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Non-Invasive Monitoring of Haemodynamics and its Changes During Systemic Infection in Neonatal Patients

SUMMARY OF DOCTORAL DISSERTATION

Medicine and health sciences,
Medicine (M 001)

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Naujagimio kraujotakos stebėsena neinvaziniu hemodinamikos monitoriumi ir jos pokyčiai sisteminės infekcijos metu

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1. INTRODUCTION

1.1. The Scientific Novelty of the Study and Implementation in Clinical Practice

During the neonatal period, the physiology of the cardiovascular system is still evolving, and cardiac function, especially in the preterm infant, differs significantly from that in the older people [1]. Not surprisingly, the monitoring, assessment, and treatment of haemodynamic disorders remain one of the greatest challenges in neonatology. Cardiac and circulatory disorders often aggravate the neonatal underlying disease and often lead to disease outcome. Correct haemodynamic assessment helps to understand the changes in central and peripheral circulation, to select the timely and most appropriate treatment in a particular clinical situation. For this purpose, pulmonary artery catheterization has long been considered the gold standard in clinical practice. However, this invasive method is not suitable for monitoring the haemodynamics of newborns, as it can cause various complications and be dangerous to the patient's health [2-4].

New, non-invasive technologies allow to assess the characteristics of haemodynamics and identify its disorders objectively and without any harm to the patient. Echocardiography is the most widely used instrumental examination to assess cardiac function in severely ill patients. Therefore, it has been agreed to consider classical echocardiography as the clinical standard for assessing cardiac function [5]. In neonatology, point-of-care echocardiography (fECHO) performed by a neonatologist is spreading rapidly. During this procedure, the newborn's cardiac output can be assessed as often as the clinical situation requires, but an accurate examination can only be performed by a physician experienced in echoscopy [6, 7]. An alternative to traditional echocardiography could be a non-invasive ultrasound cardiac output monitor based on Doppler principle USCOM (UltraSonic Cardiac Output Monitor). It is

especially useful in acute cardiovascular disorders, when it is necessary to quickly identify the main causes of these disorders and choose the most appropriate treatment: predict the amount of bolus therapy, decide which cardiovascular medications and their doses to choose. It is a device that can be used to assess all haemodynamic parameters simultaneously. The examination lasts only a few minutes, its results are easy to interpret, and no special skills are required. It is relatively recently developed, widely used in intensive care for adults and children, but is only making its way into neonatology. To date, there are few, small-scale published clinical trials in haemodynamically stable neonates, and the data collected are not sufficient to make an objective assessment of the dynamic changes in blood circulation in both preterm and full-term infants depending on their gestational age and especially when they have sepsis. Therefore, the aim of our study is to determine the haemodynamic characteristics of haemodynamically stable neonates treated at the Neonatology Center of Vilnius University Hospital *Santaros klinikos*, and its changes in both in the beginning and during the course of sepsis. Assessing the benefit-risk ratio, it is clear that the latter examination method does not pose a risk to the overall condition of the newborn, and the benefits of the examination are unquestionable.

1.2. The aims of the Study

The lack of data of neonatal haemodynamics has encouraged to carry out a larger clinical study and assess the peculiarities of haemodynamically stable neonatal blood circulation, trying to answer the question of whether non-invasive ultrasound cardiac output monitor can be an alternative method to functional echocardiography to assess neonatal cardiac function. Moreover, the USCOM manufacturer provides only recommended pediatric and estimated, plausible neonatal circulatory rates, proposing to conduct a population study in its region. And in clinical practice, observing changes in not only the general condition but also the blood circulation in patients

with systemic infectious disease has led to the idea of investigating how early the haemodynamics begins to respond to the infection and how it changes during the course of the disease.

Thus, the aim of this biomedical research is to evaluate the central and regional circulatory characteristics of haemodynamically stable and neonates with systemic infectious disease using a non-invasive ultrasound cardiac output monitor.

1.3. The objectives of the Study

1. To compare data of haemodynamics assessed during echocardiography and using non-invasive cardiac output monitor;
2. To determine the reference values of haemodynamics in haemodynamically stable neonates of different postmenstrual age treated at the Neonatology Center, measured with a non-invasive cardiac output monitor USCOM;
3. To evaluate changes of haemodynamic parameters of neonates with systemic infection.

1.4. Defended Statements

- Functional cardiac ultrasound and non-invasive ultrasound cardiac output monitoring are equally accurate.
- The reference values of haemodynamics for haemodynamically stable neonates determined using non-invasive ultrasonic cardiac output monitor can be used to assess changes in cardiac function in neonates.
- A non-invasive ultrasonic cardiac output monitor can accurately detect circulatory changes during the course of the disease in neonates with systemic infection.

2. MATERIALS AND METHODS

The prospective biomedical research presented in the dissertation was performed in 2016 – 2020 at the Clinic of Children's Diseases, Faculty of Medicine, Vilnius University. Haemodynamics monitoring of newborns have been performed at the Neonatology Center of the public institution Vilnius University Hospital *Santaros klinikos* in the period from 12 September 2017 to 30 September 2020.

2.1. Ethic aspects

The biomedical research was performed with the permission of the Vilnius Regional Biomedical Research Ethics Committee No. 158200-17-910-452 dated 12 September 2017 (Annex No. 1). Parents or guardians of newborns treated, cared for in neonatal wards were explained in detail about the objectives and course of the research. Parents or guardians who voluntarily agreed and signed an informed consent form could participate in the research of haemodynamics of their newborns. Newborns were not involved in the research without the consent of their parents or guardians.

2.2. Calculation of the Sample of the Study

The estimated sample size for the 95 per cent confidence and the 5 per cent confidence interval is 150 neonates – 60 preterm and 60 full-term haemodynamically stable neonates (**HSN**) and 30 neonates with confirmed or suspected systemic infection (**SSN**).

162 neonates were enrolled in this study. 130 participated in the HSN group study. In this group, one newborn who experienced asphyxia at birth was observed to have central circulatory disorders, and it was not possible to perform the study in a technically high-quality manner for two newborns, so they did not participate in further analysis.

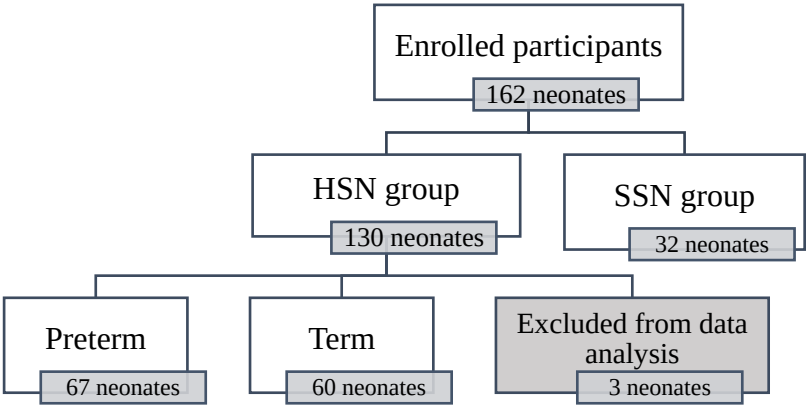


Figure 1. Participants of the study

Available data from 67 preterm and 60 full-term neonates were used to achieve the first two objectives – comparing 2 methods and setting reference values, and served as a control group for the study of 32 neonates with suspected systemic infection (Figure 1).

2.3. Selection of subjects

According to the biomedical study protocol, the study of a group of haemodynamically stable neonates included both full-term and preterm neonates of any gestational age from their seventh day of life, in whom a pediatric cardiologist had performed an anatomis echocardiography and did not detect congenital heart defects or persistent, haemodynamically significant fetal blood circulation (patent arterial duct and/or changed direction of drainage through the oval opening and/or persistent pulmonary hypertension). There were also no neonates in this group who had clinical or laboratory evidence of or suspected infection. Haemodynamics of haemodynamically stable neonates was studied to determine the age-related circulatory features of the newborn, as well as to compare two different methods

of haemodynamic monitoring. Data from this group were also used as control to assess haemodynamic changes in neonates with suspected or confirmed systemic infection.

2.4. Inclusion criteria

The group of haemodynamically stable neonates (HSN) included the following neonates:

- Those whose parents have given written informed consent;
- Male and female, preterm and full-term neonates, from week 24 of gestation, with a chronological age of seven to 140 days at the time of selection;
- Those who did not have cardiovascular disease at the time of the study and who were at least two weeks after the onset of an infectious disease.

The group of neonates with confirmed or suspected systemic infection (SSN) included neonates of the same gestational and postmenstrual age as the HSN group who had a suspected or diagnosed systemic infection according to at least one laboratory and at least two of the following clinical criteria:

Clinical criteria:

- Hypothermia (body temperature < 36 °C) or fever (> 38 °C);
- Tachycardia > 180 beats per minute or bradycardia < 100 beats per minute, or heart rate instability;
- Diuresis < 1 ml/kg/h or hypotension (assessed by postmenstrual age), or marbled skin, or prolonged capillary filling time (> 4 s);
- Hemorrhagic rash of the skin and/or mucous membranes;
- New or worsening episodes of apnea, or tachypnoea, or increasing need for supplemental oxygen, or progressive respiratory failure, which required more intensive respiratory therapy;
- Intolerance to enteral feeding or sluggish sucking, or sluggish intestinal peristalsis;

- Newborn irritability or sluggishness;
- Decrease in muscle tone.

Laboratory criteria:

- In full blood test – leukopenia $< 5 \times 10^9$/L or leukocytosis $> 34 \times 10^9$/L (0 to 7 days of life) or $> 19.5 \times 10^9$/L (7 to 28 days of life);
- Ratio of immature neutrophils to total neutrophils > 0.21;
- Platelet count $\leq 100 \times 10^9$/L;
- C-reactive protein (CRP) > 15 mg/L or procalcitonin concentration ≥ 2 ng/ml;
- Hyperglycemia or hypoglycemia;
- Metabolic acidosis;
- Positive blood culture and/or a pathogen identified by a polymerase chain reaction test.

2.5. Exclusion criteria

The research did not include:

In the HSN group:

- Neonates with any infectious disease at the time of inclusion;
- Neonates with haemodynamically significant patent ductus arteriosus;
- Neonates with unstable haemodynamics and use of cardiovascular agents to stabilize hemodynamics.

In HSN and SSN groups:

- Neonates having birth defects, congenital heart defects, vascular abnormalities;
- Neonates with inherited metabolic diseases;
- If there was no written consent of the parents to participate in this research

2.6. The Methodology of the Study

After a pediatric cardiologist had performed an anatomic echocardiography and in the absence of congenital heart defects or ductal shunting, a haemodynamically stable neonate meeting the criteria for inclusion to the HSN study group.

On the day of examination, the neonatologist performed an anthropometric examination of the newborn : the subject's length and weight were measured with the help of electronic scales SECA 233/374 (*SECA GmbH & Co.*, Germany), with an integrated length meter. Heart rate and oxygen saturation were measured with a Masimo SET LNCS (*Masimo Corp.*, California, USA) pulse oximeter tape surrounding the subject's foot. Non-invasive arterial blood pressure was measured on the right arm with a GE DINAMAP (*GE Medical Systems Information Technologies*, Wisconsin, USA) blood pressure monitor. The average of the three measurements was recorded on the patient data card (Annex No. 2). It noted the subject's main diagnosis according to the TLK-10-AM systemic disease list, respiratory therapy, supplemental oxygen demand, and subgrouping according to postmenstrual age of the subject (I – < 28 weeks, II – 28-32 weeks, III – 32-36 weeks, IV – > 37 weeks). Next, the researcher placed sensors of the near-infrared spectroscope NONIN Equanox 7600 (*Nonin Medical Inc.*, Massachusetts, USA), wrapped with an elastic cotton band, in the projection of the right forehead and right kidney on the lumbar region**.** Thus, monitoring of regional blood circulation by measuring oxygen saturation of the cerebral and right kidney was initiated.

When the newborn was at rest**,** the echocardiography was performed by neonatologist using a GE LOGIQ S8 XDclear 2.0 (*GE Ultrasound Korea Ltd*, Gyeonggi-do, Korea) ultrasound mashine with a S4-10-D (3-9 MHz) probe. Left ventricular outflow tract diameter (LVOTD) is measured from the parasternal long-axis view at the hinge point of atrioventricular annulus at end- systole. The velocity-time integral (VTI) in left ventricular outflow tract was assessed by pulse-

wave Doppler in the apical five-chamber view with the sample volume just below the aortic valve. The pulse wave Doppler recording was paused to obtain a smooth VTI envelope for exact tracing of the signal (Figure 2).

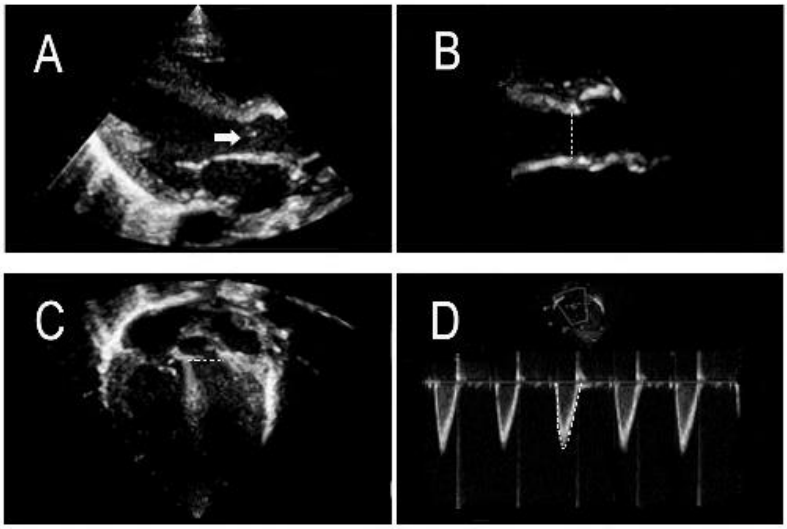


Figure 2. Assessment of left ventricular output. LVOTD is measured from parasternal long-axis view (a,b). VTI is acquired in the apical five chamber view (c,d)

Cardiac output then can be calculated by multiplying the LVOTD by the VTI of blood flow and heart rate (HR), applying these values in the equation below:

$$\textbf{CO (ml/min) = VTI (cm) × LVOTD (cm) × HR (bpm)}$$

Right after patient data, including length, weight and gender, were entered into the non-invasive USCOM device as well as blood pressure measurements during the procedure by the same investigator. To measure cardiac output by this device, Doppler flow curves were

obtained using a small transcutaneous 2.2 MHz transducer placed in the suprasternal notch to obtain an optimal flow signal at the aortic valve. The Doppler curve was displayed by the device, and the operator adjusted the angle of insonation to return the best Doppler curve. The goals of adjustment were to obtain a flow profile that was well defined at the base and peak – the highest, fullest, most complete curves indicates the best alignment with aortic valve and five these were chosen by the operator (Figure 3).

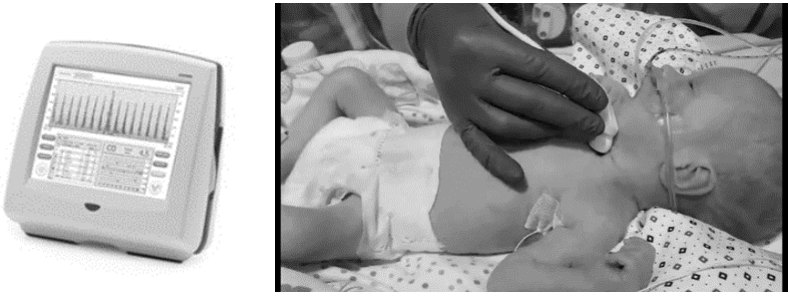


Figure 3. Non-invasive ultrasonic cardiac output monitor

The software of the device uses an algorithm based on patient‘s length to determine LVOTD. But if the length is < 50 cm, USCOM calculates aortic valve diameter based on weight, derived from Nidorf equations [5]. Based on measurements, the program calculated other parameters, reflecting preload, afterload, and inotropy presenting them in numerical form.

For SSN subjects, haemodynamic monitoring was performed only with a non-invasive ultrasound machine. It was repeated 24 hours and later in those patients who had abnormalities in the obtained data during the first and subsequent examinations and/or the patients whose clinical condition did not improve during the course of the disease. The obtained data were submitted for statistical analysis.

2.7. Statistical Analysis of Data

Statistical Package for Social Science (SPSS), version 26 (*IBM Corp*, New York, USA), *R programme*, version 3.5.2 (*The R Foundation*, Vienna, Austria) and *Microsoft Office Excel 2013* were used to analyze the study data. Quantitative characteristics, means, and standard deviations (SD) of the variable were calculated to assess the quantitative characteristics of the study sample, with data distributed according to the normal distribution and non-normal distribution expressed as medians and 10–50–90 percentiles.

The ICC – intra-class correlation coefficient was used to evaluate the relationships between the variables distributed according to the normal distribution. To compare two independent variables, Student's t criterion was used when the distribution of the variable satisfied the assumption of normality and the non-parametric Mann – Whitney U test when the distribution did not satisfy the assumption of normality.

Agreement between functional echocardiography and USCOM methods was assessed using The Bland – Altman analysis and expressed as mean difference (bias) and limits of agreement. Mean percentage error was also calculated to allow comparison with prior studies of Doppler cardiac output.

The chi-squared (x^2) test was used to determine statistically significant differences between the groups. If at least one probable number of observations in the data frequency table was less than five, the exact Fisher's exact criterion was additionally calculated.

By testing the statistical hypotheses, the significance levels (p) of the criterion were calculated to avoid the first type of errors, i. e. the likelihood of rejecting the correct statement. The statistical assumption was considered significant when $p < 0.05$.

Due to rounding, the sum of some percentages is less than or equal to one hundred per cent.

3. RESULTS

3.1. The characteristics of the groups

From 21 November 2017 to 15 September 2020, 162 both full-term and preterm neonates of various gestational ages were included in the study. Data from three subjects were not included in the analysis due to observed central circulatory impairment or failure to perform the examination in a technically qualitative manner.

Group of haemodynamically stable neonates (HSN)

127 newborns participated in the HSN group study – 53.5 per cent of girls (n = 68) and 46.5 per cent of boys (n = 59). There was no statistically significant difference in this group by the gender of participants (p = 0.535). The mean gestational age (SD; min – max) was 34.0 (4.9; 23–41) weeks. Their mean postmenstrual age (SN; min – max) on the day of examination was 36.4 (4.7; 27–44) weeks.

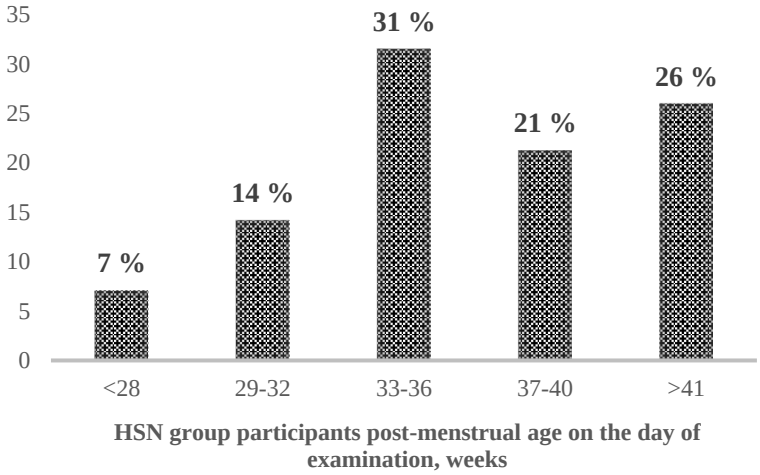


Figure 4. The distribution of subjects by postmenstrual age (%)

52.8 per cent (n = 67) of preterm neonates participated in the HSN group preterm and 47.2 (n = 60) per cent of full-term neonates, statistically evenly distributed (p = 0.528). The distribution of subjects by postmenstrual age (in per cent) is shown in Figure 4.

The mean (SN; min – max) weight of neonates in the HSN group on the day of examination was 2530 (1106; 805 - 4980) grams. Distribution data are presented in Figure 5.

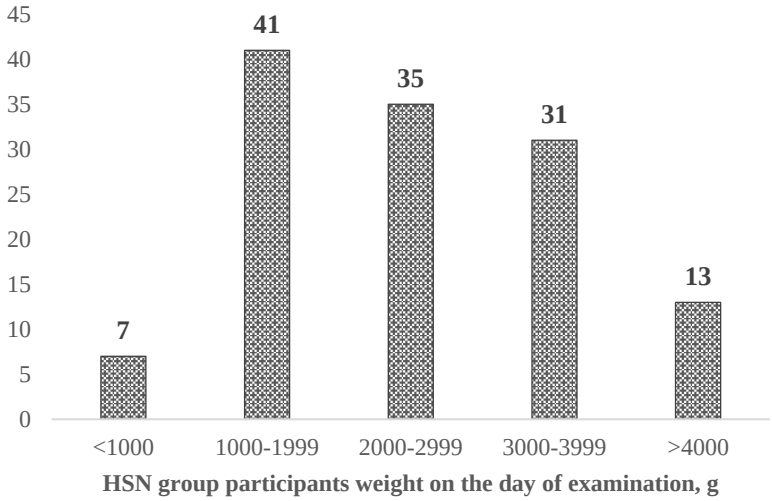


Figure 5. The distribution of subjects by their weight on the day of examination (n)

The reasons for inpatient treatment of HSN group study participants are shown in Figure 6. It provides diagnoses for hospitalization of a patient for treatment, examination, monitoring, or nursing. During the examination, all subjects were haemodynamically stable and there was no haemodynamically significant intra-cardiac shunting. Minimal non-invasive respiratory therapy was applied to the 6 smallest study participants. It was stopped during the examination, the signs of respiratory failure did not appear, so it can be stated that

the positive airway pressure did not affect the blood circulation of the subjects.

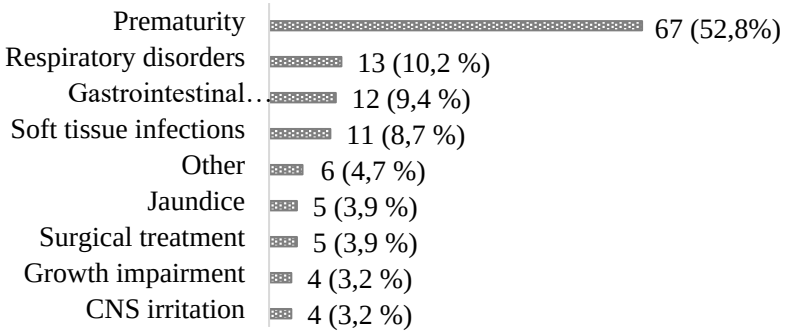


Figure 6. Diagnoses for hospitalisation of the subjects

More than half (53 per cent) of the study participants had a primary diagnosis of preterm birth. The diversity of co-morbidities, other than systemic infectious disease or haemodynamically significant condition, is not reflected in the data provided. The sub-group of preterm infants was dominated by respiratory disorders during hospitalization, but subjects no longer showed signs of respiratory failure during the examination. Due to gastrointestinal disorders, newborns were hospitalized for malnutrition, hematemesis (vomiting due to ingested blood with mother's milk), food intolerance, and a history of necrotizing enterocolitis. Eleven subjects were treated for local skin or soft tissue infections (conjunctivitis, whitlow, omphalitis, mastitis). Five neonates required surgical treatment for congenital malformations (atresia of various intestinal segments) or a postnatal condition (groin hernia, hemangioma) during the initial stage of hospitalization. Jaundice was observed in five neonates during hospitalization. Due being small for gestational age four neonates were enrolled in the study. An equal number of them were observed or treated for the signs of central nervous system irritation or inhibition. The other six neonates were hospitalized for examination

or treatment for anemia, paratrophy (excessive birth weight), postpartum trauma, and an observed episode of goiter. During the study all participants in the sub-group of preterm neonates were haemodynamically stable and in the recovery phase from the underlying hospitalization disease or condition.

Group of neonates with suspected or confirmed systemic disease (SSN)

The SSN group study included 32 neonates of various gestational and postmenstrual age who had a suspected or diagnosed systemic infection according to at least one laboratory and at least two clinical criteria. They were included in the study immediately after hospitalization or when the hospitalized patient showed the first signs of a possible infectious disease, before the start of specific treatment. In the SSN group, haemodynamic monitoring was performed on 11 preterm and 21 full-term neonates during the first two weeks of life. Eight patients in this group (25 per cent) underwent mechanical ventilation. One full-term and three of the lowest-weight preterm patients (a total of 12.5 per cent) died from complications caused by sepsis. The pathogen was identified in 59.4 per cent of patients (Table 1).

Table 1. Characteristics of SSN group

Characteristics	**SSN group**	**Undetected pathogen subgroup**	**Identified pathogen subgroup**	**Died**
	n=32	**n=13**	**n=19**	**n=4**
Gestational age, wks. (MD; min – max.)	39; 24-41	39,5; 28-40	39; 24-41	29; 24-39
Birthweight, g (MD; min – max)	2800; 650-3900	2805; 1020-3900	3460; 650-3840	680; 660-3500
Male, per cent	44,8	50	40	75

Characteristics	SSN group	Undetected pathogen subgroup	Identified pathogen subgroup	Died
	n=32	n=13	n=19	n=4
Postmenstrual age, wks. (MD; min – max)	39; 26-44	40; 29-43	39; 26-44	30; 26-39
Weight on the day of examination, g (MD; min – max)	3310; 730-3950	2902; 1020-3900	3460; 730-3950	800; 730-3500
Identified pathogen, per cent	59,4	0	100	100
Mechanical ventilation, per cent	25	8,3	35	100

Blood, cerebrospinal fluid and/or urine culture, polymerase chain reaction (PCR) assays, and complete blood count and C-reactive protein tests were performed to confirm the diagnosis. Blood cultures were performed in 90.6 per cent (n = 29) of subjects, 9.4 per cent of cases (n = 3) – PCR assay only. Ten subjects (40.6 per cent) underwent both a blood culture and a PCR assay. The pathogen was successfully grown in the blood culture in 62 per cent of cases (n = 18), no bacterial growth was observed in eleven cultures. Polymerase chain reaction studies were performed in 42 per cent (n = 13) of sick neonates, in 7.1 per cent (n = 3) of the cases, the most common pathogens causing sepsis in neonates were not found, and the pathogen was identified in ten cases. Lumbar puncture and cerebrospinal fluid culture were performed in 83.3 per cent (n = 15) of neonates after the receipt of a positive blood culture, and lumbar puncture was not performed in the remaining three as the patient‘s condition was clinically improving (Figure 7).

Sepsis caused by group B streptococcus (*Streptococcus agalactiae*) was confirmed in one third (n = 11) of patients, and five patients had it along with meningitis. Three cases of intestinal rods (*E. coli*), two *Haemophilus influenzae*, two methicillin-resistant

hemolytic staphylococci, which caused meningitis, were submitted for analysis.

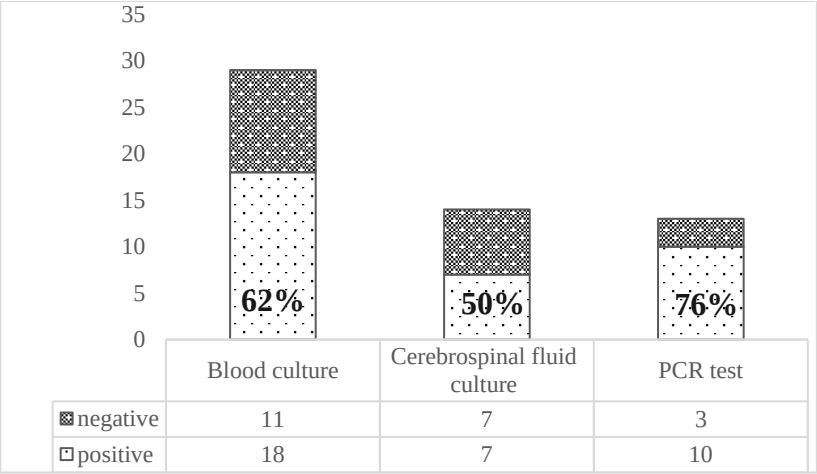


Figure 7. Tests used for detection of the pathogen

There was also one case of infection with Staphylococcus aureus, *Klebsiella pneumoniae* sepsis and respiratory syncytial virus. No pathogen, antibodies or antigens in the blood were found in eleven subjects: four were diagnosed with acute pneumonia and one was diagnosed with acute pyelonephritis. Neither the source of the infection nor the pathogen could be identified for six sick neonates, but they were included in the SSN group according to clinical and laboratory criteria for infection.

3.2.Comparison of functional echocardiography and non-invasive ultrasonic cardiac output monitor

Statistical analysis of data collected by functional echocardiography and USCOM showed a statistically significant difference between all the echocardiography and the USCOM measurements. The USCOM tended to produce higher mean estimates than echocardiography (Table 2). Despite this, there was minimal bias on the Bland – Altman analysis

Table 2. Comparison of stroke volume, velocity time integral, cardiac outputs between echocardiography and the USCOM.

	ECHO (SD)	USCOM (SD)	*p* value	ICC	BIAS (SD)	LOA	PE (%)
Stroke volume (SV), ml	3.96 (1.89)	4.25 (2.22)	<0.001	0.98	-0.3 (0.54)	-1.35 to 0.75	8.5 (7.2
Velocity time integral (VTI), cm	12.6 (2.0)	13.4 (2.2)	<0.001	0.80	-0,8 (1,34)	-3.44 to 1.81	10.2 (7.
Left ventricular output (LVO), ml/min	604 (280)	640 (321)	<0.001	0.98	-35.6 (76.1)	-184.7 to 113.6	8.4 (6.9
Left ventricular output (LVO), ml/kg/min	243 (46)	255 (53)	<0.001	0.88	-11.9 (25.3)	-61.5 to 37.8	8.3 (6.9

There was a significant difference between the stroke volume measurements obtained by echocardiography and the USCOM. The stroke volume showed a very high correlation between the USCOM and echocardiographic measurements. The mean bias was small, but with wide limits of agreement (Table 2, Figure 8).

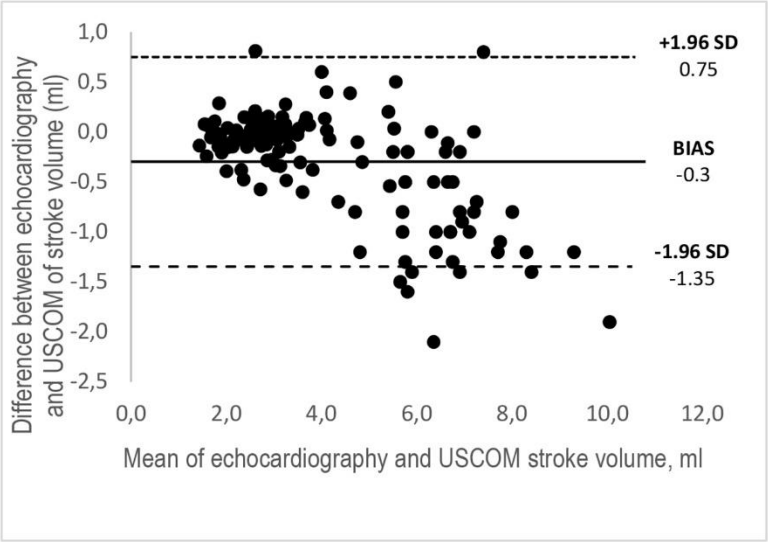


Figure 8. Bland - Altman plot for echocardiography and the USCOM measured stroke volume

The aortic valve peak velocity of the left ventricular outflow tract was larger when measured with continuous wave Doppler by the USCOM than when measured with pulse wave Doppler by echocardiography. The VTI measurements obtained by the two methods showed high correlation. The Bland - Altman plot showed that the difference between the VTI, as measured by the USCOM and echocardiography, had also small mean bias, but rather wide limits of agreement (Table 2, Figure 9).

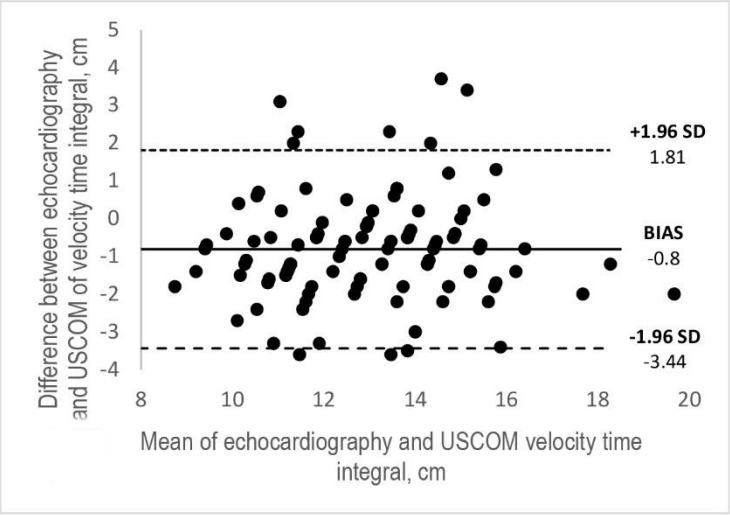
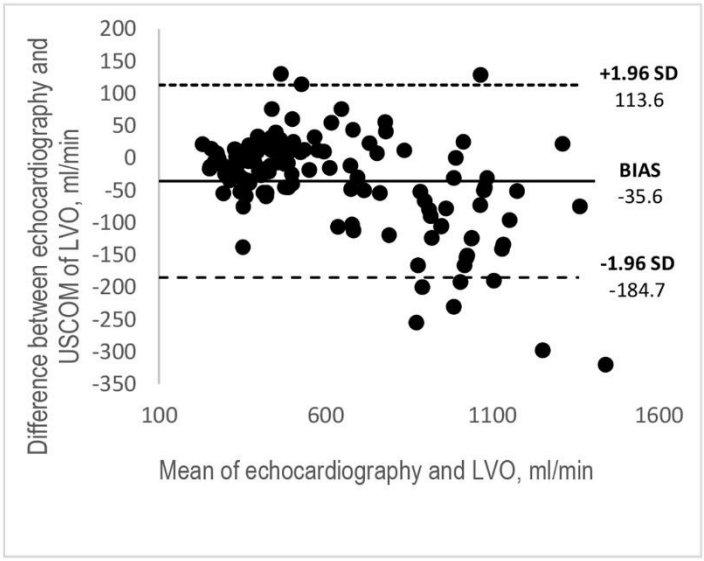


Figure 9. Bland - Altman plot for echocardiography and the USCOM measured velocity time integral

There was a significant difference between the cardiac outputs calculated from both sets of measurements. The left ventricular outputs showed a high correlation between the USCOM and echocardiographic measurements (Table 2). There was an increased mean bias with higher left ventricular output, as seen on the Bland-Altman plot (Figure 10).

Overall, when cardiac output was monitored with the USCOM using continuous wave Doppler, it overestimated the pulse wave Doppler echocardiographic measurements, especially when it came to measuring aortic valve peak velocity. The percentage error of the cardiac output of the whole sample was 8.4 ± 6.9 per cent.



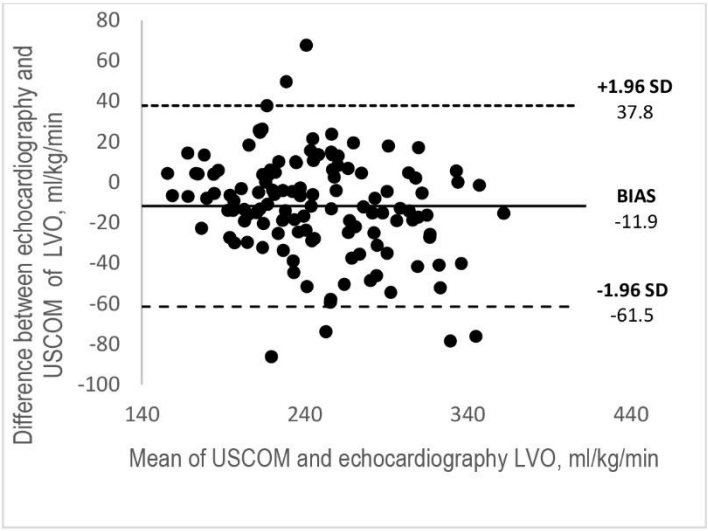


Figure 10. Bland - Altman plot for echocardiography and the USCOM measured left ventricular outputs in ml/min and in ml/kg/min

3.3. Reference values for haemodynamic parameters measured with USCOM

The same subjects of the haemodynamically stable neonatal (HSN) group were included in this part of the study. Analyzing the collected data, there was no statistically significant difference between the genders for any of the parameters ($p = 0.366 – 0.941$), so we divided the subjects into groups according to their postmenstrual age (less than 32 weeks, 32-36 weeks and 37 and more weeks) and weight on the study day (less than 1500 g, 1500–2999 g and 3000 g and more), but independent of gender. However, statistically significant differences in indexed indicators were observed only between the smallest and largest by age and weight, but not between adjacent groups. In addition, among both boys and girls, length greater than 50 cm and weight greater than 3000 g is typical of most neonates older than 37 weeks of gestation [8]. USCOM uses the length of the subject when it is greater than 50 cm to calculate the aortic valve diameter. However, if the subject's length is less than 50 cm, the device calculates the aortic diameter based on its weight [9]. Thus, both this technical factor of the USCOM and the physiological factors of the newborn determined that we divided the subjects into two groups of neonates weighing less and more 3000 g to determine the reference values. A group of 83 low-weight neonates (MSN) and 44 high-weight neonates (DSN) was formed.

Some haemodynamic parameters were distributed according to the normal distribution, some were not. Therefore, the obtained results were expressed as means ± standard deviation and as medians and percentiles. For convenience, all results were placed in a single Table No. 3.

Table 3. The USCOM reference values for haemodynamic parameters of the 127 neonates by weight.

Parameter	Mean (SD)	Weight <3000g, percentiles (n=83)			Mean (SD)	Weight ≥3000g, percentiles (n=44)			p values	U value
		10	50	90		10	50	90		
Outflow tract diameter, cm	**0.53 (0.08)**	0.44	0.51	0.61	**0.79 (0.05)**	0.76	0.79	0.83	<0.001	43
Velocity time integral, cm	**13 (2)**	10	13	16	**14 (2)**	10	14	17	0.043	1431
Peak velocity of flow, m/s	**0.9 (0.1)**	0.75	0.88	1.1	**0.95 (0.2)**	0.74	0.96	1.2	0.031	1401.5
Corrected flow time, ms	**382 (36)**	338	377	431	**382 (36)**	341	381	427	0.634	1732
Stroke volume, ml	**2.9 (1.1)**	1.7	2.7	4.1	**6.8 (1.4)**	5.1	6.9	8.7	<0.001	77.5
Stroke volume, ml/kg	**1.6 (0.3)**	1.2	1.6	2.1	**1.8 (0.3)**	1.4	1.8	2.2	0.002	1222.5
Stoke volume index, ml/m^2	**19 (4)**	15	19	24	**27 (5)**	21	27	34	<0.001	345
Minute distance, m/min	**21 (3)**	16	21	24	**21 (4)**	14	21	25	0.861	1791.5
Cardiac output, ml/min	**450 (163)**	280	420	672	**997 (226)**	705	1000	1250	<0.001	109.5
Cardiac output, ml/kg/min	**251 (54)**	192	244	326	**260 (53)**	191	257	346	0.406	1662
Cardiac index, $L/m^2/min$	**3 (0.6)**	2.3	3.0	3.8	**4 (0.8)**	2.8	4.1	5.1	<0.001	616.5
Systemic vascular resistance index, $d/s/cm^5/m^2$	**1370 (344)**	939	1340	1844	**1240 (296)**	884	1194	1700	0.024	1381
Smith-Madigan inotropy index, W/m^2	**0.6 (0.2)**	0.4	0.56	0.74	**0.9 (0.2)**	0.65	0.94	1.25	<0.001	268

As gaining the weight the aortic valve diameter was increasing – in MSN group it was 0.53 ± 0.08 and in DSN group – 0.79 ± 0.05 cm (p <0.001), also increasing the systolic and cardiac output – 2.9 ± 1.1 ml and 6.8 ± 1.4 ml, p <0.001 and 450 ± 163 and 997 ± 226 ml/min, respectively, p <0.001. However, the velocity – time integral, the peak velocity through the aortic valve, the flow time, the minute distance, systemic vascular resistance index and cardiac output for body weight remained constant regardless of neonatal gestational age or weight (Table 3). Statistically higher indexed values of haemodynamic parameters were observed with the growth of the newborn and strengthening of the heart muscle: Smith – Madigan inotropy index in the MSN group was 0.6 ± 0.2 and 0.9 ± 0.2 W/m^2, respectively, in the DSN group p <0.001, systolic volume per body weight was 1.6 ± 0.3 ml/kg and 1.8 ± 0.3 ml/kg, p = 0.002. The systolic volume index was 19 ± 4 and 27 ± 5 ml/m^2, respectively, p <0.001, and the cardiac index was 3 ± 0.6 and 4 ± 0.8 L/m^2/min, respectively, p <0.001.

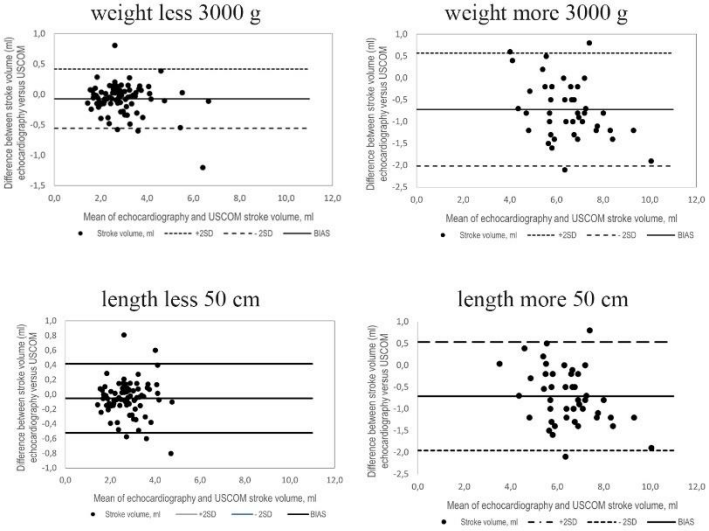


Figure 11. Bland – Altman plot for stroke volume in MSN and DSM groups according to the newborn‘s weight and length

The Bland-Altman analysis showed that the difference in bias of the systolic volume is between the MSN (weight less than 3000 g or length less than 50 cm) and DSN (weight more than 3000 g or length more than 50 cm) groups by both length and weight, however, there was no difference in either by length or weight in either group (Figure 11). In addition, in the MSN group bias was more close to zero than in the DSN group, also smaller limits of agreement. Thus, the haemodynamic parameters of newborns would be more accurate for calculations using their weight.

3.4. Haemodynamic changes during systemic infection in newborn

In order to detect the first haemodynamic changes, thirty-two neonates with clinical signs of systemic infection underwent laboratory tests for inflammation, pathogen detection, and USCOM monitoring prior to specific treatment. This examination was repeated 24 hours and later in those patients who had abnormal data during the first and subsequent monitoring and/or the patients whose clinical condition did not improve during the course of the disease. Early neonatal sepsis was suspected in 37.5 per cent (n = 12) of patients. Bacteriologically or by other laboratory methods, the diagnosis of sepsis was confirmed in 59.4 per cent (n = 19) of patients. There were found abnormalities of stroke volume index, cardiac index and systemic vascular resistance index in both – bacteriologically unconfirmed and confirmed sepsis groups (especially in vascular resistancy) that were more pronounced in the identified pathogen group (Figure 12). Although statistical significance was not achieved between these two groups due to the relatively small sample, there was a clear trend for lower systemic vascular resistance (index corresponding to < 10 percentiles) and higher stroke volume and cardiac output (index above 90 percentiles) in the group of the identified pathogen.

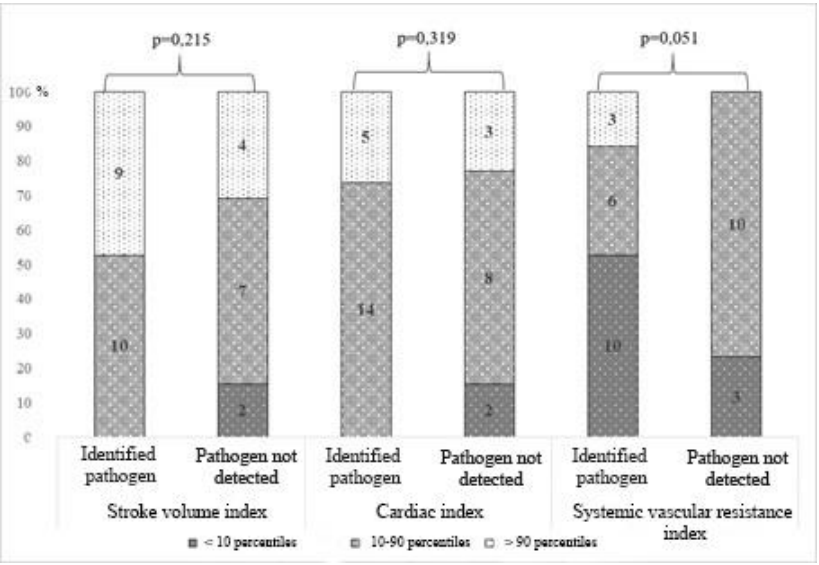


Figure 12. Stroke volume, systemic vascular resistance and cardiac indices in identified group and in the group where pathogen was not detected

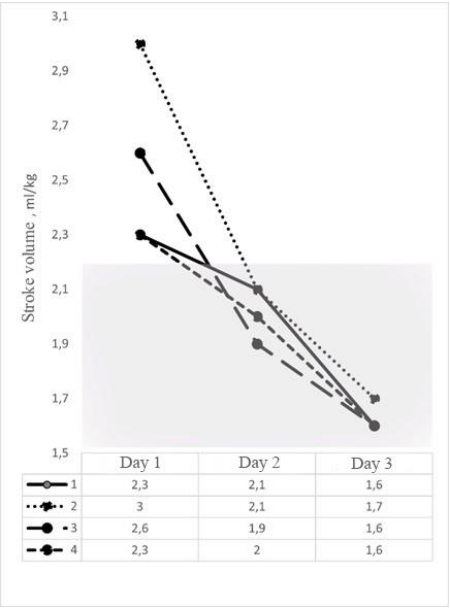
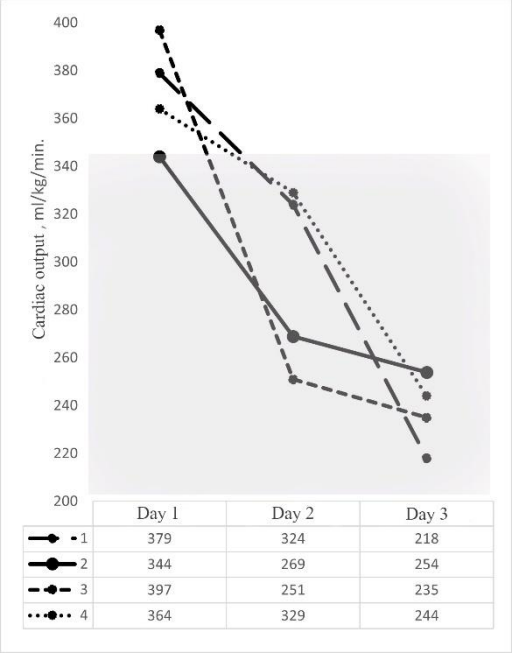


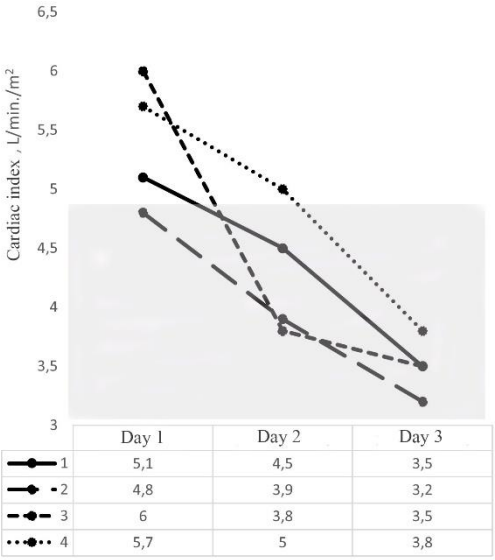
Figure 13. Dynamics of stroke volume during sepsis

Eight cases of clinically severe disease were observed in the cohort of subjects with evidence of systemic circulatory disorders during the first examination, including decreased systemic vascular resistance and simultaneously increased systolic and cardiac output. In all these cases, sepsis was bacteriologically confirmed, moreover, obvious inflammatory and clinical signs of the disease were observed. After correction of hypovolemia by fluid infusion, four of these patients were haemodynamically stable with no need for inotropes or vasoactive agents. Repeated monitoring of haemodynamics after a day and later revealed positive dynamics, with an improvement in systemic vascular tone (Figure 16) and a decrease in systolic and cardiac output to normal (Figure 13-15).



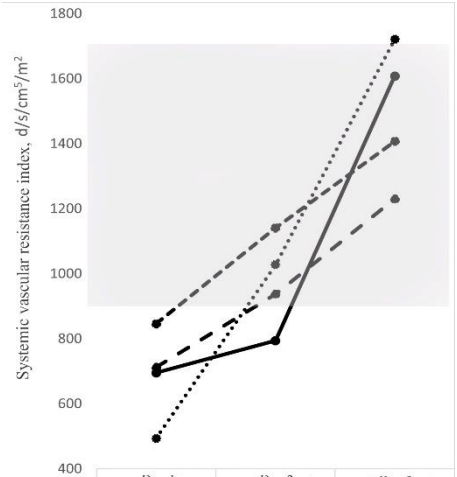
	Day 1	Day 2	Day 3
1	379	324	218
2	344	269	254
3	397	251	235
4	364	329	244

Figure 14. Dynamics of cardiac output during sepsis



	Day 1	Day 2	Day 3
1	5,1	4,5	3,5
2	4,8	3,9	3,2
3	6	3,8	3,5
4	5,7	5	3,8

Figure 15. Dynamics of cardiac index during sepsis



	Day 1	Day 2	Day 3
1	846	1141	1407
2	695	794	1608
3	494	1028	1721
4	712	937	1230

Figure 16. Dynamics of systemic vascular resistance index during sepsis

However, the other four – non-surviving – patients did not improve with intensive cardiovascular treatment and developed refractory to fluids shock. Persistent and treatment-resistant hypotension, impaired tissue perfusion, resulting in death during the first days of illness was observed in them (Figure 17).

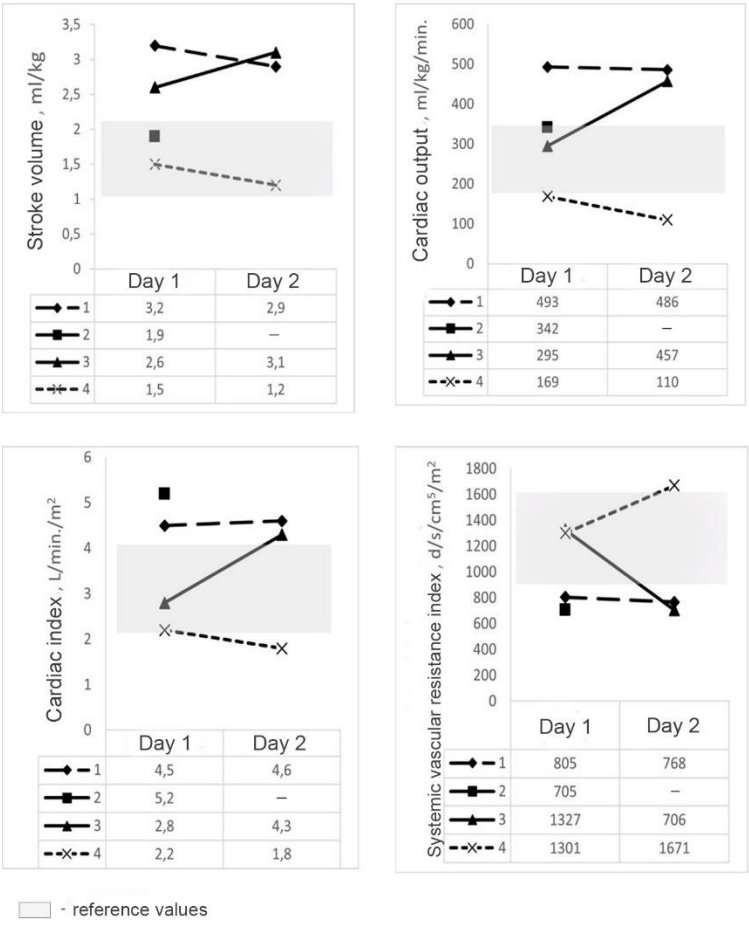


Figure 17. Haemodynamics of patients who died

4. DISCUSSION AND REVIEW OF THE RESULTS

Functional echocardiography, as a clinical standard in neonatology, is routinely used in clinical practice to assess cardiac function [10, 11]. It is accurate enough, but it is not always possible to perform this examination at the patient's bedside and as many times as the clinical situation requires, especially in a severely ill patients [12]. Accurate examination can be performed only by a specialist, usually a pediatric cardiologist who has experience in neonatal echocardiography [6]. The non-invasive ultrasonic cardiac output monitor USCOM makes the examination simpler, and any physician who understands cardiovascular physiology can learn to use it and evaluate the results obtained. This device has been validated and used to monitor hemodynamics in both adults and children, especially the severely ill ones, for more than 10 years [13]. Repeated examination at the patient's bedside can monitor changes in hemodynamics during intensive care, and assess the effectiveness and need for treatment [14]. However, to date, there has been a lack of evidence that the non-invasive ultrasonic cardiac output monitor USCOM can be as accurate as classical cardiac ultrasound in assessing cardiac output in neonates of various gestational ages. Therefore, our first aim of the study was to compare neonatal hemodynamic parameters obtained using classical echocardiography and non-invasive ultrasonic cardiac output monitor, i. e. to find out whether USCOM could partially replace classical echocardiography at the patient's bedside when there is no possibility to repeat the ultrasound examination as needed. Another thing is that neonatal reference values provided by a USCOM manufacturer are calculated based on certain formulas and algorithms rather than presented in a population-specific study. This prompted us to investigate the main hemodynamic parameters of haemodynamically stable neonates of various gestational ages at the Neonatology Center and to determine their reference values specific to this particular method. Having the reference values, we were later able to compare them with the most important indicators of

hemodynamics in neonates with systemic infection and to determine the changes during the illness.

4.1.Comparison of USCOM and Echocardiographic Measurements

Full-term and preterm haemodynamically stable neonates for whom the pediatric cardiologist has established an anatomically normal heart without congenital malformations and intra-cardiac shunting were enrolled to this prospective clinical trial. Also, subjects in the study had no signs of respiratory failure and systemic infection that could affect cardiac function, blood circulation, or vascular tone. Thus, based on the selection criteria listed above, the subjects formed a sufficiently homogeneous group.

Clinical trials in which several investigators examined the same patient with a USCOM device showed that this did not significantly affect the results, indirectly confirming that examination of the patient with a non-invasive ultrasonic cardiac output monitor is simple enough and can be widely used at the patient's bedside. [15-18]. Dey and co-authors confirmed that after 20 studies, accurate measurements are obtained with this monitor [19]. Other researchers have reported that the USCOM methodology is easy to master [16, 17, 20]. In this study, the assessment of neonatal hemodynamics was performed by one investigator, a neonatologist- intensivist who has the basics of neonatal cardiac ultrasound and uses this ultrasonic cardiac output monitor in clinical practice. We believe this has increased the value of the current study and minimized the likelihood of potential study errors.

4.2.Comparison of Left Ventricular Outflow Tract Diameter

We first compared the aortic diameter at the valve – the size of the only anatomical structure in the circulatory assessment, as measured by an echocardiography and calculated by a non-invasive

ultrasonic cardiac output monitor. Data from this study, as from many other studies, show that there is no statistically significant difference, only the minimal bias between the LVOTD measured by echocardiography and the estimated cross-sectional area of the non-invasive ultrasonic cardiac output monitor based on pre-recorded nomenclatures of Nidorf with co-authors based on patient length. If the subject's length is less than 50 cm, then the implied aortic valve diameter is calculated from its weight. [9, 21]. Fifty centimeters in length corresponds to approximately 3000 g of newborn weight. The Bland – Altman plot for aortic valve diameter shows two distinct data clusters. A more detailed analysis of the collected data showed that there were only a few subjects in the sample weighing between 2400 g and 3000 g, which corresponds to an aortic diameter of 0.6–0.76 cm at the valve. We believe that these overlaps caused such a scattering as seen in the scatterplot. Despite this scattering, the aortic valve diameter determined by both methods was almost no different.

4.3. Comparison of Velocity – Time Integral

During the study, the time–velocity integral measured by a non-invasive ultrasound blood circulation monitor was statistically significantly higher than that measured by echocardiography (13.4 ± 2.2 and 11.8 ± 2.4 cm, $p < 0.001$), but with minimal bias (Figure 9). This trend has been observed by other researchers [18, 20, 22] who have tried to explain this difference by a possible researcher's error – not very precisely mounted ultrasound sensor causing inaccurate Doppler angling [22], or different principle of operation of the devices themselves – USCOM uses continuous waves, and echocardiography uses pulse wave dopplerometry [20]. The anatomy of the newborn results in his heart, along with the aorta and its valve, being relatively close to the ultrasound window of the aortic valve of the ultrasound probe. Therefore, the influence of blood circulation of nearby organs, as well as other blood vessels, on the measurements of the time-

velocity integral is likely to be smaller [18] as well as a smaller bias than that obtained in adult measurements.

4.4.Comparison of Stroke Volume and Cardiac Output

Echoscopically measured mean systolic volume was lower and statically significantly different from that measured with a non-invasive ultrasonic cardiac output monitor, 3.96 ± 1.89 and 4.25 ± 2.22 ml, respectively, at p <0.001 (Figure 8).

A statically significant difference was also observed between cardiac output measured by both methods. This rate was also lower on cardiac ultrasound than that calculated from the USCOM study: 604 ± 280 ml/min in the echocardiography group and 640 ± 321 ml/min in the non-invasive ultrasonic cardiac output monitor group, respectively (p < 0.001) or 243 ± 46 ml/kg/min and 255 ± 53 ml/kg/min (p < 0.001), respectively (Figure 10).

However, there was a strong correlation in volumes measured by both methods, with minimal bias by the Bland – Altman analysis, although it was bigger at higher stroke volume and cardiac output.

It is known that resting or waking a newborn can affect changes in the newborn's pulse. Although manipulation of the transducer during the examination did not usually cause discomfort to the subject (it is similar to that caused by measuring arterial blood pressure using a cuff), some neonates were awake during the monitoring, which may have affected the heart rate of the subject. As is well known, heart rate is one of the determinants of cardiac output, even at stable systolic volume [20]. Thus, these factors may more or less lead to differences both between different measurement methods and between repeated measurements in the same way. Since, in this clinical study, a strong statistical relationship was found between cardiac output measured by both methods and the bias is practically the same, it can be stated that the latter factors do not affect our final data.

We agree with Cattermole and co-authors [13] that it may not be worth discussing the absence of completely similar values using

different measurement methodologies and different instruments. It is likely that the same reading measured by different methods will be of a different magnitude. It would be much more important to have their normal values and to follow in scientific and clinical practice those that are specific to a particular device. In addition, especially in clinical practice, it is not so much the absolute value of one or another indicator that is important, but the dynamic changes in that value that reflect the course of the disease, the effectiveness of treatment, etc.

4.5.Reference values for Assessing Neonatal Cardiac Output

This clinical trial involved a similar number of girls and boys, as well as full-term and preterm neonates. As already mentioned, USCOM aortic valve diameter is determined from aortic length-dependent nomograms compiled by Nidorf and co-authors [66]. However, if the subject's length is less than 50 centimeters, the device calculates the aortic diameter based on the neonate's weight. Fifty centimeters in length is common for a newborn weighing 3,000 g. In addition, both boys and girls were taller than 50 cm and weighed more than 3000 g in the majority of full-term infants [8], and there was no statistically significant difference between the genders for any of the studied indicators ($p = 0.366 - 0.941$), we divided the subjects into two weight-dependent but gender-independent groups.

To the best of our knowledge, this is the first clinical study to assess neonatal blood circulation at the end of the period of circulatory adaptation, i. e. later than the first week of life, when circulatory reorganization has already taken place and other important changes in the body in the transition from intrauterine to extraterrestrial life have ended. There are particularly limited data on the circulatory characteristics of neonates at this stage of life. Examination of neonatal haemodynamics with a non-invasive ultrasonic cardiac output monitor and analysis of the results showed that increasing myocardial power was observed as the newborn grew. This trend can

be seen in the systolic and cardiac output volumes, as well as in the derived Smith-Madigan inotropy indexed indicators, 19 ± 4 and 27 ± 5 ml/m^2, respectively, $p < 0.001$, 3 ± 0.6 and 4 ± 0.8 L/m^2/min, $p < 0.001$, and 0.6 ± 0.2 and 0.9 ± 0.2 W/m^2, $p < 0.001$ (Table 3). However, as the heart rate decreases, the cardiac output remains stable for body weight, independent of either the newborn's age or weight. This has been found by other authors in the ultrasound examination of hemodynamic parameters of neonates of different gestational age [23–25]. Cattermole and co-authors, using a non-invasive ultrasonic cardiac output monitor in both infants, older children, and adults, found that the cardiac index increases until adolescence and remains constant in older age [13, 15]. The authors concluded that the cardiac index increases during the period of most intense growth and physical activity, when tissues have the highest oxygen demand [13]. It is well known that growth is most intense during the neonatal period, so a marked increase in cardiac muscle power is observed. However, the time-velocity integral, peak velocity through the aortic valve, adjusted flow time, minute distance, and indexed systemic vascular resistance remain constant regardless of the neonatal gestational age or weight. The same changes were observed in the works by Zheng and co-authors [25]. Changes in these indicators are primarily observed in heart failure, systemic infection, or exposure to medication. Statistical analysis of our data showed that as the gestational age of the newborn increases, so does the weight of the heart muscle, but also the anatomical structure of the heart, including the aortic valve – the diameter of the aortic valve is 0.53 ± 0.08 cm of those weighing less than three kilograms in the group (MSN) and 0.79 ± 0.05 cm, respectively, $p < 0.001$ in the group of the larger ones (DSN). The results obtained do not contradict the aortic root diameter data of Calado and co-authors of ultrasound-examined neonates who were extremely lightweight [26].

This part of the clinical study was important primarily because, using a non-invasive ultrasonic cardiac output monitor, we established reference values for haemodynamically stable neonates of different

ages, which we could use as comparative in examining neonates with systemic infection. Based on USCOM measurements, we additionally calculated systolic and cardiac output for body weight (Table 3), which could be useful in assessing hemodynamics not only in systemically infected but also in other neonates with severe conditions and in making urgent treatment decisions [27 - 30].

4.6. Haemodynamic changes during systemic infection

It is known that from the very beginning of systemic infection, various biologically active substances are released, inflammatory mediators that affect both systemic and peripheral blood circulation. As the disease progresses, these biologically active substances can completely unbalance the mechanisms of circulatory regulation. Both pediatric and neonatal and adult intensivists often experience a clinical manifestation of sepsis – "cold" or "warm" septic shock – a late, decompensated sign of haemodynamics [29]. Since progressive cardiovascular failure, which eventually results in fluid refractory shock, is the leading cause of neonatal death, it is essential to anticipate and alert the progression of circulatory failure, and to select timely and targeted treatment. This could undoubtedly not only increase the chances of neonatal survival, but also help to reduce the likelihood of remote residual phenomena among survivors [31]. Innovative technologies implemented in modern devices can be used to monitor changes in common clinical vital signs, such as heart rate, before the clinical onset of systemic infectious disease [129, 130]. Clinically visible signs of sepsis are known to be an expression of advanced disease, so it is particularly important to diagnose systemic infection as early as possible and to properly assess changes in the body, including hemodynamic changes. Although there is a lot of information in the literature on various biochemical markers of blood that could serve for early diagnosis of sepsis, we have not been able to find data on how these markers may be associated with changes in hemodynamics at the onset of the disease. Ideally, those changes in

hemodynamics could be detected before the onset of clinical signs of sepsis and, or the emergence of biochemical markers of infection. However, in this case, all neonates, or at least those at higher risk of sepsis, should be monitored before the first clinical and/or laboratory signs of sepsis appear. Although in theory it is already possible to do so, in clinical practice it is hardly feasible so far.

One of the initial hypotheses of our clinical study was that in a neonate with a systemic infection, changes in hemodynamics occur very early, which, if detected early, could help not only to diagnose sepsis early, but also to manage it. In this study, we tried to include patients as early as possible at the first signs of possible disease. Difficulties in the early diagnosis of sepsis posed serious problems in seeking to include sufficient subjects in this study in a timely manner. Moreover, some subjects did not have a diagnosis of systemic infection – they were diagnosed with a local infection (pneumonia, urinary tract or soft tissue infection) or even a heart rhythm disorder that clinically mimicked early neonatal sepsis. The haemodynamic parameters of all patients with the latter diseases corresponded to the normal values for their age. However, in both bacteriologically confirmed and unconfirmed sepsis groups, nearly all haemodynamic parameters were found to deviate from the reference values (especially blood vessels), which were more pronounced in the identified pathogen group. Although statistical significance was not achieved between the two groups due to the relatively small sample size, there was a clear trend for lower systemic vascular resistance and higher systolic and cardiac output in the group of identified pathogens. Deep, de Waal and co-authors also point out that neonatal sepsis is more characterized by hyperdynamic cardiac activity, at least at the onset of the disease, and the subsequent course depends on the pathogen. [32, 33]. Summarizing the results of this part of the study, it should be noted that circulatory disorders are not characteristic of the early stage of the disease. Of the 19 subjects in whom the pathogen was identified, only eight had changes in circulatory function during the first examination, more likely with systemic vascular resistance and later

with deviations in cardiac systolic and minute volume. In all these cases, sepsis was confirmed bacteriologically, and marked inflammatory and clinical signs of the disease were observed. Decreased vascular resistance was accompanied by hypovolemia, which, when adjusted by fluid infusion, resulted in stable haemodynamics in four of these patients and no need for medications to affect cardiac function and vascular tone. Repeated monitoring after a day and later showed positive dynamics – improved systemic vascular tone, decreasing to normal stroke volume and cardiac output. However, four non-surviving patients did not improve with intensive cardiovascular treatment and developed fluids refractory shock. Persistent and unresponsive hypotension, impaired tissue perfusion, and death were observed. Other authors who have observed patients with sepsis indicate that the longer the state of shock persists, the less likely it is to survive and recover [34, 35]. Prolonged hyperdynamic cardiac work requires more extra energy, and diastolic cardiac function begins to fail, resulting in coronary insufficiency and rapidly developing heart failure [36, 37].

Although the sample of patients in our study was relatively small, the results obtained and the trends observed are similar even with different means of monitoring cardiac function and blood circulation. Many researchers indicate that the range of one or other of the same indicators reflecting hemodynamics can be very wide, as can the course of the disease itself. It must be agreed with de Waal and colleagues that there is no and cannot be a uniform scenario for the disease. Therefore, it is very important to have tools that allow a specialist to monitor hemodynamics, assess the course of the disease and steer it in the desired direction in a timely manner [38–40]. The non-invasive ultrasonic cardiac output monitor USCOM is a fairly simple, easy-learning method for neonatal monitoring of haemodynamics that can be successfully used at the patient's bedside. The device can be easily used by a medical professional who understands cardiovascular physiology, does not have the experience of an ultrasound and/or pediatric cardiologist [16, 41], who can

monitor changes in haemodynamic parameters in a trend window, especially in the context of changing disease [7, 42, 43].

5. CONCLUSIONS

1. Comparing velocity-time integral, stroke volume, cardiac output, and systemic vascular resistance measured by functional echocardiography and USCOM, a strong correlation was found, with a minimal bias and acceptible limits of agreement between the above parameters confirming the accuracy of both methods.
2. Reference values for haemodynamic parameters of haemodynamically stable neonates measured by USCOM can be used to assess the hemodynamic characteristics of sick and preterm infants, taking into account that calculating the aortic diameter based on the weight of the newborn results in a narrower limits of agreement than calculating it based on the length of the newborn.
3. The majority of patients with suspected or confirmed systemic infection had no cardiac or circulatory abnormalities at the baseline, and their primary haemodynamic parameters were within the reference range, but early and persistent changes in blood circulation indicate the severity of the disease and the possible outcome.

6. PRACTICAL RECOMMENDATIONS

- The non-invasive ultrasonic cardiac output monitor can be used by any physician who understands cardiovascular physiology. With this device, the most important components of haemodynamics (flow, vascular status and inotrophy) can be assessed simultaneously. The results of the monitoring are presented in numerical form, they are not difficult to interpret.
- After recording the subject's anthropometric data on the patient's card, the screen displays the highest, widest and straightest time–velocity integrals the operator adjusted the angle of insonation to return the best Doppler curve. The goals of adjustment were to obtain a flow profile that was well defined at the base and peak – the highest, fullest, most complete curves indicates the best alignment with aortic valve.
- Select 3–5 most regular, consecutive cycles for the analysis of the obtained data.
- It is recommended to use the reference values obtained during this study (Table 3) for the interpretation of neonatal haemodynamics.
- Indicators of stroke volume and cardiac output for body weight (Table 3) could be useful in assessing hemodynamics in neonates in severe condition and in making immediate treatment decisions.

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