European Review for Medical and Pharmacological Sciences 2018; 22: 7448-7452

Correlation of QT dispersion with serum potassium or blood sodium levels post-neonatal asphyxia

X.-B. ZHAO[1], H. WANG[1], H.-B. WU[1], X. GONG[2]

[1]Pediatrics, Zaozhuang City Maternal and Child Health Hospital, Zaozhuang, Shandong, China
[2]Nursing, Zaozhuang Municipal Hospital, Zaozhuang, Shandong, China

Xiaobing Zhao and *Hui Wang* contributed equally to this work

Abstract. – OBJECTIVE: To investigate the correlation between the corrected QT dispersion (QTcd) and serum potassium/sodium levels in order to evaluate their significance for early diagnosis of neonatal asphyxia.

PATIENTS AND METHODS: This study included 124 neonatal asphyxia patients. These patients were divided into mild and severe asphyxia groups based on their clinical features and diagnostic indexing. Sixty healthy infants were selected as controls. QTcd, and serum cardiac troponin T (cTNT), potassium and sodium levels in the three groups were compared, and the correlation between QTcd and serum potassium/sodium was analyzed by Spearman correlation tests.

RESULTS: Both mild and severe groups developed significantly higher cTnT and QTcd ($p < 0.05$), but lower serum potassium and sodium compared with control group ($p < 0.05$). The severe group had significantly higher cTnT and QTcd ($p < 0.05$), but lower serum potassium and sodium when compared with mild group ($p < 0.05$). The serum potassium and sodium were both negatively correlated with QTcd ($p < 0.05$).

CONCLUSIONS: Serum potassium and sodium can be used as indicators for neonatal asphyxia, which may markedly improve early diagnosis, prognosis and treatment efficacy.

Key Words:
Neonatal asphyxia, Serum potassium, Serum sodium, QT dispersion.

Introduction

Neonatal asphyxia is one of the leading causes of neonatal death in the perinatal period. The disease may also lead to lifetime disability in some cases. Asphyxia can cause a variety of symptoms including hypercapnia, hypoxia, and acidosis, leading to organic and functional damages in multiple organs. The heart has been known as the organ with the most serious damage during the onset of neonatal asphyxia[1]. Therefore, early diagnosis of the disease is essential for prompt, effective treatment, which can greatly reduce the damages in organs due to asphyxia and improve the prognosis in patients[2]. The selection of indicators with high sensitivity and specificity is of great clinical significance for accurate, early diagnosis of the disease[3]. Currently, neonatal asphyxia is primarily diagnosed by electrocardiogram (ECG). However, serious myocardial damage may have occurred when diagnosed, because ECG abnormities can only be detected after myocardial tissues and cardiac functions are impaired[4]. Previous studies have shown that electrolyte imbalance occurs in neonatal asphyxia in addition to hypoxic-ischemic damages. Moreover, electrolyte imbalance is more severe in infants with a higher degree of asphyxia[5]. Potassium and sodium are two important electrolytes that are involved in all activities in human bodies and may be indicators for early diagnosis of neonatal asphyxia[6]. Cardiac troponin T (cTNT) is a cardiac-specific protein that is released into the bloodstream only when myocardial cells are damaged, and is often used to evaluate the extent of myocardial injuries. In this study, the corrected QT dispersion (QTcd), and serum cTNT, potassium and sodium levels in neonatal asphyxia patients in our hospital were determined, and the correlation between QTcd and serum potassium/sodium was analyzed in order to evaluate their significance for early diagnosis of neonatal asphyxia.

Corresponding Author: Hui Wang, MD; e-mail: hanba3959539@163.com

Patients and Methods

General Information of Subjects

A total of 124 neonatal asphyxia patients who were treated in Zaozhuang City Maternal and Child Health Hospital between January 2016 and June 2017 were selected including 84 male and 40 female infants with a mean gestational age of 39.4 ± 5.2 weeks (range: 37-42 weeks). All patients were hospitalized within 24 h after onset. These patients were divided into mild (n = 72) and severe asphyxia groups (n = 52) based on their clinical features and diagnostic indexing. Sixty healthy infants were selected as controls. This investigation was approved by the Ethics Committee of Zaozhuang City Maternal and Child Health Hospital, Zaozhuang, China. All of the patients have signed the informed consents and approved this study.

Measurement of QT Dispersion

The electrocardiograph (ECG) was performed using Hewlett-Packard (HP) 12-lead ECG machine. The longest (QTmax) and shortest QT interval (QTmin) of each patient were recorded. The QTcd was calculated using the following formula: QTc = QT/(R-R) 1/2, QTcd = QTcmax-QTcmin.

Measurement of Serum cTNT Level

Blood (2 ml) was drawn from each patient by femoral vein catheterization. Serum was isolated by centrifugation and stored at -20°C until all samples are ready for lab tests. The serum cTNT level was determined using human cTNT enzyme-linked immunosorbent assay (ELISA) kits (Bio-function Inc., Beijing, China) following the manufacturer's instruction.

Determination of Serum Sodium and Potassium Level

Serum sodium and potassium levels were detected with a CL-7200 fully automatic biochemical analyzer (Shimadzu Corporation, Japan) under the following conditions: a dominant wavelength of 340 nm, a sub-wavelength of 410 nm, a *K* value of 8000, and the detection time of 2 min.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Measurement data were expressed as mean ± standard deviation (SD). The difference between groups was analyzed by the Student's *t*-tests. Tukey's post-hoc test was used to validate the ANOVA for comparing measurement data among groups. $p < 0.05$ was treated as statistical significance. Categorical data was expressed as frequency, and analyzed by x^2 tests. The correlation between QTcd and serum potassium/sodium was analyzed by Spearman correlation tests. $p < 0.05$ is considered statistically significant.

Results

Comparison of General Information of Subjects

The general information of subjects was summarized in Table I. There was no significant difference in age, gender, gestational age, and weight among the three groups ($p > 0.05$).

Comparison of QTcd, and Serum cTNT, Sodium and Potassium Levels

As shown in Table II, both mild and severe groups developed significantly higher cTnT and QTcd ($p < 0.05$), but significantly lower serum potassium and sodium compared with control group ($p < 0.05$). The severe group had a significantly higher cTnT and QTcd ($p < 0.05$), but significantly lower serum potassium and sodium when compared with mild group ($p < 0.05$).

Correlation Between QTcd and Serum Sodium/Potassium

The correlation between QTcd and serum potassium/sodium was analyzed by Spearman cor-

Table I. Comparison of general information of subjects in mild, severe asphyxia and control groups.

Group	Gender ratio (male/female)	Age (month)	Gestational age (week)	Weight (kg)
Control (n = 60)	39/21	1.65 ± 0.21	39.82 ±11.01	4.12 ± 1.01
Mild asphyxia (n = 72)	53/19	1.82 ± 0.31	39.04 ± 9.11	3.91 ± 0.32
Severe asphyxia (n = 52)	31/21	1.92 ± 0.21	40.01 ± 10.21	4.09 ± 0.94
p-value	< 0.05	< 0.05	< 0.05	< 0.05

Table II. Comparison of QTcd, and serum cTNT, sodium and potassium levels in mild, severe asphyxia and control groups.

Group	cTnT (ng/ml)	QTcd (ms)	Sodium	Potassium
Control (n = 60)	0.064 ± 0.012	20.32 ± 6.23	143.36 ± 10.25	5.32 ± 0.86
Mild asphyxia (n = 72)	0.263 ± 0.032*	37.26 ± 10.14*	132.56 ± 3.69*	4.76 ± 1.03*
Severe asphyxia (n = 52)	0.635 ± 0.025*#	66.26 ± 11.28*#	123.08 ± 5.18*#	2.21 ± 1.01*#

Note: *$p < 0.05$ compared with control group, #$p < 0.05$ compared with mild asphyxia group.

relation tests. As shown in Table III and Figure 1, the serum potassium and sodium were both negatively correlated with QTcd ($p < 0.05$).

Discussion

Neonatal asphyxia is a common neonatal disease with high mortality and morbidity that has become a serious threat to the health of newborns[7]. According to the statistics from World Health Organization (WHO), one-fourth of the 4 million global neonatal deaths is caused by neonatal asphyxia[8]. In China, the neonatal mortality is approximately 19%, and neonatal asphyxia is the second leading cause of neonatal death[9]. Currently, neonatal asphyxia has become one of the major concerns in clinical practice[10]. Neonatal asphyxia may be caused by neonatal asphyxia, fetal distress, and respiratory insufficiency and gas exchange impairment during the delivery, leading to ischemic hypoxia, which may induce organic and functional damages in multiple organs[11]. Hypoxia can initiate an anaerobic reaction in the body, resulting in the accumulation of lactic acid, and damages in cell structures and functions[12]. Therefore, early diagnosis and treatment of neonatal asphyxia are essential for the prognosis of the disease[13]. Since its first report in 1990, QTcd has become an important method for the evaluation of the degree of myocardial damages[14-16] and is widely used in the accurate assessment of ventricular re-polarization heterogeneity, and time of cardiac arrhythmia, as well as the prediction of sudden cardiac death. cTNT is a sensitive and specific biomarker for the degree of myocardial injury. In this study, the serum cTNT level was the highest in severe asphyxia group, followed successively by mild asphyxia and control group, suggesting the difference in the extent of myocardial injuries among all groups. Our

Table III. Correlation between QTcd and serum sodium/potassium in neonatal asphyxia patients.

Indicator	r-value	p-value
Serum sodium	-0.563	< 0.05
Serum potassium	-0.365	< 0.05

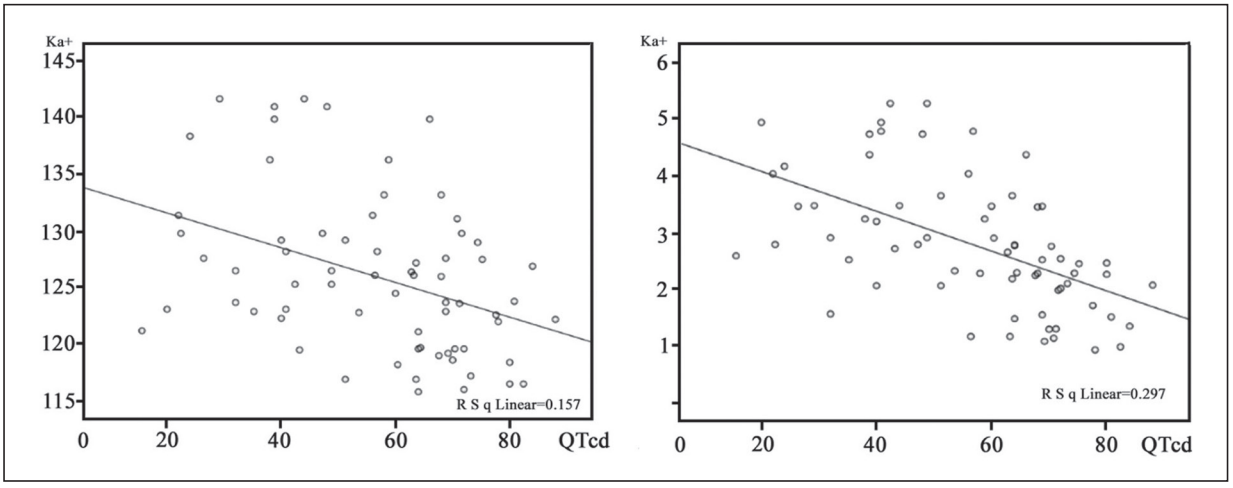

Figure 1. The correlation scatterplot showing the association between QTcd and serum sodium/potassium.

results also showed that the QTcd was increased with a higher degree of the disease, indicating a lower stability of cardiac electrical activity. The increase in QTcd might be associated with a serial of cellular and physiological changes during asphyxia, such as direct injuries of myocardial cell due to asphyxia-induced acidosis and hypoxemia, reduced intracellular ATP level caused by impaired mitochondrial oxidative phosphorylation[17], excited-uncoupling disorders induced by intracellular translocation of extra-cellular calcium ions[18] that lead to changes in the action potential of myocardial cells. Moreover, focal edema and necrosis often occur in myocardial tissues in neonatal asphyxia patients, which slow down the excited conduction in these regions[19]. In this work, the serum sodium level was negatively correlated with QTcd, suggesting that it might be used to assess the severity of asphyxia. The asphyxia-induced ischemia and hypoxia result in reduced ATP synthesis, impairment of Na^+-K^+-ATP pump, and relocation of extra-cellular electrolytes. As a result, extra-cellular sodium ions entered the cells, leading to increased intracellular, but reduced serum sodium level[20]. Moreover, the condensation function of the kidney is impaired during asphyxia, causing a reduced response to vasopressin, and hyponatremia[21]. In addition, the ANP receptors in the atrium increase upon the stimulation of ischemia and hypoxia, which induces an increased level of ANP with strong diuretic effect, and thus severe loss of serum sodium[22]. In short, the decreased serum sodium level is related to multiple biological processes in the body. Undoubtedly, serum sodium level is closely associated with changes in cardiac structures and functions, and it can be used in the assessment of the severity of neonatal asphyxia. In this research, we also found that the serum potassium level was negatively correlated with QTcd. Since the serum potassium and sodium share similar metabolism, the mechanism underlining the reduced potassium in asphyxia is close to that of sodium. Serum potassium level, therefore, can also be used to evaluate the degree of asphyxia in infants. More importantly, the quantification of serum sodium and potassium is fast and convenient, and it can be repeated throughout the treatment course. In a comprehensive study[23] on the blood and biochemical indexes in neonatal asphyxia, it has been confirmed that asphyxia cause acid-base balance disorders, and disorders in liver and kidney function as well as enzymes and glucose metabolism. In-depth studies shall be performed in search for other biomarkers with high specificity and sensitivity for further improve the accuracy of early diagnosis of the disease.

Conclusions

We found that serum potassium and sodium can be used as indicators for neonatal asphyxia, which may markedly improve early diagnosis, prognosis and treatment efficacy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Xu YJ, Ran LM, Zhai SS, Luo XH, Zhang YY, Zhou ZY, Liu YH, Ren LD, Hong T, Liu R. Evaluation of the efficacy of atosiban in pregnant women with threatened preterm labor associated with assisted reproductive technology. Eur Rev Med Pharmacol Sci 2016; 20: 1881-1887.
2) Poggi SH, Ghidini A. Pathophysiology of meconium passage into the amniotic fluid. Early Hum Dev 2009; 85: 607-610.
3) Monen L, Hasaart TH, Kuppens SM. The aetiology of meconium-stained amniotic fluid: Pathologic hypoxia or physiologic foetal ripening. Early Hum Dev 2014; 90: 325-328.
4) Yurdakök M. Meconium aspiration syndrome:do we know. Turk J Pediatr 2011; 53: 121-129.
5) van Ierland Y, de Beaufort AJ. Why does meconium cause meconium aspiration syndrome Current concepts of MAS pathophysiology. Early Hum Dev 2009; 85: 617-620.
6) Wiberg N, Källén K, Herbst A. Relation between umbilical cord blood pH,base deficit,lactate,5-minute Apgar score and development of hypoxic ischemic encephalopathy. Acta Obstet Gynecol Scand 2010; 89: 1263-1269.
7) Stigger F, Lovatel G, Marques M, Bertoldi K, Moyses F, Elsner V, Sigueira IR, Achaval M, Marcuzzo S. Inflammatory response and oxidative stress in developing rat brain and its consequences on motor behavior following maternal administration of LPS and perinatal anoxia. Int J Dev Neurosci 2013; 31: 820-827.
8) Wang H, Zhang K, Zhao L, Tang J, Gao L, Wei Z. nti-inflammatory effects of vinpocetine on the functional expression of nuclear factor-kappa B and tumor necrosis factor-alpha in a rat model of cerebral ischemia-reperfusion injury. Neurosci Lett 2014; 566: 247-251.

9) Maddahi A, Kruse LS, Chen QW, Edvinsson L. The role of tumor necrosis factor-α and TNF-α receptors in cerebral arteries following cerebral ischemia in rat. J Neuro inflammation 2011; 8: 107.

10) Hassan-Khabbar S, Vamy M, Cottart CH, Wendum D, Vibert F, Savouret JF, Therond P, Clot JP, Waligora AJ, Nivet-Antoine V. Protective effect of post-ischemic treatment with trans-resveratrol on cytokine production and neutrophil recruitment by rat liver. Biochimie 2010; 92: 405-410.

11) Siswal N , Singh K , Aruna B. Human resist in stimulates the pro-inf lammatory cytokines TNF-a and IL-12 in macropha-ges by NF-kappaB-dependent pathway. Biochem Biophys Res Commun 2005; 334: 1092-1101.

12) Voll RE, Urbonaviciute V, Herrmann M Kalden JR. High mobility group box 1 in the pathogenesis of inflammatory and autoimmune diseases. Isr Med Assoc J 2008; 10: 26-28.

13) Yang QW, Lu FL, Zhou Y, Wang L, Zhong Q, Lin S, Xiang J, Li JC, Fang CQ, Wang JZ. HMBG1 mediates ischemia-reperfusion injury by TRIF-adaptor independent Toll-like receptor 4 signaling. J Cereb Blood Flow Metab 2011; 31: 593-605.

14) Nakamura T, Yamada S, Yoshioka T. Brain hypothermic therapy dramatically decreases elevated blood concentrations of high mobility group box 1 in neonates with hypoxic-ischemic encephalopathy. Dis Markers 2013; 35: 327-330.

15) Hergenroeder GW, Redell JB, Moore AN, Dash PK. Biomarkers in the clinical diagnosis and management of traumatic brain injury. Mol Diagn Ther 2008; 12: 345-358.

16) Berger RP, Pierce MC, Wisniewski SR, Adelson PD, Clark RS, Ruppel RA, Kochanek PM. Neuronspecific enolase and S100B in cerebrospinal fluid after severe traumatic brain injury in infants and children. Pediatrics 2002; 109: E31.

17) Reddy S, Dutta S, Narang A. Evaluation of lactate dehydrogenase, creatine kinase and hepatic enzymes for the retrospective diagnosis of perinatal asphyxia among sick neonates. Indian Pediatr 2008; 45: 144-147.

18) Matter M, Abdel-Hady H, Attia G, Hafez M, Seliem W, Al-Arman M. Myocardial Performance in Asphyxiated Full-Term Infants Assessed by Doppler Tissue Imaging. Pediatr Cardiol 2010; 31: 634-642.

19) RajaJkumar PS, Vishnu Bhat B, Sridhar MG, Balachander J, Konar BC, Narayanan P, Chetan C. Electrocardiographic and echocardiographic changes in perinatal asphyxia.Indian J Pediatr 2009; 76: 261-264.

20) OhmuraA, NakajimaW, Ishida A, Yasuoka N, Kawamura M, Miura S, Takada G. Prolonged hypothermia protects neonatal rat brain against hypoxic-ischemia by reducing both apoptosis and necrosis. Brain Dev 2005; 27: 517-526.

21) Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, Strohm B, Thoresen M, Whitelaw A, Azzopardi D. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ 2010; 340: c363.

22) Licata G, Di Pasguale P, Parrinello G, Cardinale A, Scandurra A, Follone G, Argano C, Tuttolomondo A, Paterna S. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. Am Heart 2013; 145: 459-466.

23) Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor CM, She L, Yancy CW, Young J, Fonarow GC, OPTIMIZE-HF Investigators and Coordinators. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J 2007; 28: 980-988.