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Prostaglandin E1 in infants with Congenital Diaphragmatic Hernia (CDH) and life-threatening pulmonary hypertension

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1. INTRODUCTION

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 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 iso-systemic. 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 E₁ (PGE₁) may improve circulatory function (6,7). Infusion of PGE₁ 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

29 artery to descending aorta in order to promote a right-to-left shunting, improves right ventricular function
30 in children with suprasystemic PAP (9).

31

32 In the present study, we aimed at investigating the effects of PGE₁ infusion on the cardiorespiratory
33 function, in newborn infants with CDH and life-threatening pulmonary hypertension. Serial measurements
34 of cardiorespiratory variables have been recorded before and after PGE₁ infusion.

35

36 **2. POPULATION AND METHODS**

37 2.1 Population

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

40 In the Nord-Pas-de-Calais area of France (4.5 million inhabitants; 55000 births/year), all infants with a
41 diagnosis of CDH were referred to Lille University Hospital and were enrolled systematically in a prospective
42 follow-up study (cohort). We recorded data on patient demographics, Observed/Expected Lung Head Ratio
43 (collected at 24-28 and 32-34 weeks of gestational age), prenatal care and imaging, postnatal care,
44 including surgical repair, vital signs, and medication use.

45

46 2.2 Inclusion criteria

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

- 49 - An increase of more than 20% of the FiO₂ to target a preductal SpO₂ above 88%;
- 50 - Signs of circulatory failure including paleness, heart rate > 160 bpm, capillary refill time > 3 s, urine
51 output < 1ml.kg⁻¹.h⁻¹, or mean systemic blood pressure less than 40mmHg;
- 52 - Bidirectional or exclusive right-to-left shunting across the ductus arteriosus with an acceleration of
53 the blood flow > 1.5 m.s⁻¹ assessed by Doppler echocardiography;
- 54 - No response to inhaled NO;

55 2.3 Non-inclusion criteria

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

57 2.4 Ethical agreement

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

61 2.5 Primary endpoint:

- 62 • Decrease in FiO_2 to target preductal SpO_2 between 88 and 96%, 6 hours after starting PGE_1 infusion.

63 2.6 Secondary endpoints

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

67 2.7 Patient care

68 Management of the CDH infants is based on the EURO Consortium guidelines and the French Reference
69 Center guidelines (10,11).

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

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

81 Doppler echocardiography was performed by trained neonatologists with a high-frequency 12 MHz
82 transducer (Philips CX50 Compact Xtreme; Philips, Suresnes, France). The first echocardiographic

83 assessment was performed within the first hour after birth, then twice a day and for each unexplained life-
84 threatening event. We analyzed echocardiographic images and Doppler measurements after each
85 acquisition in order to adapt treatment according to hemodynamic assessment. Averages of three to five
86 consecutive readings for the flow velocities are used. The angle of isonation was less than 20°. For each
87 patient, measurements were performed by the same investigator to minimize interobserver variability.
88 Maximal blood flow velocities and flow patterns through the ductus arteriosus were assessed by pulsed
89 Doppler using a high left parasternal view. The shunting was classified into left-to-right, right-to-left or
90 bidirectional according the DA flow pattern. Systolic and diastolic pulmonary artery pressures (PAP) were
91 evaluated by measuring pressure gradient through the DA using the simplified Bernoulli formula,
92 subtracted from systolic and diastolic systemic arterial pressures. The mean pulmonary arterial pressure
93 were calculated as: $PAP = (\text{systolic PAP} + [2 \times \text{diastolic PAP}]) / 3$. These measurements were compared to
94 the systolic blood pressure measured on echocardiogram and classified as suprasystemic when mean
95 pulmonary artery pressure is \geq systemic blood pressure + 10 mmHg.

96 In our clinical setting, PGE₁ (Prostine VR®, Upjohn) is given when the maximal right-to-left blood flow
97 velocities are $> 1.5 \text{ m}\cdot\text{s}^{-1}$ in CDH infants with acute worsening of the cardiorespiratory status. In the absence
98 of evidence-based, PGE₁ is also used prophylactically at the discretion of the practitioner. PGE₁ is infused in
99 a central catheter at an initial rate of $0.025 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The infusion rate is increased to $0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$
100 if the blood flow velocities are still $> 1.5\text{m}\cdot\text{s}^{-1}$ after 1 hour of PGE₁ infusion. The infusion rate is progressively
101 decreased to $0.01 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ if the blood flow velocities are $< 1 \text{ m}\cdot\text{s}^{-1}$. PGE₁ may also be given
102 prophylactically within the first hours of birth in newborn infants with CDH considered at risk for
103 suprasystemic pulmonary hypertension (low prenatal O/E LHR). The infusion is then set at a rate of 0.01
104 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$.

105 2.8 Statistical analysis

106 The variables were collected from the charts at 12, 6 and 1 hour before, and 1, 6, 12, 24, 48 and 72 hours
107 after starting PGE₁ infusion. Each infant served as his or her own control. All statistical analyses were
108 conducted using SPSS Statistic version 24 (IBM corporation, Armonk, New York). Continuous variables were
109 described as median [range]. Baseline characteristics of PGE₁ group and non-treated group were compared
110 using Fisher's exact test for categorical data or Mann-Whitney t test for continuous data. The non-parametric

111 Friedman and Wilcoxon distribution-free with a Bonferroni correction signed rank test ($\alpha = 0.005$) was used
112 to assess the significance of differences in respiratory and hemodynamic measures between each hour
113 after starting PGE₁. Statistical significance was accepted at $p < 0.05$.

114

115 3. RESULTS

116 One hundred and two infants with CDH were identified in the Nord-Pas-de-Calais area between 2009 and
117 2015, and admitted to our institution. Sixty-eight were not eligible for the study because they never
118 received PGE₁. Sixteen were excluded because they received PGE₁ prophylactically before any clinical
119 worsening. Eighteen CDH infants were treated with PGE₁ for acute life-threatening suprasystemic
120 pulmonary hypertension during the course of the hospitalization at a median postnatal age of 11 days, IQR
121 [5-16] (Fig 1).

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

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

132 Just before starting PGE₁ these infants had symptoms of both respiratory and circulatory failure, including
133 acute increase in O₂ need (n=18), paleness (n=18), heart rate > 160 beats/min (n=11), drop in mean blood
134 pressure < 40 mmHg (n=4), decrease in urine output < 1ml.kg⁻¹.h⁻¹ (n=7), or elevation of plasma lactate
135 concentration > 2 mg.L⁻¹ (n=10). Medians and ranges of pre- and post-ductal SpO₂ were respectively 91%
136 [82 - 96] and 86% [44 - 95]. Doppler echocardiography showed a right-to-left or a bidirectional shunting
137 across the DA in respectively 11 and 7 infants. Median and range of the maximal blood flow velocities in the

138 DA were $2.2 \text{ m}\cdot\text{s}^{-1}$ [1.5-2.5].

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

145 PGE₁ was started at a median postnatal age of 11 days [5;17], at an initial rate of $0.025 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$.

146 Within 6 hours after onset of PGE₁, median FiO₂ decreased from 80% to 34% ($p<0.001$) to target pre-ductal
147 SpO₂ between 88 and 96% (Fig 2). Pre-ductal SpO₂/FiO₂ increased from 1.15 [0.9;1.9] to 2.6 [2.4;3.1]
148 ($p<0.01$) (Fig 3). Urine output increased from 1.6 to 2.9 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ($p<0.05$). Plasma lactate concentration
149 was significantly lower at H6 than just before PGE₁ infusion ($p<0.05$). Pre- and post-ductal SpO₂ and SpO₂
150 gradient, blood gases (pH, PaCO₂), arterial blood pressure, heart rate, and temperature did not change
151 significantly throughout the study period (Table 3).

152 Shunting across the DA was mainly bidirectional ($n=14$). Maximal blood flow velocities in the DA decreased
153 significantly between H1 and H6 after starting PGE₁ ($1 \text{ m}\cdot\text{s}^{-1}$ [0.55;1.2] vs $2.2 \text{ m}\cdot\text{s}^{-1}$ [1.5;2.5]; $p<0.001$) (Fig
154 4).

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

161

162 4. DISCUSSION

163 We assessed the tolerance and effects of PGE₁ in 18 newborn infants with congenital diaphragmatic hernia
164 and acute suprasystemic pulmonary arterial hypertension unresponsive to inhaled NO, by serial

165 measurements of respiratory function and hemodynamics. PGE₁ was associated with a drop in FiO₂ by 45%,
166 in plasma lactate concentration, and in maximum right-to-left blood flow velocities across the ductus
167 arteriosus within the first 6 hours of infusion. Preductal SpO₂/FiO₂ and urine output increased after initiation
168 of PGE₁. Systemic pressure did not change after starting PGE₁. These data indicate that PGE₁ may improve
169 cardiorespiratory function through decreasing pulmonary artery pressure in CDH infants with life-
170 threatening acute pulmonary hypertension. We speculate that restrictive ductus arteriosus may contribute
171 to severe hypoxic respiratory failure in infants with CDH and pulmonary hypertension. Conversely, ductus
172 arteriosus patency is required for it promotes balanced right and left pressures.

173

174 Growing evidence suggests that PGE₁ may improve cardiac function in CDH infants. In a case series, no
175 acute worsening of the cardiorespiratory function was observed in 39 infants with antenatal diagnosis of
176 CDH and prophylactically treated by PGE₁ (7). Furthermore, PGE₁ may support cardiac function in CDH
177 infants with underdeveloped left ventricle (6,12). A decrease in brain natriuretic factor plasma
178 concentration observed one day after starting PGE₁ infusion in 59 CDH infants with severe pulmonary
179 hypertension further supports the hypothesis that PGE₁ contributes to decrease right ventricle overload (8).
180 Our study provides additional information. PGE₁ has been used in case of life-threatening events, with
181 increase in O₂ need and drop in preductal SpO₂/FiO₂ ratio, and markers of circulatory failure including
182 decrease in urine output and elevation of plasma lactate concentration. The acute worsening of the
183 cardiorespiratory function was not related to technical problems, pleural effusion, late-onset sepsis, or
184 pulmonary infection.

185 The lack of change in pH or PaCO₂ provides additional evidence that the cardiorespiratory failure was not
186 triggered by change in lung ventilation. The cardiorespiratory failure was associated with a right-to-left
187 blood flow velocity between 1.5 and 2.5m.s⁻¹, which indicates – using the simplified Bernoulli formula ($|\delta P$
188 $= 4V^2|$) – a pulmonary artery and aortic pressures gradient between 10 and 25 mmHg. Such pressure
189 gradient requires at least in part that the ductus arteriosus be partly restrictive, as hemodynamic law
190 indicates that gradient pressure is proportional to resistance.

191 No change in pre- and post-ductal SpO₂ difference suggests that the right-to-left ductal flow did not
192 increase despite suprasystemic pulmonary artery pressure, which is further in accordance with restrictive

193 ductus arteriosus. Timing of the life-threatening event after birth (median 11 days) is also in accordance
194 with a cause and effect relationship between restriction of the ductus arteriosus and the cardiorespiratory
195 failure. Although the ductus arteriosus is functionally closed in 90% of healthy term babies by 72 h of life,
196 infants with PPHN have a significant delay in ductal closure (13,14).

197 In this situation of cardiopulmonary failure, ECMO was shown to be effective (15). Veno-arterial ECMO may
198 decrease pulmonary artery pressure through decrease in right ventricle preload. ECMO sustains
199 oxygenation/decarboxylation and supports systemic circulation during the period of time requires for the
200 pulmonary vascular resistance to decrease. ECMO is therefore a therapeutic option.

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

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

207 Although no change in systemic pressure was observed after starting PGE1 treatment in our study, special
208 care should be taken during PGE1 administration due to its potential side effects as vasodilation and
209 hypotension. Pre-existent biventricular dysfunction, if not adequately supported, may lead to reduced
210 cardiac output and promote right-to-left shunting across the DA giving rise to systemic hypotension,
211 acidosis, and hypoxemia.

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

219 O₂ need decreased and preductal SpO₂/FiO₂ ratio increased within the first 6 hours after initiating PGE₁
220 infusion. Preductal SpO₂ is determined by intrapulmonary shunting or right-to-left shunting through the

221 foramen ovale. Except adaptation of FiO_2 , ventilator settings were not changed within the first 6 hours of
222 the study as blood gases did not change. Therefore, it is unlikely that improvement in preductal $\text{SpO}_2/\text{FiO}_2$
223 ratio was related to decreased intrapulmonary shunting. Conversely, mechanisms can explain that PGE_1
224 may improve oxygenation in CDH infants with suprasystemic pulmonary hypertension through decrease in
225 right-to-left shunting in the foramen ovale.

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

234 Therefore, PGE_1 infusion results in a drop in pulmonary artery pressure by 18 mmHg. Indeed, PGE_1
235 contributes to large patency and low resistance of the ductus arteriosus. Increase in urine output and
236 decrease in plasma lactate concentration further support the hypothesis that PGE_1 improved circulatory
237 function. Alternatively, PGE_1 may decrease pulmonary vascular resistance, leading to an increase in
238 pulmonary blood flow, which elevates left atrial pressure. Increase in left atrial pressure contributes to
239 reduce right to left shunting in the foramen ovale. Reopening of the ductus arteriosus did not result in a
240 decrease in post-ductal SpO_2 or an increase in pre- and post-ductal SpO_2 difference, which may appear
241 surprising. The magnitude of the post-ductal desaturation is related to the right-to-left blood flow across
242 the ductus arteriosus and to the value of the mixed venous oxygen saturation. In this study, we did not
243 measure ductal flow although flow direction and velocities have been assessed. Ductal flow is proportional
244 to pulmonary and systemic pressures difference and inversely proportional to ductus arteriosus resistance.
245 PGE_1 may have improved the pulmonary circulation through 2 mechanisms: 1) DA relaxation which
246 decreases DA resistance and therefore blood flow velocities across the DA; 2) non-specific vasodilator
247 effects including pulmonary vasorelaxation which may decrease pulmonary vascular resistance and
248 pressure that in turn decreases the right to left blood flow velocities across the DA (21).

249 Alternatively, PGE1 may increase left ventricular output through: 1) improved diastolic left ventricle filling
250 associated with decreased right ventricle pressure; 2) increase in pulmonary blood flow which in turn
251 elevates left ventricle preload. Indeed, we have shown in fetal lambs that suprasystemic pulmonary artery
252 pressure induced by ductus arteriosus compression activates a potent myogenic response within the lung,
253 causing an acute increase in pulmonary vascular resistance (22,23). Reopening of the ductus arteriosus and
254 drop in pulmonary artery pressure results in a decrease in pulmonary vascular resistance and an increase in
255 pulmonary blood flow. Increase in left ventricle output contribute to elevate oxygen delivery and mixed
256 venous oxygen saturation (24). Higher venous O₂ saturation may limit post-ductal desaturation in case of
257 right to left shunting across the ductus arteriosus, and may further contribute to sustain pulmonary
258 vasodilation.

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

267 4.1 Limitations of the study

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

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

275 The use of PGE1 could be a confounding bias: infants who required PGE1 had greater markers of severity
276 including lower LHR o/e, lower pulmonary lung volume at MRI and required inhaled NO before use of PGE1.

277 Despite markers of severity, the overall survival rate in our cohort was 15 %, which is lower than others
278 reported mortality rate in this population (29). We acknowledge that indicators of respiratory morbidity
279 assessed by the length of ventilatory support, O₂ supplementation, and stay on the NICU were greater in
280 the infants treated by PGE₁ than in the infants not treated by PGE₁. We cannot exclude that early use of
281 ECMO may have prevented at least in part the respiratory morbidity or the late deaths in this population.
282 The prophylactic use of PGE₁ is associated with shorter duration of mechanical ventilation. Although these
283 data may suggest better respiratory outcome with prophylactic PGE₁, a randomized trial is yet required to
284 support this result.

285 4.2 Conclusion

286 Suprasystemic pulmonary hypertension is a life-threatening event in CDH infants, leading to impaired
287 respiratory function and failure of the right ventricle. It can occur when the ductus arteriosus becomes
288 restrictive in severe CDH. We show that PGE₁ treatment may improve cardiorespiratory failure through
289 reopening of the ductus arteriosus.

290 Acute worsening of the cardiorespiratory function should prompt echocardiographic assessment to ensure
291 the patency of the ductus arteriosus. PGE₁ should be given when evidence exists for restrictive ductus
292 arteriosus and suprasystemic pulmonary hypertension unresponsive to inhaled NO, in order to reopen the
293 ductus arteriosus and decrease pulmonary artery pressure.

294

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302

303

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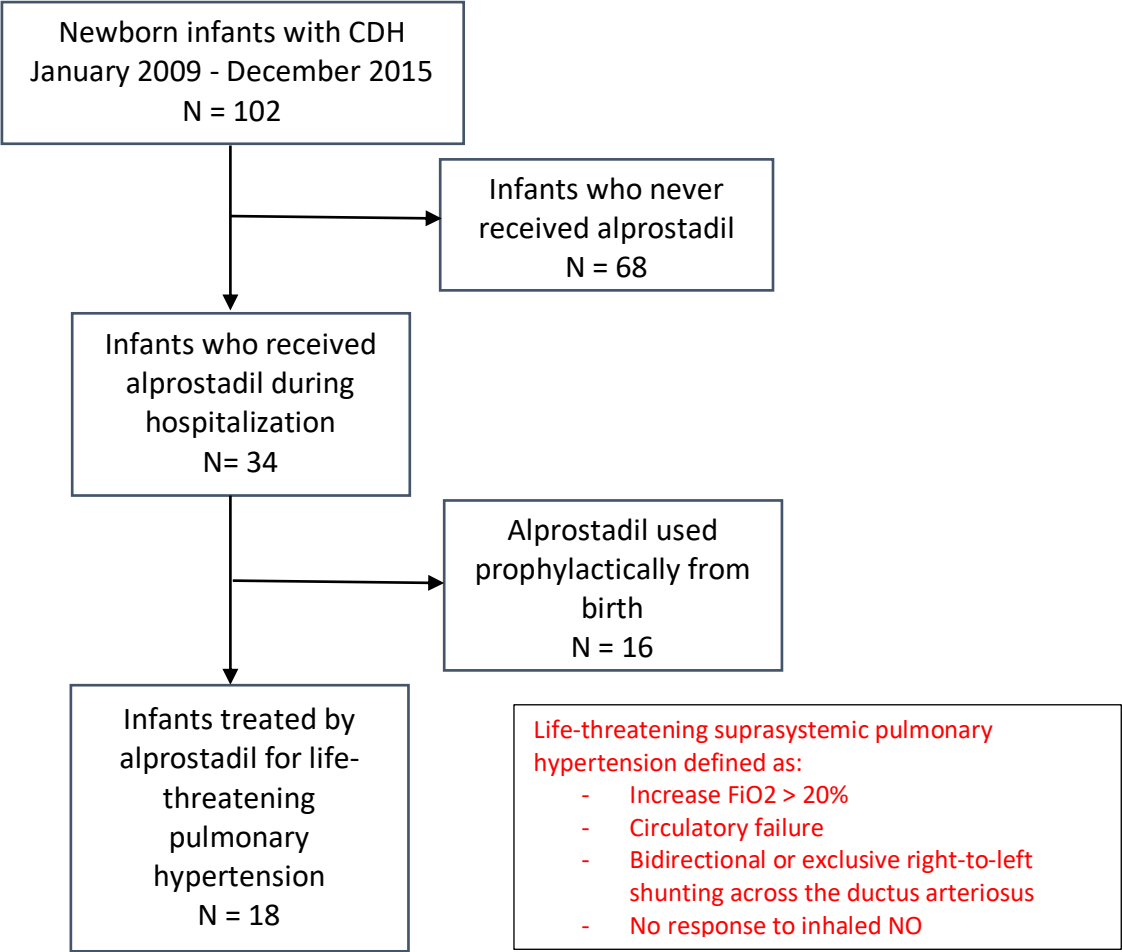
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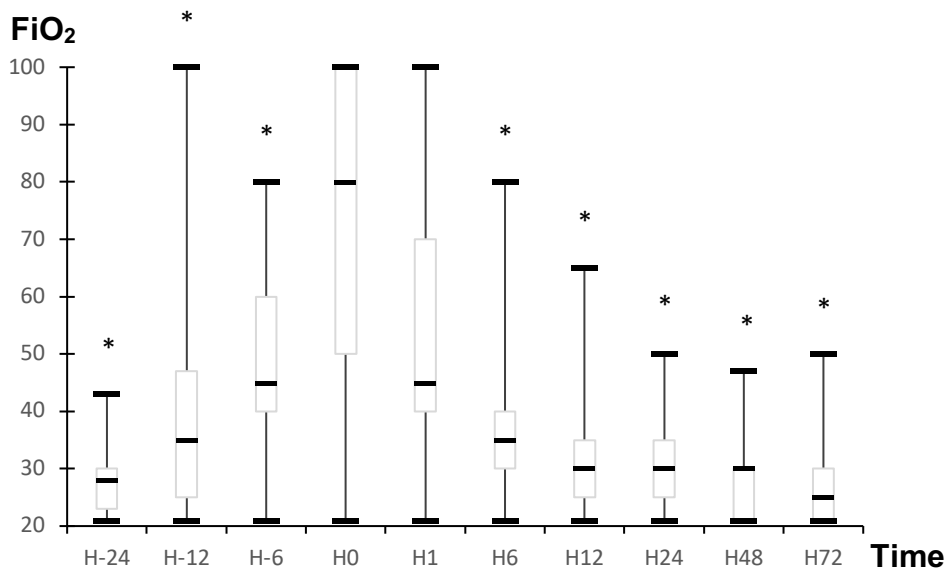
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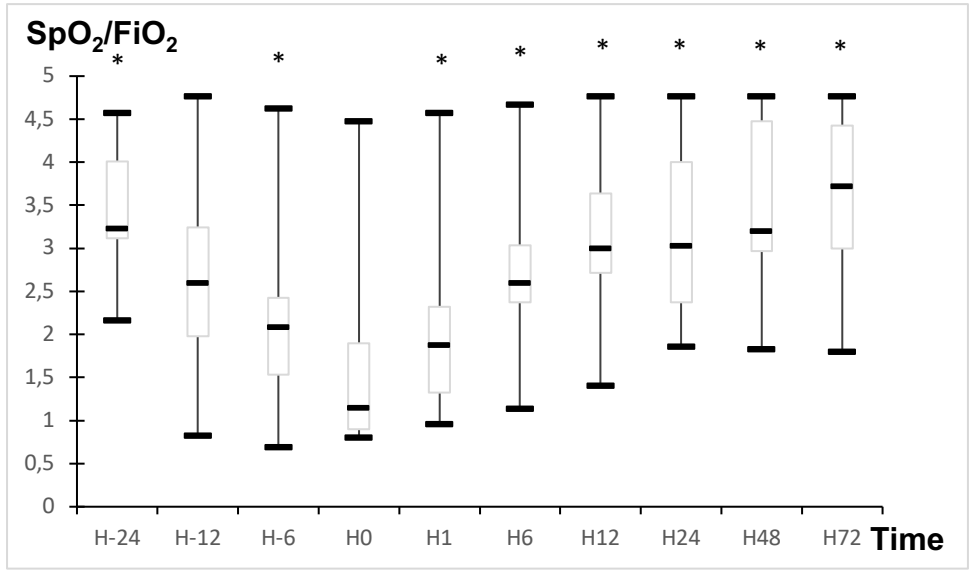
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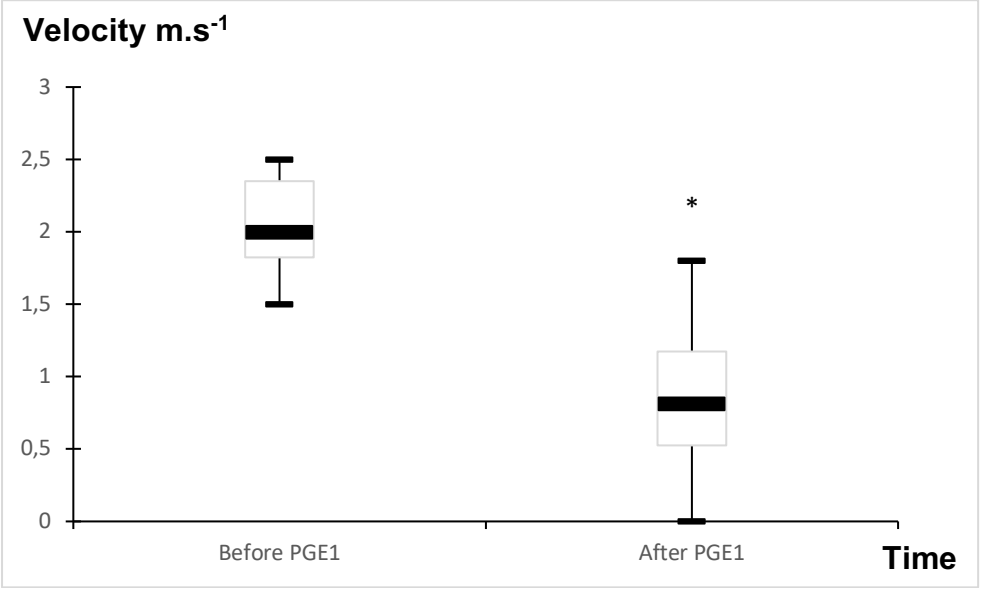
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	PGE1 group	CDH group	P value
	N=18	N=84	
Prenatal diagnosis (%)	16 (89)	66 (79)	0.33
Left CDH (%)	13 (72)	11 (16)	0.2
LHR o/e	36 [35;43]	50 [40;64]	0.001 *
Fetal MRI %	32 [30;35]	38 [30;47]	0.05 *
Liver herniation (%)	13 (72)	32 (38)	0.01 *
Male sex (%)	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 (hours)	160 [128;218]	57 [29;100]	<0.001*
Duration of O₂ (days)	45 [21;94]	3 [1;11]	<0.001*
Duration of Non Invasive 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

	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 (hours)	160 [128;218]	120 [71;168]	0.004 *
Duration of Non Invasive Ventilation (days)	12 [6;19]	3 [1;4]	0.003 *
Duration of O₂ 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

	H-24	H-12	H-6	H0	H1	H6	H12	H24	H48	H72
HR (bpm)	155	153	160	156	153	160	151	151	148	150
	[133;166]	[139;169]	[143;168]	[143;169]	[143;167]	[139;171]	[141;166]	[143;166]	[142;158]	[145;156]
MAP	48	47	49	49	49	50	50	48	51	48
(mmHg)	[44;59]	[45;50]	[43;54]	[46;56]	[45;55]	[47;57]	[45;52]	[44;58]	[46;54]	[45;52]
Preductal	94	92	93	91	93	94	95	95	95 *	97 *
SpO₂ (%)	[92;96]	[90;95]	[91;94]	[88;95]	[88;95]	[91;95]	[90;96]	[92;97]	[93;97]	[93;98]
Postductal	93	91	88	86	87	91	91	92	90	93 *
SpO₂ (%)	[83;96]	[81;95]	[80;93]	[82;91]	[79;93]	[84;93]	[87;93]	[86;95]	[86;95]	[87;96]
Diuresis	2.9 *	2.7	2.0 *	1.6	1.6	2.3 *	2.9 *	2.9	3.4	2.9
(mL.Kg⁻¹.h⁻¹)	[2.2;4.9]	[1.8;5.0]	[1.1;3.7]	[0.9;3.2]	[1.5;1.8]	[2.0;3.5]	[2.4;4.7]	[2.0;3.5]	[2.6;4.2]	[2.3;3.9]
pH	7.29	7.31	7.30 *	7.21	7.28	7.33 *	7.33 *	7.34 *	7.35 *	7.34 *
	[7.24;7.33]	[7.23;7.37]	[7.23;7.34]	[7.16;7.29]	[7.26;7.30]	[7.25;7.36]	[7.27;7.39]	[7.26;7.39]	[7.29;7.41]	[7.27;7.41]
PaCO₂	70	64	64	66	65	57	59	62	56 *	59 *
(mmHg)	[66;73]	[54;67]	[57;72]	[61;71]	[51;74]	[49;65]	[48;67]	[55;70]	[51;65]	[55;65]
Lactates	1.0	1.6	1.2 *	2	2.2	1.5	1.4 *	1.2	1.3	1.3
(mmol/L)	[0.7;1.4]	[1.6;1.7]	[0.9;2.2]	[1.3; 3]	[2.1;2.5]	[1.0;1.8]	[0.9;1.7]	[1.0;1.6]	[0.8;1.7]	[0.8;2]