

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

Kevin Le Duc, Sébastien Mur, Dyuti Sharma, Estelle Aubry, Morgan Recher, Thameur Rakza, Laurent Storme, Sixtine Gilliot, Mohamed Riadh Boukhris,

Morgane Masse, et al.

▶ To cite this version:

Kevin Le Duc, Sébastien Mur, Dyuti Sharma, Estelle Aubry, Morgan Recher, et al.. Prostaglandin E1 in infants with congenital diaphragmatic hernia (CDH) and life-threatening pulmonary hypertension. Journal of Pediatric Surgery, 2020, 55 (9), pp.1872-1878. 10.1016/j.jpedsurg.2020.01.008 . hal-03358230

HAL Id: hal-03358230 https://hal.science/hal-03358230

Submitted on 5 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Version of Record: https://www.sciencedirect.com/science/article/pii/S0022346820300336 Manuscript_c90d74f09fedcb6d765c326d3db5cb84

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

Kévin Le Duc¹, Sébastien Mur¹, Dyuti Sharma², Estelle Aubry², Morgan Recher³,

Thameur Rakza¹, Laurent Storme¹; Center for Rare Disease «Congenital Diaphragmatic Hernia»

- Department of Neonatology, Jeanne de Flandre Hospital, University Hospital of Lille, F-59000 FRANCE
- Department of Pediatric Surgery, Jeanne de Flandre Hospital, University Hospital of Lille, F-59000 FRANCE
- Paediatric Intensive Care Unit, Jeanne de Flandre Hospital, University Hospital of Lille, F-59000 France

Conflict of interest: none

Corresponding author: Kevin Le Duc Jeanne de Flandre Hospital, Lille University Hospital 1 rue Eugène Avinée F-59000 Lille Cedex, France Tel: +33 3 20 44 6199-Mail: kevin.leduc@chru-lille.fr

1 1. INTRODUCTION

2 Despite improvement in treatment options and advances in neonatal care, mortality rates in infants with 3 CDH are estimated at 20-30% in tertiary care centers (1). CDH is associated with abnormal pulmonary 4 development, including lower number of bronchial divisions and fewer pulmonary arterial branches. 5 Multiple functional abnormalities of pulmonary vessel reactivity have been reported, including decreased 6 response to vasodilator stimuli (2). Structural vascular abnormalities, namely restrictive vascular bed and 7 vascular wall remodeling, and functional abnormalities cause a failure in the cardiorespiratory transition at 8 birth. Furthermore, structural and functional left ventricle abnormalities are responsible for impaired left 9 ventricle filling and contribute to the development of pulmonary venous hypertension. This fetal-to-10 neonatal maladaptation results in persistent pulmonary hypertension of the newborn (PPHN).

11 This is associated with:

-

12

13

a right-to-left shunt through the ductus arteriosus, responsible for postductal hypoxemia, and differences in pre- and postductal arterial blood gas parameters (3);

14 - a reduction in the pulmonary venous return, resulting in a decrease in the left ventricle output.

15 The ratio of estimated PAP to the simultaneous systemic blood pressure is used to classify pulmonary 16 hypertension as subsystemic, systemic or suprasystemic. Suprasystemic pulmonary artery is a life-17 threatening event in the newborn, leading to right ventricle enlargement. Pulmonary artery pressure (PAP) 18 can rise higher than aortic pressure, in particular when ductus arteriosus becomes restrictive, resulting in 19 right-sided heart failure, which in turn alters the diastolic filling of the left ventricle, an additional factor for 20 systemic low blood flow (4). The usual treatment of pulmonary hypertension, including inhaled nitric oxide 21 (NO) or prostacyclin may fail to decrease PAP, at least in part because of the pulmonary venous component 22 of the hypertension. However, as long as the ductus arteriosus is largely patent, PAP equalizes aortic 23 pressures. Pulmonary hypertension is therefore iso-systemic. Moreover, right-to-left shunting across the 24 ductus arteriosus contributes to sustain the systemic blood flow to compensate low left ventricle output 25 (5).

Previous retrospective studies have reported that prostaglandin E_1 (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 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

In the present study, we aimed at investigating the effects of PGE₁ 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 PGE₁ infusion.

35

36 2. POPULATION AND METHODS

37 <u>2.1 Population</u>

We conducted a retrospective chart review of neonates admitted for CDH at the neonatal intensive careunit 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; 55000 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.

45

46 <u>2.2 Inclusion criteria</u>

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%;
- Signs of circulatory failure including paleness, heart rate > 160 bpm, capillary refill time > 3 s, urine
 output < 1ml.kg⁻¹.h⁻¹, or mean systemic blood pressure less than 40mmHg;
- 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;
- 55 <u>2.3 Non-inclusion criteria</u>

- 56 Infants with a polymalformative or genetic syndrome were not included in the study.
- 57 <u>2.4 Ethical agreement</u>
- 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 <u>2.5 Primary endpoint:</u>
- Decrease in FiO₂ to target preductal SpO2 between 88 and 96%, 6 hours after starting PGE₁ infusion.
- 63 <u>2.6 Secondary endpoints</u>
- Decrease in maximum right-to-left blood flow velocities across the ductus arteriosus;
- Change in pH, PaCO₂, pre- and post-ductal SpO₂, heart rate and mean arterial pressure, plasma
 lactate concentration, and urine output.
- 67 <u>2.7 Patient care</u>
- 68 Management of the CDH infants is based on the EURO Consortium guidelines and the French Reference69 Center guidelines (10,11).

Briefly, the infants are mechanically ventilated in pressure-controlled mode (STEPHANIE; Fritz Stephan GmbH Medizintechnik, Gackenbach, Germany). Pre- and post-ductal transcutaneous oxygen saturation (SpO₂), transcutaneous PtcCO₂, heart and respiratory rates, blood gases, and arterial blood pressure are monitored (IntelliVue MP70 monitor; Philips Healtcare, Suresnes, France). Fraction of inspired oxygen (FiO₂) and ventilator parameters are adjusted to target pre-ductal SpO₂ 88-96%, and PaCO₂ 45-55mmHg. 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 lateonset sepsis or pulmonary infection are ruled out. The infants receive 20ml.kg⁻¹ of saline if mean arterial
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 = (systolic PAP + [2 x 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 m.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 µg.kg⁻¹.min⁻¹. The infusion rate is increased to 0.05 µg.kg⁻¹.min⁻¹ 100 if the blood flow velocities are still > 1.5m.s⁻¹ after 1 hour of PGE₁ infusion. The infusion rate is progressively 101 decreased to 0.01 μ g.kg⁻¹.min⁻¹ if the blood flow velocities are < 1 m.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 μ g.kg⁻¹.min⁻¹.

105 <u>2.8 Statistical analysis</u>

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'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**

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 PGE₁. Sixteen were excluded because they received PGE₁ prophylactically before any clinical worsening. Eighteen CDH infants were treated with PGE₁ 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.

Just before starting PGE₁ these infants had symptoms of both respiratory and circulatory failure, including acute increase in O₂ 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 < 1ml.kg⁻¹.h⁻¹ (n=7), or elevation of plasma lactate concentration > 2 mg.L⁻¹ (n=10). Medians and ranges of pre- and post-ductal SpO₂ 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 138 DA were 2.2 m.s⁻¹ [1.5-2.5].

Table 2 compared the clinical characteristics of the infants who received PGE1 in situation of lifethreatening 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, non-invasive 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.

PGE₁ was started at a median postnatal age of 11 days [5;17], at an initial rate of 0.025 μg.kg⁻¹.min⁻¹.

Within 6 hours after onset of PGE₁, median FiO₂ decreased from 80% to 34% (p<0.001) to target pre-ductal 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] (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 PGE₁ infusion (p<0.05). Pre- and post-ductal SpO₂ and SpO₂ gradient, blood gases (pH, PaCO₂), 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 due 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).

161

162 **4. DISCUSSION**

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

165 measurements of respiratory function and hemodynamics. PGE_1 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 $Sp0_2/Fi0_2$ 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 PGE_1 (7). Furthermore, PGE_1 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. PGE_1 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.

The lack of change in pH or PaCO₂ 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 2.5m.s⁻¹, which indicates – using the simplified Bernoulli formula ($|\delta P|$ = 4V²|) – 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.

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 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).

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.

Our data highlights that PGE1 may be an alternative treatment to ECMO. As during ECMO, PGE1 promotes
 PAP decrease through DA opening and equalisation 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. 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 due to its potential side effects as vasodilation and hypotension. Pre-existent biventricular dysfunction, if not adequately supported, may lead to reduced cardiac output and promote right-to-left 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, due 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.

219 O_2 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 foramen ovale. Except adaptation of FiO₂, ventilator settings were not changed within the first 6 hours of the study as blood gases did not change. Therefore, it is unlikely that improvement in preductal SpO₂/FiO₂ ratio was related to decreased intrapulmonary shunting. Conversely, mechanisms can explain that PGE₁ may improve oxygenation in CDH infants with suprasystemic pulmonary hypertension through decrease in 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 PGE₁, blood 232 flow velocities across the ductus arteriosus decreased to below 1.5 m.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 PGE₁ improved circulatory 237 function. Alternatively, PGE1 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 PGE1 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 <u>4.1 Limitations of the study</u>

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

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.

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.

285 <u>4.2 Conclusion</u>

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 PGE₁ 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. PGE₁ 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.

294

- 295 **5. Acknowledgements**
- **296** Julien De Jonckheere for statistical analysis, advice.
- 297 Sophie Charbonnel-Bucari for careful reading and English editing,

298

299 **6.** Formatting of funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

302

303

7. <u>References</u>

1. Harting MT, Lally KP. The Congenital Diaphragmatic Hernia Study Group registry update. Semin Fetal Neonatal Med. déc 2014;19(6):370-5.

2. de Lagausie P, de Buys-Roessingh A, Ferkdadji L, Saada J, Aisenfisz S, Martinez-Vinson C, et al. Endothelin receptor expression in human lungs of newborns with congenital diaphragmatic hernia. J Pathol. janv 2005;205(1):112-8.

3. Gien J, Kinsella JP. Differences in preductal and postductal arterial blood gas measurements in infants with severe congenital diaphragmatic hernia. Arch Dis Child Fetal Neonatal Ed. juill 2016;101(4):F314-318.

4. Tourneux P, Rakza T, Bouissou A, Krim G, Storme L. Pulmonary circulatory effects of norepinephrine in newborn infants with persistent pulmonary hypertension. J Pediatr. sept 2008;153(3):345-9.

5. Kinsella JP, Steinhorn RH, Mullen MP, Hopper RK, Keller RL, Ivy DD, et al. The Left Ventricle in Congenital Diaphragmatic Hernia: Implications for the Management of Pulmonary Hypertension. J Pediatr. juin 2018;197:17-22.

6. Inamura N, Kubota A, Nakajima T, Kayatani F, Okuyama H, Oue T, et al. A proposal of new therapeutic strategy for antenatally diagnosed congenital diaphragmatic hernia. J Pediatr Surg. août 2005;40(8):1315-9.

7. Inamura N, Kubota A, Ishii R, Ishii Y, Kawazu Y, Hamamichi Y, et al. Efficacy of the circulatory management of an antenatally diagnosed congenital diaphragmatic hernia: outcomes of the proposed strategy. Pediatr Surg Int. sept 2014;30(9):889-94.

8. Lawrence KM, Berger K, Herkert L, Franciscovich C, O'Dea CLH, Waqar LN, et al. Use of prostaglandin E1 to treat pulmonary hypertension in congenital diaphragmatic hernia. J Pediatr Surg. janv 2019;54(1):55-9.

9. Aggarwal M, Grady RM, Choudhry S, Anwar S, Eghtesady P, Singh GK. Potts Shunt Improves Right Ventricular Function and Coupling With Pulmonary Circulation in Children With Suprasystemic Pulmonary Arterial Hypertension. Circ Cardiovasc Imaging. déc 2018;11(12):e007964.

10. Snoek KG, Reiss IKM, Greenough A, Capolupo I, Urlesberger B, Wessel L, et al. Standardized

Postnatal Management of Infants with Congenital Diaphragmatic Hernia in Europe: The CDH EURO Consortium Consensus - 2015 Update. Neonatology. 2016;110(1):66-74.

11. Storme L, Boubnova J, Mur S, Pognon L, Sharma D, Aubry E, et al. Review shows that implementing a nationwide protocol for congenital diaphragmatic hernia was a key factor in reducing mortality and morbidity. Acta Paediatr Oslo Nor 1992. juill 2018;107(7):1131-9.

12. Moscatelli A, Pezzato S, Lista G, Petrucci L, Buratti S, Castagnola E, et al. Venovenous ECMO for Congenital Diaphragmatic Hernia: Role of Ductal Patency and Lung Recruitment. Pediatrics. 2016;138(5).

13. Walther FJ, Benders MJ, Leighton JO. Early changes in the neonatal circulatory transition. J Pediatr. oct 1993;123(4):625-32.

14. Clyman RI, Mauray F, Heymann MA, Roman C. Influence of Increased Pulmonary Vascular Pressures on the Closure of the Ductus Arteriosus in Newborn Lambs. Pediatr Res. févr 1989;25(2):136-42.

15. Mugford M, Elbourne D, Field D. Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants. 2008;19.

16. Ly LG, Hawes J, Whyte HE, Teixeira LS, McNamara PJ. The Hemodynamically Significant Ductus Arteriosus in Critically III Full-Term Neonates. Neonatology. 2007;91(4):260-5.

17. Putnam LR, Tsao K, Morini F, Lally PA, Miller CC, Lally KP, et al. Evaluation of Variability in Inhaled Nitric Oxide Use and Pulmonary Hypertension in Patients With Congenital Diaphragmatic Hernia. JAMA Pediatr. 1 déc 2016;170(12):1188.

18. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev. 18 oct 2006;(4):CD000399.

19. Dillon PW, Cilley RE, Mauger D, Zachary C, Meier A. The relationship of pulmonary artery pressure and survival in congenital diaphragmatic hernia. J Pediatr Surg. mars 2004;39(3):307-12; discussion 307-312.

20. Lusk LA, Wai KC, Moon-Grady AJ, Steurer MA, Keller RL. Persistence of pulmonary hypertension by echocardiography predicts short-term outcomes in congenital diaphragmatic hernia. J Pediatr. févr 2015;166(2):251-256.e1.

21. Hammerman C, Aramburo MJ, Choi JH. Prostaglandin E1 selectively reduces group B beta-hemolytic streptococci-induced pulmonary hypertension in newborn piglets. Am J Dis Child 1960. mars

1989;143(3):343-7.

22. Storme L, Parker TA, Kinsella JP, Rairigh RL, Abman SH. Chronic hypertension impairs flow-induced vasodilation and augments the myogenic response in fetal lung. Am J Physiol-Lung Cell Mol Physiol. janv 2002;282(1):L56-66.

23. Storme L, Rairigh RL, Parker TA, Kinsella JP, Abman SH. In vivo evidence for a myogenic response in the fetal pulmonary circulation. Pediatr Res. mars 1999;45(3):425-31.

24. The SVO2 collaborative group. The SvO2 study: General design and results of the feasibility phase of a multicenter, randomized trial of three different hemodynamic approaches and two monitoring techniques in the treatment of critically ill patients. Control Clin Trials. févr 1995;16(1):74-87.

25. Aktas S, Ulubas D, Gumustas M, Hirfanoglu IM, Turkyilmaz C, Ergenekon E, et al. Echocardiography may cause significant pain response in preterm infants. J Matern Fetal Neonatal Med. févr 2018;31(3):267-70.

26. Houfflin-Debarge V, Delelis A, Jaillard S, Larrue B, Deruelle P, Ducloy AS, et al. Effects of nociceptive stimuli on the pulmonary circulation in the ovine fetus. Am J Physiol-Regul Integr Comp Physiol. févr 2005;288(2):R547-53.

27. Patel N, Massolo AC, Kipfmueller F. Congenital diaphragmatic hernia-associated cardiac dysfunction. Semin Perinatol. juill 2019;151168.

28. Patel N, Massolo AC, Paria A, Stenhouse EJ, Hunter L, Finlay E, et al. Early Postnatal Ventricular Dysfunction Is Associated with Disease Severity in Patients with Congenital Diaphragmatic Hernia. J Pediatr. déc 2018;203:400-407.e1.

29. Cordier A-G, Russo FM, Deprest J, Benachi A. Prenatal diagnosis, imaging, and prognosis in Congenital Diaphragmatic Hernia. Semin Perinatol. juill 2019;51163.









	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 (hours)	160 [128;218]	57 [29;100]	<0.001*
Duration of O ₂ (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	Prophylactic	
	Treatment	PGE1	P value
	N=18	N =16	
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 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

	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]
МАР	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 ⁻	[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]
1.h ⁻¹)										
рН	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]