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Prostaglandin E1 in infants with congenital diaphragmatic hernia (CDH) and life-threatening pulmonary hypertension

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ABSTRACT

Background: Suprasystemic pulmonary hypertension (PH) is highly predictive of pulmonary morbidity and death in infants with congenital diaphragmatic hernia (CDH).
Objectives: To report the effects and tolerability of Prostaglandin E_1 (PGE_1) in newborns with severe CDH and life-threatening PH.
Methods: Newborn infants with isolated CDH and life-threatening PH defined by an acute worsening of the cardiorespiratory function, and bidirectional or exclusive right-to-left shunting across the ductus arteriosus (DA) with an acceleration of the blood flow >1.5 $m.s^{-1}$ assessed by Doppler echocardiography. Serial measurements of cardiorespiratory variables have been recorded before and after PGE_1.
Results: 18 infants (out of 102 in the cohort) were included in the study (gestational age: 39 ± 2 weeks). The median FiO_2, and preductal and postductal SpO_2 were 80% [50; 100], 91% [88; 95] and 86% [82; 91], respectively, before treatment. FiO_2 decreased to 35% [30–40] ($p = 0.001$) at H6. Maximal blood flow velocities in the DA decreased after starting PGE_1 from 2.2 $m.s^{-1}$ [1.5–2.5] to 1 $m.s^{-1}$ [0.55–1.2] ($p < 0.001$).
Conclusions: PGE_1 treatment improved oxygenation and circulatory function in newborn infants with severe CDH and life-threatening PH. Our data provide evidence that restrictive DA may result in suprasystemic pulmonary hypertension in CDH infants, and that PGE_1 may improve cardiorespiratory failure through reopening of the DA.
Type of study: Treatment study.
Level of evidence: Level III.

Despite improvement in treatment options and advances in neonatal care, mortality rates in infants with CDH are estimated at 20%–30% in tertiary care centers [1]. CDH is associated with abnormal pulmonary development, including lower number of bronchial divisions and fewer pulmonary arterial branches. Multiple functional abnormalities of pulmonary vessel reactivity have been reported, including decreased response to vasodilator stimuli [2]. Structural vascular abnormalities, namely, restrictive vascular bed and vascular wall remodeling, and functional abnormalities cause a failure in the cardiorespiratory transition at birth. Furthermore, structural and functional left ventricle abnormalities are responsible for impaired left ventricle filling and contribute to the development of pulmonary venous hypertension. This fetal-to-neonatal maladaptation results in persistent pulmonary hypertension of the newborn (PPHN).

This is associated with:

- a right-to-left shunt through the ductus arteriosus, responsible for postductal hypoxemia, and differences in pre- and postductal arterial blood gas parameters [3];
- a reduction in the pulmonary venous return, resulting in a decrease in the left ventricle output.

The ratio of estimated PAP to the simultaneous systemic blood pressure is used to classify pulmonary hypertension as subsystemic, systemic or suprasystemic. Suprasystemic pulmonary artery is a life-threatening event in the newborn, leading to right ventricle enlargement. Pulmonary artery pressure (PAP) can rise higher than aortic pressure, in particular when ductus arteriosus becomes restrictive, resulting in right-sided heart failure, which in turn alters the diastolic filling of the left ventricle, an additional factor for systemic low blood flow [4]. The usual treatment of pulmonary hypertension, including inhaled nitric oxide (NO) or prostacyclin may fail to decrease PAP, at

Abbreviations: CDH, congenital diaphragmatic hernia; DA, ductus arteriosus; NO, nitric oxide; PH, pulmonary hypertension; PGE_1, prostaglandin E_1; PPHN, persistent pulmonary hypertension of the newborn; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance.

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least in part because of the pulmonary venous component of the hypertension. However, as long as the ductus arteriosus is largely patent, PAP equalizes aortic pressures. Pulmonary hypertension is therefore isosystemic. Moreover, right-to-left shunting across the ductus arteriosus contributes to sustain the systemic blood flow to compensate low left ventricle output [5].

Previous retrospective studies have reported that prostaglandin E_1 (PGE1) may improve circulatory function [6,7]. Infusion of PGE_1 has been associated with a decrease in B-type natriuretic peptide, suggesting a decrease in PAP [8]. Evidence exists that creation of a side-to-side anastomosis from the left pulmonary artery to descending aorta in order to promote a right-to-left shunting improves right ventricular function in children with suprasystemic PAP [9].

In the present study, we aimed at investigating the effects of PGE_1 infusion on the cardiorespiratory function, in newborn infants with CDH and life-threatening pulmonary hypertension. Serial measurements of cardiorespiratory variables have been recorded before and after PGE_1 infusion.

1. Population and methods

1.1. Population

We conducted a retrospective chart review of neonates admitted for CDH at the neonatal intensive care unit of Lille University Hospital (Lille, France) from January 2009 to December 2015.

In the Nord-Pas-de-Calais area of France (4.5 million inhabitants; 55,000 births/year), all infants with a diagnosis of CDH were referred to Lille University Hospital and were enrolled systematically in a prospective follow-up study (cohort). We recorded data on patient demographics, Observed/Expected Lung Head Ratio (collected at 24–28 and 32–34 weeks of gestational age), prenatal care and imaging, postnatal care, including surgical repair, vital signs, and medication use.

1.2. Inclusion criteria

Patients eligible for inclusion in the study were CDH infants with acute life-threatening suprasystemic pulmonary hypertension during the course of the hospitalization, defined by:

- An increase of more than 20% of the FiO_2 to target a preductal SpO_2 above 88%;
- Signs of circulatory failure including paleness, heart rate > 160 bpm, capillary refill time > 3 s, urine output < 1 $ml.kg^{-1}.h^{-1}$, or mean systemic blood pressure less than 40 mmHg;
- Bidirectional or exclusive right-to-left shunting across the ductus arteriosus with an acceleration of the blood flow >1.5 $m.s^{-1}$ assessed by Doppler echocardiography;
- No response to inhaled NO;

1.3. Noninclusion criteria

Infants with a polymalformative or genetic syndrome were not included in the study.

1.4. Ethical agreement

The parents were informed and consented that the data collected from their infant's chart could be used for research. The study was approved by the CNIL board (Commission nationale de l'informatique et des libertés, N° Dec 19-328).

1.5. Primary endpoint:

- Decrease in FiO_2 to target preductal SpO2 between 88 and 96%, 6 h after starting PGE_1 infusion.

1.6. Secondary endpoints

- Decrease in maximum right-to-left blood flow velocities across the ductus arteriosus;
- Change in pH, $PaCO_2$, pre- and postductal SpO_2, heart rate and mean arterial pressure, plasma lactate concentration, and urine output.

1.7. Patient care

Management of the CDH infants is based on the EURO Consortium guidelines and the French Reference Center guidelines [10,11].

Briefly, the infants are mechanically ventilated in pressure-controlled mode (STEPHANIE; Fritz Stephan GmbH Medizintechnik, Gackenbach, Germany). Pre- and postductal transcutaneous oxygen saturation (SpO_2), transcutaneous $PtcCO_2$, heart and respiratory rates, blood gases, and arterial blood pressure are monitored (IntelliVue MP70 monitor; Philips Healthcare, Suresnes, France). Fraction of inspired oxygen (FiO_2) and ventilator parameters are adjusted to target preductal SpO_2 88%–96%, and $PaCO_2$ 45–55 mmHg. Inhaled NO is given at a concentration of 20 ppm in case of persistent pulmonary hypertension (Air Liquide Santé, Lesquin, France).

In order to determine the cause of an acute worsening of the cardiorespiratory status, technical problems including tube positioning or plugging, accidental interruption of inhaled NO, pleural effusion, and late-onset sepsis or pulmonary infection are ruled out. The infants receive 20 $ml.kg^{-1}$ of saline if mean arterial pressure is <40 mmHg and heart rate > 160 $beats.min^{-1}$.

Doppler echocardiography was performed by trained neonatologists with a high-frequency 12 MHz transducer (Philips CX50 Compact Xtreme; Philips, Suresnes, France). The first echocardiographic assessment was performed within the first hour after birth, then twice a day and for each unexplained life-threatening event. We analyzed echocardiographic images and Doppler measurements after each acquisition in order to adapt treatment according to hemodynamic assessment. Averages of three to five consecutive readings for the flow velocities are used. The angle of isonation was less than 20°. For each patient, measurements were performed by the same investigator to minimize inter-observer variability. Maximal blood flow velocities and flow patterns through the ductus arteriosus were assessed by pulsed Doppler using a high left parasternal view. The shunting was classified into left-to-right, right-to-left or bidirectional according the DA flow pattern. Systolic and diastolic pulmonary artery pressures (PAPs) were evaluated by measuring pressure gradient through the DA using the simplified Bernoulli formula, subtracted from systolic and diastolic systemic arterial pressures. The mean pulmonary arterial pressure was calculated as: PAP = (systolic PAP + [2 × diastolic PAP]) / 3. These measurements were compared to the systolic blood pressure measured on echocardiogram and classified as suprasystemic when mean pulmonary artery pressure is ≥ systemic blood pressure + 10 mmHg.

In our clinical setting, PGE_1 (Prostine VR®, Upjohn) is given when the maximal right-to-left blood flow velocities are >1.5 $m.s^{-1}$ in CDH infants with acute worsening of the cardiorespiratory status. In the absence of evidence-based, PGE1 is also used prophylactically at the discretion of the practitioner. PGE_1 is infused in a central catheter at an initial rate of 0.025 $\mu g.kg^{-1}.min^{-1}$. The infusion rate is increased to 0.05 $\mu g.kg^{-1}.min^{-1}$ if the blood flow velocities are still >1.5 $m.s^{-1}$ after 1 h of PGE_1 infusion. The infusion rate is progressively decreased to 0.01 $\mu g.kg^{-1}.min^{-1}$ if the blood flow velocities are <1 $m.s^{-1}$. PGE_1 may also be given prophylactically within the first hours of birth in newborn infants with CDH considered at risk for suprasystemic pulmonary hypertension (low prenatal O/E LHR). The infusion is then set at a rate of 0.01 $\mu g.kg^{-1}.min^{-1}$.

1.8. Statistical analysis

The variables were collected from the charts at 12, 6 and 1 h before, and 1, 6, 12, 24, 48 and 72 h after starting PGE_1 infusion. Each infant

served as his or her own control. All statistical analyses were conducted using SPSS Statistic version 24 (IBM Corporation, Armonk, New York). Continuous variables were described as median [range]. Baseline characteristics of PGE_1 group and nontreated group were compared using Fisher's exact test for categorical data or Mann–Whitney *t* test for continuous data. The nonparametric Friedman and Wilcoxon distribution-free with a Bonferroni correction signed rank test ($\alpha = 0.005$) was used to assess the significance of differences in respiratory and hemodynamic measures between each hour after starting PGE_1. Statistical significance was accepted at $p < 0.05$.

2. Results

One hundred and two infants with CDH were identified in the Nord-Pas-de-Calais area between 2009 and 2015, and admitted to our institution. Sixty-eight were not eligible for the study because they never received PGE_1. Sixteen were excluded because they received PGE_1 prophylactically before any clinical worsening. Eighteen CDH infants were treated with PGE_1 for acute life-threatening suprasystemic pulmonary hypertension during the course of the hospitalization at a median postnatal age of 11 days, IQR [5–16] (Fig. 1).

The studied population is described in Table 1. The CDH defect was repaired through an abdominal approach. Surgical repair was performed at a median age of 2 days, after a short period of cardiorespiratory stabilization. Four infants had a diaphragmatic agenesis. Eleven required a Gore-Tex® patch closure. When a Gore-Tex® patch was decided, a gastrostomy was placed in the same operating time. Two of the infants needed a second surgery for recurrence. Six infants in our population had a severe gastroesophageal reflux: four of them required a Nissen fundoplication.

These 18 PGE1-treated infants had prenatal markers of moderate to severe lung hypoplasia with median O/E LHR of 36.5% [34.9;42]. Thirteen had a liver herniation in the thorax. They received pressure-controlled ventilatory support with 20 ppm inhaled NO. Twelve infants were also treated by treprostinil ($n = 11$) and/or sildenafil ($n = 7$) for sustained pulmonary hypertension.

Table 1
Fetal and neonatal characteristic of CDH patients treated with PGE_1 for a life-threatening PH ($n = 18$) and CDH patients without life-threatening PH ($n = 84$).

	PGE1 group $N = 18$	CDH group $N = 84$	P value
Prenatal diagnosis (%)	16 (89)	66 (79)	0.33
Left CDH (%)	13 (72)	11 (16)	0.2
LHR o/e	36 [35; 43]	50 [40; 64]	0.001*
Fetal MRI %	32 [30; 35]	38 [30; 47]	0.05*
Liver herniation (%)	13 (72)	32 (38)	0.01*
Male sex (%)	8 (44)	40 (48)	0.85
Gestational age (weeks)	39 [38; 40]	40 [39; 41]	0.43
Birth weight (kg)	3.5 [3.0; 3.7]	3.3 [2.9; 3.5]	0.12
Inhaled NO	18 (100)	39 (46)	<0.001*
Age at CDH repair (days)	2 [1.3; 2.8]	1 [1; 2]	0.04
Duration of Mechanical Ventilation (h)	160 [128; 218]	57 [29; 100]	<0.001*
Duration of O_2 (days)	45 [21; 94]	3 [1; 11]	<0.001*
Duration of Noninvasive Ventilation (days)	12 [6; 19]	3 [1; 8]	<0.001*
ECMO support (%)	0 (0)	4 (5)	0.91
NICU length of stay	65 [46; 109]	33 [18; 70]	0.005*
Death	5 (27)	11 (13)	0.04
Age at the death (days)	122 [57; 489]	1 [1; 5]	0.014

Categorical data expressed as *n* (%) and continuous data expressed as median and interquartile range (IQR). LHR, lung-to-head ration; o/e, observed/expected; NICU, neonatal intensive care unit; CDH, congenital diaphragmatic hernia.
* Significant difference accepted as $p \leq 0.05$.

Just before starting PGE_1 these infants had symptoms of both respiratory and circulatory failure, including acute increase in O_2 need ($n = 18$), paleness ($n = 18$), heart rate > 160 beats/min ($n = 11$), drop in mean blood pressure < 40 mmHg ($n = 4$), decrease in urine output $<1\ ml.kg^{-1}.h^{-1}$ ($n = 7$), or elevation of plasma lactate concentration $>2\ mg.L^{-1}$ ($n = 10$). Medians and ranges of pre- and postductal SpO_2 were, respectively, 91% [82–96] and 86% [44–95]. Doppler echocardiography showed a right-to-left or a bidirectional shunting across the DA in, respectively, 11 and 7 infants. Median and range of the maximal blood flow velocities in the DA were $2.2\ m.s^{-1}$ [1.5–2.5].

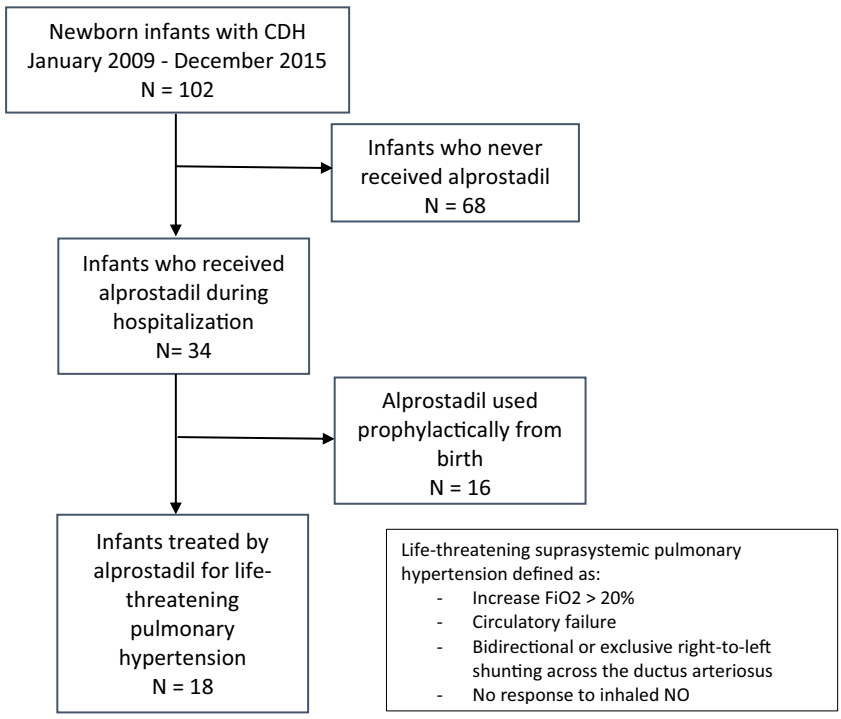

Fig. 1. Flowchart.

Table 2 compared the clinical characteristics of the infants who received PGE1 in situation of life-threatening pulmonary hypertension and the infants treated prophylactically by PGE1. Clinical characteristics were similar. No acute life-threatening events have been recorded in the PGE1 prophylactic group. Duration of mechanical ventilation, noninvasive ventilation, and O2 supplementation were shorter in the PGE1 prophylactic group than in the PGE1 rescue group. Mortality and duration of hospitalization were similar in both groups.

PGE_1 was started at a median postnatal age of 11 days [5;17], at an initial rate of 0.025 $\mu g.kg^{-1}.min^{-1}$.

Within 6 h after onset of PGE_1, median FiO_2 decreased from 80% to 34% ($p < 0.001$) to target preductal SpO_2 between 88% and 96% (Fig. 2). Preductal SpO_2/FiO_2 increased from 1.15 [0.9; 1.9] to 2.6 [2.4; 3.1] ($p < 0.01$) (Fig. 3). Urine output increased from 1.6 to 2.9 $ml.kg^{-1}.h^{-1}$ ($p < 0.05$). Plasma lactate concentration was significantly lower at H6 than just before PGE_1 infusion ($p < 0.05$). Pre- and postductal SpO_2 and SpO_2 gradient, blood gases (pH, $PaCO_2$), arterial blood pressure, heart rate, and temperature did not change significantly throughout the study period (Table 3).

Shunting across the DA was mainly bidirectional ($n = 14$). Maximal blood flow velocities in the DA decreased significantly between H1 and H6 after starting PGE1 (1 $m.s^{-1}$ [0.55; 1.2] vs 2.2 $m.s^{-1}$ [1.5; 2.5]; $p < 0.001$) (Fig. 4).

Thirteen infants were alive (73%) at the age of 3 years. Five infants died: 1) at the age of 19 days, from treatment withdrawal because of severe perinatal encephalopathy; 2) at the age of 56 days, from treatment withdrawal because of renal dysgenesis and renal failure; 3) at the age of 122 days, from severe bronchopulmonary dysplasia and chronic pulmonary hypertension in a preterm baby; 4) at the age of 489 days, from acute respiratory distress syndrome owing to viral infection; and 5) at the age of 514 days, from refractory chronic pulmonary hypertension in a context of familial CDH (5 other CDH infants).

3. Discussion

We assessed the tolerance and effects of PGE_1 in 18 newborn infants with congenital diaphragmatic hernia and acute suprasystemic pulmonary arterial hypertension unresponsive to inhaled NO, by serial measurements of respiratory function and hemodynamics. PGE_1 was associated with a drop in FiO_2 by 45%, in plasma lactate concentration, and in maximum right-to-left blood flow velocities across the ductus arteriosus within the first 6 h of infusion. Preductal $Sp0_2/Fi0_2$ and urine output increased after initiation of PGE_1. Systemic pressure did not change after starting PGE_1. These data indicate that PGE_1 may improve cardiorespiratory function through decreasing pulmonary artery pressure in CDH infants with life-threatening acute pulmonary hypertension. We speculate that restrictive ductus arteriosus may contribute to severe hypoxic respiratory failure in infants with CDH and pulmonary hypertension. Conversely, ductus arteriosus patency is required for it promotes balanced right and left pressures.

Growing evidence suggests that PGE_1 may improve cardiac function in CDH infants. In a case series, no acute worsening of the cardiorespiratory function was observed in 39 infants with antenatal diagnosis of CDH and prophylactically treated by PGE_1 [7]. Furthermore, PGE_1 may support cardiac function in CDH infants with underdeveloped left ventricle [6,12]. A decrease in brain natriuretic factor plasma concentration observed one day after starting PGE_1 infusion in 59 CDH infants with severe pulmonary hypertension further supports the hypothesis that PGE_1 contributes to decrease right ventricle overload [8].

Our study provides additional information. PGE_1 has been used in case of life-threatening events, with increase in O_2 need and drop in preductal SpO_2/FiO_2 ratio, and markers of circulatory failure including decrease in urine output and elevation of plasma lactate concentration. The acute worsening of the cardiorespiratory function was not related to technical problems, pleural effusion, late-onset sepsis, or pulmonary infection.

The lack of change in pH or $PaCO_2$ provides additional evidence that the cardiorespiratory failure was not triggered by change in lung ventilation. The cardiorespiratory failure was associated with a right-to-left blood flow velocity between 1.5 and 2.5 $m.s^{-1}$, which indicates – using the simplified Bernoulli formula ($|\delta P = 4\ V^2|$) – a pulmonary artery and aortic pressures gradient between 10 and 25 mmHg. Such pressure gradient requires at least in part that the ductus arteriosus be partly restrictive, as hemodynamic law indicates that gradient pressure is proportional to resistance.

No change in pre- and postductal SpO_2 difference suggests that the right-to-left ductal flow did not increase despite suprasystemic pulmonary artery pressure, which is further in accordance with restrictive ductus arteriosus. Timing of the life-threatening event after birth (median 11 days) is also in accordance with a cause and effect relationship between restriction of the ductus arteriosus and the cardiorespiratory failure. Although the ductus arteriosus is functionally closed in 90% of healthy term babies by 72 h of life, infants with PPHN have a significant delay in ductal closure [13,14].

In this situation of cardiopulmonary failure, ECMO was shown to be effective [15]. Venoarterial ECMO may decrease pulmonary artery pressure through decrease in right ventricle preload. ECMO sustains oxygenation/decarboxylation and supports systemic circulation during the period of time required for the pulmonary vascular resistance to decrease. ECMO is therefore a therapeutic option.

Our data highlight that PGE1 may be an alternative treatment to ECMO. As during ECMO, PGE1 promotes PAP decrease through DA opening and equalization to systemic pressure. Furthermore, PGE1 contributes to support systemic circulation through promoting right to left shunting across the DA.

PGE1 treatment should not be delayed once the diagnosis of DA restriction-induced life-threatening pulmonary hypertension is made. Failure to open the DA may require cannulation to ECMO. In our study, none of these 5 children died of pulmonary hypertension, where ECMO could have been an alternative treatment.

Although no change in systemic pressure was observed after starting PGE1 treatment in our study, special care should be taken during PGE1 administration owing to its potential side effects as vasodilation and hypotension. Preexistent biventricular dysfunction, if not adequately supported, may lead to reduced cardiac output and promote right-to-left

Table 2
Fetal and neonatal characteristic of CDH patients treated with PGE_1 for a life-threatening PH ($n = 18$) and CDH patients treated with prophylactic PGE1 ($n = 16$).

	PGE1 Rescue Treatment $N = 18$	Prophylactic PGE1 $N = 16$	P value
Prenatal diagnosis (%)	16 (89)	12 (75)	0.06
Left CDH (%)	13 (72)	13 (81)	1.0
LHR o/e	36 [35; 43]	38.5 [28.5; 65.4]	0.93
Fetal MRI %	32 [30; 35]	42 [28; 53]	0.12
Liver herniation (%)	13 (72)	7 (43)	0.74
Male sex (%)	8 (44)	7 (43)	0.75
Gestational age (weeks)	39 [38; 40]	39.9 [38.4; 41.3]	0.6
Birth weight (kg)	3.5 [3.0; 3.7]	3.2 [2.7; 3.5]	0.14
Inhaled NO	18 (100)	11 (68)	0.02
Age at CDH repair (days)	2 [1.3; 2.8]	1 [0; 2]	0.13
Duration of Mechanical Ventilation (h)	160 [128; 218]	120 [71; 168]	0.004*
Duration of Noninvasive Ventilation (days)	12 [6; 19]	3 [1; 4]	0.003*
Duration of O_2 supplementation (days)	45 [21; 94]	15 [7; 41]	0.05*
ECMO support (%)	0 (0)	1 (6)	1.0
NICU length of stay	65 [46; 109]	52 [36; 92]	0.38
Death	5 (27)	1 (6)	0.18

Categorical data expressed as n (%) and continuous data expressed as median and IQR. LHR, lung-to-head ration; o/e, observed/expected; NICU, neonatal intensive care unit; CDH, congenital diaphragmatic hernia.

* Significant difference accepted as $p \leq 0.05$.

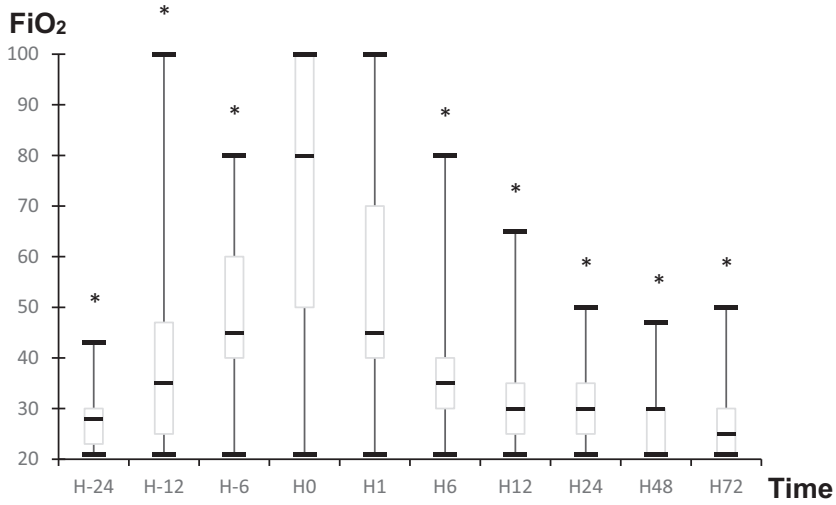

Fig. 2. Effect of PGE_1 on FiO_2 course. FiO_2 has been set to target preductal SpO_2 between 88% and 96%. PGE_1 infusion started just after H0. FiO_2 decreased within the first 6 h after starting PGE_1. FiO_2 (%) expressed as median and interquartile. H, hour; D, Day. * $p < 0.005$.

shunting across the DA giving rise to systemic hypotension, acidosis, and hypoxemia.

Cases of right ventricular failure have been reported when the ductus arteriosus closes in newborn infants with PPHN [16]. In our study, pulmonary hypertension did not respond to inhaled NO. Failure of NO treatment to decrease pulmonary pressure has been reported previously in CDH infants, owing at least in part to impaired vascular relaxation of the hypoplastic lungs [17,18]. Late PH is associated with a strikingly poor prognosis. Late PH is the main cause of mortality after the neonatal period in infants with CDH [19,20]. Therefore, there is clearly a need for new therapeutic strategies in this particular subgroup of infants with CDH and suprasystemic pulmonary hypertension.

O_2 need decreased and preductal SpO_2/FiO_2 ratio increased within the first 6 h after initiating PGE_1 infusion. Preductal SpO_2 is determined by intrapulmonary shunting or right-to-left shunting through the foramen ovale. Except adaptation of FiO_2, ventilator settings were not changed within the first 6 h of the study as blood gases did not change. Therefore, it is unlikely that improvement in preductal SpO_2/FiO_2 ratio was related to decreased intrapulmonary shunting. Conversely, mechanisms can explain that PGE_1 may improve oxygenation in CDH infants with suprasystemic pulmonary hypertension through decrease in right-to-left shunting in the foramen ovale.

Suprasystemic pulmonary hypertension may impair right ventricular function. Pulmonary artery pressure can elevate above aortic pressure, in particular when ductus arteriosus becomes restrictive, resulting in failure of the right ventricle, which in turn alters the diastolic filling of the left ventricle, an additional factor for systemic low blood flow [4]. Impaired right ventricle function elevates diastolic pressure that in turn promotes right-to-left shunting in the foramen ovale. Decrease in pulmonary artery pressure may improve the right ventricular function. Our results are in accordance with this hypothesis. After starting PGE_1, blood flow velocities across the ductus arteriosus decreased to below 1.5 $m.s^{-1}$, indicating that the difference in pressure between pulmonary artery and aorta was less than 10 mmHg.

Therefore, PGE_1 infusion results in a drop in pulmonary artery pressure by 18 mmHg. Indeed, PGE_1 contributes to large patency and low resistance of the ductus arteriosus. Increase in urine output and decrease in plasma lactate concentration further support the hypothesis that PGE_1 improved circulatory function. Alternatively, PGE_1 may decrease pulmonary vascular resistance, leading to an increase in pulmonary blood flow, which elevates left atrial pressure. Increase in left atrial pressure contributes to reduce right to left shunting in the foramen ovale. Reopening of the ductus arteriosus did not result in a decrease in postductal SpO_2 or an increase in pre- and postductal SpO_2 difference,

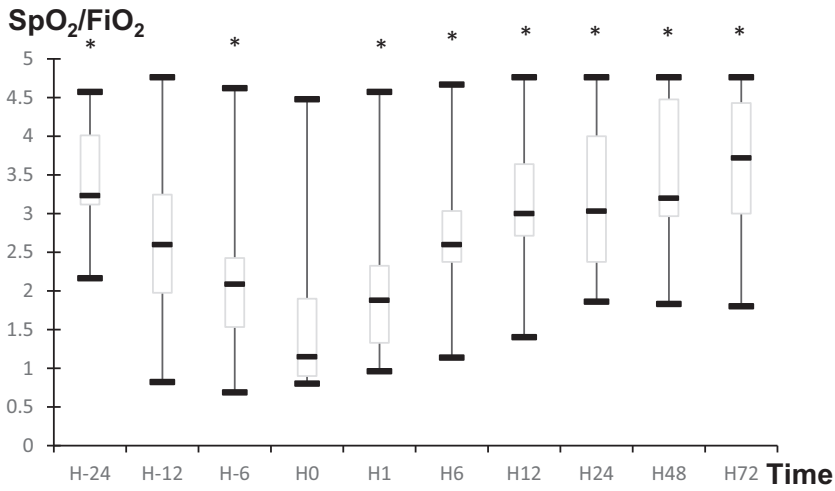

Fig. 3. Effect of PGE_1 on SpO_2/FiO_2 course. FiO_2 has been set to target preductal SpO_2 between 88 and 96%. PGE_1 infusion started just after H0. SpO_2/FiO_2 increased within the first 6 h after starting PGE_1. SpO_2/FiO_2 expressed as median and interquartile. H, hour; D, Day. * $p < 0.005$.

Table 3
Change of the cardiorespiratory variables before and after onset of Alprostadil. Alprostadil was started just after H0.

	H-24	H-12	H-6	H0	H1	H6	H12	H24	H48	H72
HR (bpm)	155 [133; 166]	153 [139; 169]	160 [143; 168]	156 [143; 169]	153 [143; 167]	160 [139; 171]	151 [141; 166]	151 [143; 166]	148 [142; 158]	150 [145; 156]
MAP (mmHg)	48 [44; 59]	47 [45; 50]	49 [43; 54]	49 [46; 56]	49 [45; 55]	50 [47; 57]	50 [45; 52]	48 [44; 58]	51 [46; 54]	48 [45; 52]
Preductal SpO_2 (%)	94 [92; 96]	92 [90; 95]	93 [91; 94]	91 [88; 95]	93 [88; 95]	94 [91; 95]	95 [90; 96]	95 [92; 97]	95* [93; 97]	97* [93; 98]
Postductal SpO_2 (%)	93 [83; 96]	91 [81; 95]	88 [80; 93]	86 [82; 91]	87 [79; 93]	91 [84; 93]	91 [87; 93]	92 [86; 95]	90 [86; 95]	93* [87; 96]
Diuresis ($mL.kg^{-1}.h^{-1}$)	2.9* [2.2; 4.9]	2.7 [1.8; 5.0]	2.0* [1.1; 3.7]	1.6 [0.9; 3.2]	1.6 [1.5; 1.8]	2.3* [2.0; 3.5]	2.9* [2.4; 4.7]	2.9 [2.0; 3.5]	3.4 [2.6; 4.2]	2.9 [2.3; 3.9]
pH	7.29 [7.24; 7.33]	7.31 [7.23; 7.37]	7.30* [7.23; 7.34]	7.21 [7.16; 7.29]	7.28 [7.26; 7.30]	7.33* [7.25; 7.36]	7.33* [7.27; 7.39]	7.34* [7.26; 7.39]	7.35* [7.29; 7.41]	7.34* [7.27; 7.41]
$PaCO_2$ (mmHg)	70 [66; 73]	64 [54; 67]	64 [57; 72]	66 [61; 71]	65 [51; 74]	57 [49; 65]	59 [48; 67]	62 [55; 70]	56* [51; 65]	59* [55; 65]
Lactates (mmol/L)	1.0 [0.7; 1.4]	1.6 [1.6; 1.7]	1.2* [0,9; 2.2]	2 [1.3; 3]	2.2 [2.1; 2.5]	1.5 [1.0; 1.8]	1.4* [0.9; 1.7]	1.2 [1.0; 1.6]	1.3 [0.8; 1.7]	1.3 [0.8; 2]

Data expressed as median and IQR. HR, heart rates; MAP, mean arterial pressure.
* Significant difference accepted as $p \leq 0.005$.

which may appear surprising. The magnitude of the postductal desaturation is related to the right-to-left blood flow across the ductus arteriosus and to the value of the mixed venous oxygen saturation. In this study, we did not measure ductal flow although flow direction and velocities have been assessed. Ductal flow is proportional to pulmonary and systemic pressures difference and inversely proportional to ductus arteriosus resistance. PGE1 may have improved the pulmonary circulation through 2 mechanisms: 1) DA relaxation which decreases DA resistance and therefore blood flow velocities across the DA; 2) nonspecific vasodilator effects including pulmonary vasorelaxation which may decrease pulmonary vascular resistance and pressure that in turn decreases the right to left blood flow velocities across the DA [21].

Alternatively, PGE1 may increase left ventricular output through: 1) improved diastolic left ventricle filling associated with decreased right ventricle pressure; 2) increase in pulmonary blood flow which in turn elevates left ventricle preload. Indeed, we have shown in fetal lambs that suprasystemic pulmonary artery pressure induced by ductus arteriosus compression activates a potent myogenic response within the lung, causing an acute increase in pulmonary vascular resistance [22,23]. Reopening of the ductus arteriosus and drop in pulmonary artery pressure result in a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow. Increase in left ventricle output contributes to elevate oxygen delivery and mixed venous oxygen saturation [24]. Higher venous O_2 saturation may limit postductal desaturation in case of right to left shunting across the ductus arteriosus, and may further contribute to sustain pulmonary vasodilation.

There is increasing evidence of postnatal LV dysfunction in CDH. LV dysfunction has been hypothesized as one of the mechanisms contributing to worsening after pulmonary vasodilators administration [5]. A primary LV dysfunction may itself lead to increased pressure in the pulmonary veins, contributing to increased PVR independently of the structural abnormalities in the pulmonary vasculature, which in turn may contribute to RV dysfunction. This might suggest that the use of cardiotropes with inotropic and lusitropic effects, such as milrinone, may improve cardiorespiratory function. In our study, we could not test this hypothesis as none of CDH infant received milrinone, although seven infants required norepinephrine infusion to support systemic hemodynamic.

3.1. Limitations of the study

Only direction and velocities of the blood flow across the ductus arteriosus have been assessed routinely in this study, according to our local guidelines. Additional measurements would have provided further meaningful evidence to explain the effects of PGE1. However, extensive Doppler echographic assessment may induce stress and pain, which in turn may worsen pulmonary hypertension [25,26].

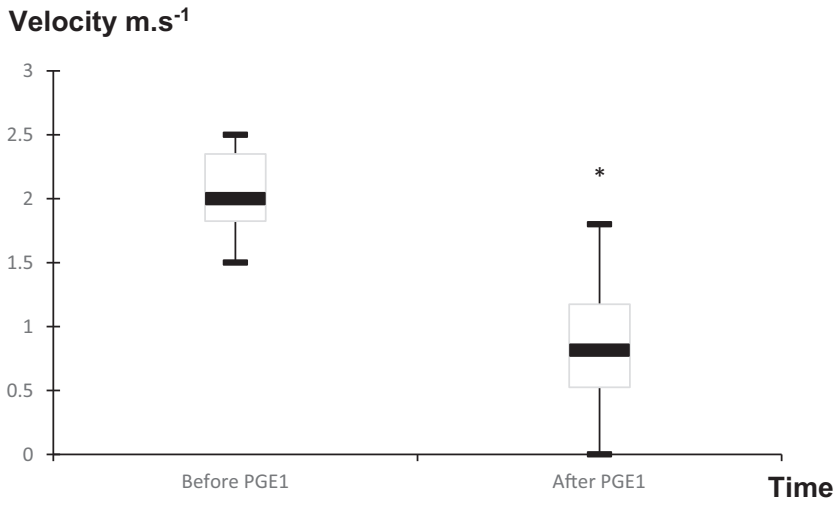

Fig. 4. Maximum right-to-left blood flow velocities across the ductus arteriosus ($m.s^{-1}$). The blood flow velocities decreased significantly after starting alprostadil. Values are expressed as median and IRQ. * $p < 0.05$.

Evidence exists that lack of response to pulmonary vasodilators may result from left ventricle dysfunction as recently reported [5,27,28]. It would be interesting to explore the effects of PGE1 on the left ventricular function. Further studies are needed to assess this parameter.

The use of PGE1 could be a confounding bias: infants who required PGE1 had greater markers of severity including lower LHR o/e, lower pulmonary lung volume at MRI and required inhaled NO before use of PGE1. Despite markers of severity, the overall survival rate in our cohort was 15%, which is lower than others reported mortality rate in this population [29]. We acknowledge that indicators of respiratory morbidity assessed by the length of ventilatory support, O2 supplementation, and stay on the NICU were greater in the infants treated by PGE1 than in the infants not treated by PGE1. We cannot exclude that early use of ECMO may have prevented at least in part the respiratory morbidity or the late deaths in this population.

The prophylactic use of PGE1 is associated with shorter duration of mechanical ventilation. Although these data may suggest better respiratory outcome with prophylactic PGE1, a randomized trial is yet required to support this result.

3.2. Conclusion

Suprasystemic pulmonary hypertension is a life-threatening event in CDH infants, leading to impaired respiratory function and failure of the right ventricle. It can occur when the ductus arteriosus becomes restrictive in severe CDH. We show that PGE_1 treatment may improve cardiorespiratory failure through reopening of the ductus arteriosus.

Acute worsening of the cardiorespiratory function should prompt echocardiographic assessment to ensure the patency of the ductus arteriosus. PGE_1 should be given when evidence exists for restrictive ductus arteriosus and suprasystemic pulmonary hypertension unresponsive to inhaled NO, in order to reopen the ductus arteriosus and decrease pulmonary artery pressure.

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