N-terminal Prohormone Brain Natriuretic Peptide-proBNP Levels in Ventricular Arrhythmias in Children

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ABSTRACT

Background: Ventricular arrhythmias are the most common consequences of structural and functional heart diseases, but cases with no evident pathology are also observed. A parameter indicating asymptomatic circulatory failure could support decisions related to possible treatment of ventricular arrhythmias.

Hypothesis: The study objective was the evaluation of N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels in children with ventricular arrhythmias and an attempt to determine if this parameter may be used for diagnosis and prognosis of ventricular arrhythmias.

Material and methods: The study population was comprised of 36 children age 5 to 17.5 years old with idiopathic ventricular arrhythmias (Group B) graded mild or potentially malignant; 29 patients with mild ventricular arrhythmias were included into Group B1; and 7 patients with potentially malignant cases into Group B2. In all the patients, NT-proBNP assays were performed.

Results: The NT-proBNP levels in Groups B, B1, B2 and the control group (Group K) were as follows: 41.5 ± 15.1 pg/mL, 35.5 ± 18.5 pg/mL, 66.3 ± 24.9 pg/mL and 31.5 ± 15.1 pg/mL, respectively. Between the groups with and without arrhythmias (Group B vs Group K), no statistically significant differences in NT-proBNP levels were found. However, markedly higher NT-proBNP levels were shown in the children with potentially malignant arrhythmias (Group B2) compared to the patients with mild arrhythmias (B1) and the control group (Group K).

Conclusions: The level of NT-proBNP increases with the severity of ventricular arrhythmia. NT-proBNP assays can be helpful for diagnosing and grading the severity of ventricular arrhythmias.

Introduction

Ventricular arrhythmias are the most common consequences of structural and functional heart disease as well as primary electrophysiological changes. However, in a large group of children with chronic ventricular arrhythmias, no evident heart pathology is observed. Such conditions are defined as idiopathic ventricular arrhythmias, and their clear treatment criteria have not been established yet. The severity of ventricular arrhythmias is commonly graded by means of Lown Score or Bigger and Morganroth Score. In the evaluation of pediatric patients, the Bigger et al system is more frequently used, grading ventricular arrhythmias mild, potentially malignant, and malignant. However, though useful, this classification does not solve all the concerns. It does not show, for instance, the evident necessity for management of arrhythmias graded between mild and potentially malignant. A parameter indicating asymptomatic circulatory failure could support decisions related to possible treatment or use of other therapeutic methods for management of ventricular arrhythmias.

The effect of ventricular arrhythmias on cardiac hemodynamics may lead to circulatory failure. In chronic circulatory failure, compensatory mechanisms are activated, resulting in myocardial remodeling and damage. Thus, symptomatic circulatory failure is preceded by a period of asymptomatic left ventricular dysfunction.²

The fact that natriuretic peptides are involved in circulatory compensation has been used for cardiac failure diagnosing.³ Brain natriuretic peptide (BNP) and its N-terminal (NT-proBNP) fragment have been proven sensitive and equivalent markers of left systolic and diastolic ventricular impairment.⁴ Brain natriuretic peptide is described as an independent marker of circulatory failure, and it is useful for identification of patients at the highest risk of adverse cardiovascular events.⁵⁻⁹ Hence, this parameter seems important for the evaluation of circulatory status in children with ventricular arrhythmias. The effect of ventricular arrhythmias on BNP levels in children has not been of common interest so far and data worldwide are rare.

Objectives

The study objective was the evaluation of N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels in children with ventricular arrhythmias as well as an attempt to determine if this parameter may be used for diagnosis and prognosis of ventricular arrhythmias.

Material and Methods

The study population was comprised of a group of previously pharmacologically untreated children (group B) with ventricular arrhythmias graded mild or potentially malignant (by Bigger et al). The eligible patients were children with no comorbid circulatory pathology and no manifestations

Table 1. Comparison of BNP Values in Groups Determined According to the Number of Premature Ventricular Contractions

Parameter	Group K	Group A	Group B	Group C
BNP (pg)				
PVC	...	5788 ± 2006	13 267 ± 3379	30 250 ± 10 687
X	31.49	34.28	37.89	61.68
n	20	16	12	8
SD	15.13	17.30	21.14	27.72
Min-Max	7.01–58.13	10.70–67.77	9.96–81.70	27.89–99.22
Group C vs K, A, B	0.0102	0.0275	0.0449	...
Mann-Whitney test				
Abbreviations: BNP, brain natriuretic peptide; Group A, PVC <10 000/ day; Group B, PVC 10 000–20 000/ day; Group C, PVC >20 000/ day; n, number of children; PVC, premature ventricular contractions; SD, standard deviation; X, mean BNP level.				

of circulatory failure, showing normal arterial pressure values, and no abnormalities on physical examination except arrhythmia. The patients were 5 to 17.5 years old (average 12.4 ± 3.4). A total of 29 children were included into the mild arrhythmia group (group B1). They demonstrated isolated premature ventricular contractions 2400 to 22000/ day. A total of 7 children were included into the potentially malignant arrhythmia group (group B2). They showed complex ventricular arrhythmias: premature ventricular contractions 20000 to 40000/ day accompanied by ventricular couplets, episodes of nonsustained ventricular tachycardia (6 children), and active ventricular rhythm (1 child). All patients >7 years old underwent repeated electrocardiography, Holter monitors, echocardiography, chest x-rays, and exercise stress tests. Blood biochemistry tests were also performed including: blood count, electrolytes, glucose, ALT, glucose, alanine transaminase, aspartate transaminase, creatine kinase, and its cardiac fraction CK-MB.

The study group was also divided, on the basis of the number of premature ventricular contractions only, into group A (below 10 000/d), group B (10 000–20 000/d), and group C (above 20 000/d). The groups were comprised of 16, 12, and 8 children, respectively (Table 1). The control group (group K) was comprised of 20 healthy children 7 to 17.5 years old (12.8 ± 3.5), who underwent the same diagnostic tests as mentioned above.

For all the study groups, serum NT-proBNP levels were using ELISA assays (Medica Gruppe, Austria). Blood samples were collected and serum centrifuged and stored at -70°C . All the samples were assayed simultaneously.¹⁰ The results are presented in Table 2.

The statistical analysis was performed with the use of nonparametric tests. The study parameters among the groups were compared by means of the Mann-Whitney test, and the parameter correlations were estimated using the Spearman rank correlation coefficient, the significance level was $P < 0.05$.

The present study was approved by the bioethics committee at the Medical University of Silesia in Katowice, Poland.

Results

The study groups showed similarities in age, gender, and body mass index (BMI). The echocardiography performed in children with ventricular arrhythmias (group B) and the control group (group K) showed no abnormalities—left ventricular contractility was within standard limits in all the patients. Shortening fraction (FS) values were as follows: group B1: $40.1\% \pm 3.8\%$, group B2: $41.4\% \pm 4.2\%$, and group K: $41.3\% \pm 3.4\%$. The laboratory results did not show inflammation or electrolyte disorders.

Chest x-rays were also performed and showed no abnormalities and normal cardiothoracic ratios. Bruce stress tests were performed in 26 patients from group B1 and 7 patients from group B2. Physical efficiency of children from group B1 ranged from poor to very good (III–V workload levels). During the exercise stress test, arrhythmia did not resolve in only 3 children. The other patients did not demonstrate arrhythmia or it resolved at increased heart rate. In the second group (group B2), arrhythmia did not resolve in 4 patients and it maintained throughout the whole test. Ventricular arrhythmia was enhanced in 1 child and more complex forms occurred, therefore the test was discontinued.

In the whole group of patients with ventricular arrhythmias (group B), the NT-proBNP levels were 41.5 ± 15.1 pg/mL, while in the control group the levels were 31.5 ± 15.1 pg/mL. Between the study groups (group B vs group K), no statistically significant differences in NT-proBNP levels were shown. The results for group B1 and group B2 were 35.5 ± 18.5 pg/mL and 66.3 ± 24.9 pg/mL respectively, showing that the children with potentially malignant arrhythmias (group B2) had statistically significant higher levels of NT-proBNP compared to the levels in patients with mild arrhythmias (group B1) as well as the control group (group K; $P < 0.01$; Table 2).

Table 2. Parameters of Healthy Children (Group K) and Children with Ventricular Arrhythmias (Group B) Graded Mild (Group B₁) or Potentially Malignant (Group B₂)

	n	Gender		Age (years)	BMI (kg/m ²)	FS (%)	NT-proBNP (pg/mL)
		Boys	Girls				
Group K	20	12	8	12.8 ± 3.5	18.6 ± 2.9	41.3 ± 3.4	31.5 ± 15.1
		60.0%	40.0%	7 ± 17.5	14.0 ± 23.1	36 ± 47	7.0 ± 53.2
Group B	36	18	18	12.4 ± 3.4	18.5 ± 3.2	40.4 ± 3.9	41.5 ± 15.1
		50.0%	50.0%	5 ± 17.5	13.4 ± 24.5	32 ± 50	9.6 ± 99.2
Group comparison		NS		NS	NS	NS	NS
Group B ₁	29	13	16	11.9 ± 3.9	18.4 ± 3.4	40.1 ± 3.8	35.5 ± 18.5
		44.8%	55.2%	5 ± 17.5	13.4 ± 24.5	32 ± 50	9.9 ± 81.7
Group B ₂	7	5	2	13.0 ± 7.8	19.0 ± 2.5	41.4 ± 4.2	66.3 ± 24.9
		71.4%	28.6%	8.5 ± 17.0	15.9 ± 23.3	38 ± 50	41.7 ± 99.2
Group comparison	B ₁ -B ₂	NS		NS	NS	NS	<i>P</i> < 0.01
	B ₁ -K	NS		NS	NS	NS	NS
	B ₂ -K	NS		NS	NS	NS	<i>P</i> < 0.01

Abbreviations: BMI, body mass index; FS, shortening fraction; Group B, children with ventricular arrhythmias; Group B₁, children with mild ventricular arrhythmias; Group B₂, children with potentially malignant ventricular arrhythmias; Group K, healthy children; n, number of children; NS, not significant; NT-proBNP, N-terminal prohormone brain natriuretic peptide; p, statistical significance level.

Table 3. NT-proBNP vs Age

Age and NT-proBNP (pg/mL)	Number of Patients, n	Spearman Rank Correlation Coefficient		
		R	t (N-2)	Level <i>p</i>
Group K	20	0.1109002	0.473439	0.641591
Group B	36	-0.227311	-1.36107	0.182444
Group B ₁	29	-0.228776	-1.22114	0.232588
Group B ₂	7	-0.750000	-2.535446	0.052181

Abbreviations: Group B, children with ventricular arrhythmias; Group B₁, children with mild ventricular arrhythmias; Group B₂, children with potentially malignant ventricular arrhythmias; Group K, healthy children; NT-proBNP, N-terminal prohormone brain natriuretic peptide; p-level, statistical significance level; R, Spearman rank correlation coefficient; t (N-2), statistic t-value.

In the study subgroups, no statistically significant correlations between NT-proBNP values and age were found (Table 3).

The comparison of group C (determined according to the number of premature ventricular contractions only) with groups K, A, and B yielded statistically significant differences: *P* = 0.0102, *P* = 0.0275, and *P* = 0.0449 respectively (Table 1). In group C, the mean BNP level was 61.68 pg; in group B, it was 37.89 pg; and in group A, the mean BNP level was 34.28 pg.

Discussion

Brain natriuretic peptide is a natriuretic peptide released by ventricular and atrial myocytes due to increased myocardial wall stress induced by pressure load and increased cardiac blood volume. Natriuretic peptides enhance glomerular filtration, have natriuretic effect, dilate the vascular bed, and inhibit the renin-angiotensin-aldosterone system.⁵⁻⁸

Elevation in BNP levels occurs in circulatory failure with both systolic and diastolic ventricular impairment. Abnormal BNP values are demonstrated even in the asymptomatic

period of circulatory failure and they rise after a prolonged time of increased ventricular wall stress.^{11–15} BNP levels do not change due to temporary ventricular wall stress abnormalities, whereas they increase with age^{16,17} and in such diseases as arterial hypertension, pulmonary hypertension, Kawasaki disease,¹⁸ congenital cardiac shunts,^{9,11,19–22} and many other conditions related to increased ventricular wall stress. A BNP level has been considered as an independent marker of adverse cardiac events for a long time.^{5,8,9}

In the present study, no correlation of NT-proBNP level with age was found. The patients were 5 to 17.5 years old. In the literature data, aging-related BNP elevation has been reported.^{16,17} Undoubtedly, the determinants of elevated BNP levels are: the aging process, cardiac structural changes, stress changes, and a growing number of collagen filaments. Children demonstrate elevated BNP levels on the first days after birth which stabilize between 4 months and 15 years of life. In children 5 to 17.5 years old (the study group age), no remarkable changes in the circulatory system seem to have occurred yet, hence the study groups did not show a correlation between age and BNP levels.

Many reports show BNP elevation in cases of low cardiac contractility as well as left ventricular systolic and diastolic dysfunction. A BNP level increases with reduced shortening fraction (FS) and reduced ejection fraction (EF).^{5,22} In our study, the children with ventricular arrhythmias demonstrated FS within standard limits $41.5\% \pm 3.9\%$. Therefore, the effect of cardiac contractility on BNP levels cannot be evaluated here. Compared to the healthy children (group K) and the patients with mild arrhythmia (group B1), the children with enhanced arrhythmia (group B2) demonstrated significantly higher levels of NT-proBNP (Table 2).

The comparison of groups determined according to the number of premature ventricular contractions only (groups A, B, and C) yielded a statistically significant difference between the group of 20 000/day (group C) and the other groups K, A, and B (Table 1). The BNP levels increased with the growing number of premature ventricular contractions.

These study results are consistent with the literature data. Sutovsky et al studied a heterogeneous group of 52 adult patients with ventricular arrhythmias and no manifestations of circulatory failure.²³ They found higher BNP levels in the group of patients with more severe arrhythmias. Despite comparable EF values in both groups, the patients with enhanced arrhythmia showed greater left ventricular end-systolic (LVESD) and greater left ventricular end-diastolic (LVEDD) diameters. Hiroshi and Tada²⁴ have reported similar results. They found higher BNP levels in patients with ventricular tachycardia and premature ventricular contractions originating from the left rather than the right ventricle. Controlled BNP levels were significantly lower after successful ablation. No correlation of BNP levels with age, left ventricular ejection fraction, and left ventricular mass index were found. Nevertheless, it should be

noted that the reports referred to patients with comorbidities, such as hypertension or atherosclerosis. As mentioned before, adult patients show increased cardiac mass, greater-sized myocytes, and increased number of collagen filaments causing higher BNP levels than in children. It is worth mentioning that in the original study, the group of children was homogenous and none of the above-mentioned factors that could affect the study outcomes occurred.

These results prove a significant effect of ventricular arrhythmia on BNP levels. Enhanced ventricular arrhythmia, even if not leading to circulatory failure, is suggested to result in remodeling and lesions in ventricular wall stress. Children do not show aging-related ventricular dysfunction, so elevated BNP levels seem to be induced by another factor. In regular ventricular activation, the earliest activated region is the middle part of the left interventricular septal endocardium. Almost simultaneously, left ventricular apical-posterior and anterior muscular activation occurs. Activation of other structures is slightly delayed. This activation sequence determines normal ventricular systolic function. In premature ventricular contractions, a different activation sequence is shown, which induces asynchronous contractions, asynchronicity of atrial and ventricular functions, atrioventricular valvular regurgitation, coronary flow reduction, contractility impairment, and cardiac output reduction accompanied by the increase in heart rate. Ventricular arrhythmias change ventricular wall stress, while mechanical stress enhances ventricular hypertrophy. For these conditions, increased expression of the BNP gene and augmented stimulation of BNP production have been described.^{25,26}

The effect of ventricular arrhythmias on hemodynamics has been proven by the studies that included echocardiography. They showed the increase in LVEDD, significant left ventricular contractility reduction, and impairment of systolic motion in the left ventricular wall during premature ventricular contractions. The severity of those changes increased with the shortened coupling interval of premature ventricular contractions and prolonged QT time. In the same patients, the above changes usually did not occur during sinus rhythm.^{27–29}

The study results suggest that BNP assays in children with ventricular arrhythmias could contribute to arrhythmia severity grading. They can be useful for choices related to possible arrhythmia therapy implementation as well as for treatment efficacy monitoring in patients receiving the therapy (also for many other conditions, such as circulatory failure and congenital cardiac shunts).³⁰ Shiga et al found that patients with ventricular arrhythmias who received amiodarone therapy demonstrated reduced BNP levels. That effect was shown even in those patients who did not show a significant change in the left ventricular diameter or shortening fraction during the therapy.³¹ The elevation of BNP levels in ventricular arrhythmia could

also be an argument supporting the choice of a possible electrophysiological examination and ablation.

However, the study conclusions must be very cautious. The small number of the patients involved in the study should be considered, specifically those with potentially malignant arrhythmias. No myocardial biopsy or cardiac MRI was performed, while possible abnormal results could exclude idiopathic arrhythmia in some cases.³² Despite these limitations, the usefulness of BNP assays for children with ventricular arrhythmias should be emphasized.

Conclusions

Levels of BNP increase with the severity of ventricular arrhythmia in children. BNP assays can be helpful in diagnosing and grading the severity of ventricular arrhythmias.

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