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Original article

Hematocrit: another important factor in systemic neonatal cardiovascular adaptation

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Abstract

Background: Global cardiovascular adaptation of normal healthy term newborns is rarely studied from a multiorgan and hematological point of view.

Aims: To evaluate comprehensive neonatal cardiovascular adaptation during the first days of life with echocardiography and renal-cerebral echo color-Doppler and to correlate it with hematocrit (Ht) changes.

Study design: A prospective observational study was conducted on 35 healthy term neonates with a mean ± SD gestational age and birth weight of 39.5 ± 1.1 weeks and 3,400 ± 330 g, respectively. All infants underwent serial echocardiograms at 15 ± 4 hours (day 1) and 72 ± 4 hours (day 3) of age. At the same time, cerebral and renal Doppler parameters were acquired and Ht was sampled.

Results: The weight and Ht declined by 220 g (189-251) and 8.1% (6.7-9.5), respectively. Systolic and diastolic diameters of the right ventricle and diastolic left ventricle posterior wall thickness showed a reduction, while the

diastolic diameter of the left ventricle showed a small increase. The Doppler cardiac evaluation showed an increase in the mitral E/A ratio and pulmonary acceleration time, a reduction of late transmitral flow peak velocity, aortic peak systolic velocity (PSV), aortic peak systolic pressure gradient, aortic velocity-time integral, aortic mean pressure gradient and pulmonary mean acceleration. We also found a reduction of cerebral resistance parameters and an increase in PSV, end-diastolic velocity, and time-averaged velocity. Other measured parameters remained unchanged.

Conclusion: Systemic cardiovascular evaluation about changes in Ht is an essential approach to study newborns, especially during the first days of life when Ht shows a significant decrease. Knowledge of the laws of physics related to the effect of Ht changes on vascular parameters is another important factor in understanding the pathophysiology of neonatal disease states. Further studies are useful to help physicians make evidence-based decisions in the management of newborns in Neonatal Intensive Care Units (NICUs).

Keywords

Cardiac function, cardiovascular adaptation, newborn.

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Introduction

Echography is a well-established technique for the evaluation of newborns in Neonatal Intensive Care Units (NICUs) which allows repeated and safe assessments of hemodynamics. Pulsed Doppler technique can be used to examine the pattern of blood flow velocity with good reproducibility in the major vessels of the brain [1] as well as the visceral organs [2] in neonates. Echocardiographic quantification is crucial in the diagnosis and management of patients with acquired and congenital heart disease (CHD) [3]. Information from cardiovascular changes allows the neonatologists to make an early diagnosis and provide specific treatments [4, 5]. Echocardiography can provide real-time hemodynamic information by assessing cardiac function, loading conditions, and cardiac output [5]. Two-dimensional echocardiography is considered the clinical reference investigation to evaluate neonatal ventricular size and function. The most common echocardiographic methods used to assess dimensions of atria and ventricles are M- and B-mode. Cardiac function is usually studied with continuous-pulsed Doppler. Emerging techniques like speckle-tracking require post-processing analysis [6-8], and for this reason they are not very useful in contexts such as NICU, where a rapid response is necessary [9]. Although many studies investigate hematocrit (Ht) change during the transitional period [10-14], the cardiovascular effect of Ht change is rarely contextualized with neonatal cardiovascular adaptation [15]. Since the two main fetal shunts are closing during the first hours of life, the neonatal cardiovascular change is challenging to study, and another confounder effect on the calculation of systemic vascular resistance is added. Few parameters are usually used to define a healthy newborn, such as Apgar score, weight, etc. Few studies used transcutaneous pO_2 ($tcpO_2$) and pCO_2 ($tcpCO_2$) to define an average population of neonates [16]. We aimed to evaluate a comprehensive cardiovascular adaptation in healthy neonates during the first days of life by studying the Ht change, and its correlation with echocardiography and renal, cerebral echo color-Doppler parameters.

Methods

This prospective, observational study was carried out in San Giovanni Addolorata Hospital, Rome, Italy over 3 months in 2018. The institutional research ethics board approved the study, and the parents of eligible infants provided consent within 12 hours of birth. Eligible newborns included healthy, term, singleton neonates born after uncomplicated, low-risk pregnancies with a gestational age ranging between 37 and 42 weeks and birth weights between the 10^{th} and 90^{th}

percentiles for the given gestation. The following non-invasive parameters were evaluated to study the standard adaptation to extrauterine life: Apgar score, weight, body surface area (BSA), Ht, blood pressure, $tcpO_2$ and $tcpCO_2$ (**Tab. 1**). We excluded newborns with the following characteristics: newborns born to mothers with medical conditions that could influence the infant's cardiac function or physiological postnatal transition (diabetes mellitus/gestational diabetes, pre-eclampsia, clinical chorioamnionitis, absent/reversed end-diastolic flow in the umbilical arteries on the most recent fetal ultrasound examination, use of antidepressant medication), 5-minute Apgar score of ≤ 5 or need for active resuscitation, $tcpO_2$ < 65 mmHg and $tcpCO_2$ > 45 mmHg, Ht < 42% or > 69%, systemic blood pressure over 2 standard deviations according to international guidelines, admission to the NICU for any length of time, evidence of congenital malformations or chromosomal abnormalities, and CHD other than a small patent foramen ovale. We also excluded newborns with patent ductus arteriosus of any diameter and included newborns with closed or very small foramen ovale. None of the patients enrolled in this study were exposed to an antenatal course of corticosteroids. Each infant underwent 2 transthoracic echocardiographic evaluations at a mean ± SD age of 15 ± 4 hours of age (range 11-20, day 1) and 72 ± 4 hours of age (range 68-76, day 3) using an iE33 ultrasound system and a S12-4 MHz phased-array transducer (Philips Medical Systems) by a single sonographer. All examinations included an electrocardiographic trace, and all measurements were determined from an average of 3 consecutive cardiac cycles. These times were based on the fact that, at our institute, the majority of healthy newborns are discharged home on day 3 of age. Discharge from the hospital was not explicitly delayed for this study. All patients were examined using an aimed neonatal protocol to assess all the dimensional-functional parameters. Infants were in a quiet resting state during the examination. Simultaneous blood pressure was recorded just before performing the echocardiogram using an oscillometric method (DINAMAP™ V100; GE Healthcare). Finally, $tcpO_2$ and $tcpCO_2$ were acquired using the Radiometer Copenhagen TCM3.

Cardiac dimensions

Cardiac dimensions were obtained in systole and end-diastole from the apical 4-chamber view, the long axis parasternal view, and the short axis parasternal view. The ventricular diameters, interventricular septum thickness, left ventricle (LV) posterior wall thickness, aortic diameter were determined using M-mode of the long and short axis parasternal views at the level of the mitral valve (MV) leaflet tips [17].

Conventional echocardiography functional assessment

The following conventional LV function measurements were made: shortening fraction (SF) from the long axis parasternal view; ejection fraction (EF) using Simpson Biplane Method from the apical 4- and 2-chamber views; MV

Table 1. Population parameters on days 1 and 3 of age and p-value in healthy term neonates.

Measure	N day 1	N day 3	Mean ± SD day 1			Mean ± SD day 3			p-value
Apgar 1 minute	35	-	8.5	±	0.5	-		-	-
Apgar 5 minute	35	-	9	±	0.5	-		-	-
Weight (g)	35	35	3,440	±	330	3,220	±	340	**< 0.01**
BSA (m^2)	35	35	0.22	±	0.01	0.21	±	0.01	**< 0.01**
Ht (%)	35	35	61.8	±	7.8	53.7	±	7.8	**< 0.01**
SBP (mmHg)	35	35	73	±	8	74	±	5	0.43
DBP (mmHg)	35	35	47	±	7	51	±	6	0.29
MAP (mmHg)	35	35	56	±	7	58	±	5	0.25
$tcpO_2$ (mmHg)	35	35	82	±	13	79	±	7	0.68
$tcpCO_2$ (mmHg)	35	35	32	±	4	34	±	4	0.23

Values are presented as mean ± SD.
BSA: body surface area; DBP: diastolic blood pressure; Ht: hematocrit; MAP: mean arterial pressure; SBP: systolic blood pressure; $tcpCO_2$: transcutaneous carbon dioxide pressure; $tcpO_2$: transcutaneous oxygen pressure.

E-wave velocity, A-wave velocity, E/A ratio, MV velocity time integral (VTI) obtained from the apical 4-chamber view using pulse wave Doppler with the sample gate of 2 mm placed approximately at the level of the tips of the MV leaflets. The LV ejection time, acceleration time, aortic velocity-time integral, aortic peak systolic velocity (PSV) were measured from the apical 5-chamber view at the level of the aortic valve using pulsed wave Doppler. Peak gradient, mean gradient, stroke volume, cardiac output, and mean aortic acceleration were calculated by the echocardiography. Systemic vascular resistance corrected by BSA was calculated with a standard formula [17-19].

The following conventional right ventricle (RV) function measurements were made: tricuspid valve (TV) E-wave velocity, A-wave velocity, E/A ratio, TV VTI obtained from the apical 4-chamber view using pulse wave Doppler with the sample gate of 2 mm placed approximately at the level of the tips of the TV leaflets. The RV ejection time, acceleration time, pulmonary velocity-time integral, and pulmonary PSV were measured from the parasternal short axis view at the level of the pulmonary valve using pulsed wave Doppler. Peak pulmonary gradient, mean pulmonary gradient and mean pulmonary acceleration (peak pulmonary velocity/acceleration time) were calculated by the echocardiography.

Cerebral and renal perfusion assessment

Systolic-diastolic velocity and time-averaged velocity (TAV) were sampled in standard view on the anterior cerebral artery (ACA) and renal artery using pulse wave Doppler with a sample gate of 2 mm. Pulsatility and resistance indices and systolic/diastolic ratio were calculated by the echocardiography. Three Doppler traces of three cardiac cycles were obtained in the ACA and renal artery [19, 20].

Statistical analysis

Values were tested for normality by using the Shapiro-Wilk test as well as visualization of histogram presentation of the data and reported as mean values ± SD or median values as appropriate. Values from day 3 scans were compared with those from day 1 using paired Student t-tests or the Wilcoxon test, as appropriate. We accepted p-values < 0.05 as significant. SPSS® version 21 (SPSS Inc, Chicago, Illinois) was used to perform the statistical analysis.

Results

Thirty-five infants with a mean ± SD gestational age and birth weight of 39.5 ± 1.1 weeks and 3,400 ± 330 g, respectively, were included. Mean maternal age was 35.5 ± 5 years. Seventeen (49%) were males, and 18 (51%) were females; 29 (83%) were delivered vaginally, and 6 (17%) by cesarean section. The mean 1-minute Apgar score was 8.5 ± 0.5, and the mean 5-minute Apgar score was 9 ± 0.5. Weight on day 3 was significantly lower (-220 ± 90 g; $p < 0.01$) with a mean weight loss of 6.4% ± 2.6%. There was no difference in heart rate (125 vs 133; $p = 0.13$), systolic blood pressure (73 ± 8 mmHg vs 74 ± 5 mmHg; $p = 0.43$), or diastolic blood pressure (47 ± 7 mmHg vs 51 ± 6 mmHg; $p = 0.29$) between the 2 time points. We found no significant difference in $tcpO_2$ and $tcpCO_2$ between day 1 and day 3 ($p > 0.05$) (**Tab. 1**).

Left ventricle dimensions

LV dimensions were measurable from all scans. We found a reduction in diastolic LV posterior wall thickness on day 3 and an increase of LV internal diastolic diameter. The other measurements had no change between the 2 time points (**Tab. 2**).

Right ventricle dimensions

RV dimensions were measurable from all scans. We found a significant decrease in RV diastolic and systolic diameter. The other measurements remained unchanged (**Tab. 2**).

Left ventricle function

All measurements of LV function were feasible from each scan. Except for aortic peak velocity, aortic peak gradient, aortic VTI, aortic mean gradient, mitral peak velocity A and mitral E/A ratio, all measured functional indices remained unchanged on day 3 (**Tab. 2**).

Right ventricle function

All measurements of RV function were feasible from each scan. Except for pulmonary acceleration time and pulmonary mean acceleration, all mea-

Table 2. Cardiac parameters on days 1 and 3 of age and p-value in healthy term neonates.

Measure	N day 1	N day 3	Mean ± SD day 1			Mean ± SD day 3			p-value
RVWd (cm)	35	35	0.37	±	0.07	0.34	±	0.08	0.94
RVWs (cm)	35	35	0.56	±	0.13	0.53	±	0.15	0.32
RVDd (cm)	35	35	0.68	±	0.19	0.55	±	0.13	**< 0.01**
RVDs (cm)	35	35	0.57	±	0.11	0.45	±	0.15	**< 0.01**
IVSTd (cm)	35	35	0.50	±	0.10	0.47	±	0.08	0.17
IVSTs (cm)	35	35	0.63	±	0.12	0.65	±	0.10	0.38
LVDd (cm)	35	35	1.68	±	0.18	1.75	±	0.11	**0.04**
LVDs (cm)	35	35	1.05	±	0.19	1.12	±	0.21	0.36
LVPWd (cm)	35	35	0.39	±	0.09	0.33	±	0.07	**0.007**
LVPWs (cm)	35	35	0.52	±	0.11	0.49	±	0.07	0.80
EF (%)	35	35	70	±	10	70	±	11	0.40
SF (%)	35	35	37	±	8	37	±	8	0.51
SV (ml)	35	35	5.79	±	1.53	6.06	±	1.07	0.53
CO (l/min)	35	35	0.72	±	0.22	0.80	±	0.18	0.97
HR (bpm)	35	35	125	±	19	133	±	23	0.42
SVRI	35	35	1,217	±	409	1,081	±	276	0.33
AOd (cm)	35	35	0.93	±	0.11	0.92	±	0.10	0.75
AOs (cm)	35	35	1.27	±	0.15	1.19	±	0.16	0.37
AOs/AOd	35	35	1.38	±	0.19	1.30	±	0.22	0.77
Aortic PSV (m/s)	35	35	0.72	±	0.13	0.62	±	0.13	**< 0.01**
Aortic peak gradient (mmHg)	35	35	2.2	±	0.7	1.6	±	0.6	**< 0.01**
Aortic VTI (m)	35	35	0.12	±	0.03	0.10	±	0.02	**0.02**
Aortic mean gradient (mmHg)	35	35	1.02	±	0.35	0.78	±	0.32	**0.02**
Aortic mean acceleration (m/s^2)	35	35	7.91	±	2.88	7.34	±	2.97	0.88
Aortic AT (ms)	35	35	82.5	±	31.5	77.2	±	19.4	0.25
Aortic ET (ms)	35	35	248.2	±	41.8	238.6	±	34.6	0.55
Aortic AT/ET	35	35	0.323	±	0.075	0.321	±	0.054	0.13
MV VTI (m)	35	35	0.10	±	0.02	0.10	±	0.03	0.76
MV mean gradient (mmHg)	35	35	0.57	±	0.19	0.57	±	0.22	0.60
E (m/s)	35	35	0.52	±	0.11	0.53	±	0.11	0.08
A (m/s)	35	35	0.54	±	0.09	0.48	±	0.07	**0.009**
E/A	35	35	0.96	±	0.18	1.09	±	0.15	**< 0.01**
Pulmonary PSV (m/s)	35	35	0.93	±	0.17	0.89	±	0.14	0.40
Pulmonary peak gradient (mmHg)	35	35	3.5	±	1.3	3.3	±	1.0	0.47
Pulmonary VTI (m)	35	35	0.20	±	0.18	0.16	±	0.03	0.17
Pulmonary mean gradient (mmHg)	35	35	1.8	±	0.6	1.6	±	0.5	0.56
Pulmonary mean acceleration (m/s^2)	35	35	10.25	±	5.09	6.63	±	2.89	**0.003**
Pulmonary AT (ms)	35	35	80.2	±	31.8	94.5	±	18.5	**0.026**
Pulmonary ET (ms)	35	35	247.3	±	65.0	263.9	±	32.4	0.70
Pulmonary AT/ET	35	35	0.342	±	0.140	0.361	±	0.073	0.23
TV VTI (m)	35	35	0.11	±	0.01	0.12	±	0.09	0.47
TV mean gradient (mmHg)	35	35	0.6	±	0.2	0.6	±	0.2	0.63
TV peak velocity (m/s)	35	35	0.54	±	0.10	0.52	±	0.09	0.29
TV peak gradient (mmHg)	35	35	1.2	±	0.4	1.1	±	0.4	0.44

Values are presented as mean ± SD.

A: late transmitral flow peak velocity; AT: acceleration time; AOd: aortic diastolic diameter; AOs: aortic systolic diameter; CO: cardiac output; E: early diastolic transmitral flow peak velocity ; EF: ejection fraction; ET: ejection time; HR: heart rate; IVSTd: diastolic interventricular septum thickness; IVSTs: systolic interventricular septum thickness; LVDd: left ventricle internal diastolic diameter; LVDs: left ventricle internal systolic diameter; LVPWd: diastolic left ventricle posterior wall thickness; LVPWs: systolic left ventricle posterior wall thickness; MV: mitral valve; PSV: peak systolic velocity; RVDd: right ventricle internal diastolic diameter; RVDs: right ventricle internal systolic diameter; RVWd: right ventricle wall diastolic thickness; RVWs: right ventricle wall systolic thickness; SF: shortening fraction; SV: stroke volume; SVRI: systemic vascular resistance index; VTI: velocity time integral; TV: tricuspid valve.

sured functional indices remained unchanged on day 3 (**Tab. 2**).

Cerebral parameters

All cerebral measurements were feasible from each scan. We found a small but significant reduction of pulsatility index, resistance index, systolic-diastolic ratio (S/D), and an increase of PSV, end-diastolic velocity (EDV), and TAV (**Tab. 3**).

Renal parameters

All renal measurements were feasible from each scan. Signal quality was eligible for analysis in 14 and 12 babies on day 1 and 3 respectively. We have found no significant change in parameters of renal arterial flow (**Tab. 4**).

Discussion

We used a comprehensive echocardiographic protocol that included global cardiovascular quantitative measures easy to acquire and useful in neonatal care units of different complexity. Our study population was composed of healthy term neonates selected out by clinical information or non-invasive instrumental parameters: Apgar index, gestational age, weight, $tcpO_2$, $tcpCO_2$, Ht, non-invasive blood pressure (NIBP) measurement, closed ductus arteriosus, absent or very small foramen ovale shunts, differently from some other studies that didn't acquire transcutaneous partial gas pressures [21, 22] and included newborns with patent ductus arteriosus that can influence systemic vascular resistance index (SVRI) and cardiac function. We decided to acquire the measures on the 1st and the 3rd day of life because babies are usually discharged

Table 3. Cerebral parameters on days 1 and 3 of age and p-value in healthy term neonates.

Measure	N day 1	N day 3	Mean ± SD day 1			Mean ± SD day 3			p-value
PSV (m/s)	35	35	0.29	±	0.08	0.37	±	0.08	**0.01**
EDV (m/s)	35	35	0.09	±	0.04	0.13	±	0.03	**0.02**
TAV (m/s)	35	35	0.16	±	0.05	0.21	±	0.04	**0.02**
PI	35	35	1.31	±	0.23	1.03	±	0.28	**0.01**
RI	35	35	0.70	±	0.05	0.66	±	0.05	**0.01**
S/D	35	35	3.43	±	0.55	2.95	±	0.39	**0.01**

Values are presented as mean ± SD.
EDV: end-diastolic velocity; PI: pulsatility index; PSV: peak systolic velocity; RI: resistance index; S/D: systolic-diastolic ratio; TAV: time-averaged velocity.

Table 4. Renal artery parameters on days 1 and 3 of age and p-value in healthy term neonates.

Measure	N day 1	N day 3	Mean ± SD day 1			Mean ± SD day 3			p-value
Left PSV (m/s)	14	12	0.46	±	0.07	0.47	±	0.06	0.13
Left EDV (m/s)	14	12	0.10	±	0.02	0.11	±	0.02	0.21
Left TAV (m/s)	14	12	0.20	±	0.04	0.23	±	0.03	0.47
Left PI	14	12	1.15	±	0.44	1.12	±	0.40	0.39
Left RI	14	12	0.75	±	0.08	0.74	±	0.10	0.81
Left S/D	14	12	3.49	±	1.65	3.38	±	1.76	0.59
Right PSV (m/s)	14	12	0.45	±	0.09	0.46	±	0.08	0.53
Right EDV (m/s)	14	12	0.11	±	0.02	0.11	±	0.04	0.32
Right TAV (m/s)	14	12	0.22	±	0.06	0.22	±	0.06	0.39
Right PI	14	12	1.24	±	0.43	1.05	±	0.49	0.90
Right RI	14	12	0.74	±	0.11	0.74	±	0.10	0.26
Right S/D	14	12	3.80	±	1.50	3.68	±	1.81	0.94

Values are presented as mean ± SD.
EDV: end-diastolic velocity; PI: pulsatility index; PSV: peak systolic velocity; RI: resistance index; S/D: systolic-diastolic ratio; TAV: time-averaged velocity

from hospital 72 hours after birth. We found that population parameters were similar to other studies [21-24]. We found an increase in cerebral blood flow despite no significant change in SVRI. The same result has been observed in other studies [21, 24]. We did not evaluate the influence on cerebral vascular resistance of postprandial time. No significant renal vascular change was found between the 1st and the 3rd day. We also have to consider the fact that we were not able to obtain a sufficient number of values related to renal parameters. For this reason, we might not have been able to demonstrate an increase in renal blood flow during the first days of life, as have been shown in Ilves et al. study [25]. Two-dimensional echocardiography is considered the gold standard for the assessment of heart function. Although recent reports have highlighted the feasibility of quantifying RV function in healthy neonates with more sophisticated techniques like speckle-tracking [26-32], we decided to study the newborn using a simple, fast and comprehensive approach through 2D echocardiographic views plus functional Doppler integrated with a simple hematological parameter such as Ht. We found a significant Ht reduction of 8.1% from the first hours of life to the 3rd day. Ht is one of the main factors that influence the whole blood viscosity. From the empiric curve of Christensen et al. [12], we can estimate an approximative reduction of viscosity of 15%. Hagen-Poiseuille's law shows the relationship between viscosity and hydraulic resistance:

$$R = \frac{8\eta d}{\pi r^4}$$

where η is the viscosity, d the diameter of the tube, r the radius of the tube, R the resistance.

So, in our case, we should have a 15% reduction in pulmonary and systemic vascular resistance. As largely demonstrated in the literature, during the transitional period, there is a fall in pulmonary vascular resistance (PVR) [33-35]. One of the main factors is the decrease in PVR due to the change in pulmonary blood vascular properties. The resistance is defined as the ratio of the pressure decrease across the vascular bed to the flow of the fluid that runs through it:

$$R = \frac{P_1 - P_2}{Q}$$

where R is the resistance, P_1 the pressure before the vascular bed, P_2 the pressure at the end of the vascular bed, Q the flow. We found no significant flow change (cardiac output), so, considering this physics law, either pulmonary or systemic pressure should decrease. The systemic pressure didn't change, meaning that there is a vascular regulation (vasoconstriction) to maintain optimal tissue perfusion pressure. In opposition, on the pulmonary side, indirect parameters of pulmonary pressure decrease were found; a rise in pulmonary acceleration time, a decrease in mean pulmonary acceleration and RV end systolic and diastolic diameters, the first two according to Jain et al. [22] and other studies that evaluated the cardiopulmonary dynamic in pulmonary hypertension [36-39]. These results highlight that there is a less autonomic regulation on the pulmonary compared to the systemic vascular tone. According to these results, there is the well-known absent sympathetic and parasympathetic pulmonary innervation in opposition to systemic circulation where carotid baroreceptors play an important role.

Nevertheless, normal vascular maturation and remodeling play an important role in the development of physiological pulmonary circulation also [38]. The level of circulating blood volume is another crucial factor that affects hemodynamic changes in the transitional period. Usher et al. [39] demonstrated that during the first 4 hours of life there is a constriction of total blood volume due to a reduction of plasma volume and from 4 to 24 hours an augmentation with a constant red blood cell component especially in newborns who had early cord clamping. However, our study was performed in infants with immediate cord clamping and later than 12 hours after birth. Blood volume change during our study period was expected to have been negligible.

Conclusions

Better neonatal right cardiac function is mainly due to a drop in Ht and PVR related to the change in pulmonary vascular properties. Systemic vascular resistance remained unchanged despite a significant Ht reduction, demonstrating compensatory vasoconstriction, which was absent in the pulmonary circulation. Other factors, such as total blood volume and vascular remodeling, are presumed to play an important role in neonatal cardiovascular adaptation. Better cerebral perfusion was found despite no change in renal vascular function. It is necessary to carry out

further studies with a large sample size to establish correlations of cardiac parameters with Ht and new reference z score curves corrected by Ht.

Study limitations

This study has several limitations. We included cases with a small opened foramen ovale in our study, so we could not entirely exclude an influence of shunting. We couldn't also exclude a smaller effect of sex on functional indices and a possible change in renal measures, because of a limited sample size.

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Statement of Ethics

Parents or guardians have given their written informed consent.
The research institute's committee on human research has approved the study protocol.

Declaration of interest

The Authors have no conflicts of interest to declare. There were no fundings, contracts and other forms of financial support. There were no relationships with industries.

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