

Natalia Kretsu, Olena Koloskova, Tetiana Bilous

## Peculiarities of changes in the cardiovascular system in the course of sepsis in newborns

### Specyfika zmian w układzie krążenia w przebiegu sepsy u noworodków

Department of Paediatrics and Children Infectious Diseases, Bukovinian State Medical University, Chernivtsi, Ukraine

Correspondence: Tetiana, Department of Paediatrics and Children Infectious Diseases, Bukovinian State Medical University, Teatralna sq., 2, Chernivtsi, 58002, Ukraine,

tel.: +380502213516, e-mail: bilous.tetiana@bsmu.edu.ua

#### ORCID iDs

1. Natalia Kretsu <https://orcid.org/0000-0003-0241-0700>

2. Olena Koloskova <https://orcid.org/0000-0002-4402-8756>

3. Tetiana Bilous <https://orcid.org/0000-0002-9469-401X>

#### Abstract

The issues of early diagnostics of cardiovascular disorders in neonates with sepsis using up-to-date methods of examination are relevant today and will remain so in the future. They can be used as screening methods with the purpose to verify the possible development of cardiovascular dysfunction. **Aim of the study:** The study aimed to investigate the peculiarities of possible changes in the cardiovascular system and physiological electrical heart activity in neonates with signs of generalised infectious-inflammatory process, and to assess possible diagnostic methods and use of electrocardiography to verify cardiovascular disorders in newborns with neonatal sepsis. **Materials and methods:** To achieve the study objective, we followed up a total of 69 neonates with signs of generalised infectious-inflammatory process. Group I (32 patients – 46.4%) included neonates with a term of gestation of 37–42 weeks, and group II included 37 preterm neonates (53.6%) with a term of gestation under 36 weeks inclusive. **Results:** Generalised infectious-inflammatory process during the neonatal period of term infants is accompanied by electrocardiographic signs of left ventricular overload associated with the female sex ( $r = 0.30$ ), delivery by cesarean section ( $r = 0.27$ ), and assessment of neonatal condition by a 5-minute Apgar score ( $r = -0.33$ ). The study demonstrates that increased values of lactate dehydrogenase activity in the blood plasma both in the term and preterm neonates are associated with left ventricular overload among the former, and the right ventricular overload among the latter, that is, preterm neonates. **Conclusions:** Increased values of lactate dehydrogenase activity in the blood serum of both term and preterm neonates are associated with left ventricular overload in term neonates, while right ventricular overload in preterm infants thus can be considered as a marker of cardiovascular dysfunction caused by neonatal sepsis, especially in the subpopulation of term patients considering its diagnostic value. Changes found in electrophysiological heart activity promote the necessity of routine use of electrocardiography in neonates with signs of the septic process.

**Keywords:** neonatal sepsis, newborns, cardiovascular system

#### Streszczenie

Wczesna diagnostyka zaburzeń układu krążenia u noworodków z sepsą przy wykorzystaniu dostępnych metod badań ma istotne znaczenie dziś i można przyjąć, że będzie tak również w przyszłości. Metody te mogą być wykorzystywane w ocenie przesiewowej w celu weryfikacji ewentualnych zaburzeń w obrębie układu krążenia. **Cel pracy:** Celem pracy była analiza specyfiki potencjalnych zmian w układzie krążenia i czynności elektrofizjologicznej serca u noworodków z objawami sepsy oraz ocena dostępnych metod diagnostycznych i przydatności elektrokardiografii przy weryfikacji zaburzeń w obrębie układu krążenia u noworodków z sepsą. **Materiał i metody:** Obserwacją objęto łącznie 69 noworodków z objawami sepsy. Grupa I (32 dzieci – 46,4%) obejmowała noworodki urodzone o czasie, w 37.–42. tygodniu ciąży, a grupa II – 37 wcześniaków (53,6%) urodzonych do 36. tygodnia ciąży włącznie. **Wyniki:** Sepsie w okresie noworodkowym u dzieci urodzonych w terminie towarzyszą objawy elektrokardiograficzne przeciążenia lewej komory, które wykazują zależność z płcią żeńską ( $r = 0,30$ ), porodem przez cesarskie cięcie ( $r = 0,27$ ) oraz oceną stanu noworodka w skali Apgar w 5. minucie życia ( $r = -0,33$ ). Badanie wykazało, że podwyższone wartości aktywności dehydrogenazy mleczanowej w osoczu krwi zarówno u noworodków urodzonych o czasie, jak i wcześniaków wiążą się z przeciążeniem lewej komory w pierwszej z wymienionych grup oraz przeciążeniem prawej komory w drugiej grupie ( wcześniaczej). **Wnioski:** Podwyższone wartości aktywności dehydrogenazy mleczanowej w surowicy krwi

zarówno u noworodków urodzonych w terminie, jak i wcześniaków wiąże się z przeciążeniem lewej komory u noworodków urodzonych w terminie oraz przeciążeniem prawej komory u wcześniaków. Na tej podstawie można uznać je za marker zaburzeń układu krążenia wywołanych sepsą noworodkową, zwłaszcza w podpopulacji dzieci urodzonych w terminie, biorąc pod uwagę ich wartość diagnostyczną. Stwierdzone zmiany w elektrofizjologicznej czynności serca przemawiają za koniecznością rutynowego wykonywania elektrokardiografii u noworodków, u których występują objawy rozwoju procesu septycznego.

**Słowa kluczowe:** sepsa noworodkowa, noworodki, układ krążenia

## INTRODUCTION

Cardiovascular disorders during the neonatal period are the total sum of disorders occurring in neonates within the cardiovascular system in response to a concomitant pathology or other pathological conditions. The topicality of the issue is determined by a high rate of occurrence of the nosology and polymorphism of clinical signs. Therefore, clinical assessment of haemodynamic disorders is complicated. It is subjective, and furthermore it often leads to missing the early disorders of the cardiovascular system<sup>(1)</sup>.

Cardiac rhythm disturbances occurring during the neonatal period are most typically associated with extracardiac causes and reflect the state of physiological tension or instability of the vital functions<sup>(2)</sup>. Cardiac dysfunction is a common complication after severe sepsis and septic shock. At the same time, the available literature contains only a limited amount of studies dealing with sepsis-induced myocardial dysfunction in neonatology<sup>(3)</sup>. Pathogenesis of the disease is multifactorial. It is characterised by complicated dynamics, a wide spectrum of multiple organic and functional-metabolic disturbances controlling the disease at the organ, cellular and molecular levels. The infectious-inflammatory process is a major damaging factor resulting in disturbance of energy metabolism at the cellular level, reduced formation of high-energy bonds in the cardiac histiocyte mitochondria, and cellular death processes occurring through apoptosis<sup>(4)</sup>.

Myocardial dysfunction mediated by sepsis is one of the most common components of multiple organ inequality in cases of severe sepsis and septic shock<sup>(5)</sup>. The mortality rate due to sepsis has been found to increase twice in patients developing cardiovascular dysfunction and septic shock<sup>(6)</sup>. Therefore, the issues of early diagnostics of cardiovascular disorders in neonates with sepsis using up-to-date methods of examination are relevant today and will remain so

in the future. They can be used as screening methods with the purpose to verify the possible development of cardiovascular dysfunction with generalised infectious-inflammatory process.

## AIM OF THE STUDY

To investigate the peculiarities of possible changes in the cardiovascular system and physiological electrical heart activity in neonates with signs of generalised infectious-inflammatory process, and to assess possible diagnostic methods and use of electrocardiography to verify cardiovascular disorders in newborns with neonatal sepsis.

## MATERIALS AND METHODS

To achieve the study objective, we followed up a total of 69 neonates with signs of generalised infectious-inflammatory process in the Neonatal Intensive Care Unit, Department of Neonatal Pathology, and Department of Preterm Neonatal Care at the Regional Clinical Non-Profitable Institution «Chernivtsi Regional Children's Clinical Hospital» in the town of Chernivtsi. Group I (32 patients – 46.4%) included neonates with a term of gestation of 37–42 weeks, and group II included 37 preterm neonates (53.6%) with the term of gestation under 36 weeks inclusive. The general characteristic of the groups is presented in Tab. 1.

Differences between the groups according to their gestational age and parameters of physical neonatal development were considered to be natural, and they reflected correct formation of the study groups. Boys were found to suffer from sepsis reliably more often among term neonates, and no such regularity was found among preterm infants. Tab. 1 shows that the average age of mothers in the groups compared did not differ significantly. At the same time, delivery by cesarean section was more common in the group of preterm infants.

Parameter	Group I (n = 32)	Group II (n = 37)	p
Term of gestation [weeks]	38.5 ± 0.24	32.4 ± 0.40	<0.05
Boys [%]	68.75%	51.35%	>0.05
Body weight at birth [g]	3,297.3 ± 115.84	1,810.9 ± 80.46	<0.05
Body length at birth [cm]	52.5 ± 0.75	42.2 ± 0.69	<0.05
Cesarean section [%]	28.1%	56.76%	<0.05
Mother's age [years]	30.9 ± 1.24	29.5 ± 1.08	>0.05

Tab. 1. General characteristic of the study groups (M ± m)

Parameter	Group I (n = 32)	Group II (n = 37)	Control group (n = 26)	p
1-minute Apgar score	6.25 ± 0.37	5.92 ± 0.19	7.16 ± 0.23	$p_{I,II} > 0.05$ $p_{I,II,Contr.} < 0.05$
5-minute Apgar score	7.18 ± 0.41	6.21 ± 0.34	8.32 ± 0.17	$p_{I,II} > 0.05$ $p_{I,II,Contr.} < 0.05$
Proportion of neonates undergoing resuscitation in the delivery room [%]	32.3%	64.9%	11.54%	$p_{I,II} < 0.05$ $p_{I,II,Contr.} < 0.05$
Proportion of neonates requiring ALV [%]	38.7%	37.5%	-	> 0.05
Proportion of neonates requiring administration of inotropic drugs in the maternity home [%]	23.3%	28.6%	-	> 0.05

Tab. 2. Characteristics of infants' condition at birth

Using a pairing method and after receiving parents' written consent, a total of 26 neonates of similar sex and age (under 28<sup>th</sup> day of life) from the neonatal departments of the Regional Children's Clinical Hospital were included in the control group. Infectious-inflammatory diseases in these infants were ruled out, and the prevailing nosological forms were hypoxic-ischaemic encephalopathy, feeding disturbances, etc. Their mean age was  $38.7 \pm 0.23$  weeks, and male neonates constituted 53.8% of the group. The body weight at birth was  $3,237.1 \pm 111.17$  g, the body length was  $52.3 \pm 0.58$  cm, the mother's mean age was  $26.8 \pm 1.20$  years, and delivery by cesarean section occurred in 26.9% of cases. The patients with neonatal sepsis were examined and treated according to the current international recommendations and directives<sup>(7,8)</sup>. In addition to clinical examination, biochemical detection of ischaemic myocardial lesion markers in the blood serum was performed for all the neonates in the biochemical laboratory of the Regional Clinical Non-Profitable Institution «Chernivtsi Regional Children's Clinical Hospital,» using a biochemical analyser HTI BioChem FC-200 (USA) and reagents produced by Cormay (Poland), guided by the specified standards of the markers examined<sup>(9)</sup>. Thus, lactate dehydrogenase activity (LDH, norm 225–430 un/L) was determined in compliance with the recommendations of the German Society for Clinical Chemistry (Deutsche Gesellschaft für Klinische Chemie, DGKC).

To study the myocardial functional state electrocardiography (ECG) was used in the standard Einthoven's leads (I, II, III), in the intensified unipolar extremity Goldberg's leads (aVR, aVL, aVF) and in 6 chest Wilson's leads (V1–V6) with the velocity of 50 mm/sec. ECG was performed using the electrocardiograph Nihon Kohden's Cardiofax C (Japan) after feeding a neonate. Electrocardiograms were recorded and assessed according to the common method accepted in neonatology<sup>(10)</sup>, and the duration of the PQ interval and the P, R, S waves were determined. All the values were compared with those of healthy neonates according to the term of gestation<sup>(11)</sup>.

The study was conducted using the case-control method in parallel groups based on simple randomised sampling and after obtaining the parents' written consent. The research protocol and the informed consent form were approved by the Commission on Biomedical Ethics in biomedical scientific research of the Bukovinian State Medical University

(Minute No. 7, dated 19.04.2018). The results of the study were processed statistically using the variation statistics methods to calculate the arithmetic mean ( $M$ ) and standard mean error ( $m$ ). Spearman's method was used to evaluate correlations between qualitative parameters by calculating the binding force ( $r$ ) and its probability ( $p$ ). The parameters of clinical-epidemiological risk were assessed by determining the odds ratio (OR) and relative risk (RR) considering their 95% confidence interval (95% CI), and the value of attributive risk (AR). Data were processed statistically using the program StatSoft Statistica v 6.0., with a certain number of observations ( $n$ ). The critical significance level  $p$  for checking the statistical hypotheses in the study was  $p < 0.05$ .

## RESULTS

To assess myocardial involvement in the course of the infectious-inflammatory process in neonatal sepsis, examination of anamnesis or previous history of sick neonates was considered to be important, since some of them exhibited certain differences in clinical condition at birth which could be associated with generalised infection<sup>(12)</sup>. Tab. 2 presents the major clinical characteristics reflecting the adaptation of patients from the clinical groups under comparison to the extrauterine conditions of life, and the amount of therapy needed to support the main vital functions.

Despite the lack of reliable differences in the adaptation parameters of children to the extrauterine conditions of life determined according to the Apgar score, a tendency for lower scores was marked both at the 1<sup>st</sup> and 5<sup>th</sup> minutes of life among the representatives of group II. In our opinion, it is indicative of poorer adaptation of preterm neonates to the extrauterine conditions, which was confirmed by a reliably higher percentage of such patients who required cardiopulmonary resuscitation ( $p < 0.05$ ). Preterm neonates suffering from neonatal sepsis received inotropic support in the maternity home more frequently. At the same time, the duration of inotropic support for preterm neonates was reliably longer and lasted  $4.3 \pm 0.54$  days in group II and  $2.3 \pm 0.57$  days in group I ( $p < 0.05$ ). An average therapeutic dose of dobutamine in group I was  $6.2 \pm 0.85$  µg/kg/min, and in group II –  $4.7 \pm 0.67$  µg/kg/min ( $p > 0.05$ ), which reflected certain peculiarities of administration of inotropic drugs considering the terms of gestation that severity

Parameter	Group I (n = 32)	Group II (n = 37)	Control group (n = 26)	p
Sinus tachycardia [%]	-	13.5%	-	
Atrial extrasystole [%]	-	5.4%	-	
Incomplete block of the right bundle of His [%]	33.3	35.7	3.85	$p_{I:II} > 0.05$ $p_{I:Contr.} < 0.05$
Disturbances of repolarisation processes [%]	78.6	86.7	23.1	$p_{I:II} > 0.05$ $p_{I:Contr.} < 0.05$
Amplitude of P wave in II lead [mm]	1.80 ± 0.10	2.01 ± 0.12	1.36 ± 0.14	$p_{I:II} > 0.05$ $p_{I:Contr.} < 0.05$
Duration of PQ interval [sec]	0.10 ± 0.003	0.09 ± 0.004	0.09 ± 0.004	$p_{I:II} = 0.05$ $p_{I:Contr.} < 0.05$
Shortening of PQ interval [%]	4.0	13.8	-	>0.05
Amplitude of RV1 wave [mm]	12.60 ± 1.06	10.48 ± 0.84	15.0 ± 1.48	$p_{I:II} > 0.05$ $p_{I:Contr.} < 0.05$
Amplitude of SV1 wave [mm]	7.40 ± 1.07	6.52 ± 0.74	8.71 ± 2.26	$p_{I:II} > 0.05$
Amplitude of RV6 wave [mm]	13.00 ± 1.15	12.52 ± 0.93	12.0 ± 1.38	$p_{I:II} > 0.05$
Amplitude of SV6 wave [mm]	8.96 ± 0.63	7.38 ± 0.57	7.57 ± 0.75	$p_{I:II} = 0.05$
Left ventricle overload [%]	76.0	48.3	3.85	$p_{I:II} < 0.05$ $p_{I:Contr.} < 0.05$
Right ventricle overload [%]	68.0	93.1	23.1	$p_{I:II} < 0.05$ $p_{I:Contr.} < 0.05$

Tab. 3. Major electrocardiographic changes found in patients in the two study groups

of disturbances within the cardiovascular system in patients with neonatal sepsis. At the same time, an average total dose of the drug with positive inotropic support obtained under conditions of the maternity home for preterm neonates was 20.21 µg/kg/min, and for term neonates – 14.29 µg/kg/min ( $p < 0.05$ ). In our opinion, it reflected a more serious degree of damage to the cardiovascular system due to generalised infectious-inflammatory process in preterm neonates. In the control group, severe general condition after birth was found in 11.5% of cases, and moderately severe condition in 38.5%, though the neonates did not require inotropic support in any of the cases.

Of note, the indicated therapy did not lead to any substantial improvement in the cardiac function, which was manifested by statistically reliable differences in the values of the mean arterial blood pressure which was  $49.2 \pm 1.00$  mm Hg in the group of term neonates, and  $46.8 \pm 0.51$  mm Hg among preterm neonates ( $p < 0.05$ ). Under conditions of neonatal intensive care units, where patients suffering from

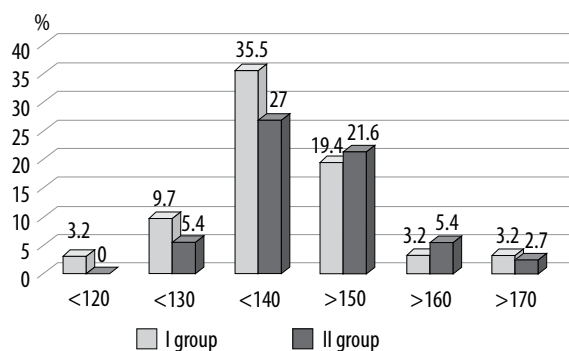


Fig. 1. Distribution of heart rate in children from the study groups (%)

neonatal sepsis were transported from the maternity homes of the region, inotropic support was used in both clinical groups with approximately the same frequency: 23.3% in group I and 14.7% in group II ( $p > 0.05$ ), and the ejection fraction of the heart by the results of echocardiography was higher in the group of preterm infants:  $77.6 \pm 0.94\%$  against  $73.7 \pm 1.07\%$  in the group of term patients ( $p < 0.05$ ).

Tab. 3 presents the major electrocardiographic changes found in patients from the clinical groups under comparison.

The data presented in Tab. 3 indicate that sinus tachycardia and atrial extrasystole occurred among preterm neonates exclusively, which was associated with disturbances of the repolarisation processes and relative shortening of the PQ interval, which might be explained by the effect of infectious factors on the excitability and conductivity of the electric impulse in the myocardium. A clear tendency for an increased P amplitude in II standard lead in the groups under comparison concerning the control group might be associated with cardiac distress and initiated resuscitation, as well as with morphological-functional immaturity and tension of the adaptation processes (in group II). Thus, the cases of shortening of the PQ interval to less than 0.08 s were found to prevail among the patients in group II (17.2%) against 4.0% among term infants. Duration of the PQ interval shorter than 0.1 s was found in 48.0% of children from group I and 79.3% of preterm neonates ( $p < 0.05$ ). Though statistically reliable differences in the distribution of the heart rate in the clinical groups compared were lacking, the tendencies found reflected the above supposition concerning the involvement of the electric excitability and myocardial conducting system of preterm neonates with accelerated generation and conduction of the electric impulse and shortening of the PQ interval.

Parameter	OR (95% CI)	RR (95% CI)	AR
LDH higher than 400 un/L group I: control	15.8 (7.82–31.73)	3.59 (2.26–5.71)	0.60
LDH higher than 400 un/L group II: control	11.0 (5.55–21.60)	2.91 (1.82–4.64)	0.53
LDH higher than 430 un/L group I: control	34.5 (14.71–80.92)	4.23 (2.15–8.30)	0.69
LDH higher than 430 un/L group II: control	18.9 (8.27–43.30)	3.04 (1.53–6.02)	0.60

Tab. 4. Parameters of risk of an increased lactate dehydrogenase (LDH) activity in children with neonatal sepsis

Fig. 1 illustrates the distribution of the heart rate in children from the two clinical groups, which is indicative of an insignificant predominance of bradycardia in patients in group I and a tendency for more frequent registration of tachycardia of more than 160 beats per minute in preterm children.

## DISCUSSION

The data presented above indicate that the generalised infectious-inflammatory process in the neonatal period among term infants is associated with electrocardiographic signs of the left ventricular overload, and among preterm infants – the right ventricular overload, which can be explained by the anatomical-physiological features of such children – persisting foetal circulation, and relative pulmonary hypertension in particular. It can be partially confirmed by study<sup>(13)</sup> describing heart rate variability in preterm infants with sepsis. The correlation analysis conducted in the study indicates a slight correlation between the signs of the left ventricular overload among the neonates suffering from sepsis and the female sex ( $r = 0.30$ ,  $p = 0.02$ ), delivery by cesarean section ( $r = 0.27$ ,  $p = 0.04$ ), and assessment of the neonate by the 5-minute Apgar score ( $r = -0.33$ ,  $p = 0.01$ ).

It should be noted that electrocardiographic markers of the right ventricular overload occurring mainly among preterm children were associated with a considerable shift of the leukogram to the left, which was manifested by the presence of statistically significant correlations between the signs of such overloads in the heart chambers and the relative content of metamyelocytes in the blood of neonates suffering from sepsis ( $r = 0.85$ ,  $p = 0.03$ ) and stab

neutrophils ( $r = 0.33$ ,  $p = 0.01$ ). At the same time, since the mentioned relationships can be partially explained by the anatomical-physiological peculiarities of the haematopoietic system of neonates with different gestational ages, than a statistically reliable connection of the electrocardiographic signs of the right cardiac side overload with lactate dehydrogenase activity in the blood serum ( $r = 0.42$ ,  $p = 0.001$ ) can be determined as a marker of cellular instability of the myocardial cells alone.

Fig. 2 illustrates the analysis of the distribution rate of low parameters of the serum lactate dehydrogenase activity in the two study groups.

The data presented above indicate that cases of the lowest lactate dehydrogenase activity are found in the control group. The frequency of low parameters of this enzyme activity was lower among the neonates suffering from sepsis, and first of all, among the term children. On this basis, it could be suggested that higher values of lactate dehydrogenase activity, on the one hand, are associated with electrophysiological markers of the right ventricular overload (found in 93.1% of preterm neonates), and on the other hand, they can be considered as risk criteria of the generalised infectious-inflammatory process available in the cohort of neonates.

The study demonstrates that increased values of lactate dehydrogenase activity in the blood plasma both in the term and preterm neonates are associated with the left ventricular overload among the former, and the right ventricular overload among the latter, that is, preterm neonates. Thus, lactate dehydrogenase activity in the blood plasma among the representatives of group I, whose electrocardiograms showed markers of the left ventricular overload was  $728.6 \pm 56.95$  un/L, and in children without any signs of overload –  $455.3 \pm 77.02$  un/L ( $p < 0.05$ ). Similar differences occurred in the group of preterm children who experienced the right ventricular overload and their mean values of lactate dehydrogenase activity in the blood plasma were  $725.4 \pm 72.12$  un/L, and in the case the overload was lacking –  $424.1 \pm 65.10$  un/L ( $p < 0.05$ ).

On this assumption, in Tab. 4, we examined the prognostic parameters of the risk of neonatal sepsis in neonates based on the assessment of lactate dehydrogenase activity in the blood plasma.

Therefore, increased lactate dehydrogenase activity can be used in as part of complex diagnostic procedures to verify neonatal sepsis, especially in the subpopulation of term patients. Some research shows the effectiveness of this marker for both term and preterm neonates for the prognosis of severe conditions<sup>(14)</sup>. Thus, the sensitivity of this

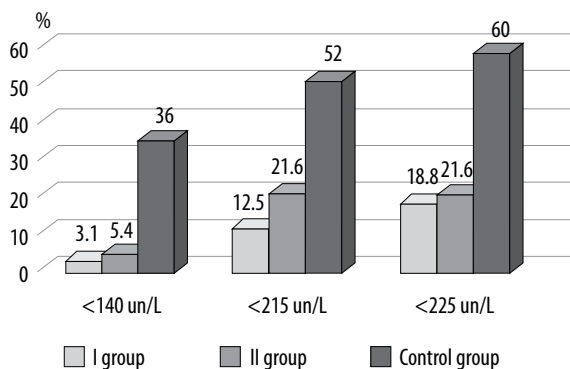


Fig. 2. Distribution of serum lactate dehydrogenase activity in the study groups

test to make the diagnosis of neonatal sepsis with lactate dehydrogenase activity higher than 400 un/L in the group of term children was 75.0%, with a positive prediction of the test value of 82.4%, and in the group of preterm children – 67.6%, respectively, with a positive prediction of the test value of 80.9%. For this distinctive point, the parameters of test specificity were similar in both clinical groups and reached 84.0%, with a negative prediction of the result value in the group of term children – 77.1%, and in the group of preterm children – 72.2%. For this distinctive point of lactate dehydrogenase activity in the blood plasma higher than 430 un/L in the group of term children, the parameters of sensitivity were 75.0%, with a positive prediction of the test value of 90.4%, and the specificity of the test – 92.0% with a negative prediction of the test value 78.6%. In the subpopulation of preterm neonates, the above parameters of the diagnostic value of lactate dehydrogenase activity in the blood plasma higher than 430 un/L were 62.2%, 88.6%, 92.0%, and 70.9%, respectively.

## CONCLUSIONS

1. Neonatal sepsis, often accompanied by the development of myocardial dysfunction which in term neonates is associated with electrocardiographic signs of the left ventricular overload is also connected with the female sex ( $r = 0.30$ ), delivery by cesarean section ( $r = 0.27$ ) and neonatal assessment according to the 5-minute Apgar score ( $r = -0.33$ ).
2. Increased lactate dehydrogenase activity in the blood serum can be considered a marker of cardiovascular dysfunction caused by neonatal sepsis, especially in the subpopulation of term patients, considering its diagnostic value.
3. Changes found in electrophysiological heart activity promote the necessity of routine use of electrocardiography in neonates with signs of the septic process.

**Prospects for further studies:** timely diagnostics of cardiovascular disturbances in neonates with clinical signs of the generalised infectious-inflammatory process is one of the mainstays of rational therapy focused on the elimination of these disturbances and prevention of possible complications.

### Conflict of interest

*The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.*

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