

The diagnostic and prognostic role of amino-terminal pro-brain type natriuretic peptides in pediatric cardiac diseases and pulmonary hypertension

Kayirnis Tilemanbetova¹, Taalaibek Kudaiberdiev¹, Jalil Sheishenov², Damirbek Abibillaev^{1,3}

¹ Scientific-Research Institute of Heart Surgery and Organ Transplantation, Bishkek, Kyrgyzstan

² National Center of Cardiac Surgery and Transplantation, Taraz, Kazakhstan

³ Medical Faculty, International Ala-Too University, Bishkek, Kyrgyzstan

Abstract

Objective: Several studies showed that N-terminal pro-brain type natriuretic peptide (NT-pro-BNP) as the reliable marker both in diagnostic and prognostic workup of pediatric patients with congenital heart disease complicated by pulmonary hypertension. Furthermore, it has well assisted both in therapeutic and surgical management of children with congenital heart diseases. In this review, we aimed to analyze recent studies concerning the role of the NT-pro-BNP in pediatric cardiac patients with pulmonary hypertension.

Methods: PubMed, Cochrane, Science Direct and Google Scholar databases were used with the searching of the following words: "amino terminal pro brain type natriuretic peptide", "pediatric pulmonary hypertension", "congenital heart diseases", emphasizing on original research articles published within recent 15 years and in English language. We critically analyzed and summarized the retrieved studies.

Conclusion: NT-pro-BNP remains as the reliable diagnostic and prognostic marker of pulmonary hypertension and congenital heart diseases in pediatric patients. NT-pro-BNP and BNP remain as the universal marker of cardiovascular pathology in pediatric population. Improvement of their effectiveness in diagnostic workup in patients with CHD and PH undergoing surgery needs further clarification.

Key words: pediatric pulmonary hypertension, N-terminal pro-brain type natriuretic peptide, congenital heart disease

(Heart Vessels Transplant 2021; 5: 21-6. doi: 10.24969/hvt.2020.244)

Introduction

Natriuretic peptides are hormonal molecules produced in cardiac chambers in response to myocardial wall stretching during pressure or volume load. In physiological circumstances, these molecules maintain homeostasis of the cardiovascular system. The natriuretic peptides produced by ventricles, or brain type peptides have been used widely in clinical medicine, due probably to longer half-lives compared to atrial peptides (1).

Basically, any cardiovascular pathology or cardiac involvement of systemic disease that cause myocardial stretching easily stimulate the increased production of brain natriuretic peptides. Thus, both brain natriuretic peptide (BNP) and its product, namely amino-terminal pro-brain natriuretic peptide (NT pro-BNP) have been found as the reliable markers in the diagnostic and prognostic spectrum of many cardiovascular conditions, including congestive heart failure, congenital heart diseases (CHD) and pediatric pulmonary hypertension (PPH) (2-4).

Address for Correspondence: Damirbek Abibillaev, Scientific Research Institute of Heart Surgery and Organ Transplantation, Bishkek, Kyrgyzstan, Email: kg.damir.da@gmail.com

Received: 18.11.2020 **Revised:** 26.01.2021 **Accepted:** 27.01.2021

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Nonetheless, according to several evidence-based guidelines, the most rational use of natriuretic peptides has been justified for the differential diagnosis of the congestive heart failure (CHF) with established cut-off values (2, 5). The routine use of BNP and NT pro-BNP was not supported by guidelines in CHD and PPH. Furthermore, confirmation of diagnosis or assessment of prognosis is impossible solely on the basis of these laboratory markers.

Reference ranges and cut-off values remained under the influence of several determinants, including the age, gender, body mass index, renal disease (6-9).

In pediatric cardiology, most of the data is obtained from the observational or small cohort studies in contrast to large-scale trials conducted on adult populations.

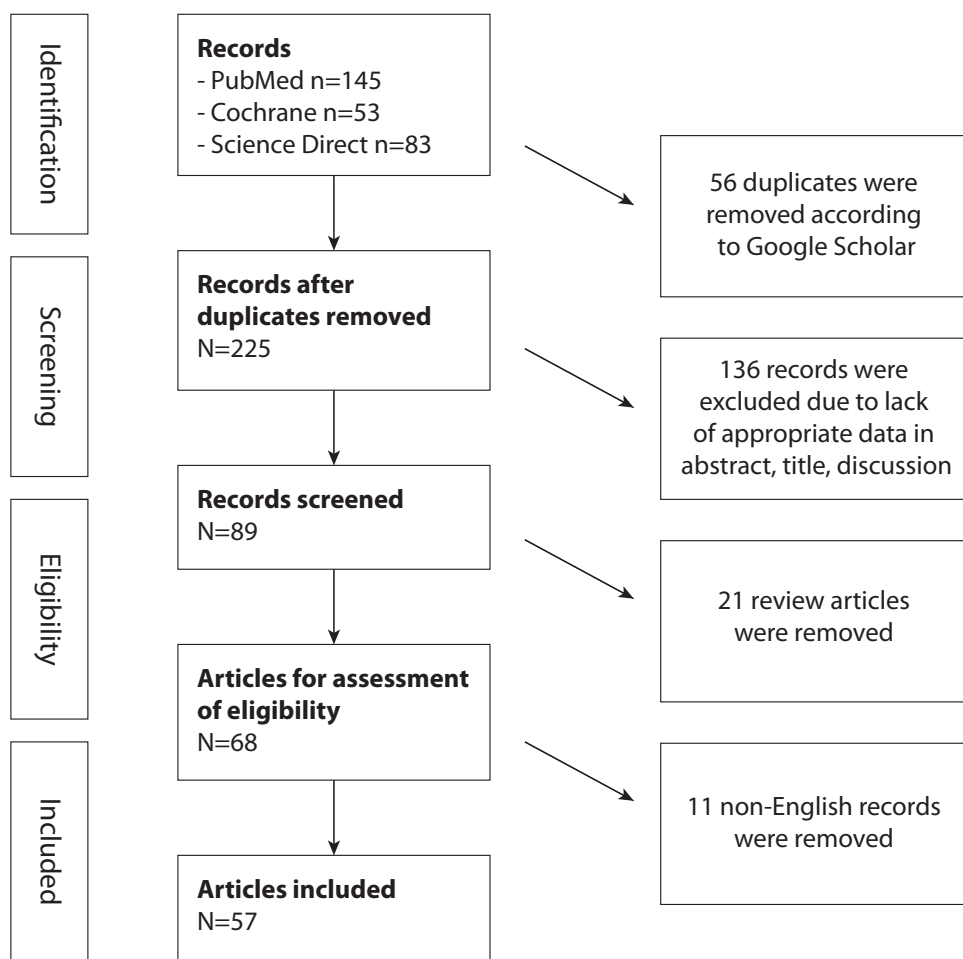


Figure 1. Flowchart of search and inclusion of studies in analysis

In this article, we aimed to review the diagnostic and prognostic roles of NT pro-BNP assay in the management of pediatric pulmonary hypertension associated with pediatric cardiovascular disorders including congenital heart diseases.

Evidence search method (Fig. 1)

PubMed, Science Direct and Cochrane library databases were searched from 2005 to 2020 for primary studies. Search terms included “pediatric pulmonary hypertension”, “amino terminal natriuretic peptides”, “congenital heart disease”. Duplicates were removed according to Google Scholar. All study designs

were included except review articles. Eligibility criteria included studies published only in English language.

The overall role of NT-pro-BNP in the pediatric cardiac disease management (Table 1)

The literature body confirmed the efficacy of BNP’s in workup of children with dyspnea (10, 11).

In infants, Cohen et al. demonstrated the diagnostic accuracy of peptide in differential diagnosis of acute heart failure from pulmonary diseases with cut-off value of 2940 pg/ml (10). A cohort study conducted on children of 1-3 years

with pneumonia accompanied by heart failure revealed the invaluable finding that NT-pro-BNP is a diagnostic evaluative marker in management of patients with concomitant diseases (12).

Both BNP and NT-pro-BNP reflected the severity of heart failure, but NT-pro-BNP was found superior in correlation of modified Ross functional class of heart failure (13). Furthermore, NT-pro-BNP served as a diagnostic marker in case of cardiac involvement of pediatric non-cardiac systemic conditions, such that cystic fibrosis, thalassemia (14, 15).

Serial NT pro-BNP analysis was recommended as the prognostic rationale. According to Medar et al. degree of decline of NT pro-BNP in the first week was strongly associated with adverse cardiovascular events in pediatric patients with myocardial

dysfunction and acute decompensated heart failure (16).

The studies conducted on adults with the objective of “NT pro-BNP guided therapy” could not reach the primary end-point, whereas in pediatric populations such kind of study was not available (17). Recently Januzzi et al. stated the exploratory results of modification of NT-pro-BNP concentration on the background of angiotensin receptor-neprilysin inhibitor (ARNI) treatment in a large cohort of adults with congestive heart failure (18). Again, no rationalized approach has been proposed yet in pediatric patients. In conclusion, the pediatric heart failure is the well-studied branch of pediatric cardiology regarding to natriuretic peptides. Still, gaps in the predictive evidence of peptides exist, especially for the “NT pro-BNP guided therapy” regimen.

Table 1. Diagnostic and prognostic cut-off points of NT-pro BNP for various cardiac conditions in children

Authors	Age, gender, ethnicity or other specific aspects	NT pro-BNP differentiation cut-off points
Cohen et al ¹⁰	Differentiation of heart failure from lung diseases in infants (1-36mth) with respiratory distress	2940pg/ml
Rodriguez-Gonzales et al ¹⁹	Predictor of poor outcome in children <12yrs with myocarditis	2000pg/ml
Sugimoto et al ¹³	Correlation of NT pro-BNP with modified Ross classification	younger than 3yrs: 438 pg/ml (\geq grade II), 1,678 pg/ml (\geq grade III) 7.734 pg/ml (grade IV) elder than 3 yrs: 295 pg/ml (\geq grade II), 1.545 pg/ml (\geq grade III) 3.617 pg/ml (grade IV)
Jung et al ²⁰	Prediction of the coronary artery dilation in hyperacute phase of Kawasaki disease	515.4 pg/mL

NT pro-BNP - amino-terminal pro-brain natriuretic peptide

Congenital heart disease and NT-pro-BNP

In adult congenital heart disease (CHD), the prognostic role of NT-pro-BNP was well investigated in contrast to pediatric population. NT-pro-BNP strongly predicted postoperative adverse events in corrected complex defects (21-23). Brain type natriuretic peptide has been found as a good prognostic marker of critical adverse events after atrial switch operations (23).

Physiologically the level of NT-pro-BNP is elevated up to several days immediately after birth, then it decreases and equals to the adult's level for whole life (3). Nevertheless, some studies revealed that, NT-pro-BNP was significantly elevated in infants with congenital heart diseases compared to neonates without CHD (24).

In a relatively large cohort of pediatric patients underwent congenital heart surgery (CHS), Qu et al confirmed the

predictive role of NT pro-BNP. The marker was strongly associated with prolonged duration of mechanical ventilation, intensive care unit stay and inotropic therapy within different perioperative timelines: before surgery, 1 hour, 12 hours and 36 hours after surgery (25).

Furthermore, Lin et al conducted more sophisticated analysis on children underwent CHD surgery by taking into account the temporal trajectory. According to them, two phenotypes of marker were distinguished: “rapidly-rising” with 5.4-fold increase in prolonged intensive care unit stay in contrast to “slowly-rising” one: (aOR=0.40, p=0.003) (26).

Our center of cardiovascular surgery recently published the study, in which potential relationships of NT pro-BNP with variety of CHD were analyzed. Due to small sample size no statistical tests were conducted. Nevertheless, higher

modified Ross classes, mortality and complication rates were noted in children with NT pro-BNP level >250pg/ml (27).

To conclude, diagnostic and prognostic roles of natriuretic peptides in the management of congenital heart diseases are already shown. Large-scale trials are needed for development of recommendations for proper management of CHDs for daily practice of pediatric cardiologists and related specialties.

NT-pro-BNP as a prognostic marker of pediatric pulmonary hypertension

Conventionally in adults, pulmonary arterial hypertension is defined as a pulmonary arterial pressure of ≥ 25 mm Hg at rest in the presence of normal pulmonary capillary wedge pressure (≤ 15 mm Hg) and increased pulmonary vascular resistance ≥ 3 Wood Units. Due to variability in post-natal pulmonary circulation these criteria are accepted after 3 months of age in pediatric patients (28, 29). About 10% of CHD cases are complicated by pulmonary hypertension (PH) and 8% by Eisenmenger syndrome (30, 31). According to recent guidelines, PH associated with CHDs is classified in several groups: septal defects with left-to-right shunts in group 1, congenital post-capillary obstructive lesions in group 2 and complex congenital anomalies in group 5 (28).

According to recent study, in a large cohort of adults NT-pro-BNP along with other two markers has been found to be additive prognostic marker of left-sided heart failure in PH group 1 (32).

Natriuretic peptides might be used as the prognostic markers both in therapeutic, interventional and surgical management of PH. NT-pro-BNP is also successfully used in randomized clinical trials conducted on the basis of target-therapy of PH (4, 33, 34). According to Kriechbaum et al, initially elevated NT-pro-BNP level decreased following balloon pulmonary angioplasty for inoperable chronic thromboembolic PH (35).

To sum up, NT-proBNP can be used for the diagnosis of pulmonary hypertension and as a prognostic marker in children undergoing cardiac surgery; however, to date, there are insufficient large-scale studies with heterogeneous patient groups, and diverse outcome measures.

Conclusion

NT-pro-BNP and BNP remain as the universal marker of cardiovascular pathology in pediatric population. Improvement of their effectiveness in diagnostic workup in patients with CHD and PH undergoing surgery needs further clarification.

Peer-review: External and internal

Conflict of interest: None to declare

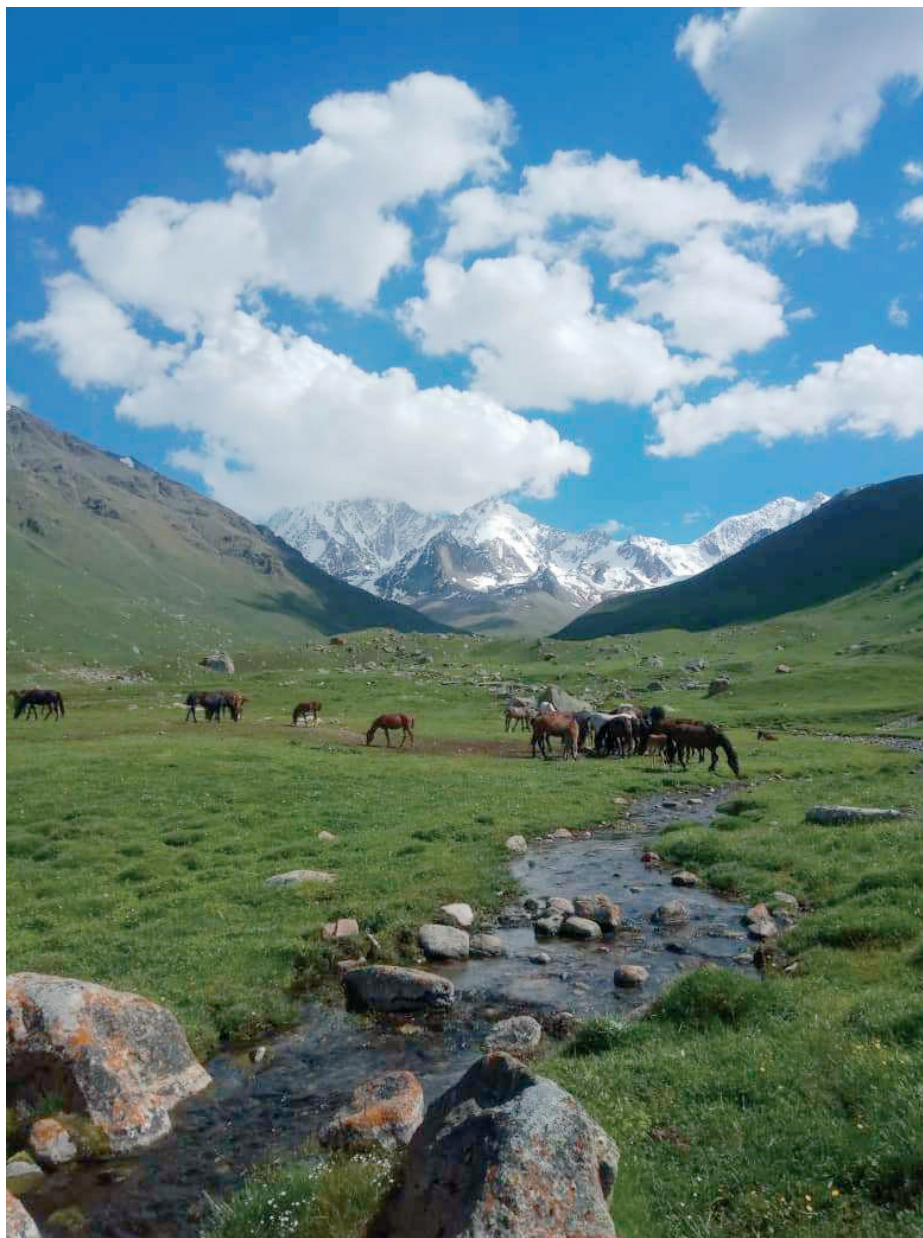
Authorship: K.T., T.K., J.S., D.A. are equally contributed to article preparation

Acknowledgement and funding: None to declare

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Horses on watering place at Chon Kemin jailoo, Kyrgyzstan. Summer 2020. Taalaibek Kudaiberdiev, Bishkek, Kyrgyzstan