

# Cerebral Haemodynamic Changes in Symptomatic Patent Ductus Arteriosus – Doppler Ultrasonographic Evaluation

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**Objectives:** Patent ductus arteriosus (PDA) is a relatively frequent finding in distressed newborns, especially premature infants. Its importance is due to hemodynamic changes that take place in the systemic circulation, influencing cardiac output, and in cerebral blood flow due to blood steal at the level of the patent ductus. This can rise the risk of brain injury among infants with hemodynamically significant left to right shunting. Our goal was to evaluate transfontanellar eco-Doppler appearance in these babies, interpreting measurements from the clinical point of view.

**Materials and methods:** We measured by transfontanellar ultrasonography the eco-Doppler parameters of cerebral blood flow (CBF) at the level of the Anterior Cerebral Artery (ACA) in 15 prematures with demonstrated haemodynamically significant ductus arteriosus, and compared the results with normal values for the age measured in 30 healthy prematures with the same gestational age.

**Results:** We found in all infants with significant left to right shunt at the level of the PDA low levels of end-diastolic velocities, even negative values in 4 cases due to blood steal in the PDA. Later clinical symptoms showed a direct correlation with the grade of left-to-right shunt and cerebral changes.

**Conclusions:** Our results demonstrate the importance of monitoring the effects of PDA on CBF in the indication for medical or surgical closure of the ductus arteriosus, due to the correlation between the severity of the PDA and decrease of CBF, transfontanellar Doppler assessment being a useful tool in centers where echocardiography is not available.

**Keywords:** patent ductus arteriosus, cerebral blood flow, transfontanellar eco-Doppler, prematurity

## Introduction

Patent ductus arteriosus is a vital shunt between the Aorta and left branch of the Arteria Pulmonalis during intrauterine life, it closes in the first 72 hours in 90% of newborns among 30 weeks gestational age, but may persist months in sick or premature infants [1]. Failure of postnatal closure of the ductus arteriosus (DA) remains a common complication of very preterm birth, of which about a third will develop clinical signs of a patent DA (PDA) that requires therapy [2]. Hemodynamic importance of PDA is due to a significant left to right shunt through the ductus, that may result decrease of blood flow to the systemic circulation, affecting especially the brain, lungs and gastro-intestinal tract in the sick prematures [3,4].

The major regulatory mechanisms for cerebral blood flow (CBF) in infants are autoregulation, arteriolar  $\text{CO}_2$ ,  $\text{O}_2$  delivery, blood glucose, and neural activity. It has also been shown that the cardiovascular system regulates CBF through variation in cardiac output (CO) and distribution of blood flow [5,6]. As CBF in preterm infants is a pressure passive system, autoregulation being impaired, variations in cardiac output are directly transposed to CBF.

Despite improvements in the assistance and treatment of preterm infants, periventricular leucomalacia and/or intraventricular hemorrhage (IVH) remain frequent complications among patients with hemodynamically significant PDA, due to great variations in cardiac output [7], and the most severe IVH cases are related to a high risk of neu-

rodevelopmental handicaps. In fact, mental retardation, seizures, and cerebral palsy have been reported for 45% to 86% of preterm infants with parenchymal IVH involvement [8,9,10,11].

Accurate diagnosis of PDA can be done by echocardiography, measuring the diameter of the ductus being the most specific and sensible tool, especially for the reason that the evidence suggests that clinical signs are of limited accuracy, particularly in the first 3 to 4 days after delivery [12,13,14].

The morphological approach to cerebral lesions is a routine examination with simple gray-scale ultrasonography, but their appearance is a late finding, after hemodynamic changes [15]. Because morphologic changes are related to changes in cerebral blood flow (CBF), a hemodynamic study is required, an active investigation that can be oriented toward early diagnosis and prognosis. Doppler ultrasonography is a non-invasive method, which allows repeated and safe assessment of neonatal cerebral hemodynamics and shows consistent changes in cerebral blood flow velocities (CBFv) in infants with PDA [16]. It also can be done at the patient's bedside, without the need of any sedation or other premedication, it is relatively low-cost, can be repeated at any time, and does not influence the status or the treatment of the infant [16,17].

The aim of our study was to investigate cerebral hemodynamics in infants diagnosed with hemodynamically significant patent ductus arteriosus, to assess the efficacy of transfontanellar Doppler ultrasonography in identification of patent ductus arteriosus and find correlations between the supposed changes in other hemodynamic pa-

**Table I.** Statistical indicators in infants with PDA and control groups regarding pCO<sub>2</sub>, pO<sub>2</sub> and MBP

72 h/ group	Measured variables					
	PCO <sub>2</sub>		PO <sub>2</sub>		MBP	
	Mean ± SD	min-Max	Mean ± SD	min-Max	Mean ± SD	min-Max
control	40.4±5.0	27.3–55.0	73.8±10.4	46.8–91.4	39.4±7.4	30–51
PDA	43.7±4.3	37.5–49.5	76.9±8.9	65.8–98.4	34.4±3.7	27–43
p	>0.05		>0.05		>0.05	

pCO<sub>2</sub>: arterial pressure of carbon dioxide; pO<sub>2</sub>: arterial pressure of oxygen; MBP: mean blood pressure

rameters, also to evaluate later outcome related to these findings.

## Materials and methods

The study was a prospective one between January 1, 2006 and December 31, 2009, conducted in Mures County Emergency Hospital, Neonatology and Obstetrics and Gynecology Departments.

We studied the parameters of two groups: 1. The group of patients with hemodynamically significant PDA included 15 preterm newborns, presenting clinical signs and diagnosed by echocardiographic evaluation. We excluded newborns with restrictive PDA, infants unstable on assisted ventilation, modified blood gases or low systemic blood pressure. 2. The control group summarized 30 stable premature newborns, with hemodynamic and acid-base parameters within normal values.

Infants included in the study were examined at birth, Apgar scores, and gestational age based on Ballard score were assigned. Complete physical examination were done at birth and repeated daily or whenever needed, noting the clinical and ultrasonographic findings, also the evolution of the case was mentioned. Premees with PDA, also had different degrees of respiratory distress syndrome (RDS) and were cared for in our neonatal intensive care unit (NICU) for maintenance of adequate ventilation and oxygenation by assisted ventilation, constant monitoring of the vital signs, fluid administration, maintenance of cardiac function and blood pressure with inotropic medication such as dopamine and/or dobutamine as needed, temperature control and maintenance of normal acidobase balance. The control group, also treated in the NICU, received routine care with minimal ventilatory support.

We measured the arterial pH, pCO<sub>2</sub> (mmHg), pO<sub>2</sub> (mmHg), mean arterial blood pressure (MBP in mmHg), in the first 12 hours, at 24, 48, and after 72 hours of life. PDA diagnosis was made by echocardiography in the first 12–72 hours, a ductal diameter ≥2mm being assigned as hemodynamically significant PDA.

Cerebral blood flow velocity recordings were made by color duplex Doppler scanner manufactured by Philips, with En-Visor B.0.1. software. We used 5–12 MHz frequency sectorial transducers. The high-pass filter, used to remove low frequency noise was set at the level of 50–100

**Table II.** Cerebral hemodynamic parameters in studied groups in the first 72 h of life

Group	Mean	SD	ES	Min	Max	Q25	Median	Q75
PSV								
PDA	41.9	5.3	1.4	32.8	49.6	39.0	42.5	45.6
Control	38.6	4.7	0.3	23.4	49.6	35.4	38.4	41.9
p	0.047432							
EDV								
PDA	1.1	2.4	0.6	-3.5	4.3	0.7	0.8	3.7
Control	12.0	2.9	0.2	7.1	23.4	10.1	11.8	14.2
p	0.00000							

Hz. Recordings of CBF velocities were made in the supine position. Observations were made when the infants were in the quiet state, eyes closed and with no gross body movements. Anterior cerebral artery was visualized in the sagittal plane through the anterior fontanel and the signals were recorded from the point midway between the inferior-most border of the corpus callosum and the vessel origin from the circle of Willis. The angle correction was performed and the angle was always less than 30°. The data reported represent the average of three determinations. We measured the peak systolic velocity (PSV), end-diastolic velocity (EDV). The resistive index (RI) was calculated according to the formula  $RI = (PSV - EDV) / PSV$ . In lack of intravenous indomethacin and ibuprofen, our therapeutic possibilities were reduced to oral ibuprofen, after the infant reached total enteral feeding and in some cases surgical ligation, made in the NICU, at the patient's bedside. Most oral ibuprofen protocols recommend an initial dose of 20 mg/kg ibuprofen followed by two doses of 10 mg/kg, administered at 24 hours interval between them, protocol also respected in our unit.

ANOVA and Newman-Keuls test was used for statistical analysis to compare data at different moments in asphyxiated and healthy infants. p values of <0.05 were considered statistically significant at a confidence interval of 95%. We obtained informed consent from at least one parent of the newborn, and respected confidence regarding the identity of the patients.

## Results

Gestational age was 28.6±1.6 SD weeks, in both studied groups, while birth weight was 1082.1±280.5 SD in the first group, and 1329.7±214.7 SD in the control group. There was no statistically significant difference between the groups (p>0.05).

PDA and control groups were compared by pO<sub>2</sub>, pCO<sub>2</sub>, MBP, systolic and end-diastolic peak flow velocities and RI values in anterior cerebral arteries in the first 72 hours of life. We found no statistical difference between the groups in all moments of examination regarding the means of main parameters of hemodynamics and blood gases as shown in Table I.

There was statistically significant difference (p<0.05) between the groups in anterior cerebral artery both systolic

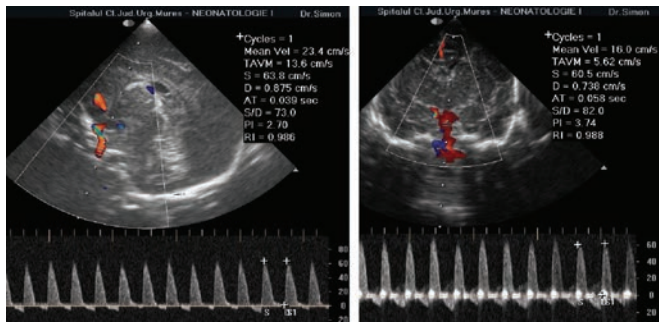


Fig. 1. Low, even negative end-diastolic velocity values are pathognomonic in hemodynamically significant (nonrestrictive) PDA

and end-diastolic flow velocity in the first days, especially the end-diastolic velocities had lower values in the first 72 hours, as a pathognomonic sign for PDA. Statistical mean, minimum, maximum, median and standard deviation for each variable are listed on Table II.

Resistive index values were significantly higher in the measured vessel in the first group compared with controls due to very low values, even negative ones of EDV (Figure 1). We determined that RI values of anterior cerebral artery were 0.62–0.80 in healthy infants and 0.98–1.19 in infants with hemodynamically significant PDA during the first 3 days of life.

We also found significant direct correlation between echocardiographic diagnosed PDA, and decrease of end-diastolic velocity measured in ACA by pulsed Doppler in the first 72 hours confirmed by the correlation coefficient  $r > 0.5$  and  $p < 0.05$  also direct correlation with the increased values of RI ( $r > 0.5$ ;  $p < 0.05$ ), and no correlation between clinical signs and hemodynamic parameters, as clinical signs for a nonrestrictive PDA became evident after this period.

In our studied group of infants with hemodynamically significant PDA 2 cases (13.33%) underwent surgical ligation of the ductus, 4 (26.66%) died in lack of proper treatment due to pulmonary hemorrhage or grade IV intraventricular hemorrhage (IVH). Nine cases (60%) had lower grades of IVH or PVL survived with different grades of neuropsychomotor sequelae. Morphological changes of the brain were different grades of IVH, and/or PVL, as shown in Figure 2.

## Discussion

In preterm infants, a hemodynamically important patent ductus arteriosus that requires therapy is a common problem in the first week of life. Excessive pulmonary flow increases the ventilatory dependency and decreases systemic flow, causing alterations in cerebral perfusion. Clinical parameters, such as hyperactive precordium, wide pulse pressure, cardiac murmur, and tachycardia, are not very reliable signs to properly diagnose PDA [18]. To prove whether a hemodynamically important ductus arteriosus exists, echocardiography should be used.

Because infants with PDA have lower blood pressures and "ductal steal" phenomena leading to less blood flow

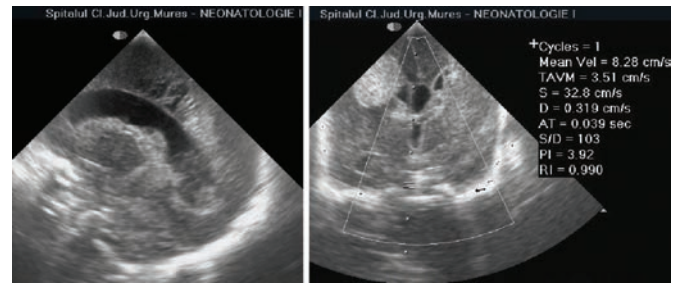


Fig. 2. Periventricular leukomalacia and grade IV intraventricular hemorrhage in two cases with nonrestrictive PDA

directed to organs such as the brain, it is a risk factor for periventricular/intraventricular hemorrhage and white matter damage [19]. Low cardiac output and decreased myocardial contractility have been reported in preterm infants with respiratory distress syndrome [20,21,22]. In these patients, patent ductus arteriosus represents a major challenge for postnatal cardiovascular adaptation, and its adverse ischemic effects on cardio-pulmonary status have been well demonstrated [23,24].

Doppler investigation plays an important role in the accurate evaluation of effects on cerebral blood flow of a nonrestrictive PDA, especially that sonographic morphological changes require 24–48 hours to appear after the hemodynamic changes. Although transfontanellar Doppler ultrasonography cannot substitute the echocardiological diagnose, an increased RI with decreased velocities and diastolic amplitude in a premature infant with respiratory distress syndrome, constitutes a good approach for determining the immediate potential severity and later prognosis, and may help neonatologist in the decision to conduct therapeutic approach [15,16,25].

Our personal experience is based on examination of 15 neonates with confirmed nonrestrictive PDA. In these infants we observed systolic and diastolic velocities below normal in the first 72 hours of life, along with unstable arterial blood pressure. These changes could be explained with loss of cerebral autoregulation in sick premature infants. Our data personal data confirms the direct correlation between high RI values and severity of brain injury. We found strong inverse correlation between diastolic velocities and ductal left to right shunt, as a sign for ductal steal. Loss of autoregulation was demonstrated by the pressure passive character of the cerebral blood flow velocities throughout the examination, corresponding to literature data. The degree of later sequelae was directly correlated to brain tissue destructions, a disadvantage in this respect was the grade of immaturity of included newborns, in conformity with literature studies. Lack of intravenous indomethacine or ibuprofen worsened the prognosis of our preemies, oral ibuprofen being administered only after complete gastric tolerance.

## Conclusions

Cerebral artery Doppler ultrasonography is a useful tool in evaluating cerebral hemodynamics in newborns admitted

to the neonatal intensive care unit. The degree of cerebral hemodynamic alterations and their durations are in direct correlation with later outcome. RI and velocity changes are specific in nonrestrictive PDA. Early Doppler investigation may be important in neonatal screening in premature infants, especially with RDS to find the risk group, and it may lead the clinicians' treatment in respect for clinical and imaging findings especially in neonatal centers where echocardiography is not available.

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