Hypotension in Preterm Infants with Significant Patent Ductus Arteriosus: Effects of Dopamine

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Objective To study the effects of dopamine on systemic arterial pressure (SAP) and systemic blood flow (SBF) (estimated with the superior vena cava [SVC] flow) in preterm infants with hypotension and patent ductus arteriosus (PDA).

Study design Clinical and echocardiographic variables were measured before and 2 hours after starting dopamine in premature infants <32 weeks gestational age with PDA and systemic hypotension.

Results Seventeen premature infants were included (gestational age, 28±2 weeks; birth weight, 1030 ± 400 g). A mean rate of 8 ± 2 μg/kg/min of dopamine raised SAP from 30 ± 3 to 41 ± 5 mm Hg ($P < .05$), and the pulmonary artery pressures from 25 ± 5 to 32 ± 8 mm Hg ($P < .05$). The SVC flow increased by 30% (from 130 ± 40 to 170 ± 44 mL/kg/min; $P < .05$). The left ventricular output and the end-diastolic and mean left pulmonary artery blood flow velocities did not change despite the increase in pulmonary artery pressure.

Conclusion In preterm infants with hypotension and PDA, dopamine (<10 μg/kg/min) increases the systemic blood pressure and the systemic blood flow. Our results suggest that dopamine decreases left-to-right shunting across ductus arteriosus, caused by a rise in pulmonary vascular resistances. *(J Pediatr 2008;153:790-4)*

The incidence of patent ductus arteriosus (PDA) in preterm infants ranges from 20% to 60%, depending on the diagnostic criteria used and the population studied.[1-2] Significant left-to-right shunting across the DA in premature infants is associated with increased morbidity, such as intraventricular hemorrhage, necrotizing enterocolitis, kidney injury, heart failure, and chronic lung disease.[3-7] Proposed mechanisms include decreased systemic artery pressure, decreased peripheral organ perfusion, and increased pulmonary perfusion. The risk of adverse outcomes depends, at least in part, on the level of the systemic vascular steal through the ductus arteriosus (DA). The ductal flow is proportional to the DA diameter and to the imbalance between the systemic and pulmonary vascular resistances (SVR/PVR).[8]

Hemodynamically significant PDA is generally treated with medical or surgical treatment.[9] However, symptoms of poor tolerance such as systemic hypotension and respiratory or renal failure may occur despite starting the medical treatment for ductal closure. There are still many controversial and unresolved issues about the effectiveness of additional medical treatment. Although not evidence-based, fluid restriction, correction of anemia with red blood cell transfusion, and prevention from respiratory alkalosis-induced drop in PVR have been proposed in the preterm infant with significant PDA.[9,10] There are no data to support the use of inotropic/vasopressor agents in the preterm infant with symptomatic PDA.[10]

Dopamine is widely used in neonates with circulatory failure.[11-13] Growing evidence suggests that dopamine has the potential to raise the pulmonary vascular resistance and the pulmonary artery pressure in some newborns.[14,15] In symptomatic PDA, an increase in the pulmonary vascular resistance may reduce the left-to-right shunting and the systemic vascular steal across DA.

We hypothesized that dopamine increases the systemic blood flow through the elevation in pulmonary vascular resistance in premature infants with significant PDA.

DA	Ductus arteriosus	SAP	Systemic arterial pressure
LA: Ao	Left atrial /aortic root ratio	SBF	Systemic blood flow
PAP	Pulmonary artery pressures	SpO_2	Oxygen saturation
PDA	Patent ductus arteriosus	SVC	Superior vena cava
PVR	Pulmonary vascular resistance	SVR	Systemic vascular resistances

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The authors declare no conflicts of interest.

Submitted for publication Jan 2, 2008; last revision received May 8, 2008; accepted Jun 17, 2008.

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0022-3476/$ - see front matter

10.1016/j.jpeds.2008.06.014

METHODS

We conducted an observational prospective study in the neonatal intensive care units of the University Hospitals of Lille (France), between March 2006 and March 2007. The study was approved by the Institutional Research Ethics Committee. Because the present protocol was part of the usual treatment of premature newborn infants in our neonatal intensive care unit, no written consent was required, but all parents were informed and provided their oral consent to inclusion in the study.

Newborns eligible for inclusion were preterm infants born before 32 weeks of gestation with a large left-to-right shunt across the PDA and systemic hypotension. Other etiologies of systemic hypotension, such as sepsis and congenital heart diseases, were exclusion criteria.

Significant left-to-right shunting through the DA was defined by the detection of at least 4 of these 6 echocardiographic criteria[8]: ductal diameter (B mode and color Doppler) ≥1.4 mm/kg; left atrial /aortic root ratio (LA: Ao) ≥1.4; pulsatile low blood flow velocity in the DA (maximal ductal blood flow velocity <1.5 m/s); mean and an end-diastolic blood flow velocities in the left pulmonary artery ≥0.45 m/s and ≥0.20 m/sec, respectively; and low or retrograde diastolic flow in the middle cerebral and superior mesenteric arteries. Systemic hypotension was defined as a mean systemic artery pressure (SAP) lower than the infant's gestational age (expressed in weeks) during the first 2 days after birth, or mean SAP <10th percentile of the reference range for birth weight and postnatal age.[16,17]

On the basis of the aforementioned criteria, significant PDA was treated with intravenous Ibuprofen (Pedea Orphan Europe; loading dose of 10 mg/kg; then 2 maintenance doses of 5 mg/kg at 24-hour intervals). Additional medical treatment included special care to prevent a respiratory alkalosis-induced drop in PVR, fluid restriction, and the correction of anemia with red blood cell transfusion.[10]

Dopamine was infused for persistent systemic hypotension. Dopamine (diluted in 5% dextrose to a concentration of 1 mL = 1000 μg) was infused in a central catheter at an initial rate of 5 μg/kg/min. The rate of infusion was increased every 30 minutes until the mean SAP was higher than the target SAP. Clinical, biological, and echocardiographic data were recorded before and 2 hours after the normalization of the mean SAP. The ventilator settings were kept constant during the study period, except for the FiO_2, which was adjusted to maintain transcutaneous oxygen saturation (SpO_2) between 88% and 94%. The rate of fluid administration was not changed during the study period.

These clinical and biological variables were recorded: heart rate, SAP, SpO_2, oxygen requirement and mean airways pressure, blood gas values, and plasma lactate concentrations. Urine output was collected the 12 hours before and after starting dopamine.

Echocardiographic data were collected by using a General Electric VIVID echocardiographic system (GE Healthcare, Buckinghamshire, UK) with a high-frequency 10-MHz transducer. Measurements were performed by the same investigator immediately before and 2 hours after the normalization of mean SAP. An average of 3 to 5 consecutive readings for the vessel diameter and flow velocity integrals was used. The angle of insonation was less than 20°. These Doppler echocardiographic variables were measured: 1) LA:Ao, from a parasternal long axis view; 2) internal diameter of the DA (mm/kg) with both B mode and color Doppler ultrasound scanning were obtained from the high left parasternal view[8]; 3) Mean and end diastolic blood flow velocities of the left pulmonary artery were measured with pulsed Doppler ultrasound scanning by using a high left parasternal view; 4) left ventricular output was obtained from subaortic diameter of the tract measured from a parasternal long axis view by using the leading edge technique; flow velocity time integral was measured from the apical view with the sample volume placed in the left ventricular output and the heart rate measured from peak to peak intervals of the Doppler velocity time signals; 5) superior vena cava (SVC) flow was measured as previously described[18]; because of the variation in the vessel diameter through the cardiac cycle, a mean of the maximum and minimum diameter within 10 cardiac cycles was used to calculate the flow; the flow was imaged from a low subcostal view; the Doppler sample volume was placed at the junction of the SVC and right atrium. SVC flow value was calculated as: SVC flow (mL/kg/min) = (velocity time integral × [π × (mean SVC diameter^2/4) × heart rate])/ body weight; 6) blood flow velocities in the middle cerebral artery and superior mesenteric artery were imaged and the resistance index was calculated (RI = [systolic blood flow velocity − diastolic blood flow velocity) / systolic blood flow velocity); and 7) systolic and diastolic pulmonary artery pressures (PAP) were evaluated by measuring pressure gradient through the DA by using the simplified Bernoulli formula,[19,20] subtracted from systolic and diastolic systemic arterial pressures. The mean pulmonary arterial pressure was calculated as: PAP = (systolic PAP + [2 × diastolic PAP]) / 3.

Results were expressed as means ± SD. Each included infant was used as his or her own control. A Wilcoxon signed-rank test was used to compare paired data before and during the dopamine infusion at the rate that allowed correction of the systemic hypotension. *P* values <.05 were consideredn to be significant.

RESULTS

Seventeen premature infants were included in the study. The mean gestational age and birth weight were 28 ± 2 weeks and 1030 ± 400 g, respectively. The median postnatal age at enrollment was 5 days (range, 1-25 days). The infants received a mean fluid intake of 110 ± 35 mL/kg/day at the entry of the study. Respiratory support was mechanical ventilation (n = 5), nasal CPAP (Infant-Flow driver; n = 9), or nasal cannula (n = 3) with a median O_2 need of 21% (range, 21%-40%). A mild respiratory acidosis was found on the baseline blood gases (Table I). Basal mean SAP was 30 ± 3 mm Hg at inclusion. Basal urine output was 1.9 mL/kg/hour.

Table I. Clinical and biological variables before and 2 hours after starting dopamine infusion in premature infants with significant patent ductus arteriosus (n = 17)

	Baseline	After starting dopamine	*P* value
Heart rate (bpm)	148 ± 11	160 ± 12	<.001
FiO_2 (%)	21 (21-40)	21 (21-40)	NS
SaO_2(%)	96 ± 3	96 ± 3	NS
pH	7.26 ± 0.1	7.25 ± 0.1	NS
$PaCO_2$(mm Hg)	47 ± 11	48 ± 9	NS
Systolic SAP (mm Hg)	47 ± 8	57 ± 9	<.001
Diastolic SAP (mm Hg)	21 ± 4	31 ± 6	<.001
Mean SAP (mm Hg)	30 ± 3	41 ± 5	<.001

Dopamine was associated with an increase in heart rate and mean SAP.
Values are expressed as mean ± SD, except FiO_2expressed as median and range.
NS, Not significant.

Doppler echocardiographic markers for a large left-to-right shunting through the DA were found in each included infant (Table II). A mean dopamine infusion rate of 8 ± 2 μg/kg/min was required to raise the mean SAP higher than the target value (from 30 ± 3 to 41 ± 5 mm Hg; $P < .05$; Figure). All the newborns had an increase in blood pressure 2 hours after starting Dopamine infusion.

The O_2 need and the blood gas values did not change after starting the dopamine infusion (Table I). Despite an increase in heart rate by 8% (95% CI, 3%-13%; $P < .05$), the left ventricular output did not change after starting treatment (340 ± 89 versus 340 ± 107 mL/kg/min; Table II). Dopamine infusion was associated with an increase in SVC flow by 30% (95% CI, 7%-51%; from 130 ± 40 to 170 ± 44 mL/kg/min; $P < .05$; Table II). DA diameter did not change after starting Dopamine infusion (2.6 ± 1.1 versus 2.7 ± 1.2 mm/kg). LA:AO and the left ventricular shortening fraction did not change significantly.

Mean PAP increased by 31% (95% CI, 7-54) from 25 ± 5 to 32 ± 8 mm Hg ($P < .05$), without change in end-diastolic or mean blood flow velocities in the left pulmonary artery (respectively, 0.26 ± 0.09 versus 0.27 ± 0.09 m/sec and 0.64 ± 0.24 versus 0.63 ± 0.19 m/sec). Mean PAP over mean blood flow velocity in the LPA ratio, used as an index of pulmonary vascular resistance, increased by 35% (95% CI, 9%-57%; $P < .05$).

Mean mesenteric and cerebral artery resistance index decreased from 0.95 ± 0.15 to 0.83 ± 0.17 and from 0.92 ± 0.20 to 0.77 ± 0.18, respectively, after starting treatment ($P < .05$). Before starting dopamine, 13 of 17 infants had a resistance index >0.90 with low or retrograde diastolic blood flow velocity in the cerebral artery, superior mesenteric artery, or both. After starting dopamine, 5 of 17 infants had a resistance index >0.90. Urine output increased from 1.9 ± 1.2 to 2.9 ± 1.4 mL/kg/h ($P < .05$). A trend in decreased plasma lactate concentration was found during the study period (reference range for plasma lactate concentrations, <2 mmol/L at our institution).

Table II. Echocardiographic variables before and 2 hours after starting dopamine in premature newborn infants with systemic hypotension and significant patent ductus arteriosus (n = 17)

	Baseline	After starting dopamine	*P* value
DA diameter (mm/kg)	2.6 ± 1.1	2.7 ± 1.2	NS
Mean PAP (mm Hg)	25 ± 5	32 ± 8	<0.001
LPA mean blood flow velocity (m/sec)	0.64 ± 0.24	0.63 ± 0.19	NS
End-diastolic LPA blood flow velocity (m/sec)	0.26 ± 0.09	0.27 ± 0.09	NS
Mean PAP/LPA mean blood flow velocity ratio	42 ± 13	55 ± 19	<0.001
LA/Ao ratio	1.71 ± 0.3	1.67 ± 0.3	NS
LV shortening fraction (%)	39 ± 7	39 ± 9	NS
LV Output (ml/kg/min)	340 ± 89	340 ± 107	NS
SVC flow (ml/kg/min)	130 ± 40	170 ± 44	0.002
Mesenteric artery RI	0.95 ± 0.15	0.83 ± 0.17	0.05
Cerebral artery RI	0.92 ± 0.20	0.77 ± 0.18	0.004
Lactate (mmol/L; reference range <2 mmol/L)	1.8 ± 1.5	1.4 ± 1.1	0.055

Dopamine infusion was associated with an increase in mean PAP and an increase in SVC flow, whereas the left pulmonary artery blood flow velocities did not change.
Values are expressed as means ± SD.
LPA, Left pulmonary artery; *LA/Ao ratio,* left atrium/aorta ratio; *LV,* left ventricle; *RI,* resistance index.

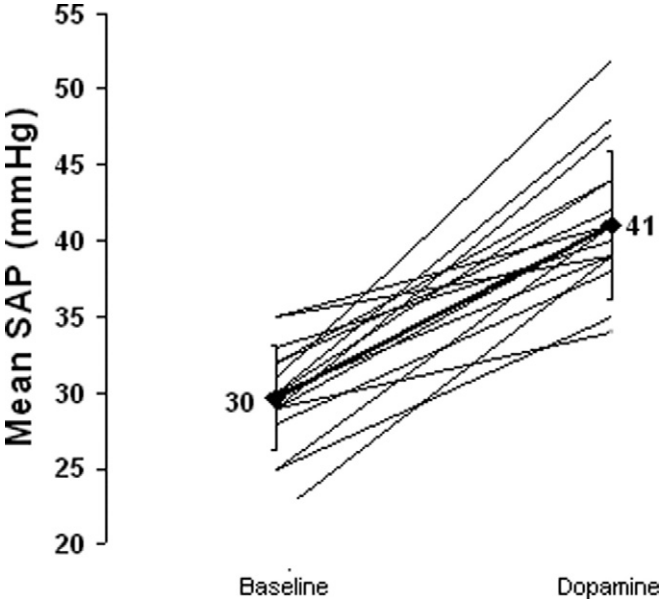

Figure. Median ± IQ (*black dots*) and individual mean SAP in 17 premature newborn infants with hypotension and significant PDA, before and 2 hours after starting Dopamine ($P < .05$).

DISCUSSION

We found that dopamine infusion was associated with an increase in SAP and in SVC flow. The left ventricular

output did not change during the study period. These results suggest that dopamine increased the SBF and reduced the left-to-right shunting through the DA. Furthermore, we found that the left pulmonary artery blood flow velocity did not change despite an increase in PAP. Taken together, our results support the hypothesis that dopamine increases the systemic blood flow in preterm infants with PDA-induced systemic hypotension through elevation in pulmonary vascular resistances, resulting in a drop in the left-to-right shunting across the DA.

This is evidence to support the use of inotropic/vasopressor agents in the preterm infant with symptomatic PDA. We showed that dopamine not only increases SBP, but also elevates SVC flow. SVC flow represents the blood flow returning to the heart from the upper part of the body. Thus, it helps to evaluate the cardiac input which is not influenced by either ductal or atrial shunting.[18] The decrease in mesenteric and cerebral artery resistance index (ie, an increase in diastolic arterial flow) and the increase in urine output provide additional evidence for an increase in tissue perfusion and oxygenation with dopamine.

Dopamine-induced elevation in a SBF could result from either an increase in left ventricular outflow, or a decrease in left-to-right shunting through the DA. The left ventricular output, left atrium/aorta ratio, and left ventricular function did not change after starting dopamine. Thus, the increase in SBF results from a decrease in ductal flow. In accordance with this hypothesis, the mean and end-diastolic left pulmonary artery blood flow velocities, the left atrium/aorta ratio, and the left ventricular output did not change during the study period, suggesting that dopamine did not alter either the pulmonary blood flow or the pulmonary venous return. In the same way, lack of change in the left pulmonary artery blood flow velocities despite an increase in systemic blood flow (ie, an increase in venous return to the right atrium and an increase in right ventricular output) further suggest that dopamine decreased left-to-right shunting across the DA.

The mechanisms by which dopamine reduces left-to-right shunting across the DA remain speculative. Blood shunting through the DA is proportional to the DA diameter and to the balance between vascular resistances in both sides of the DA. As ductal diameter was not altered with dopamine, dopamine may have modified the balance between pulmonary and systemic vascular resistances. Previous experimental and clinical studies have shown that dopamine has the potential to raise the pulmonary vascular resistance and the PAP in the newborn. Dopamine elevates pulmonary vascular resistance in fetal lambs, in newborn goats, and in adult dogs.[14,21,22] In preterm infants with hypertension and PDA, dopamine increases the PAP/SAP ratio.[15] Our data showed that dopamine elevated the PAP without changing the left pulmonary artery blood flow velocities. The finding that the PAP/pulmonary artery blood flow velocities ratio increased after starting dopamine strongly support the hypothesis that dopamine increased the pulmonary vascular resistance. This change was not explained by a modification in ventilation management or blood gases.

The study has some limitations. PAP was assessed by measuring pressure gradient through the DA. This method has not been rigorously validated in the population of preterm infants. However, a good correlation was reported between tricuspid regurgitant Doppler velocity and PAP measured with transductal gradient pressure in the newborn infant.[19] In children with various types of aortic-pulmonary shunts (some had PDA), measurement of PAP with the pressure drop across the shunt was found highly correlated with invasive measurements.[23] Our data provide evidence for a pulmonary vasoconstrictor effect of dopamine in preterm infants with PDA; however, there is no information at present that dopamine administration results in clinically relevant and significant increases in PAP in preterm or term neonates without significant left to right shunting across the PDA. Despite the large left-to-right shunting across the PDA causing systemic hypotension, no evidence for inappropriate organ perfusion before dopamine treatment was found in this study. In particular, SVC flow was slightly higher than the values reported earlier in preterm infants with PDA.[18] In a recent study, a large ductal shunt in a preterm infant was not associated with decreased SVC flow during the first 2 days after birth, suggesting that upper body perfusion may be preserved despite large left-to-right shunting across the PDA.[24] Evidence exists that SVC flow increases from day 1 to day 2 after birth.[18] In this study, the median postnatal age at enrollment was 5 days. No reference range for SVC flow has been reported in preterm infants after the third day after birth. Thus, whether or not basal SVC flow was normal in our population is difficult to assess. However, dopamine increased SVC flow in our population of preterm infants with large left-to-right shunting across PDA. High resistance index in the cerebral artery and superior mesenteric artery suggests that the regional vascular resistance was not decreased in the studied population. However, a distributive shock cannot be excluded, because we did not measure systemic vascular resistance. Thus, dopamine-induced elevation in a SBP could result from both an increase in SBF and systemic vascular resistances. Evidence exists that high doses of dopamine (20 μg/kg/min) increase left ventricular afterload and left ventricular stress.[25] Although we found that a low infusion rate of dopamine ($<$10 μg/kg/min) increases SBF, we cannot exclude that higher doses may have adverse effects.

Our study indicates that dopamine infusion can raise the SAP and the SBF in preterm infants with PDA-induced hypotension. We speculate that dopamine improves tissue perfusion through an increase in the pulmonary vascular resistance and a decrease in the ductal flow in the preterm infant with significant PDA.

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