Pulmonary Circulatory Effects of Norepinephrine in Newborn Infants with Persistent Pulmonary Hypertension

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Objective To evaluate the respiratory and the pulmonary circulatory effects of norepinephrine in newborn infants with persistent pulmonary hypertension (PPHN)-induced cardiac dysfunction.

Study design Inclusion criteria were: 1) Newborn infants >35 weeks gestational age; 2) PPHN treated with inhaled nitric oxide; and 3) symptoms of circulatory failure despite adequate fluid resuscitation. Lung function and pulmonary hemodynamic variables assessed with Doppler echocardiography were recorded prospectively before and after starting norepinephrine.

Results Eighteen newborns were included (gestational age: 37 ± 3 weeks; birth weight: 2800 ± 700 g). After starting norepinephrine, systemic pressure and left ventricular output increased respectively from 33 ± 4 mm Hg to 49 ± 4 mm Hg and from 172 ± 79 mL/kg/min to 209±90 mL/kg/min ($P < .05$). Although the mechanical ventilatory variables have not been changed, the post-ductal transcutaneous arterial oxygen saturation increased from 89% ± 1% to 95% ± 4%, whereas the oxygen need decreased from 51% ± 24% to 41% ± 20% ($P < .05$). The pulmonary/systemic pressure ratio decreased from 0.98 ± 0.1 to 0.87 ± 0.1 ($P < .05$). Mean left pulmonary artery blood flow velocity increased by 20% ($P < .05$).

Conclusion Norepinephrine may improve lung function in newborn infants with PPHN through a decrease in pulmonary/systemic artery pressure ratio and improved cardiac performance. *(J Pediatr 2008;153:345-9)*

Persistent pulmonary hypertension of the newborn (PPHN) results from the failure of the pulmonary circulation to dilate at birth. This syndrome is characterized by sustained elevation of pulmonary vascular resistance, causing extrapulmonary right-to-left shunting of blood across the ductus arteriosus (DA) and foramen ovale, and severe hypoxemia.[1] PPHN is frequently associated with low systemic pressure and low cardiac output because of increased right ventricular afterload and myocardial dysfunction.[1-4] PPHN-induced circulatory failure further impairs oxygen delivery to the tissues and contributes to significant mortality and morbidity in newborn infants with PPHN.[1,2]

Management requires adequate lung recruitment and alveolar ventilation, inhaled nitric oxide (NO), and appropriate fluid and cardiovascular resuscitation.[5] Early initiation of inotropic and vasoactive agents is commonly used to increase cardiac output, maintain adequate blood pressure, and enhance oxygen delivery to the tissue.[6,7] However, there are many controversial and unresolved issues about the most effective drugs. Although dopamine is the sympathomimetic amine most frequently used in newborn infants who are hypotensive and hypoxemic,[7] no clinical study supports the use of dopamine in PPHN. Moreover, concerns exist about the potential adverse effect of dopamine of raising pulmonary vascular resistance and pulmonary/systemic arterial pressure ratio.[8] In the same way, dobutamine has no or limited effects on systemic pressure, although it increases cardiac output.[9] Thus, particular clinical conditions may require the use of other vasoactive drugs.

Experimental studies in fetal lambs showed that norepinephrine may decrease the basal pulmonary vascular tone and elevate the pulmonary blood flow through the activation of α_2-adrenoceptors and NO release.[10,11] A pulmonary vasodilator response to norepinephrine was observed after acute hypoxia in isolated perfused lung in various models.[12,13] In newborn lambs with PPHN, norepinephrine improves post-natal circulatory adaptation at birth both by increasing systemic artery pressure and by increasing

DA	Ductus arteriosus	PPHN	Persistent pulmonary hypertension of the newborn
LPA_{Vel}	Left pulmonary artery blood flow velocity		
LVO	Left ventricular output	SAP	Systemic artery pressure
NO	Nitric oxide	SpO_2	Transcutaneous arterial oxygen saturation
PAP	Pulmonary artery pressure		

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pulmonary blood flow.[14] In adult patients with refractory pulmonary hypertension, norepinephrine was found to induce a dramatic drop in pulmonary vascular resistance and in pulmonary-to-systemic vascular resistance index ratio.[15]

The aim of this study was to evaluate the respiratory and the pulmonary circulatory effects of norepinephrine in newborn infants with PPHN-induced cardiac dysfunction.

METHODS

This observational prospective study was approved by the institutional research ethics committee of Amiens University Hospital. The study was conducted in the Neonatal Intensive Care Units of Lille's and Amiens' University Hospital, France. Newborn infants eligible for inclusion were: 1) >35 weeks' gestation and <1 month old; 2) admitted in the neonatal intensive care unit between Jan 1, 2005, and Dec 31, 2006; 3) received inhaled NO for severe respiratory failure and PPHN; 4) had symptoms of circulatory failure despite adequate fluid resuscitation; and 5) were mechanically ventilated and sedated. Circulatory failure was defined as systemic hypotension (mean systemic artery pressure [SAP] less than an infant's gestational age in weeks during the first 2 days of life, then SAP <10th percentile of the reference range for birth weight and postnatal age)[16] with at least 3 of these criteria for decreased perfusion: 1) tachycardia (heart rate >160 beats/min); 2) abnormal peripheral pulses; 3) modified coloration of the extremities; 4) prolonged capillary refill time >3 seconds; 5) urine output <1 mL/kg/h; 6) arterial plasma lactate concentration >2 mmol/L. Hypovolemia (assessed with echocardiographic measurement of ventricular kinetics and size) were treated before inclusion. Exclusion criteria were: 1) congenital structural heart disease, except patent ductus arteriosus; 2) cardiac arrest or terminal disease (transcutaneous arterial oxygen saturation [SpO_2] <60%; arterial pH <6.80; bradycardia <90 beats/min; no measurable blood pressure) before inclusion in the study; or 3) start of norepinephrine before inclusion in the study.

Norepinephrine (diluted in 5% dextrose to a concentration of 1 mL = 100 μg) was infused in a central catheter at an initial rate of 0.5 μg/kg/min. The rate of infusion was eventually increased every 30 minutes until the target SAP was obtained (Mean SAP higher than an infant's gestational age in weeks during the first 2 days of life, or mean SAP >10th percentile of the reference range for birth weight and postnatal age). Clinical, biological, and echocardiographic data were measured before and 1 hour after the normalization of mean SAP.

Inhaled NO concentration and ventilator settings were kept constant during the study period, except for the fraction of inspired oxygen, which was adjusted to maintain transcutaneous arterial oxygen saturation (SpO_2) between 92% and 97%. No change in fluid administration was performed during the study.

The following clinical and biological variables were recorded just before and 1 hour after the correction of hypotension: heart rate, mean SAP, pre- and post-ductal transcutaneous arterial oxygen saturations (pre- and post-ductal SpO_2) measured with pulse oxymetry, oxygen requirement and mean airway pressure, blood gas values, and plasma lactate concentrations. Echocardiographic data collection was carried out with a VIVID echocardiographic system with a high-frequency 7.5-MHz transducer (General Electric, Stockton, California). An average of 3 to 5 consecutive readings for the vessel diameter and flow velocity integrals was used. The angle of insonation was <20 degrees. These variables were collected: mean left pulmonary artery blood flow velocity (LPA_{Vel}), left ventricular shortening fraction, left ventricular output (LVO), end diastolic left ventricular diameter, DA diameter, maximal systolic and diastolic blood flow velocities in the DA (visualized in high left parasternal view on cross-sectional echocardiogram, and velocity was obtained with a pulsed-wave Doppler sample placed at the pulmonary end of the ductus). Mean LPA_{Vel} was used as an estimate of pulmonary blood flow.[17] Systolic and diastolic pulmonary artery pressures (PAP) were evaluated by measuring pressure gradients through the DA with the simplified Bernouilli formula.[8,18,19] In the case of bidirectional ductal shunting (right-to-left systolic shunting and left-to-right diastolic shunting), the systolic pressure gradient was added to the systolic systemic pressure to evaluate the systolic PAP, and the diastolic value was subtracted from the diastolic systemic pressure to evaluate the diastolic PAP. The mean PAP was then calculated as (systolic PAP + [2 x diastolic PAP]) / 3).[8]

Patient outcome was evaluated with ExtraCorporeal Membranous Oxygenation requirement and survival at discharge from the unit. Results were expressed as the mean ± SD, except as noted. Each infant was used as his or her own control. Data were analysed by using the $\chi 2$ test for categorical data. A Wilcoxon signed-rank test was used to compare paired data before and during norepinephrine infusion at the rate that allowed for the correction of the systemic hypotension. Serial data were analyzed by using repeated-measures and factorial analysis of variance (StatView for PC, SAS Institute, Cary, New Hampshire). Linear regression was used to assess the relationship between the baseline values of LVO and LPA_{Vel} and the percentage of change for these variables after starting norepinephrine. The significance level was set to $P < .05$.

RESULTS

Eighteen newborns were included in the study (mean gestational age, 37 ± 3 weeks; mean birth weight, 2800 ± 700 g). The mean Apgar score was 6 ± 3 and 8 ± 3 at 1 and 5 minutes after birth, respectively. Respiratory failure was caused by meconium aspiration syndrome in 2 cases, congenital diaphragmatic hernia in 6 cases, and early onset sepsis in 10 cases. The mean O_2 requirement was 51% ± 20% at the entry of the study. Each of the newborn infants required vascular expansion with saline or 10% albumin before inclusion (mean volume expansion, 35 ± 18 mL/kg). One infant received dobutamine at an infusion rate of 9 μg/kg/min before inclusion. High frequency oscillation ventilation was

Table I. Respiratory and pulmonary circulatory variables before and after starting norepinephrine infusion in 18 newborn infants with persistent pulmonary hypertension of the newborn and circulatory failure

	Before norepinephrine	After norepinephrine	*P* value
Mean airway pressure (cm H_20)	16 ± 4	16 ± 4	NS
FiO_2	51 ± 20	41 ± 20	<.01
iNO (ppm)	12 ± 7	12 ± 7	NS
Pre-ductal $SpO_{2\ (\%)}$	94 ± 4	95 ± 4	<.05
Post-ductal $SpO_{2\ (\%)}$	88 ± 2	95 ± 4	<.05
PH	7.32 ± 0.12	7.32 ± 0.09	NS
PCO_2 (mm Hg)	38 ± 10	40 ± 10	NS
Mean PAP (mm Hg)	33 ± 4	42 ± 5	<.001
Mean PAP/SAP ratio	0.98 ± 0.10	0.87 ± 0.10	<.001
Mean LPA_{Vel} (m/s)	0.30 ± 0.11	0.36 ± 0.09	<.05

Norepinephrine infusion was associated with a decrease in the O_2 need and in the mean PAP/SAP ratio and an increase in the mean LPA_{Vel}.
Results are shown as mean ± SD.
iNO, inhaled nitric oxide; *pre- and post-SpO_2,* pre- and post-ductal transcutaneous arterial oxygen saturations.

used in 11 infants. Just before starting norepinephrine infusion, mean SAP and PAP were respectively 33 ± 4 and 33 ± 4 mm Hg, and mean heart rate was 139 ± 23 beats/min. The mean urine output was <1 mL/kg/h during the 3 hours before the norepinephrine infusion, except in 1 infant. Prolonged capillary refill time (> 3 seconds) was found in 16 infants before treatment. The direction of the shunt through DA was bidirectional in 15 infants and unidirectional right-to-left in 3 infants. Furthermore, the mean arterial pH was 7.32 ± 0.12, and the mean arterial lactate concentration was 3.5 ± 1.7 mmol/L.

The initial norepinephrine infusion rate was 0.5 μg/kg/min. The norepinephrine infusion rate had to be increased to 0.75 μg/kg/min in 1 infant, and to 1.0 μg/kg/min in 3 infants to reach the target SAP. The median duration of norepinephrine use was 50 ± 26 hours (range, 18-103 hours).

After starting norepinephrine infusion, the mean SAP increased from 33 ± 4 to 49 ± 4 mm Hg ($P < .05$), whereas the heart rate did not change significantly (before 139 ± 23 versus after 142 ± 16 beats/min; $P = .20$). Either systolic SAP (before 47 ± 7 versus after 63 ± 7 mm Hg; $P < .001$) and diastolic SAP (before 27 ± 4 versus after 41 ± 5 mm Hg; $P < .001$) increased significantly after starting norepinephrine. LVO increased by 22% (before 172 ± 79 versus after 209 ± 90 mL/kg/min; $P < .05$). End diastolic left ventricular diameter increased from 12 ± 4 mm to 13 ± 4 mm ($P < .05$). Cerebral and mesenteric resistance index decreased from 0.81 ± 0.11 to 0.67 ± 0.14, and from 0.76 ± 0.09 to 0.67 ± 0.09 respectively ($P < .05$). The median urine output increased from 0.7 mL/kg/h (range, 0-1.4) during the 3 hours before the norepinephrine infusion, to 1.5 mL/kg/h (range, 0-2.4) during the 3 hours after the beginning of treatment ($P < .05$). The plasma lactate concentration did not change significantly after starting infusion of norepinephrine (before 3.5 ± 1.7 versus after 3.0 ± 1.6 mmol/L; $P = .06$).

The O_2 need decreased from 51% ± 20% to 41% ± 20%, whereas pre- and post-ductal SpO_2 increased 2 hours after starting norepinephrine ($P < .05$; Table I). The mean airway pressure and the blood gas variables did not change (Table I). The mean PAP increased from 33 ± 4 mm Hg to 42 ± 5 mm Hg ($P < .001$; Table I). Mean PAP/SAP ratio decreased from 0.98 ± 0.10 to 0.87 ± 0.10 ($P < .001$; Figure 1; Table I). Mean LPA_{Vel} increased by 20% ($P < .05$; Figure 2; Table I). The rise in mean LPA_{Vel} was inversely correlated to the value before norepinephrine infusion (Figure 3). After starting norepinephrine, the direction of DA shunting switched from bidirectional to exclusive left-to-right in 8 infants. DA diameter did not change (before 3.0 ± 0.7 mm versus after 3.2 ± 0.9 mm; $P = .27$).

After pre- and post-treatment data recordings, further serial recordings of the clinical variables showed a progressive decrease in the median O_2 need (at H6, 38% [25-80]; at H24, 31% [23-80]; at H48, 27% [21-60]; at H72, 25%[21-60]; $P < .05$), an increase in median urine output (at H6, 1.4 mL/kg/h [0-2.1]; at H24, 1.7 mL/kg/h [0.8-2.4]; at H48, 2.1 mL/kg/h [1.1-3.2]; at H72, 2.7 mL/kg/h [1.6-3.9]; $P < .05$). Mean systemic artery pressure remained higher than the target pressure during the period of norepinephrine infusion. Three newborn infants required further increase in norepinephrine infusion rate (from 0.75 μg/kg/min to a maximum of 3.3 μg/kg/min), and 1 infant required an additional fluid loading to maintain the target systemic artery pressure. Median plasma lactate concentrations were 2.6 mmol/L (range, 1.7-8) at H6, and 1.9 mmol/L (range, 0.9-7) at H24. No ischemic distal lesion was observed during norepinephrine infusion. No infant required ExtraCorporeal Membranous Oxygenation for PPHN. All the included newborn infants were alive at the discharge of the unit.

DISCUSSION

The purpose of this observational study was to investigate the respiratory and the hemodynamic effects of norepinephrine in newborn infants with PPHN and circulatory failure. Although the mechanical ventilatory settings were not changed, we found that the use of norepinephrine was associated with a significant decrease in the oxygen requirement. Despite a rise in both pulmonary and systemic artery pressure, the PAP/SAP ratio decreased after starting norepinephrine.

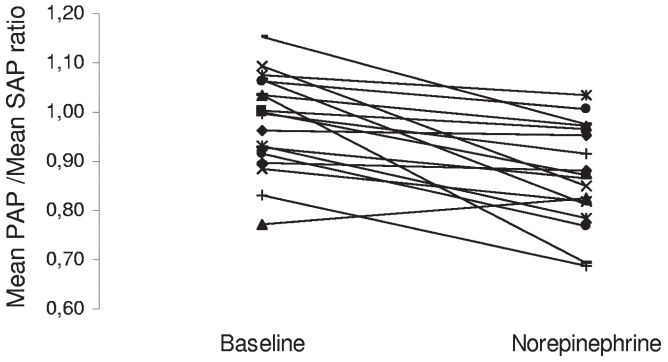

Figure 1. Mean pulmonary artery pressure over mean systemic artery pressure ratio before and after starting norepinephrine infusion in 18 newborn infants with PPHN and circulatory failure. Norepinephrine infusion was associated with a decrease in mean PAP/SAP ratio (from 0.98 ± 0.10 to 0.87 ± 0.10; $P < .001$).

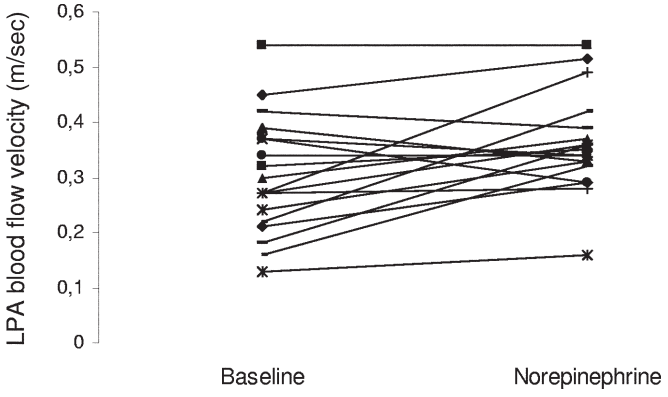

Figure 2. Individuals' left pulmonary artery (*LPA*) blood flow velocity before and after starting norepinephrine in 18 newborn infants with PPHN and circulatory failure. The median ± interquartile LPA blood flow velocity increased from 0.27 ± 0.16 m/sec to 0.35 ± 0.07 m/sec ($P < .05$).

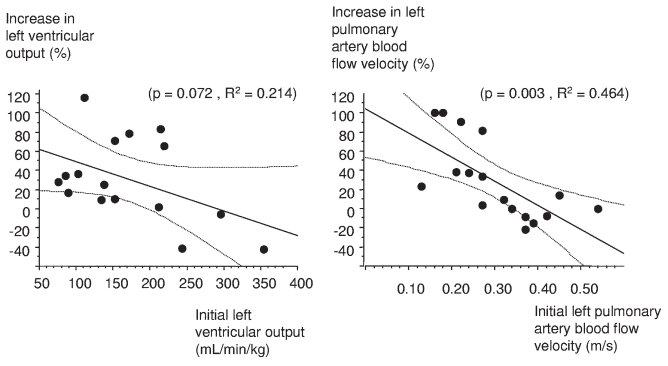

Figure 3. LVO (*left panel*) and LPA_{Vel} (*right panel*) before and after starting norepinephrine. Lower is the baseline LPA_{Vel}, greater is the response to norepinephrine ($P < .05$).

The increase in the blood flow velocity in the left pulmonary artery, in the end-diastolic diameter of the left ventricle, and in the LVO suggests that norepinephrine may improve lung function in PPHN through elevation in the pulmonary blood flow and improve cardiac performance.

We found that norepinephrine elevated both systemic and pulmonary artery pressures. Norepinephrine was found to increase systemic arterial blood pressure, cardiac output, oxygen delivery, and regional blood flow including mesenteric and renal blood flow in adult septic shock.[20-23] Furthermore, a pulmonary vasodilator response to norepinephrine has been shown, in animal studies[10,12-14,24] and in human studies.[15] This data provide additional evidence for potential beneficial effects of norepinephrine in PPHN. The rise in PAP was lower than SAP, because the PAP/SAP ratio decreased after starting norepinephrine. A drop in the PAP/SAP ratio explains why the direction of DA shunting changed in half the included infants after starting norepinephrine. Moreover, increases in the LPA_{Vel}, in the end diastolic left ventricular diameter, and in the LVO indicate that norepinephrine may increase pulmonary blood flow. Indeed, both the end diastolic left ventricular diameter and the LVO are related, at least in part, to the pulmonary venous flow. The increase in the pulmonary blood flow may result from elevation of the left-to-right part of the shunting across the DA. We also found that norepinephrine infusion was associated with a decrease in the O_2 need. Because the mechanical ventilatory settings and the blood gases did not change during the study, the decrease in the O_2 need observed after starting norepinephrine was caused neither by change in lung recruitment or ventilation nor by a change in pH/$PaCO_2$-induced alteration in pulmonary circulation. Taken together, these data suggest that improvement in the O_2 requirement after starting norepinephrine resulted from decreased PAP/SAP ratio and right-to-left shunting and from an elevation in pulmonary blood flow. No earlier study on the effect of norepinephrine has been reported in newborn infants, except in a single case report.[25] In this study, no ischemic distal lesion was observed during norepinephrine administration. Furthermore, urine output increased and cerebral and mesenteric resistance index decreased after starting norepinephrine, supporting the hypothesis that norepinephrine may improve tissue perfusion and oxygenation. Thus, our data show that norepinephrine may raise perfusion pressure, and may improve lung function in newborn infants with PPHN and circulatory failure.

Several potential mechanisms may explain the beneficial effect of norepinephrine in newborn infants with PPHN and cardiac failure. First, increased right ventricular afterload may impair cardiac output and alter perfusion pressure in newborn infants with PPHN.[3,4] Mechanisms may include leftward shift of the interventricular septum impairing the left ventricular filling, decreased left ventricular preload resulting from decreased pulmonary venous flow, and/or decreased coronary artery perfusion resulting from increased right ventricular transmural pressure.[26] Norepinephrine activates both α (α_1 and α_2) and β_1-adrenoceptors. Alpha-adrenoceptors participate in the sympathetically mediated vasoconstriction.[27] Activation of β_1-adrenoceptors increases cardiac contractility and cardiac output.[27] Both α_1- and β_1-adrenoceptors activa-

tion explain the increase in systemic pressure observed in our study. In adult dogs with acute right ventricular hypertension, an elevation of aortic pressure was found to reverse right ventricular failure by restoring right coronary flow.[26] In newborn piglets with right ventricular hypertension, an elevation in systemic arterial blood pressure reduced right to left foramen ovale shunt and increased pulmonary blood flow and systemic O_2 delivery.[28] Our data are consistent with these studies because the increase in the systemic artery pressure during norepinephrine infusion was associated with an increase in LVO and a decrease in the O_2 need, suggesting that a norepinephrine-induced rise in aortic pressure may be associated with improvement of PPHN-induced cardiac dysfunction. Second, PPHN is characterized by a sustained elevation of pulmonary vascular resistance, causing extrapulmonary right-to-left shunting of blood across the DA and foramen ovale and hypoxemia. Several lines of evidence suggest that norepinephrine may induce a vasodilation in the perinatal lung. A pulmonary vasodilator response to norepinephrine has been observed in several pulmonary hypertensive animal models.[12,13,24] Moreover, norepinephrine induces a NO-dependent pulmonary vasodilation in the ovine fetus through activation of α_2-adrenoceptors.[10,11] Compared with dopamine, norepinephrine has the additional ability to activate vascular α_2-adrenoceptors.[11,29,30] Our results support the hypothesis that norepinephrine may have pulmonary vasodilator properties, as the LPA_{Vel}, the end diastolic left ventricular volume, and the LVO increased after starting norepinephrine infusion. In the *in vitro* studies, preconstriction of the pulmonary vessels was clearly a prerequisite for the norepinephrine to induce pulmonary vessels relaxation.[12,13,24] We speculate that the more elevated the basal pulmonary vascular tone is, the greater the norepinephrine-induced pulmonary vasodilation would be. Our results support this hypothesis because the change in the LPA_{Vel} was enhanced in the newborns with the lowest basal LPA_{Vel}.

This prospective observational study indicates that norepinephrine can reduce O_2 requirement and normalize the systemic artery pressure in newborn infants with PPHN-induced cardiac dysfunction. We speculate that norepinephrine-improved lung function in PPHN results from an improved cardiac performance through increased systemic pressure and increased pulmonary blood flow.[16]

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