Original research

STATE OF RENAL BLOOD FLOW IN PREMATURE CHILDREN WITH HEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS

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Abstract: *Introduction:* Hemodynamically significant patent ductus arteriosus (HSPDA) lowers the renal circulation because of the "ductal stealing phenomenon," which can change the renal blood flow.
The aim: To study the state of blood flow in the main renal artery and interlobar renal artery in premature infants with HSPDA.
Materials and methods: 74 preterm newborns (gestational age 29-36 weeks) were divided into three groups: I - 40 children with HSPDA, II - 17 children with patent ductus arteriosus (PDA) without hemodynamic disorders, III - 17 children with closed ductus arteriosus. Color ultrasound Doppler scan of the vascular bed of the kidneys was performed using a microconvex sensor with a frequency of 5-8 MHz ("TOSHIBA" Nemso XG model SSA-580A (Japan) from the main renal artery to the interlobar renal arteries of the right kidney. The following parameters of renal blood flow were studied: peak systolic velocity (PSV), end-diastolic velocity (EDV), resistance index (RI).
Results: Peak systolic velocity (PSV) in the main renal artery and interlobar renal arteries did not differ significantly between groups. On the first, third, and tenth days of life, there was a significant decrease in the EDV of blood flow and increased RI in the main renal artery. The EDV of blood flow and RI in the interlobar renal artery on the first day of life did not differ depending on PDA's presence and its hemodynamic significance. On the third and tenth days of life and in the interlobar renal artery, a significant decrease in EDV of blood flow and increased RI were noted. These renal blood flow characteristics were closely related to the size of the PDA on the first day of life.
Conclusion: A feature of renal hemodynamics in HSPDA in premature infants is a decrease in the EDV of blood flow in the main renal artery and interlobar renal artery, as well as an increase in the RI of these vessels, directly correlating with the size of the PDA in the first day of life. During the first ten days of life, dynamic control revealed a slowed process of restoration of renal blood flow in babies with HSPDA, despite the PDA's closure.

Keywords: renal blood flow, hemodynamically significant patent ductus arteriosus, premature infants

INTRODUCTION Ductus arteriosus is one of the main components of the fetus circulation, which in healthy term newborn spasms and closes spontaneously soon after labor. The rate of spontaneous closure of the ductus arteriosus in preterm infants is delayed. The ductus arteriosus remains open at the age of 4 days in about 10% of premature babies with a gestational age of 30 to 37 weeks, 80% of premature babies with a gestation of 25-28 weeks. By the 7th day after birth, these indexes decrease to about 2% and 65%, respectively [1].

Hemodynamically significant patent ductus arteriosus (HSPDA) is a state in which the ductus arteriosus is open, and the volume of the transductal shunt is big enough to cause hemodynamic disorders [2]. The blood shunts from left to right, promoting excessive circulation in lungs and developing "ductal stealing phenomenon" with perfusion

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depletion of the organs situated postductal, like kidneys and gastrointestinal tract [2-5]. This creates pathogenetic prerequisites for developing such complications of HSPDA, such as acute kidney injury and necrotizing enterocolitis [6].

In this regard, HSPDA requires accurate and timely diagnosis to prevent multiple organ damage [7]. Several studies have shown that Doppler assessment of renal artery blood flow in premature infants with HSPDA is more likely to confirm the presence of systemic hypoperfusion than blood flow in the descending aorta [8-11].

In connection with the above, the purpose of our study was to study the state of blood flow in the main renal artery and interlobar renal artery in premature infants with HSPDA.

MATERIALS AND METHODS A cohort, prospective study was conducted in 2018-2019 based on the Department of Anesthesiology and Intensive Care of Newborns in the Dnepropetrovsk Regional Children's Clinical Hospital and was approved by the regional commission on medical ethics.

Inclusion criteria: preterm infants at 29-36 weeks gestation with a closed ductus arteriosus, patent ductus arteriosus (PDA), and HSPDA, signed informed parental consent to participate in the study.

The study's exclusion criteria were: congenital malformations, intraventricular and intracranial hemorrhages of III-IV-degree, sepsis, severe asphyxia, skin diseases, intrauterine growth retardation.

We examined 74 preterm infants. All children were admitted to observation on the first day of life. The examined patients were divided into three groups depending on PDA's presence and its hemodynamic significance: I group - 40 children with HSPDA, II group - 17 children with PDA without hemodynamic disorders, III group - 17 children with a closed ductus atreriosus.

The observation period was ten days. Eight children dropped out of the study because of the developed exclusion criteria: 4 - grade III-IV intraventricular hemorrhage, 4 - neonatal sepsis.

To close the PDA, all children received restrictive therapy [12]. In addition, 32 (80, 0%) premature infants at the end of the first day of life were prescribed ibuprofen three-day course at doses of 10-5-5 mg/kg/day intravenously or 20-10-10 mg/kg/day in the rectal form [12]. On the fourth day of life in all children, the PDA was closed.

The clinical-laboratory examination included gestational age, weight, physical examination, CBC. Instrumental methods of examination - echocardiography with Doppler, ultrasound Doppler of renal vessels.

Echocardiographic and Doppler examination with broadband microconvex probe with a frequency of 5-8 MHz («TOSHIBA» Nemso XG model SSA-580A (Japan) was made to all children at admission to the department (5-11 hour of life) and daily after that to determine the PDA, its size and hemodynamic significance. Echocardiographic and Doppler criteria of HSPDA are: large ductal size (>1.5 mm in a newborn with weight < 1500 g, >1.4 mm/kg in a newborn with weight ≥ 1500 g), demonstration of left to right shunt, growing or pulsatile shunt pattern, increased left atrial to aortic root ratio (LA:Ao>1.4), retrograde descending aortic flow [13].

Color ultrasound Doppler scan of the vascular bed of the kidneys was performed immediately after echocardiography using a microconvex sensor with a frequency of 5-8 MHz ("TOSHIBA" Nemso XG model SSA-580A (Japan) from the main renal artery to the interlobar renal arteries of the right kidney, visualized from the flank region in the position of the child on his back. The flow velocity curves were obtained at the optimal viewing angle (<50 °).

The following renal blood flow parameters were studied: peak systolic velocity (PSV), end-diastolic velocity (EDV). To minimize the variability of the parameters, the average value of 3 measurements was used. The resistance index (RI) was calculated by the formula: RI = [PSV - EDV] / PSV) [14].

To solve the tasks mentioned above and test the initial assumptions, a set of statistical research methods was used, namely: the Mann-Whitney U-test, as a nonparametric analog of the one-way analysis of variance method for independent samples, the Wilcoxon signed-rank test for related samples, the $\chi 2$ test and Fisher's exact test for contingency tables, Spearman's correlation for assess the degree of dependence between variables. The normal distribution of quantitative samples was checked using the Kolmogorov-Smirnov test. Statistical processing of the results was performed using the software product STATISTICA 6.1 (StatSoft Inc., serial number AGAR909E415822FA).

RESULTS The clinical characteristics of the examined children are presented in Table 1.

Index	I group, n=40	II group, n=17	III group, n=17	p_{I-II}<	p_{I-III}<	p_{II-III}<
Gestational age, M±s (Me; Q_1-Q_3) in weeks	32.6±1.93 (33; 32-34)	32.8±2.28 (33; 31,5-34,5)	33.9±1.22 (34; 33-35)	ns	0.03	ns
• 35 – 36 w, n (P)	7 (17,5 %)	4 (23,5 %)	6 (35,3 %)	ns	ns	ns
• 32 – 34 w, n (P)	24 (60,0 %)	9 (52,9 %)	11 (64,7 %)	ns	ns	ns
• 29 – 31 w, n (P)	9 (22,5 %)	4 (23,5 %)	0 (0,0 %)	ns	0.04	0.04
Weight, M±s (Me; Q_1-Q_3) in g	2037.8±552.60 (1950; 1620-2437.5)	1856.5±424.63 (1900; 1485-2175)	2047,1±356,58 (1980; 1825-2300)	ns	ns	ns
• More than 2400 g, n (P)	10 (25.0 %)	2 (11.8 %)	3 (17.6 %)	ns	ns	ns
• 1501 – 2400 g, n (P)	23 (57.5 %)	9 (52.9 %)	13 (76.5 %)	ns	ns	ns
• ≤ 1500 g, n (P)	7 (17.5 %)	6 (35.3 %)	1 (5.9 %)	ns	ns	0.04
Boys, n (P)	28 (70.0 %)	8 (47.1 %)	7 (41.2 %)	0.05	0.05	ns
Girls, n (P)	12 (30.0 %)	9 (52.9 %)	10 (58.8 %)			
Apgar score on 1 minute, M±s (Me; Q_1-Q_3) in points	6.1±1.28 (7; 5-7)	5.7±1.21 (6; 5-7)	6.5±0.51 (6; 6-7)	ns	ns	ns
Apgar score on 5-minute, M±s (Me; Q_1-Q_3) in points	6.8±1.04 (7; 6-8)	6.5±0.87 (7; 6-7)	7.0±0.61 (7; 7-7)	ns	ns	ns
Respiratory distress syndrome	27 (67.5 %)	14 (82.4 %)	15 (88.2 %)	ns	ns	ns
Intrapartum asphyxia	7 (17.5 %)	3 (17.6 %)	0 (0,0 %)	ns	ns	ns
Intrauterine infection	6 (15.0 %)	0 (0.0 %)	2 (11.8 %)	ns	ns	ns
PDA size on day 1, M±s (Me; Q_1-Q_3) in mm	2.36±0.834 (2.1; 1.7-2.7)	1,11±0,154 (1; 1-1.25)	—	0.001	—	
PDA size on day 3, M±s (Me; Q_1-Q_3) in mm	0,50±0,816 (0; 0-1)	0,06±0,243 (0; 0-0)		0.03		

Note. Mann-Whitney U-test, the χ2 test and Fisher's exact test are used («ns» – significant difference not observed).

Table 1. Clinical characteristics of the examined children

Distribution by sex: boys - 43 (58.1%), girls - 31 (41.9%). It is interesting to note the significant predominance of boys in the group with HSPDA. The average gestational age was 32.9 ± 0.22 weeks. The largest number of children had a gestational age of 32-34 weeks. The number of premature babies with a gestational age of 29–31 weeks was the same in the group with PDA and HSPDA. There were no children with such gestational age in the third group, which can be explained by the fact that almost all premature babies have PDA with a gestational age of 29-31 weeks. At birth, the average body weight was 1998.2 ± 56.55 g; there was no significant difference between the groups. More than half of the children examined had low body weight. Very low body weight (≤ 1500 grams) was observed in almost every fifth infant and much more often in samples with PDA. There were no differences in Apgar scores at the first and fifth minutes between the study groups. Respiratory distress syndrome was observed in 75.7%, newborn asphyxia - in 13.5%, intrauterine infection - in 10.8% of children. The incidence of these diseases between the study groups did not differ significantly.

The size of PDA on the first day in children of the first group (Table 1), on average, exceeded that in the second group by more than two times ($p<0.001$). On the third day of life, the size of the PDA significantly decreased in both groups. Simultaneously, the PDA size in the first group was still significantly larger than that in the second group ($p<0.03$). On the tenth day of life, ductus arteriosus was closed in all patients.

Estimating average values of the blood flow's main parameters in the main renal artery allowed to reveal several features (Table 2).

Peak systolic velocity (PSV) had no significant differences between the groups. In the dynamics, there was a significant increase in this parameter in all subjects. The end-diastolic blood flow velocity (EDV) in the main renal artery throughout the observation period varied significantly depending on the presence of HSPDA: in group I, the EDV of blood flow was significantly lower than that of groups II and III. The minimum value of EDV in children with HSPDA was observed on the first day of life. Subsequently, despite its increase in group I in the third and tenth days, there was a decrease in EDV in the main renal artery compared with groups II and III. Changes in the ratio of PSV and EDV in children with HSPDA contributed to an increase in the main renal artery's RI on the first, third, and tenth day of life. This parameter in children of group I was higher than in groups II and III and did not change in dynamics.

Parameter	Day	I group, n=40 (34)	II group, n=17 (17)	III group, n=17 (15)	$p_{I-II}<$	$p_{I-III}<$	$p_{II-III}<$	Total
Peak systolic velocity (PSV), cm/sec	I	22.7±6,38 (22; 19-25,8)	25.4±4,02 (27; 21,5-28)	24.1±4,30 (23; 21-26,5)	ns	ns	ns	23.6±5.54 (23; 21-27)
	III	27.5±6,09 (28; 22-32) ***	26.5±5,52 (26; 24.5-29)	27.2±4.94 (27; 24-30) *	ns	ns	ns	27.2±5.66 (27; 24-31.3) ***
	X	30.4±5.15 (30.5; 26-34) *** ^^	30.4±3.83 (31; 26.5-33.5) *** ^^	31.7±5.69 (29; 27-39) ** ^	ns	ns	ns	30.7±4.93 (31; 26-34) ***^^^
End diastolic velocity (EDV), cm/sec	I	5.8±3.14 (5; 3-8)	10.1±4.71 (10; 7-11,5)	10.1±2.60 (10; 8-12)	0.001	0.001	ns	7.8±4.02 (8; 4.8-11)
	III	7,5±3,62 (7; 5-9.8) **	10,2±3,38 (11; 7.5-12)	9,8±2,27 (9; 8-11.5)	0.007	0.006	ns	8.6±3.51 (8; 6-11.3)
	X	7.9±2.58 (7; 6-10) ***	11.7±3 (12; 10.5-13.5)	12.2±3.23 (11; 11-15)	0.001	0.001	ns	9.8±3.48 (10.5; 7-12) *** ^^
Resistance index (RI)	I	0.747±0.1114 (0.75; 0.68-0,84)	0,591±0,1967 (0.59; 0.53-0.73)	0,581±0,0846 (0.59; 0.52-0.64)	0.003	0.001	ns	0.673±0.1523 (0.67; 0.58-0.81)
	III	0.724±0.1246 (0.73; 0.63-0.83)	0.618±0.0739 (0.6; 0.58-0.68)	0.636±0.0754 (0.67; 0.58-0.69)	0.002	0.008	ns	0.679±0.1146 (0.68; 0.59-0.77)
	X	0.739±0.0823 (0.74; 0.68-0.8)	0.613±0.0927 (0.59; 0.56-0.65)	0.613±0.0800 (0.59; 0.56-0.66)	0.001	0.001	ns	0.678±0.1048 (0.67; 0.59-0.77)

Note: 1. The sample size for the 10th day is given in parentheses.
2. When comparing independent samples, the Mann-Whitney test was used ("ns" - no significant difference was observed).
3. *, **, *** - significant difference from the level of the 1st day; ^, ^^, ^^^ - from the level of the 3rd day, respectively $p<0.05$, $p<0.01$ and $p<0.001$ according to the criterion of sign ranks of Wilcoxon.

Table 2. Dynamics of blood flow parameters in the major renal artery in premature infants with HSPDA

Parameter	Day	I group, n=40 (34)	II group, n=17 (17)	III group, n=17 (15)	$p_{I-II}<$	$p_{I-III}<$	$p_{II-III}<$	Total
Peak systolic velocity (PSV), cm/sec	I	14.2±4.86 (13.6; 10.6-18.5)	16.0±2.97 (16; 13,5-19)	16.2±2.33 (16; 14,5-18)	ns	ns	ns	15.1±0.47 (15.65; 12-18.23)
	III	17.1±4.9 (17.5; 12.3-21) ***	18,9±4,41 (17; 16-22) *	19,3±3,57 (19; 16.5-21.5) **	ns	ns	ns	18.0±0.53 (18; 16-21.25) ***
	X	21.8±5.84 (21; 18.8-24.3) *** ^^^	23.0±3.72 (22; 21-25.5) *** ^^^	23.1±3.44 (23; 21-26) *** ^^	ns	ns	ns	22.4±0.59 (22; 19-25) *** ^^^
End diastolic velocity (EDV), cm/sec	I	4.2±2.76 (4; 2-5.6)	4.5±1.73 (5; 3-5.6)	5.1±2.24 (5; 3-6.6)	ns	ns	ns	4.5±0.28 (4.7; 2.9-5.9)
	III	4.5±2.05 (4.5; 3-6)	6.2±2.34 (7; 3.8-8)*	7.1±1.85 (6.1; 6-8.1) **	0.01	0.001	ns	5.5±0.27 (6; 3.1-7) **
	X	5.7±3.18 (5; 3-8)*	7.8±2.37 (8; 5-10) **	8.6±2.59 (8; 7-10) **^	0.008	0.002	ns	6.9±0.38 (7; 5-9) *** ^^
Resistance index (RI)	I	0.719±0.1371 (0.73; 0.62-0.82)	0.715±0.098 (0.72; 0.64-0.79)	0.688±0.1125 (0.69; 0.58-0.78)	ns	ns	ns	0.711±0.0143 (0.72; 0.62-0.80)
	III	0.732±0.1358 (0.71; 0.69-0.83)	0.666±0.1195 (0.65; 0.56-0.76)	0.631±0.0658 (0.63; 0.57-0.68)	0.02	0.001	ns	0.693±0.0146 (0.69; 0.63-0.80)
	X	0.746±0.1067 (0.74; 0.68-0.80)	0.651±0.1135 (0.65; 0.55-0.74)	0.632±0.0766 (0.65; 0.59-0.69)	0.006	0.001	ns	0.696±0.014 (0.69; 0.61-0.79)

Notes: 1. The sample size for the 10th day is given in parentheses.
2. When comparing independent samples, the Mann-Whitney test was used ("ns" - no significant difference was observed).
3. *, **, *** - significant difference from the level of the 1st day; ^, ^^, ^^^ - from the level of the 3rd day, respectively $p<0.05$, $p<0.01$ and $p<0.001$ according to the criterion of sign ranks of Wilcoxon.

Table 3. Dynamics of blood flow parameters in the interlobar renal artery in premature infants with HSPDA

We have studied the state of intrarenal hemodynamics at the level of the interlobar renal artery (Table 3). As shown in Table 3, the PSV value of blood flow in the interlobar renal artery did not differ between the groups. There was an increase in PSV blood flow on the first, third and tenth days of life of premature infants, regardless of the presence of PDA and its hemodynamic significance. End diastolic velocity (EDV) of blood flow in the interlobar renal artery on the first day of life did not differ in the groups. Subsequently, this parameter increased significantly in the

II and III groups on the third and tenth day of life. At the same time, in children with HSPDA, on the third day of life, low indicators of EDV of blood flow in the interlobar artery remained, and only by the 10th day, an increase in this parameter was noted, which remained significantly lower than in groups II and III. These findings were reflected in the interlobar renal artery's RI, which on the third and tenth days of life was significantly higher in patients with HSPDA compared with children of groups II and III.

on the tenth day of life as compared with similar data of the II and III groups (Table 3, Table 4).

Interesting results were obtained in the correlation analysis between PDA size on the first day of life and parameters of renal blood flow. As for the PSV of blood flow, an inverse relationship was established between the size of the PDA and this indicator on the first day of life in the major renal artery ($\rho = -0.283$, $p<0.01$) and interlobar

Parameter	ρ	p
EDV of blood flow in the main renal artery		
- first day of life	-0,5825	0,000
- third day of life	-0,404	0,000
- tenth day of life	-0,629	0,000
EDV of blood flow in the interlobar renal artery		
- first day of life	-0,355	0,.002
- third day of life	-0,589	0,000
- tenth day of life	-0,559	0,000
RI in the main renal artery		
- first day of life	0,553	0,000
- third day of life	0,344	0,003
- tenth day of life	0,662	0,000
RI in the interlobar renal artery		
- first day of life	0,229	0,05
- third day of life	0,528	0,000
- tenth day of life	0,585	0,000

Table 4. Correlation between the size of PDA in the first days of life of premature infants and EDV of renal blood flow in the dynamics

It should be noted that despite the closure of the PDA by the fourth day of life, a decrease in the EDV of blood flow in the main renal artery and interlobar renal artery, an increase in the RI of these renal vessels was still observed

artery ($\rho = -0.410$, $p<0.000$). Attention was drawn to the inverse relationship between the EDV parameters of blood flow, both in the main renal artery and in the interlobar renal artery, and the PDA size on the first day of life

(Table 4). The renal vessel's RI was directly dependent on the size of the PDA on the first day of the life of premature infants (Table 4).

DISCUSSION Hemodynamically significant patent ductus arteriosus in preterm infants because of left-to-right blood shunting leads to enhanced blood flow in the lungs and volume overload in the left ventricle due to venous return to the pulmonary circulation. Despite the immature myocardium in premature infants, the heart is able to increase the cardiac output, mainly by increasing stroke volume [7]. Since peak systolic velocity (PSV) is the maximum velocity achieved during the cardiac cycle, it can vary with stroke volume changes [15]. The increase in stroke volume in premature infants with HSPDA explains the data obtained in our study: the PSV value of blood flow in the main renal artery and interlobar renal artery did not differ depending on the presence of HSPDA. Meanwhile, it should be emphasized that on the first day of life, there was an inverse relationship between the size of the PDA and the PSV value of the blood flow in the main renal artery ($\rho = -0.283$, $p<0.01$) and interlobar artery ($\rho = -0.410$, $p<0.0001$).

Although in the study of T. Bömelburg, G, Jorch [11], it was shown that in children with HSPDA before surgery, the PSV value of blood flow in the main renal artery exceeded that in the control group, which is most likely associated with more pronounced hemodynamic disorders in the examined children, because they needed the operational closure of the PDA.

However, an increase in stroke volume does not increase or maintain effective systemic perfusion in HSPDA [7]. Experimental and clinical studies have shown impairment in blood flow in organs (intestines, brain, kidneys) due to a combination of a decrease in perfusion pressure and local vasoconstriction [8-10,16]. It has been proved that with significant shunting, systemic blood flow decreases, despite a constant increase in left ventricular ejection. The universal hemodynamic response to systemic hypoperfusion increases arterial blood vessels' resistive characteristics, which is reflected in a decrease of the EDV value of the blood flow [7,15].

According to our data, the "duct stealing phenomenon" in HSPDA led to a noticeable decrease in blood flow's EDV value. It increased RI in the main renal artery and interlobar renal artery. The same results were obtained by other researchers [11,17,18]. It should be noted that only on the first day of life, the EDV value of the blood flow and RI in the interlobar renal artery did not differ depending on PDA's presence and hemodynamic significance. This can be explained by compensatory mechanisms associated with an increase in stroke volume.

Our study also demonstrated that a decrease in EDV parameters of blood flow and an increase in renal blood flow resistance from the main to interlobar renal arteries were closely related to the PDA size. K.H. Hsu et al. [8] found that a PDA size> 2.0 mm is associated with an 8.0-fold increase in the risk of an abnormal renal blood flow index (95% CI 1.6–39.4).

It should be noted that in the examined premature infants, despite the closure of the PDA by the fourth day of life, a decrease in the EDV of blood flow and an increase in the RI of the renal arteries on the tenth day of life persisted, while directly correlating with the size of the PDA on the first day of life. Thus, dynamic control during the first ten days of life allowed revealing a delayed restoration of renal blood flow in children with HSPDA. It is possible that this process could be influenced by the combined effect of damaging factors in the perinatal period.

CONCLUSIONS Thus, a feature of renal hemodynamics in HSPDA in premature infants is a decrease in the EDV value of blood flow in the main renal artery and interlobar renal artery and an increase in the RI of these vessels. These renal blood flow characteristics were closely related to the PDA size on the first day of life. During the first ten days of life, dynamic control revealed a slowed-down process of restoration of renal blood flow in children with HSPDA, despite the PDA's closure.
The study of the state of renal blood flow in premature infants with HSPDA makes it possible for early diagnosis of renal hypoperfusion, which creates the prerequisites for timely nephrological examination and effective drug correction to prevent the development of acute kidney damage.

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