT route to be certain of the dose deposited in the lung. Despite potential limitation on distribution, PAP responses were seen within a minute in all of our studies and lasted 5–11 min (PGI_2 half life of 90–120 s) of administration of the drug, indicating the effectiveness of the IT route of administration in these experiments. The doses of PGI_2 used were extrapolated from clinical and animal studies of inhaled PGI_2. In our study, all doses of IT PGI_2 effectively and selectively reduced PAP and PVR with minimal effect on SBP. As PAP and resistance decreased and pulmonary blood flow increased, it is probable that systemic blood flow and oxygen delivery increased. We failed to demonstrate any improvement in oxygenation with PGI_2 either alone or with milrinone. This could be related not only to the significant intracardiac shunting of blood from right to left *via* the foramen ovale secondary to significant PH but also to intrapulmonary shunting in an instrumented, sick postoperative newborn lamb. Also, IT administration of the drug preferentially deposits the drug to a poorly ventilated, dependent part of the lung, limiting its effects on oxygenation.

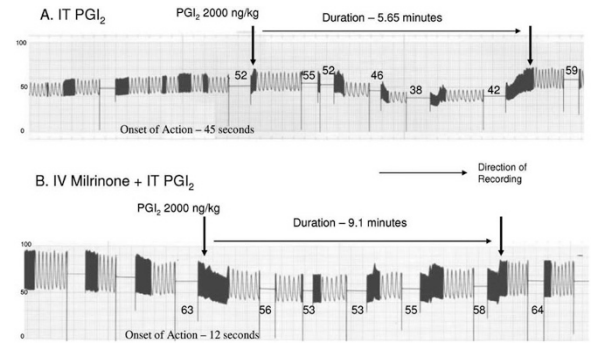

Figure 8. Graphic depiction of a representative study demonstrating the effects of PGI_2 on PAP. The kinetic information about the duration of response to PGI_2 alone (*A*) is compared with same dose of PGI_2 in the presence of intravenous milrinone (*B*). Intravenous milrinone shortens the onset and prolongs the duration of action of PGI_2. The numbers adjacent to the recording indicate mean PAP in mm Hg.

In adult patients following cardiac surgery milrinone increased cardiac index and reduced pulmonary artery occlusion pressure and systemic vascular resistance (25). It decreased pulmonary arterial and venous vascular tone without increasing cardiac work or impairing pulmonary oxygenation in hypoxic dogs (26). A single 50 μg/kg i.v. bolus of milrinone produced a 31% reduction in PVR, a 42% increase in cardiac output, and a 12% reduction in mean PAP in adult patients with severe left ventricular dysfunction (27). Inhaled milrinone did not affect systemic arterial pressure in cardiac surgical patients with pulmonary hypertension (28). Milrinone as a loading dose of 50 μg/kg followed by an infusion of 0.5 μg/kg/min decreased PVR and SVR and increased cardiac index in neonates with low cardiac output following cardiac surgery (29). Dipyridamole, a PDE5 inhibitor had significant hemodynamic effects in both the pulmonary and systemic circulations of newborn lambs with PH (12). In our experiments, intravenous milrinone by itself decreased PVR and increased PBF with no significant affect on SBP. Our data demonstrate a good response in a lamb model of PPHN.

The use of PDE inhibitors for maintenance of the PGI_2 induced second messenger cAMP may offer the possibility of prolonging and increasing the vasodilatory effect of nebulized PGI_2 in the lung vasculature. A graphic depiction of decrease in PAP following IT PGI_2 (2000 ng/kg) from a representative study both in the presence and absence of intravenous milrinone is shown in Figure 8. In our studies, the onset of action was significantly shorter and the duration of action was significantly longer with PGI_2 in the presence of intravenous milrinone compared with PGI_2 alone. Co-administering PGI_2 with a systemic PDE3 inhibitor not only produced a greater decrease in PVR at lower doses, but also prolonged the action of PGI_2 on PAP. The shorter time to onset of action (measured in seconds) may not be clinically relevant but its longer duration of action (measured in minutes) may be of clinical interest. The short half-life of PGI_2 makes it imperative to administer it as a continuous inhalation for sustained clinical benefit. Our study validates the use of this combination therapy in a newborn lamb model of PH. Administration of PGI_2 by IT bolus is clinically impractical, but its administration by continuous nebulization along with intravenous milrinone seems relevant and practical in certain clinical situations.

Several studies have addressed the role of systemic PDE inhibitors in combination with inhaled PGI_2 in adults (30–33). Doses in our experiments are similar to the doses used in the clinical management of patients with cardiac failure and cardiogenic or septic shock. Subthreshold systemic doses of monoselective PDE3 (motapizone), PDE4 (rolipram) and PDE5 (zaprinast), and dual-selective PDE 3/4 inhibitors cause

significant amplification of the pulmonary vasodilatory response to inhaled PGI_2, while limiting the hypotensive effect to the systemic circulation (31). Co-administration of PDE inhibitors with inhaled iloprost, a prostacyclin analogue, markedly enhanced the prostanoid-induced pulmonary artery pressure decrease while maintaining the lung selectivity of the vasodilatory response (32). The absence of data on cardiac output makes it difficult to comment on vascular selectivity in our experiments. The lack of cardiac output and systemic vascular resistance (SVR) measurements is a significant limitation to the study, which is a result of a conscious decision to not perform double thoracotomies (to measure cardiac output) in these sick newborn lambs. In the absence of SVR data we used PAP/SBP ratio as a marker of vascular selectivity. Even though a declining PAP/SBP ratio is helpful, it does not prove that SVR did not drop significantly. PAP to SBP ratio decreased with PGI_2 both in the presence and absence of intravenous milrinone. The ratio was lower at lower doses when PGI_2 was administered alone or with milrinone. However, the ratio increases at higher doses of PGI_2 with a concomitant decrease in SBP and this effect could be exaggerated by intravenous milrinone. This observation has clinical implications. The clinician should avoid higher doses of PGI_2 especially when it is co-administered with intravenous PDE3 inhibitor.

There is paucity of data on PGI_2 with PDE3 inhibitors in newborn human or animals. We have demonstrated that IT PGI_2 and intravenous milrinone each decrease PVR in a well-established newborn lamb model of PPHN. Systemic administration of milrinone in combination with IT PGI_2 produced a synergistic response in reduction in PVR, more so at clinically relevant doses of 200 and 500 ng/kg (extrapolates to 20–50 ng/kg/min over 10 min by aerosol). Combination of systemically administered milrinone with lower doses of PGI_2 may enhance the pulmonary hemodynamic response with probably minor and clinically not relevant side effects on the systemic vasculature. These findings may be of relevance in the clinical management of infants with pulmonary hypertension.

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