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Selected cardiac biomarkers in newborns with perinatal asphyxia symptoms

Wybrane markery sercowe u noworodków z objawami niedotlenienia okołoporodowego

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Abstract

Perinatal hypoxia is one of the more common complications of the early adaptation period. This condition is defined as a disorder of tissue oxygenation during labour and is responsible for approximately 23% of neonatal mortality. Perinatal hypoxia can cause injury and failure of many organs, including the brain, heart and kidneys, mainly in the mechanism of the ischaemic-reperfusion injury. Currently, biochemical markers are more frequently incorporated in neonatal diagnostics. Routinely used in adult patients, these organ-specific chemicals enable diagnosis with high sensitivity and specificity. The manuscript presents a review of research on the use of cardiac markers (N-terminal fragment of pro-B-type natriuretic peptide, cardiac troponins I and T, and cardiac creatine kinase isoenzyme) in selected neonatal diseases. Still, no cutoff values have been established for any of the markers described in this paper. Therefore, for routine use of cardiac markers in the neonatal population, further studies are needed to determine the range of cutoff values and factors that may cause their fluctuation.

Keywords: perinatal asphyxia, newborn, NT-proBNP, cardiac troponin, creatine kinase

Streszczenie

Niedotlenienie okołoporodowe stanowi jedno z częstszych powikłań wczesnego okresu adaptacji. Stan ten definiowany jest jako zaburzenie utlenowania tkanek podczas porodu i odpowiada za około 23% przypadków śmiertelności wśród noworodków. Niedotlenienie okołoporodowe może być przyczyną uszkodzenia oraz niewydolności wielu narządów, w tym mózgu, serca i nerek, przede wszystkim w mechanizmie uszkodzenia niedokrwienno-reperfuzyjnego. Obecnie w diagnostyce neonatologicznej coraz powszechniej wykorzystuje się markery biochemiczne. Dotąd standardowo stosowane u pacjentów dorosłych, te specyficzne narządowo związki chemiczne umożliwiają ustalenie rozpoznania z wysoką czułością i swoistością. W pracy przedstawiono przegląd badań dotyczących wykorzystania markerów sercowych (N-końcowego fragmentu propeptydu natriuretycznego typu B, troponin sercowych I i T oraz izoenzymu sercowego kinazy kreatynowej) w wybranych zaburzeniach okresu noworodkowego. Jednak dla żadnego spośród opisanych w niniejszym artykule markerów wciąż nie ustalono wartości referencyjnych dla noworodków. Aby możliwe było zatem rutynowe i powszechne ich oznaczanie w tej grupie pacjentów, niezbędne są dalsze badania, pozwalające określić zarówno zakres wartości referencyjnych, jak i czynniki wpływające na fluktuację stężenia markerów sercowych w populacji neonatologicznej.

Słowa kluczowe: niedotlenienie okołoporodowe, noworodek, NT-proBNP, troponina sercowa, kinaza kreatynowa

INTRODUCTION

Perinatal asphyxia (PA) is one of the most common complications of the early adaptation period, resulting from abnormal tissue oxygenation during the first and second stages of labour. Complications of PA include a high frequency of hypoxic-ischaemic encephalopathy (HIE), bronchopulmonary dysplasia (BPD), and persistent pulmonary hypertension of newborns (PPHN) as well as patent ductus arteriosus (PDA) among cardiovascular disorders. According to the available literature, PA is responsible for approximately 23% of all neonatal deaths[1]. A low Apgar score is one of the criteria for the PA diagnosis. However, it is important to remember that the use of this scale for assess in the patient's clinical condition is subjective, and some studies have shown that it reflects neither the severity of PA nor the risk for developing HIE[2]. Laboratory tests of parameters determined both from umbilical cord blood and the venous blood from newborns in the first hours of life are characterised by much higher sensitivity and specificity in the detection of PA[1,2].

Perinatal hypoxia can cause damage to all body systems, and the most dangerous is impaired functioning of vital organs, including the brain, heart, and kidneys. Many authors have documented that myocardial damage can be observed in as much as 60–82% of hypoxic newborns[3–5]. As a consequence of systemic hypoxia, energy production inside cells occurs in a less efficient anaerobic mechanism. Combined with a compensatory increase in myocardial contractility, this leads to overload and damage to the heart. Additionally, hypoxia leads to the formation of a large number of oxygen free radicals, which cause ischaemia-reperfusion injury to tissues, intensifying myocardial dysfunction, resulting in a decrease in cardiac output, as well as impaired organ perfusion[3]. This pathomechanism may lead to acute heart failure, myocardial ischaemia or PPHN in the youngest patients[3].

Organ-specific biochemical markers have found broad use in the adult population, both in diagnostics and in monitoring the course of cardiac disease therapy. According to the literature, the ideal markers are the molecular, genetic or biochemical factors that are highly expressed in response to cardiac tissue damage, and can be detected with high clinical sensitivity and specificity in the blood early after the onset of symptoms[6]. However, their routine use in the diagnostic and therapeutic process in neonatology is still limited. Before the standard use of biomarkers in neonatal departments is possible, it is necessary to specify their reference values and to learn about the factors affecting the changes in their concentration in the body.

NATRIURETIC PEPTIDES IN NEONATOLOGY

B-type natriuretic peptide (BNP) is one of the 6 natriuretic oligopeptides known to date. BNP was initially isolated from pig brains in 1988. Under physiological conditions, BNP significantly improves diuresis and natriuresis, regulating the water and electrolyte balance by reducing the secretion of vasopressin and adrenocorticotropic hormone, and inhibiting the renin–angiotensin–aldosterone system[7]. The professional literature shows that the local production of proBNP prohormone is increased due to elevated ventricular pressure and the mechanical response of the heart to myocardial stretch. Enzymatic hydrolysis with proBNP leads to the production of BNP and the N-terminal pro-B-type natriuretic peptide (NT-proBNP) at equimolar concentrations. As a biochemically inactive product of metabolism, NT-proBNP has a half-life 6 times longer than that of BNP. In this respect, this parameter has found broad use in clinical practice as a diagnostic marker for heart disease in adults[7]. However, the reference values of BNP and NT-proBNP serum concentrations for the population of newborns and the youngest children have not been clearly defined[8].

Irmak et al. studied the relationship between serum pH value and NT-proBNP concentration. The researchers documented a correlation between lowering the pH value and the concentration of the peptide in the serum of both umbilical cord blood and venous blood of neonates collected in the first minutes of life[9]. Kariyappa and Shivarudrappa found that the NT-proBNP concentrations in the first days of life are significantly increased in neonates who were later diagnosed with HIE. The results are presented as mean [standard deviation]: for HIE degree I – 1,502.9 [3,581.2] pg/mL, HIE degree II – 4,916.3 [8,001.7] pg/mL, and for HIE degree III – 8,912.4 [13,927.2] pg/mL. Furthermore, the authors showed that the value of this marker was positively correlated with the severity of HIE[5]. Many researchers have observed a significant increase in NT-proBNP concentration in neonates with myocardial injury due to PA[10,11].

Researchers from other centres reported significantly increased levels of NT-proBNP, measured in both blood and urine samples, in preterm newborns with PDA[12,13]. In the study by Letshwiti et al., the median NT-proBNP level of neonates with PDA was 11,469 ng/L (interquartile range, IQR: 2,971–19,299 ng/L), and in the group of healthy children 898 ng/L (IQR: 649–2,524 ng/L)[12]. The authors also reported a significant correlation between the width of PDA and the concentration of the discussed marker. It was also observed that NT-proBNP could also serve as a specific marker of PDA closure[12,13].

NT-proBNP concentration was also used as a marker of BPD development[14–16]. Studies consisting of repeating the determinations of NT-proBNP concentration on individual days of life of newborns with very low birth weight showed the highest correlation between the diagnosis of BPD and the value of this marker found on the 14th day of life (sensitivity 100% and specificity 86% for the concentration of 2,264 pg/mL)[17]. NT-proBNP levels above 17,800 pg/mL, measured in the first 3 days of life, were associated with a 4-fold increased risk of BPD and mortality[18].

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Perinatal hypoxia can lead to PPHN. It has been shown that the determination of NT-proBNP in diagnostics of this disease is characterized by high sensitivity and specificity[19]. Natriuretic peptides have also found application in monitoring the effectiveness and efficiency of PPHN treatment and predicting disease recurrence. Furthermore, the authors propose to determine the concentration of natriuretic peptides in neonates with symptoms of respiratory distress, as their elevated concentrations may indicate a developing PPHN[20].

CARDIAC TROPONINS IN NEONATOLOGY

Troponins are a complex of structural proteins present in striated muscle cells responsible for proper muscle contraction. Cardiac isoforms of troponin T and I have been studied thoroughly in adult patients. Modern cardiology considers the determination of cardiac troponins as the reference method in the diagnosis of myocardial damage[21,22]. So far, no reference values have been established for cardiac troponin T (cTnT) for the neonatal population[22]. However, numerous studies point to the usefulness of this marker in certain complications of the early adaptation period.

Joseph et al. examined a cohort of 120 full-term newborns with symptoms of PA, and determined cTnT concentration in the 4th hour of life. The results indicate the usefulness of determining cTnT concentration in this group of patients in the diagnosis – with high sensitivity and specificity – of myocardial ischaemia, confirmed by echocardiography at 24 hours of life (sensitivity 92.4% and specificity 94.1% for 0.1145 ng/mL, i.e. 114.5 ng/L). Furthermore, a statistical relationship was observed between the concentration of cTnT and the degree of HIE, and the increased mortality in this study group[23,24].

Jiang et al. analysed cardiac troponin I (cTnI) concentration in children with PA and HIE, and showed significantly higher concentrations of this marker in this group compared to healthy neonates. Analysis of the receiver operating characteristic (ROC) curve showed that cTnI concentration of more than 87 ng/L allows the diagnosis of myocardial dysfunction in the early adaptation period with a sensitivity of 55.6% and specificity of 95.5%[4].

CREATINE KINASE MYOCARDIAL BAND (CK-MB) IN NEONATOLOGY

Creatine kinase (CK), which is composed of 2 subunits, is one of the main enzymes responsible for cellular energy homeostasis. The cardiac isoenzyme of creatine kinase myocardial band (CK-MB) is one isoform of the enzyme that occurs mainly in the cardiac muscle cytosol. Increased levels of CK-MB in the blood, noticeable as early as 4–8 hours after the activity of the damaging factor, is a long-recognised marker of hypoxia of the cardiac muscle cells[25].

Similarly to adult patients, more and more publications indicate the usefulness of CK-MB determination in neonates with suspected PA damage. Bhasin and Kohli showed a statistically significant relationship between serum CK-MB concentrations and the occurrence and severity of HIE. The results are presented as mean [standard deviation]: for HIE degree I – 88.2 [15.0] U/L, HIE degree II – 450.9 [184.8] U/L, and for HIE degree III – 746.1 [106.5] U/L[26–28]. However, Sadoh et al. observed a significant increase in the concentration of CK-MB in the case of damage to the cardiac muscle, not only in children with PA, but also in children with acute kidney injury. The demonstrated low specificity of CK-MB, despite its high sensitivity, significantly limits its usefulness as a biochemical marker of cardiac failure[29].

CONCLUSION

The increased interest in the possibility of the broad use of biomarkers to assist diagnosis of neonatal diseases, observed in recent years, has contributed to the enormous development of knowledge in this field. Organ-specific biochemical compounds, so far used mainly in the diagnosis and treatment of adults, are now being increasingly used in paediatric patients.

Perinatal hypoxia is a common complication of the early adaptation period and in many cases may contribute to multiorgan failure. One of the major contributors to this condition is impaired cardiac function. Therefore, research aimed at the possibility of using biochemical markers in the diagnosis of cardiac complications of PA is extremely important. Inclusion of the determination of laboratory indicators of cardiac function in the daily, routine neonatal practice would allow for the early implementation of therapy, significantly reducing both the risk of further organ and neurodevelopmental complications in the later period and mortality among newborns.

Conflict of interest

The authors report no financial or personal connections with other persons or organisations that could adversely affect the content of the publication and claim the right to this publication.

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