



The role of biochemical markers as early indicators of cardiac damage and prognostic parameters of perinatal asphyxia

Uloga biohemijskih markera kao ranih indikatora oštećenja srca i prognostičkih parametara perinatalne asfiksije

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Abstract

Background/Aim. In recent years, the focus of interest of the scientific community is the application of heart markers as early indicators and prognostic parameters of perinatal asphyxia (PA). The aim of this study was to evaluate the significance of clinical application of heart markers in term newborns with perinatal asphyxia. **Methods.** During a 3-year period we analyzed 91 full-term newborns (55 with and 36 without perinatal asphyxia). In all the subjects within the first 24–48 h after birth, we simultaneously determined serum concentrations of cardiac troponin I, brain natriuretic peptide, MB fraction of creatine kinase (CK-MB) and C-reactive protein. **Results.** In the group of full-term neonates with PA significantly higher levels of cardiac troponin I ($p = 0.000$), CK-MB fraction ($p = 0.000$), brain natriuretic peptide ($p = 0.003$) and C-reactive protein ($p = 0.017$) were found, compared to the group of healthy full-term newborns. In merged group ($n = 91$) cardiac troponin I level correlated with the fifth minute Apgar score ($r = -0.637$, $p = 0.000$) and the serum lactate concentration in the first 12h after birth ($r = 0.529$, $p = 0.000$). Early increase in cardiac troponin I $> 0.135 \mu\text{g/L}$ predicted the risk of death with the sensitivity of 84.6% and specificity of 85.9%, while the increase in CK-MB fraction, brain natriuretic peptide and C-reactive protein did not have a predictive value with respect to a mortality outcome. **Conclusion.** Among the tested cardiac markers, cardiac troponin I is the most sensitive and the only reliable early predictor of mortality in full-term neonates with perinatal asphyxia.

Key words: perinatology; asphyxia; biological markers; heart failure; troponin I; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Poslednjih godina u žiži interesovanja naučne javnosti je primena srčanih markera kao ranih indikatora i prognostičkih parametara perinatalne asfiksije. Cilj ovog rada bio je da se proceni značaj kliničke primene srčanih markera kod terminske novorođenčadi sa perinatalnom asfiksijom. **Metode.** Tokom trogodišnje studije analizirano je 91 terminsko novorođenče (55 sa i 36 bez perinatalne asfiksije). Kod svih ispitanika određivana je simultano serumska koncentracija srčanog troponina-I, moždanog natriuretskog peptida, MB frakcije kreatin kinaze i C-reaktivnog proteina u prvih 24–48 h po rođenju. **Rezultati.** U grupi terminske novorođenčadi sa perinatalnom asfiksijom registrovan je značajno viši nivo srčanog troponina-I ($p = 0,000$), CK-MB frakcije ($p = 0,000$), moždanog natriuretskog peptida ($p = 0,003$) i C-reaktivnog proteina ($p = 0,017$), u odnosu na grupu zdrave, terminske novorođenčadi. Nivo srčanog troponina-I bio je u korelaciji sa Apgar skorom u petom minutu ($r = -0,637$; $p = 0,000$) i koncentracijom laktata u prvih 12 h po rođenju ($r = 0,529$; $p = 0,000$). Rani porast srčanog troponina-I $> 0,135 \mu\text{g/L}$ ukazivao je na rizik od smrtnog ishoda, sa senzitivnošću 84,6% i specifičnošću 85,9%, dok porast CK-MB frakcije, moždanog natriuretskog peptida i C-reaktivnog proteina nije bio pouzdan prediktor mortaliteta. **Zaključak.** Srčani troponin-I je najsenzitivniji i jedini pouzdan prediktor mortaliteta kod terminske novorođenčadi sa perinatalnom asfiksijom.

Ključne reči: perinatologija; gušenje; biološki pokazatelji; srce, insuficijencija; troponin I; testovi, prognostička vrednost.

Introduction

Three groups of cardiac markers are routinely used in adult clinical cardiology: markers of cardiac function, markers of necrosis and inflammation markers¹. Markers of cardiac function (cardiac natriuretic peptides) are used in diagnosis, monitoring, prognosis and treatment of heart failure^{1, 2}. Markers of myocyte necrosis, cardiac troponin I (cTnI) and cardiac troponin T (cTnT), are included in the new international guidelines for diagnosis and treatment of acute myocardial infarction^{1, 3}. Markers of inflammation, particularly C-reactive protein (CRP), play an important role in risk stratification and application of appropriate therapy in acute coronary syndrome^{1, 4}.

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from unstable angina, to non-ST-segment elevation myocardial infarction (NSTEMI) and, finally, to ST-segment elevation myocardial infarction (STEMI). Patients with unstable angina can be separated from those with NSTEMI by measuring the levels of troponin as cardiac-specific markers which can reveal minimal (microscopic) myocardial necrosis. With that in mind, it is of paramount importance to determine troponin reference values and detection limits, which is the subject of extensive evaluation and standardization at the international level⁵.

The application of biochemical markers in perinatal asphyxia (PA) has not been sufficiently studied in the literature. McAuliffe et al.⁶ in the study of 110 infants, mean gestational age of 39.9 weeks (33.4–42.3 weeks), were analyzed for cTnI levels and correlated with intrapartum risk factors and blood pH levels. These authors found a significant difference in the level of cTnI in the observed groups. In 84/110 (76%) of the newborns they found the mean value (median) of cTnI to be 0.03 ng/mL (0.03–0.881 ng/mL) and in 26/110 (23.6%) it was 0.5 ng/mL (0.00–4.3 ng/mL). Also, they found that 90 percentile for healthy neonatal population represents the value of cTnI < 0.05 ng/mL, reported in 12/110 (10.9%) of respondents, on the basis of their results. In 5/110 (4.5%) of respondents in this study, the cTnI value was registered > 0.1 ng/mL, which according to the reference values for adults, might indicate cardiac morbidity and significant consequences. Comparing the group of patients with normal and high concentrations of cTnI, McAuliffe et al.⁶ noted significantly lower blood pH (7.24 ± 0.09) in the patients with intrapartum risk factors and high levels of serum cTnI, compared with the group of healthy term newborns ($pH = 7.32 \pm 0.07$). The results of these and other authors suggested that troponin I could be used as early indicator of PA^{6–10}.

Most of the neonatal studies are focused on changes in serum concentrations of cardiac troponins (cTnI/cTnT) and natriuretic peptides (BNP/NT-pro-BNP) with respect to gestational age, patent ductus arteriosus, degree of respiratory distress syndrome and/or perinatal asphyxia, applied ventilatory, inotropic and other therapies. It was found that the increase in these biochemical markers was often in proportion with the diameter of patent ductus arteriosus, degree of respiratory distress syndrome and perinatal asphyxia, hypoxic is-

chemic encephalopathy and other serious conditions which are the cause of significant mortality and long-term morbidity^{7, 11–18}.

In adult patients with chronic heart failure, increased levels of cardiac troponins or BNP / NT-pro-BNP have a prognostic significance. High values of these biomarkers were demonstrated to be associated with higher mortality and higher rates of repeated hospitalizations^{1, 3, 19–22}. Elevated levels of these biomarkers in acute coronary syndrome were also associated with increased mortality and increased incidence of recurrent ischemic events^{23, 24}.

In neonatal studies, increased BNP / NT-pro-BNP levels, as markers of heart failure, positively correlated with elevated levels of serum troponins as markers of myocyte necrosis, indicating severe myocardial damage with possible fatal outcome¹³.

C-reactive protein is a highly sensitive but not a specific marker of acute inflammation^{4, 25}. In newborn infants infection is a common cause of neonatal morbidity and mortality. Early and rapid diagnosis of systemic infection is very important for the timely treatment, and the role of CRP, as an early marker of inflammation, is very important. On the other hand, a well-known prognostic significance of increased CRP levels in adults with coronary ischemia open the discussion on the possibilities of implementing CRP as a prognostic marker of post-asphyctic myocardial lesions in newborns²⁵.

The aim of this study was to assess whether there is a significant difference in serum cardiac troponin I, creatine kinase MB fraction, brain natriuretic peptide and CRP between the groups of term neonates, with and without PA. The aim of this study was also to precisely determine the predictive value of each of the above mentioned biomarkers with respect to fatal outcome in the examined group of term newborns with PA.

Methods

This study was conducted at the Center of Neonatology, Pediatric Clinic and Maternity Gynecology and Obstetrics Clinic, Clinical Centre Kragujevac, during the period August 2007 – January 2010. The study was retrospective-prospective and non-interventional. Not a single diagnostic procedure was performed solely for the purpose of the study but was conducted within the framework of referent neonatal protocols and was approved both by the parents written consent, and the Ethics Committee, Clinical Center in Kragujevac, No. 01-613.

A previously conducted pilot study, determined that to get a statistically significant difference in the level of troponin I compared to the group of neonates without PA (power of the study 80%, statistical significance 0.05), the minimal number of examinees in the group of neonates with PA was 36.

During a 3-year study we analyzed 108 subjects, 17 neonates were excluded from the study. Exclusion criteria were: proven congenital heart defect (1 hypoplastic left heart syndrome, ventricular septal defect and pulmonary artery

stenosis and 2 atrial septal defects), chromosomal aberrations (1 Edwards and 2 Downs syndrome), and conatal sepsis (9 patients with positive blood cultures).

The study included a total of 91 full-term neonates (55 with and 36 without perinatal asphyxia). The clinical diagnosis of PA was based on the criteria Caliskan et al.¹² and Zupan Simunek²⁶.

Inclusion criteria for the study were: the history of fetal asphyxia and gynecology/obstetric complications; cardiorespiratory and neurological depression defined by Apgar score < 4 in the 1st minute and < 7 in the 5th minute after delivery; metabolic acidosis (defined as a lactate level > 3.7 mmol/L in the first 1–12 hours after birth); respiratory distress; convulsions, coma or hypotonia in the first 48 h after birth; hypotension and/or oliguria; multiorgan failure.

Following variables were analyzed in both the groups of examinees: the 5th minute Apgar score; blood lactate levels in the first 1–12 h after birth (capillary blood sample, analyzed by a gas analyzer Gem Premier 3000; reference values 0.3–3 mmol/L); serum level of the second generation troponin I (cTnI-Ultra) determined simultaneously with other biomarkers (CK-MB, BNP and CRP) in the first 24–48 h after birth [enzyme-linked immunosorbent method on a Biomerieux mini Vidas ELFA (“enzyme-linked fluorescent assay”)]. For this type of analyzer in the adult population, normal values (99. percentile) of serum level of cTnI-Ultra were < 0.01 µg/L with coefficient of variation of 10% (from 0.01 to 0.11 µg/L)²⁷. For the neonatal population, the reference value for the second-generation cTnI is still not known, whereas the first generation cTnI reference range is from 0.01 to 2.8 µg/L, depending on authors^{28–30}; creatine kinase MB fraction (CK-MB) level was determined by a biochemical analyzer Beckman Coulter. For such analysis, the adult population reference range is 2–25 U/L, while for the neonatal population 95th percentile for healthy full-term newborns is 72 U/L¹⁰; The level of “brain” natriuretic peptide (BNP) was determined from the same sample of blood on the immunochemical analyzer Axsym. In the adult population BNP reference value is < 108 pg/mL while in the neonatal population it varies from 231.6 ± 197.5 pg/mL in the first week of life, to 48.449 ± 49.1 pg/mL in the later period³¹; serum concentration of C-reactive protein (CRP) was determined by the biochemical analyzer Beckman Coulter. The reference value in the Clinical Center Kragujevac laboratory, irrespective of age, is < 5 ng/mL.

To analyse of basic respondent’s clinical characteristics we used descriptive statistics – mean and standard deviation.

To display the mean values of biochemical markers and other variables, whose distribution was not normal we used descriptive statistics – median and quartiles. To compare the mean values of variables two populations were used: Mann-Whitney-test and ANOVA. The correlation of two numerical characteristics was examined using Spearman's and Pearson's correlation coefficient. The suitability of numeric variables was tested using ROC (receiver operating characteristic) curves.

Results

In the group of 55 asphyxiated newborn infants there were 31 (56.4%) males and 24 (43.6%) females. The average gestational age (GA) was 39.5 ± 1.3 weeks and the average birth-weight (BW) 3429 ± 571 g. All of them presented with fetal distress syndrome and/or abnormal obstetric history. Furthermore, all had clinical signs of cardiorespiratory and neurological disability [i.e., Apgar score recorded at the first minute < 4, Apgar score at the 5th minute < 7, seizures (< 48 h after birth), hypotonia or comma, hypotension and/or oliguria and multiorgan dysfunction with postnatal blood lactate level > 3.7 mmol/L (1–6 h after birth)]. Nineteen out of 55 newborns (34.5%) were delivered by caesarean section. Thirty-one out of 55 (56.4%) newborns required respiratory and 23 (41.8%) pressure support; 13 (23.6%) had critical cardiorespiratory problems or multiorgan dysfunction and died. The median 5th minute Apgar score in this group of newborn infants was 5 (range 3–7), and mean value of lactate levels 8.63 ± 4.43 mmol/L. Median CRP concentration was 4.2 mg/L (range 1.9–12.1 mg/L). The median value of CK in the same group of neonates was 1,550 U/L (range 608–4736 U/L) and the mean value of CK-MB fraction 240.7 ± 212.1 U/L. The median level of cTnI in the group of asphyxiated newborn infants (both survived and non-survived) was 0.08 µg/L (range 0.02–0.17 µg/L).

In the control group of 36 non-asphyxiated healthy newborn infants there were 17 males and 19 females. The average BW was 3,455 ± 352 g and GA 39.8 ± 1.1 weeks. All the participants had Apgar score > 8 at 5th minute (median 9) and their lactate levels were 1.04 ± 0.36 mmol/L.

Table 1 shows the average serum concentrations of the analyzed biochemical markers in the groups of full-term newborns with and without perinatal asphyxia, measured during the first two days of life. There was a statistically significant difference in concentrations of all the investigated biochemical markers (CRP, cTnI, CK-MB and BNP) between the examined groups of neonates.

Table 1

Average value of the analyzed biochemical markers in the observed groups

Analyzed biochemical markers	Asphyxiated newborns (n = 55)	Healthy newborns (n = 36)	<i>p</i>
Lactate (mmol/L), $\bar{x} \pm SD$	8.63 ± 4.43	1.04 ± 0.36	0.000
C-reactive protein (mg/L)	4.20 (IQR 1.9–12.1)	2.60 (IQR 0.8–4.8)	0.017
Cardiac troponin I (µg/L)	0.08 (IQR 0.02–0.17)	0.01 (IQR 0.01–0.01)	0.000
Creatine kinase-MB (U/L), $\bar{x} \pm SD$	240.69 ± 212.13	78.83 ± 39.14	0.000
B-type natriuretic peptide (pg/mL), $\bar{x} \pm SD$	993.05 ± 1259.51	278.98 ± 190.47	0.003

p – statistical significance; IQR – interquartile range.

In both groups of patients ($n = 91$), all the investigated biochemical parameters (CRP, cTnI, CK-MB and BNP) correlated with the parameters of perinatal asphyxia (5th minute Apgar score and lactate concentration) (Table 2). However,

0.345, a PA group $r = 0.290$), whereas there was no correlation between the concentrations of cTnI and BNP (unified group $r = 0.279$; group with PA $r = 0.115$) (Tables 2 and 3).

Table 2
Correlation of perinatal asphyxia indicators with cardiac damage parameters showed by correlation coefficients (r) in the merged group (newborns with and without perinatal asphyxia) ($n = 91$)

Analyzed markers	Lactate	CRP	cTnI	CK-MB	BNP
Apgar scores at 5th min	$r = -0.839$ $p = 0.000$	$r = -0.228$ $p = 0.032$	$r = -0.637$ $p = 0.000$	$r = -0.449$ $p = 0.000$	$r = -0.341$ $p = 0.022$
Lactate (mmol/L)	–	$r = 0.348$ $p = 0.001$	$r = 0.529$ $p = 0.000$	$r = 0.533$ $p = 0.000$	$r = 0.613$ $p = 0.000$
CRP (mg/L)	–	–	$r = 0.345$ $p = 0.001$	$r = 0.337$ $p = 0.002$	$r = 0.340$ $p = 0.021$
cTnI ($\mu\text{g/L}$)	–	–	–	$r = 0.507$ $p = 0.000$	$r = 0.279$ $p = 0.061$
CK-MB (U/L)	–	–	–	–	$r = 0.405$ $p = 0.005$

p – statistical significance; CRP – C-reactive protein; cTnI – cardiac troponin I; CK-MB – creatine kinase-MB; BNP – B-type natriuretic peptide.

in the group of full-term neonates with perinatal asphyxia, 5th minute Apgar score and lactate concentration significantly correlated only with cTnI and CK-MB levels (Tables 2 and 3).

cTnI level negatively correlated with the 5th minute Apgar score (unified group $r = -0.637$; group with PA $r = -0.318$), and positively correlated with the serum lactate level ($r = 0.529$ in unified group and $r = 0.399$ in PA group) and the concentration of CK-MB ($r = 0.507$ in the unified group and $r = 0.410$ in the PA group). The correlation between cTnI and CRP was less pronounced (unified group $r =$

0.181) and BNP ($p = 0.095$) there were no reliable predictors of death. CK-MB had a borderline predictive value for a mortality outcome ($p = 0.017$). Among the tested biochemical markers only the cardiac troponin I with the area under the ROC curve of 0.896 and serum lactate levels with an area under the ROC curve of 0.894 had a highly significant predictive value for fatal outcome ($p = 0.000$) (Table 4). For a threshold of 0.135 mg/L, cTnI was a predictor of death with sensitivity of 84.6% and specificity 85.9%.

Table 3
Correlation of indicators of perinatal asphyxia with cardiac damage parameters showed by correlation coefficients (r) in the group with perinatal asphyxia ($n = 55$)

Analyzed markers	Lactate	CRP	cTnI	CK-MB	BNP
Apgar score 5th min	$r = -0.423$ $p = 0.000$	$r = -0.086$ $p = 0.541$	$r = -0.318$ $p = 0.019$	$r = -0.286$ $p = 0.051$	$r = -0.408$ $p = 0.148$
Lactate (mmol/L)	–	$r = 0.242$ $p = 0.090$	$r = 0.399$ $p = 0.004$	$r = 0.318$ $p = 0.035$	$r = 0.494$ $p = 0.073$
CRP (mg/L)	–	–	$r = 0.290$ $p = 0.033$	$r = 0.279$ $p = 0.057$	$r = 0.203$ $p = 0.469$
cTnI ($\mu\text{g/L}$)	–	–	–	$r = 0.410$ $p = 0.004$	$r = 0.115$ $p = 0.684$
CK-MB (U/L)	–	–	–	–	$r = 0.277$ $p = 0.317$

p – statistical significance; CRP – C-reactive protein; cTnI – cardiac troponin I; CK-MB – creatine kinase-MB; BNP – B-type natriuretic peptide.

Table 4
Analysis of serum biochemical markers after asphyxia as a predictor of death by ROC (receiver operating characteristic) curve in the merged groups of patients ($n = 91$)

Analyzed biochemical markers	AUC	Statistical values			
		p	Cut-off	Sensitivity	Specificity
Lactate (mmol/L)	0.894	0.000	8.65	83.3%	84.0%
CRP (mg/L)	0.616	0.181	5.0	61.5%	71.4%
Troponin I ($\mu\text{g/L}$)	0.896	0.000	0.135	84.6%	85.9%
CK-MB (U/L)	0.717	0.017	126	83.3%	63.9%
BNP (pg/mL)	0.791	0.095	372.45	100%	65.1%

p – statistical significance; AUC – area under the curve; CRP – C-reactive protein; cTnI – cardiac troponin I; CK-MB – creatine kinase-MB; BNP – B-type natriuretic peptide.

Discussion

The diagnosis of myocardial damage in newborn infants was previously based on clinical examination, suggestive electrocardiographic or echocardiographic examinations and increasing value CK-MB isoenzyme. Numerous studies have shown that CK-MB isoenzyme, and particularly total creatine kinase, cannot be regarded as specific cardiac enzymes in the neonatal period, but the interpretation of their increasing concentrations in infants must be viewed with extreme caution³².

Major goals of neonatal studies were both to define normal values of cardiac biochemical markers in the neonatal population, and to evaluate factors that may have impact on their serum concentrations^{6-10, 28-30}.

In our study the reference value of troponin I Ultra in healthy newborn infants was 0.0183 ± 0.026 ; mediana 0.01 (0.01–0.01) $\mu\text{g/L}$. A statistically significant higher mean concentration of cTnI and others investigated biochemical markers of perinatal asphyxia (lactate, CRP, CK-MB and BNP) was found in the group of asphyxiated full-term newborn infants compared to the group of healthy full-term neonates. Similar to our results, Costa et al.³³ and Rajakumar et al.³⁴ in two separate studies found a correlation of increased cTnI and signs of myocardial damage in newborns with PA. Szymankiewicz et al.³⁵ studied 39 asphyxiated newborn versus 44 nonasphyxiated newborns and tried to relate the cTnI to echocardiographic findings of myocardial damage. The cTnI was measured within 12 and 24 hours of life. Asphyxiated infants had higher levels of cTnI (0.141 versus 0.087 ng/mL) nonasphyxiated infants ($p < 0.01$).

In asphyxiated newborns heart failure is the consequence of "hypoxic-ischemic lesions or hypotensive necrosis"³³, and it can accurately be assessed through measurement of cardiac troponin I serum concentrations. At birth, cardiac troponin I is not found in skeleton muscles and other tissues, but only in the myocardium, and its level does not change under the influence of regenerative or degenerative processes in muscles^{30, 32, 33}. Iacovidou et al.³⁶ analyzed changes in the level of cTnI in fetuses with intrauterine arrest, due to chronic malnutrition and hypoxia of the fetus, and found a correlation between cTnI levels in neonates and pregnant women, assuming that the increase in neonatal cTnI level is the result of transplacental cTnI transit from mother to fetus. On the other hand, Trevisanuto et al.³⁷, similar to our results, showed a significant increment in cTnI level in asphyxiated newborn infants. Comparing levels of cTnI in asphyxiated full-term neonates (gestational age 34–40 weeks), with cTnI levels in serum of their mothers, these authors found no significant association, which is similar to the results of Alexandre et al.³⁸, who also founded that transplacental cTnI passage is not possible. Based on such findings Trevisanuto et al.³⁷, concluded that increased cTnI level is not related to the mother, but is strictly the consequence of increased fetal and neonatal production due to organ lesions in perinatal asphyxia.

In the group of full-term neonates with PA we found a significant correlation between increased serum cTnI levels and standard clinical markers of perinatal asphyxia such as

the 5th minute Apgar score and serum lactate levels^{6, 15}. The 5th minute Apgar score and serum lactate levels also positively correlated with serum CK-MB levels but less significantly than with cTnI, similar to other authors. This is in agreement with recently published reports showing that CK-MB is both less specific and less sensitive in detecting cardiac involvement and in early prediction of poor outcome/death in neonates with PA^{10, 12, 39}.

We found that cTnI is a highly sensitive and specific marker of myocardial damage as part of terminal multi-system failure^{8, 10, 12, 15, 16}.

In recent years, an increasing number of neonatal study is trying to determine the value of cardiac troponin I and T, as early indicators of critically ill newborns with PA, which would in future allow monitoring of therapeutic response and improvement of cardioprotective strategies.

Türker et al.⁴⁰ in their original study compared the levels of cTnI in 109 critically ill (mechanically ventilated neonates) with cTnI levels in the control group (48 healthy and 48 newborn infants requiring only the first stage of intensive care unit). According to the results of these authors in a group of critically ill, mechanically ventilated infants, there was a significant increase in cTnI (median 1.4 ng/mL, the min. 0 to max. 13.0 ng/mL; $p < 0.001$), compared to the control group (median 0, min from 0 to max. 1.84 ng/mL). Also in the group of critically ill children with fatal outcome there has been a significant increase in cTnI ($p < 0.001$), (6.6 ng/mL; 1.3–13.0 ng/mL) compared to the patients who survived (1.3 ng/mL; 0–8.0 ng/mL). Receiver-operator curve showed that early increase in cTnI could be a sensitive predictor of death in critically ill newborns with the confidence interval of 96%.

Similar to other authors, we found an association of increased cTnI values with several variables related to illness severity. A statistically significant higher mean concentration of cTnI was associated with the need of respiratory support: 0.11 $\mu\text{g/L}$ (0.04–0.18); $p = 0.039$ and to the use of inotropic drugs: 0.15 $\mu\text{g/L}$ (0.06–0.56); $p = 0.006$, compared to the group without cardio-respiratory support: 0.01 $\mu\text{g/L}$ (0.01–0.04). The results of our study suggest that early increase in cTnI could be used as an important prognostic marker, since serum cTnI > 0.135 mg/L predicted a mortality outcome with sensitivity of 84.6% and specificity 85.9%^{40, 41}.

CRP, as a non-specific indicator of tissue damage⁴², and BNP, as insufficiently sensitive indicator of perinatal asphyxia, neither correlated with 5th minute Apgar score and serum lactate levels, nor were reliable predictors of mortality outcome in neonates with PA, in our study. One-time blood samples in a wide interval of 24–48 h could have a limiting effect on results analysis according to the different period of elimination of observed biochemical markers⁴³. On the other hand, such findings could be explained by the fact that BNP is secreted primarily from the myocardium of heart chambers in response to pressure/volume overload^{1, 2, 13}, while the increase in cTnI is the result of hypoxia and/or myocardial ischemia^{1, 3, 5, 29, 33, 43}. Heart failure is a complex clinical syndrome and a single biochemical marker, such as BNP, may not reflect all of its features. Measurement of both serum BNP levels, as markers of cardiac load, and cTnI levels, as

markers of myocardial damage, could open new perspectives in diagnosis, prognosis and monitoring of critically ill asphyxiated newborns with heart failure⁴⁴.

Conclusion

Cardiac troponin I, a highly specific and sensitive marker of myocardial damage, can be used as a prognostic marker of perinatal asphyxia in full-term newborn infants. Increase in cardiac troponin I > 0.135 mg/L in the first 24–48 h after birth may predict fatal outcome with sensitivity of 84.6% and specificity 85.9%.

Creatinine kinase MB fraction is both sensitive and specific marker of myocardial damage, but its predictive value is less significant than cTnI.

C-reactive protein is not sensitive indicator of perinatal asphyxia and, accordingly, its increase in the serum cannot be used for early prediction of outcome.

The increase in serum BNP levels in the population of full-term newborns, in our study did not appear to be a reliable predictor of perinatal asphyxia. Further studies on more patients are necessary to assess its predictive capacity in terms of mortality outcome in full-term neonates with perinatal asphyxia.

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