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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Relationship between N-terminal B-type natriuretic propeptide and right ventricular performance assessed by tissue Doppler imaging and speckle tracking echocardiography in children after surgical repair of tetralogy of Fallot

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Abstract

Background and aim: The relationship between plasma levels of N-terminal B-type natriuretic propeptide (NT-proBNP) and parameters of right ventricular (RV) function was evaluated in patients after surgical repair of tetralogy of Fallot (ToF).

Methods: 52 children comprised the study group (SG). The control group (CG) included 32 healthy children. Patient histories, measured NT-proBNP levels and transthoracic echocardiography parameters were analysed.

Results: Tissue Doppler imaging (TDI) demonstrated significant differences ($p < 0.01$) between SG and CG in regard to the following systolic and diastolic function parameters: peak systolic myocardial velocity (S', 5.9 ± 1.6 cm/s vs. 9.8 ± 2.3 cm/s), peak early diastolic velocity (E', 6.6 ± 2.9 cm/s vs. 11.6 ± 3.1 cm/s), and peak atrial diastolic velocity (A', 3.8 ± 1.6 cm/s vs. 6.6 ± 2.8 cm/s). Mean values of peak longitudinal strain (ε) were significantly higher ($p < 0.01$) in SG compared to CG, including basal lateral segment (BL, –32.8 ± 12.1% vs. –51.5 ± 15.5%), medial lateral segment (ML, –23.8 ± 9.5% vs. –40.4 ± 14.9%), and apical lateral segment (AL, –16.9 ± 7.5% vs. –35.8 ± 13.43%). Mean plasma NT-proBNP level also differed significantly ($p < 0.01$) between SG and CG (286.0 ± 269.2 pg/mL vs. 153.1 ± 170.5 pg/mL, respectively). NT-proBNP levels were significantly higher ($p < 0.01$) in SG subjects with reduced effort tolerance (639.2 ± 357.1 pg/mL) compared to those with normal effort tolerance (181.8 ± 97.2 pg/mL), and in patients in whom a transannular patch was used for surgical correction (488.9 ± 317.19 pg/mL) compared to those treated without the use of a transannular patch (228.1 ± 217.5 pg/mL). Significant correlations between plasma NT-proBNP level and S' ($r = –0.40$, $p < 0.01$), E' ($r = –0.50$, $p < 0.01$), BL ε ($r = 0.36$, $p < 0.05$), and AL ε ($r = 0.35$, $p < 0.05$) were found.

Conclusions: 1. Increased plasma NT-proBNP levels in patients after surgical repair of ToF are related to RV systolic dysfunction, as determined by the S' wave velocity of the tricuspid annulus and longitudinal strain of the RV. 2. Children after surgical repair of ToF showed increased plasma NT-proBNP levels associated with RV diastolic dysfunction as evaluated by TDI.

Key words: tetralogy of Fallot, NT-proBNP, tissue Doppler imaging, speckle tracking, longitudinal strain

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INTRODUCTION

In patients after surgical repair of tetralogy of Fallot (ToF), various residual haemodynamic sequels are seen despite good surgical results, including pulmonary regurgitation, residual right ventricular outflow tract obstruction, and tricuspid regurgitation, which may lead to cardiac dysfunction at long-term follow-up. A risk factor for haemodynamic disturbances related to the surgical technique is the use of a transannular patch [1, 2].

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There are reports in the literature regarding the usefulness of N-terminal B-type natriuretic propeptide (NT-proBNP) to evaluate and predict the risk of the development of heart failure before clinical symptoms apear in patients after surgical repair of ToF but no data are available on the relationship between NT-proBNP levels and right ventricular (RV) function parameters as evaluated using speckle tracing echocardiography [3–7].

Evaluation of clinical symptoms, surgical approach used, and RV function using modern echocardiographic techniques along with measurements of plasma NT-proBNP levels might allow new insights into the usefulness of this peptide in the evaluation of RV function in children after surgical correction of ToF.

The aim of this study was to evaluate the relationship between plasma NT-proBNP levels and selected parameters of RV function in children after surgical correction of ToF.

METHODS

Patients

We studied 52 children after surgical correction of ToF (22 girls and 30 boys) aged 8–18 years (mean age 13.7 ± 3.42 years). The mean patient age at the time of surgical correction was 12.0 ± 8.9 months. Evaluation was performed at mean 12.9 ± 3.3 years after the surgery. Transannular patch was used in 11 (21.1%) patients. The control group included 32 healthy children (15 girls and 17 boys) aged 8–18 years (mean age 13.7 ± 2.95 years).

In all children in the study and control groups, we evaluated heart failure stage using the New York Heart Association (NYHA) classification and measured plasma NT-proBNP level using the immunoenzymatic method (ELISA SK-1204, Biomedica). NT-proBNP level measurements were expressed in pg/mL.

Echocardiographic evaluation

Echocardiographic examinations included 2-dimensional, conventional Doppler, and tissue Doppler imaging (TDI). The latter was performed using an iE33 machine (Philips) and a S5-1 sector transducer. Images were optimised to achieve the highest possible frame rate (minimum desired value was 100 Hz) with simultaneous scanning of the evaluated wall, so as to allow the maximum angle between the direction of the ultrasound beam and the direction of strain not exceeding 15°. Examinations were stored digitally on DVDs.

Evaluation of regional systolic and diastolic function using TDI and speckle tracing echocardiography was performed in stored 2-dimensional and colour tissue Doppler images in the apical 4-chamber view with focus on the RV, using QLAB Advanced Quantification software (Philips). The results were arithmetic means from 3 consecutive cardiac cycles, calculated automatically by the software.

Using TDI at the lateral aspect of the tricuspid annulus, we measured:

- peak systolic myocardial velocity (S');
- isovolumic acceleration (IVA) during isovolumetric contraction (IVC), evaluated automatically after determination of two points on the upslope of the myocardial velocity curve during IVC. The IVC wave was defined as a positive deflection of the myocardial velocity curve that coincided with the QRS complex in the electrocardiogram;
- peak early diastolic myocardial velocity (E');
- peak atrial diastolic velocity (A').

To calculate the E/E' ratio, we also analysed the spectrum of tricuspid inflow, measuring peak early (E) wave velocity by pulse wave Doppler in the apical 4-chamber view, with the sample volume at the level of valve leaflets.

Peak longitudinal myocardial strain (ε) was measured using the Free Strain tool of the Cardiac Motion/Mechanics Quantification function at the basal lateral segment (BL), medial lateral segment (ML), and apical lateral segment (AL) of the RV wall.

Statistical analysis

All statistical calculations were performed using the STATISTICA software, version 10.0 (StatSoft, Inc.), the R statistical package, version 2.15.2, and the Excel spreadsheet.

Quantitative variables were characterised by the arithmetic mean and standard deviation (SD), and for non-normally distributed variables also by the median and range. Qualitative variables were characterised by frequencies and percentages.

The Shapiro-Wilk test was used to verify normal distribution of quantitative variables. Significance of differences between the two groups was evaluated using the Student *t* test, or the Mann-Whitney U test for non-normally distributed variables.

$P < 0.05$ was considered statistically significant.

Pearson correlation coefficients were calculated to evaluate the presence, strength, and direction of associations between variables. The study was approved by the respective university bioethics committee. A written informed consent was obtained from all patient guardians, and children above 15 years of age in the study and control groups.

RESULTS

Among 52 patients in the study group, reduced effort tolerance was noted in 10 (19.2%) patients, all categorised as NYHA class II, with no children categorised as NYHA class III or IV. Reduced effort tolerance was not found in any children in the control group. The mean E wave velocity in the study group was significantly higher ($p < 0.01$) compared to the control group (92.9 ± 18.3 cm/s vs. 62.7 ± 13.8 cm/s). Systolic and diastolic function parameters evaluated by tissue Doppler echocardiography are shown in Table 1.

In patients after surgical repair of ToF, S' wave velocity was significantly lower ($p < 0.01$) compared to healthy children. Mean IVA was also significantly lower ($p < 0.01$) in the study

Table 1. Systolic and diastolic function parameters evaluated by tissue Doppler echocardiography

Parameter	Study group	Control group	P
S' [cm/s]	5.5 ± 1.6	9.8 ± 2.3	< 0.01
IVA [cm/s^2]	81.9 ± 53.9	139.3 ± 28.6	< 0.01
E' [cm/s]	6.6 ± 2.9	11.6 ± 3.0	< 0.01
A' [cm/s]	3.8 ± 1.6	6.6 ± 2.8	< 0.01
E/E'	16.6 ± 8.0	5.6 ± 1.6	< 0.01

S' — peak systolic myocardial velocity; IVA — isovolumetric acceleration; E' — peak early diastolic velocity; A' — peak atrial diastolic velocity; E — peak early diastolic tricuspid inflow velocity

Table 2. Peak longitudinal strain (ε)

Segment	Study group [%]	Control group [%]	P
Basal lateral	–32.8 ± 12.1	–51.5 ± 15.7	< 0.01
Medial lateral	–23.8 ± 9.5	–40.4 ± 15.1	< 0.01
Apical lateral	–16.6 ± 6.4	–35.8 ± 13.5	< 0.01

group compared to the control group. Mean E' wave velocity in the study group was significantly lower ($p < 0.01$), and mean E/E' was significantly higher ($p < 0.01$) compared to the control group. In children after surgical repair of ToF, mean A' wave velocity was also significantly lower compared to the healthy children ($p < 0.01$). Mean peak longitudinal strain (ε) was higher (i.e., less negative) in the study group compared to the control group. These changes were significant ($p < 0.01$) for all evaluated myocardial segments (Table 2).

Mean NT-proBNP level in the study group was 286.0 ± ± 269.2 (median 215.0, range 45.3–1109.7) pg/mL, compared to 153.1 ± 170.5 (median 116,5, range 1.0–996.0) pg/mL in the control group, a statistically significant difference ($p < 0.01$).

We found significantly higher ($p < 0.01$) plasma NT-proBNP levels in patients with reduced effort tolerance (mean 639.2 ± 357.1 pg/mL, median 621 pg/mL, range 134––1109 pg/mL) compared to those with normal effort tolerance (mean 181.8 ± 97.2 pg/mL, median 212 pg/mL, range 45–1034 pg/mL). In patients who underwent repair with the use of a transannular patch, plasma NT-proBNP levels (mean 488.9 ± 317.19 pg/mL, median 317.5 pg/mL, range 187–1109 pg/mL) were significantly higher $p < 0.01$) compared to those in whom ToF was repaired without the use of a transannular patch (mean 228.1 ± 217.5 pg/mL, median 170 pg/mL, range 45–1038 pg/mL).

Figure 1 shows the relationships between plasma NT-proBNP level and selected parameters of RV function. Among the evaluated systolic function parameters, we found a significant negative correlation between plasma NT-proBNP level and S' wave velocity ($r = –0.43$, $p < 0.01$), and significant ($p < 0.05$) positive correlations between plasma NT-proBNP level and BL ε ($r = 0.36$) and AL ε ($r = 0.35$). We found no significant correlation between plasma NT-proBNP level and ML ε.

We also find a significant negative correlation between plasma NT-proBNP level and E' wave velocity ($r = –0.49$, $p < 0.01$), and a significant positive correlation between plasma NT-proBNP level and the E/E' ratio ($r = 0.41$, $p < 0.05$). We found no significant correlation between plasma NT-proBNP level and A' wave velocity.

DISCUSSION

Haemodynamic disturbances in patients after surgical repair of ToF are asymptomatic for many years. In our study, a slight limitation of exertion tolerance was seen in only 10 (19%) patients, with no patients in NYHA class III or IV.

It may be suspected that few clinical symptoms regardless of residual changes or haemodynamic disturbances in children after surgical repair of ToF are related to the fact that these patients are adapted to functioning at a lower level of physical activity and are able to control their exercise in adequate proportion to their RV function. In addition, children with restrictive RV physiology typical for ToF are known to show better exertion tolerance.

Our TDI findings showed reduced peak systolic myocardial velocity (S' wave) and IVA in patients after surgical repair of ToF. These results are consistent with the study by Harada et al. [4] who, based on exercise testing, found that S' wave velocity measurements are useful for the identification of patients with reduced systolic reserve. These authors showed a decreased increment of S' wave velocity at the lateral aspect of the tricuspid annulus during exercise in patients after surgical repair of ToF.

IVA is considered a parameter directly associated with myocardial damage and does not depend on volume overload or changes in the RV geometry [5]. As a parameter of the presystolic phase, it may be useful in the evaluation of myocardial function before a reduction in ejection fraction occurs [6–10].

Using speckle tracing echocardiography, we showed reduced longitudinal strain (ε) in all evaluated myocardial segments. Kempny et al. [11] found that evaluation of this parameter by magnetic resonance imaging in patients after surgical repair of ToF is a sensitive approach to assess RV systolic function. In that study, RV lateral wall contractility evaluated by longitudinal strain worsened while the RV ejection fraction remained unchanged. Literature data indicate, however, that longitudinal strain is related not only to myocardial damage but also depends on RV preload. When evaluating cardiac systolic function by speckle tracing technique in patients with RV volume overload, e.g. due to atrial septal defect, absolute values of longitudinal strain are increased compared to healthy subjects [12].

The use of TDI allows more precise evaluation of diastolic function and earlier detection of impaired relaxation before it becomes evident in conventional echocardiography. In the

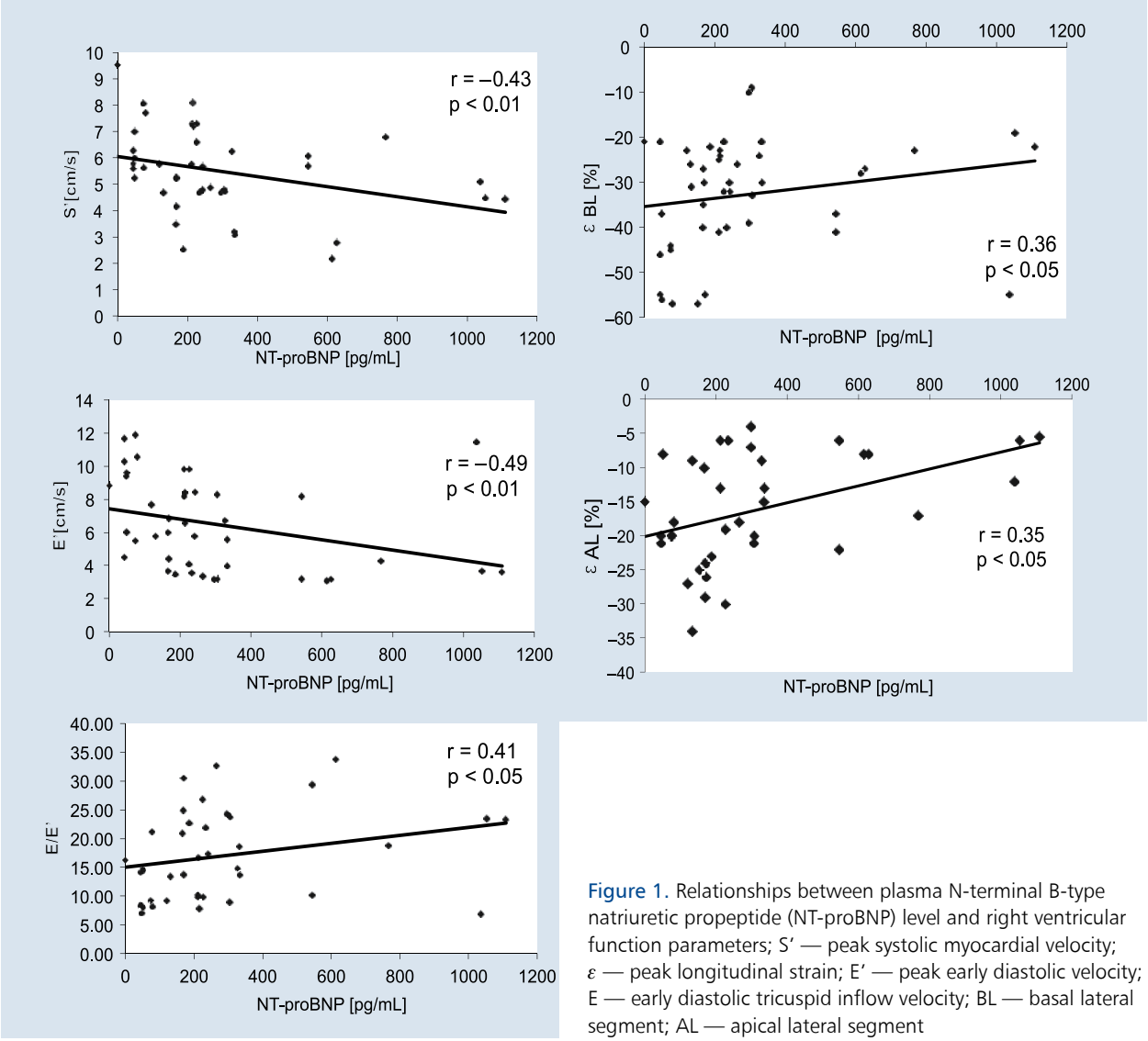

Figure 1. Relationships between plasma N-terminal B-type natriuretic propeptide (NT-proBNP) level and right ventricular function parameters; S′ — peak systolic myocardial velocity; ε — peak longitudinal strain; E′ — peak early diastolic velocity; E — early diastolic tricuspid inflow velocity; BL — basal lateral segment; AL — apical lateral segment

current study, we found a reduction in both early and late diastolic myocardial velocities. Due to the fact that mean early diastolic inflow velocity as measured by conventional echocardiography in children after surgical repair of ToF was higher compared to the control group, the E/E′ in the study group was much increased compared to healthy subjects. In studies performed in adult subjects, increased E/E′ values were found to closely related to RV filling pressures [13]. These results are discordant with the findings by Hayabuchi et al. [14] using TDI and invasive measurements. These authors were unable to find a relationship between the E/E′ ratio and both RV pressure and mean right atrial pressure in children after surgical repair of ToF but that study was performed in a group of young children at the mean age of 3 years. In light of the present findings and reports by other authors, it may be suspected that myocardial compliance reduces with age, leading to increasing diastolic dysfunction (as evidenced by decreased E′ wave velocity and increased E/E′ ratio) and increases in the RV diastolic pressure and right atrial pressure in patients after surgical repair of ToF.

In turn, reduction of myocardial A′ wave velocity may be related to exhaustion of the compensatory capacity of the right atrial myocardium. In patients after surgical repair of ToF, A′ wave velocity increase during dobutamine stress was shown to be lower compared to healthy subjects [15].

In our study, plasma NT-proBNP levels were significantly higher in the study group compared to the control group. In patients with reduced exertion tolerance, mean plasma NT-proBNP level was higher than in patients with normal exertion tolerance. Plasma NT-proBNP level is an indicator of ventricular and atrial dilation, including that of the RV, which occurs with volume overload seen commonly in children after surgical repair of ToF. We found that in children in whom a transannular patch was used for surgical repair, plasma

NT-proBNP level was higher compared to those patients who were operated without the use of a transannular patch. These results are in concordance with our previous findings [16]. An increase in plasma NT-proBNP level is probably related to more severe pulmonary regurgitation seen in patients treated with the use of a transannular patch compared to those in whom repair did not involve the use of a transannular patch.

In the present study, we found a moderate but significant correlation between plasma NT-proBNP level and S' wave velocity. The results of previous studies in adult patients after surgical repair of ToF are unclear in this regard [2, 4]. The observed relationship may be secondary to reduced systolic reserve associated with cardiomyocyte overstretching in patients after surgical repair of ToF [17–20]. According to the literature data, children with surgically repaired ToF who show impaired systolic reserve are characterised not only by the above mentioned reduction in S' wave velocity, but also by an increase in plasma NT-proBNP level compared to healthy subjects and those patients after surgical repair of ToF in whom systolic reserve is normal [21–24].

On the other hand, Apitz et al. [25] found a weak correlation between plasma NT-proBNP level and reduced systolic reserve as evaluated during cardiac catheterisation after adrenergic stimulation with dobutamine, but these findings were based on evaluation of only 5 patients.

In the studies by Norozi et al. [26, 27], an increase in plasma NT-proBNP level in patients after surgical repair of ToF was found to occur prior to the development of clinical symptoms and to show a relation with the RV end-diastolic volume. Koch et al. [28] found a reduction in plasma NT-proBNP level following pulmonary valve replacement due to severe regurgitation.

Of note, in patients after surgical repair of ToF with RV overloading due to pulmonary regurgitation, plasma NT-proBNP level is reduced by angiotensin-converting enzyme inhibitors. This observation holds promise for drug treatment to delay progression of myocardial damage in patients with severe pulmonary regurgitation [29].

In our study, we showed for the first time a significant positive correlation between plasma NT-proBNP level and RV myocardial strain evaluated using speckle tracing technique in children after surgical correction of ToF.

We also found a relationship between plasma NT-proBNP level and parameters of RV diastolic function evaluated using TDI. Plasma NT-proBNP level rose with a reduction of early diastolic myocardial velocity and an increase in the E/E' ratio.

All these findings are consistent with the results of experimental studies showing that NT-proBNP release from the cells is related to both diastolic overload and systolic myocardial strain [30].

Despite numerous studies showing usefulness of various echocardiographic parameters to detect early RV haemodynamic disturbances in patients after surgical repair of ToF, their value during patient selection for reintervention has not been clearly established. Measurements of plasma NT-proBNP level along with evaluation using TDI and speckle tracking echocardiography might be useful to develop a diagnostic algorithm to determine optimal timing of reintervention in case of increasing haemodynamic disturbances in patients after surgical repair of ToF.

When deciding upon treating residual changes, potential benefits related to the avoidance of irreversible myocardial damage should also be taken into account.

Limitations of the study

Due to a complex nature of ToF, it is difficult to evaluate all factors which might have affected our findings. In our study, we did not evaluate the effect of various surgical techniques, e.g. the use of Blalock-Taussig anastomosis before the surgical correction, on haemodynamic disturbances, and the effect of residual changes and surgical sequels such as arrhythmia, residual ventricular septal defect or significant tricuspid regurgitation, as the number of patients with these factors was low.

In addition, both NT-proBNP level and echocardiographic parameters were evaluated at only single occasion. Serial measurements and long-term follow-up will be a subject of further studies.

CONCLUSIONS

1. Increased plasma NT-proBNP levels in children after surgical repair of ToF are related to RV systolic dysfunction, as evidenced by lower S' wave velocity at the lateral aspect of the tricuspid annulus and increased longitudinal strain within the lateral wall of the RV.
2. Plasma NT-proBNP levels increase with the severity of RV diastolic dysfunction as evaluated by TDI.

Conflict of interest: *none declared*

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Analiza zależności między stężeniem N-końcowego propeptydu natriuretycznego typu B w surowicy a funkcją prawej komory ocenianą metodami doplera tkankowego i śledzenia markerów akustycznych u dzieci po operacji tetralogii Fallota

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Streszczenie

Wstęp i cel: Celem pracy była ocena związku między stężeniem N-końcowego propeptydu natriuretycznego typu B (NT-proBNP) w surowicy a wybranymi parametrami funkcji prawej komory u dzieci po korekcji zespołu Fallota (ToF).

Metody: Badaniem objęto 52 dzieci w wieku 8–18 lat po korekcji ToF (grupa badana). Do grupy kontrolnej włączono 32 dzieci zdrowych. U wszystkich zebrano wywiad i oceniono stężenie NT-proBNP w surowicy oraz wykonano badanie echokardiograficzne.

Wyniki: U pacjentów po korekcji ToF i u dzieci zdrowych średnie wartości maksymalnej prędkości miokardialnej fali skurczowej (S') wynosiły odpowiednio 5,9 ± 1,6 cm/s i 9,8 ± 2,3 cm/s ($p < 0,01$), wczesnorozkurczowej (E'): 6,6 ± 2,9 cm/s i 11,6 ± 3,1 cm/s ($p < 0,01$), a późnorozkurczowej (A') — 3,8 ± 1,6 cm/s i 6,6 ± 2,8 cm/s ($p < 0,01$). Średnie wartości maksymalnej wielkości odkształcenia podłużnego (ε) u dzieci w grupie badanej wynosiły w segmentach ściany bocznej: podstawnym (BL) –32,8 ± 12,1%, środkowym (ML) –23,8 ± 9,5%, koniuszkowym (AL) –16,9 ± 7,5%, a u dzieci zdrowych: BL –51,5 ± 15,5%, ML –40,4 ± 14,9%, AL –35,8 ± 13,3%. Różnice były istotne statystycznie ($p < 0,01$). Średnie stężenia NT-proBNP w surowicy u dzieci w grupach badanej i kontrolnej wynosiły odpowiednio 286,0 ± 269,2 pg/ml i 153,1 ± 170,5 pg/ml ($p < 0,01$). Średnie wartości stężenia NT-proBNP były statystycznie istotnie wyższe ($p < 0,01$) u pacjentów z obniżoną tolerancją wysiłku, w porównaniu ze stężeniem u pacjentów z prawidłową tolerancją wysiłku: 639,2 ± 357,1 *vs*. 181,8 ± 97,2 pg/ml. U pacjentów, u których podczas korekcji zastosowano łatę przezpierścieniową, stężenie tego peptydu wynosiło 488,9 ± 317,19 pg/ml i było istotnie statystycznie wyższe ($p < 0,01$) niż u dzieci po korekcji ToF, operowanych bez użycia łaty, u których wynosiło 228,1 ± 217,5 pg/ml. U pacjentów z grupy badanej uzyskano korelacje między stężeniem NT-proBNP a S' ($r = –0,40$; $p < 0,01$), stężeniem NT-proBNP a E' ($r = –0,50$; $p < 0,01$) oraz stężeniem NT-proBNP a ε w BL ($r = 0,36$; $p < 0,05$) i AL ($r = 0,35$; $p < 0,05$).

Wnioski: 1. Wyższe wartości stężenia NT-proBNP w surowicy u dzieci po korekcji ToF wiążą się z zaburzeniami funkcji skurczowej prawej komory pod postacią spadku prędkości fali S' bocznej części pierścienia zastawki trójdzielnej oraz wzrostu wielkości odkształcenia podłużnego w obrębie ściany bocznej prawej komory. 2. Stężenie NT-proBNP wzrasta wraz z nasilaniem się zaburzeń funkcji rozkurczowej ocenianej za pomocą parametrów doplera tkankowego.

Słowa kluczowe: tetralogia Fallota, NT-proBNP, dopler tkankowy, metoda śledzenia markerów akustycznych, odkształcenie podłużne

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