Hemodynamic Effects of Fluid Restriction in Preterm Infants with Significant Patent Ductus Arteriosus

Julie De Buyst, MD[1], Thameur Rakza, MD[2,3], Thomas Pennaforte, MD[2], Anne-Britt Johansson, MD[1], and Laurent Storme, MD[2,3]

Objective To determine the hemodynamic impact of fluid restriction in preterm newborns with significant patent ductus arteriosus.

Study design Newborns ≥24 and <32 weeks' gestational age with significant patent ductus arteriosus were eligible for this prospective multicenter observational study. We recorded hemodynamic and Doppler echocardiographic variables before and 24 hours after fluid restriction.

Results Eighteen newborns were included (gestational age 24.8 ± 1.1 weeks, birth weight 850 ± 180 g). Fluid intake was decreased from 145 ± 15 to 108 ± 10 mL/kg/d. Respiratory variables, fraction of inspired oxygen, blood gas values, ductus arteriosus diameter, blood flow-velocities in ductus arteriosus, in the left pulmonary artery and in the ascending aorta, and the left atrial/aortic root ratio were unchanged after fluid restriction. Although systemic blood pressure did not change, blood flow in the superior vena cava decreased from 105 ± 40 to 61 ± 25 mL/kg/min ($P <$ .001). The mean blood flow-velocity in the superior mesenteric artery was lower 24 hours after starting fluid restriction.

Conclusions Our results do not support the hypothesis that fluid restriction has beneficial effects on pulmonary or systemic hemodynamics in preterm newborns. *(J Pediatr 2012;161:404-8)*.

The incidence of patent ductus arteriosus (PDA) ranges from 55% to 70% in extremely low birth weight infants.[1,2] Several studies reported an association between PDA and major complications of prematurity including bronchopulmonary dysplasia,[3-5] intraventricular hemorrhage,[6,7] and necrotizing enterocolitis .[8-10] There are still many controversial and unresolved issues regarding the management of significant PDA.[11-14] Correction of anemia with red blood cell transfusion and avoidance of a respiratory alkalosis–induced drop in pulmonary vascular resistance (PVR) have been proposed to prevent excessive left-to-right shunting through ductus arteriosus (DA) and overload of the pulmonary circulation.[2,11] Although fluid restriction with PDA has been widely recommended,[12,14-16] its benefit-to-risk ratio has not been systematically assessed. A large left-to-right shunt across PDA causes a systemic circulatory steal toward the pulmonary circulation, resulting in both a decrease in systemic blood flow and an overload of the pulmonary circulation, which in turn may cause pulmonary edema and respiratory failure. Fluid restriction may decrease circulating blood volume and the overload of the pulmonary circulation that in turn may improve the respiratory function. A decreased fluid intake in the first few days after birth decreased the occurrence of PDA and the risk of bronchopulmonary dysplasia.[17] Alternatively, fluid restriction may result in a decrease in left ventricular outflow through a decrease in left ventricle preload that in turn may cause a reduction in systemic blood flow. However, the actual hemodynamic effects of fluid restriction have not been systematically explored in the preterm infants with significant PDA.

Therefore, we performed serial echocardiographic measurements of pulmonary and systemic hemodynamics before and 24 hours after starting fluid restriction (ECHO 2) in a prospective observational multicenter study of preterm infants with significant PDA. Systemic blood flow was estimated by measuring the superior vena cava (SVC) blood flow.[18]

Methods

The study was conducted in the 2 neonatal intensive care units (NICUs) of Lille University Hospital, France, and of Brussels University Children Hospital Reine Fabiola, Belgium, between August 31, 2009, and August 31, 2011. The study was approved

CPAP	Continuous positive airway pressure	LPA	Left pulmonary artery
DA	Ductus arteriosus	MCA	Middle cerebral artery
ECHO 1	Superior vena cava flow measured before starting fluid restriction	NICU	Neonatal intensive care unit
		PDA	Patent ductus arteriosus
		PVR	Pulmonary vascular resistance
ECHO 2	Superior vena cava flow measured 24 hours after starting fluid restriction	RI	Resistance index
		SVC	Superior vena cava
		SVR	Systemic vascular resistance
LA:Ao	Left atrial/aortic root ratio		

From the [1]Neonatal Intensive Care Unit, Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium; [2]Pôle Femme Mère Nouveau-né, Hôpital Jeanne De Flandre, CHRU Lille, Lille, France; and [3]UPRES EA4489, Faculté de Médecine, IFR 114, Université de Lille 2, Lille, France

The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2012.03.012

by the Institutional Research Ethics Committee. Informed consent was obtained from the parents.

Newborns eligible for inclusion have: (1) a gestational age ≥24 weeks and <32 weeks; (2) >10 days after birth; (3) ≥1 clinical symptom attributable to significant PDA (ie, respiratory failure requiring supplemental O_2, continuous positive airway pressure (CPAP) or mechanical ventilation, hypotension defined by a mean arterial pressure <35 mm Hg, intestinal ileus, cardiac/thoracic ratio >0.6 on the chest radiograph); (4) significant left-to-right shunting through the DA defined by the detection of the following concomitant 4 echocardiographic criteria (ie, ductal diameter [B mode and color Doppler] >1.5 mm/kg,[12] left atrial/aortic root ratio [LA:Ao] >1.4,[19,20] pulsatile low blood flow-velocity in the DA, end-diastolic blood flow-velocity of the left pulmonary artery [LPA] >0.20 m/s); and (5) failure of 2 successive courses of intravenous ibuprofen (Pedea Orphan Europe [Paris, France] loading dose of 10 mg/kg then 2 maintenance doses of 5 mg/kg at 24-hour intervals).

Exclusion criteria included: (1) congenital structural heart disease; (2) poor hemodynamic tolerance requiring infusion of catecholamine; (3) hypernatremia ≥145 mEq/L; (4) fluid restriction before inclusion; and (5) renal failure defined by creatinine >8 mg/L.

The infants were referred to the NICU for echocardiographic evaluation and possible surgical closure of the DA. The total fluid intake was between 140 and 160 mL/kg/d (as usual in our NICUs) for ≥24 hours and then was decreased to 100-120 mL/kg/d (fluid restriction). Fluid restriction is part of the routine care with a diagnosis of a significant PDA for an preterm infant admitted in the NICU. Na^+, K^+, glucose, and blood gases were measured every 8 hours (i-Stat; Abbott, Paris, France). Fluid restriction was discontinued for hypernatremia >147 mEq/L or for an increase of Na^+ >4 mEq/L every 8 hours. The following Doppler echocardiographic variables were measured before starting fluid restriction (ECHO 1) and ECHO 2: (1) internal diameter of DA by both B-mode and color Doppler, and maximal blood flow-velocity in DA with pulsed Doppler, from a high left parasternal view; (2) mean and end-diastolic blood flow-velocities in LPA, measured with pulsed Doppler using a high left parasternal view; (3) LA:Ao by M mode, using a parasternal long-axis view; (4) mean blood flow-velocity in ascending aorta, measured with pulsed Doppler from an apical 5-chamber view; and (5) SVC flow measured as previously described.[19] 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; (6) left ventricular shortening fraction, measured from a parasternal long-axis view; (7) resistance index (RI) and mean blood flow-velocity of the middle cerebral artery (MCA), visualized using color Doppler in the middle sagittal plane from the anterior fontanel; and (8) RI and mean blood flow-velocity of the superior mesenteric artery, measured at the proximal portion of the artery near its origin from the aorta.

Doppler echocardiography was with a General Electric VIVID (GE Healthcare, Buckinghamshire, United Kingdom) echocardiographic system with a high-frequency 10-MHz transducer. Measurements were performed by the same investigator. Averages of 3-5 consecutive readings for the vessel diameter and flow-velocity integrals were used. The angle of isonation was <20°.

Clinical and physiologic variables (oxygen requirement, ventilatory settings, blood pressure, diuresis, blood gases) were collected at the time of the 2 Doppler echocardiograms. The ventilatory mode and medical treatment were not changed between the first and the second echocardiogram. Inspired oxygen concentration was set to maintain oxygen saturation between 88% and 95%.

Results are expressed as mean ± SD or median ± interquartile. Each included infant was used as his or her own control. A Wilcoxon signed-rank test was used to compare paired data before and ECHO 2. $P < .05$ was considered to be significant.

Results

The mean gestational age of the 18 evaluated newborns was 24.8 ± 1.1 weeks and mean birth weight was 850 ± 180 g. The postnatal age at ECHO 1 was 26.5 ± 1.3 weeks, and the weight was 970 ± 210 g. Eight newborn infants were mechanically ventilated, and nasal CPAP was used for the other 10 infants (variable flow CPAP). No vasopressor or inotropic drugs were used. The basal fluid intake at ECHO 1 was 145 ± 15 mL/kg/d. The total fluid intake was decreased to 108 ± 10 mL/kg/d for 24 hours before ECHO 2 ($P < .05$). None of the newborns was excluded because of adverse effects of fluid restriction.

There was no significant difference in the systolic, diastolic, and mean arterial blood pressures between the 2 times of evaluation (Table I). Fraction of inspired oxygen, pH, $Paco_2$, base excess, and blood bicarbonate concentrations did not change significantly after 24 hours of fluid restriction. The urine output decreased by 60% during the fluid restriction period ($P < .05$).

The mean internal diameters of the DA as well as the maximal flow-velocity in the DA did not change after fluid

Table I. Change in hemodynamic and respiratory variables for ECHO 1 and ECHO 2 (N = 18)

	ECHO 1	ECHO 2
Fio_2, (%)	26 ± 4	24 ± 3
pH	7.29 ± 0.1	7.28 ± 0.09
$Paco_2$ (mm Hg)	51 ± 5	53 ± 6
Heart rate (beats/min)	156 ± 12	160 ± 10
Systolic blood pressure (mm Hg)	53 ± 10	54 ± 7
Diastolic blood pressure (mm Hg)	32 ± 9	32 ± 4
Mean blood pressure (mm Hg)	41 ± 7	40 ± 4
Urine output (mL/kg/h)	2.5 ± 1.1	1.0 ± 0.6*

FIO2, fraction of inspired oxygen.
Data are expressed as mean ± SD.
*$P < .05$.