SRYAHWA PUBLICATIONS

Archives of Pediatrics and Neonatology
ISSN: 2638-5155 | Volume 6, Issue 1, 2023
https://doi.org/10.22259/2638-5155.0601004

RESEARCH ARTICLE

Relationship between N-terminal B-type Natriuretic Propeptide and Echocardiographic Assessment of Right Ventricular Function in Children after Surgical Repair of Tetralogy of Fallot

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Received: 22 September 2023 Accepted: 03 October 2023 Published: 06 October 2023
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Abstract

Aim: To examine the relationship between plasma levels of N-terminal proB type natriuretic peptide (NTproBNP) value in patients after surgical correction of Tetralogy Fallot with the dimensions of the right heart chambers, the volume load of the right heart chamber and the severity of pulmonary regurgitation

Methods: The research include 39 patients aged 1-17 years, 1±17 years after the primary surgical correction of the tetralogy Fallot, divided into two groups: Group I- patients who underwent surgical correction less than 10 years ago beginning of the study and Group II-patients who underwent operative correction in a period longer than 10 years before beginning of the study. Patient histories, measured NT-proBNP levels and transthoracic echocardiography parameters were analysed.

Results: 39 patients participated in the study, with an average age of 9.1±4.63 years, and a range of 1 to 17 years. Of the mentioned number of patients, 20 (51.3%) underwent surgery less than 10 years ago, on average 4.85 years ago, while 19 (48.7%) respondents underwent surgery more than 10 years ago, on average 11.74 years ago. In relation to the gender distribution of the respondents, it was determined that in the group of respondents who underwent surgery within 10 years, 18 (90%) respondents were female. In the group of respondents who underwent surgery more than 10 years ago, 11 (57.9%) respondents were female. It was found that there is a significant statistical difference in gender representation between the two investigated groups (x2=5.267; p=0.022). Of the 20 subjects who were operated on within 10 years, 7 of them (35%) use some form of therapy, while among the subjects who were operated on 10 years or more ago, 2 of them (10.5%) use some form of therapy. No significant statistical difference was found in the frequency of therapy consumption (x2=3.288; p=0.070). Dysrhythmias were not found in any patient. Pericardial effusion was also not found in any patient. In relation to the elapsed time since the operation, significantly higher values of PVR were found in subjects who had the operation performed ten or more years ago (p=0.022). Significantly higher values of FS-RVOT (%) (p=0.009) and significantly higher values of RV-FAC (%) were also determined; p=0.012. A significant correlation between the value of NTproBNP and the E"/A" index was determined, r=0.468; p=0.037. The relationship was evaluated as a medium-strong relationship, with a positive sign.

Citation: Halimic M, Dzubur A, Orucevic S, *et al*. Relationship between N-terminal B-type Natriuretic Propeptide and Echocardiographic Assessment of Right Ventricular Function in Children after Surgical Repair of Tetralogy of Fallot. Archives of Pediatrics and Neonatology. 2023;6(1): 16-25.

Conclusions: Quantification of right heart function is possible and should be routinely performed using a combination of different parameters. Increased plasma NT-proBNP levels in patients after surgical repair of ToF are related to RV systolic and dyastolic dysfunction, evaluated by 2D-, M-mode and TDI.

Keywords: Tetralogy Fallot, Right Heart, NTpro BNP, Echocardiography.

1. Introduction

Tetralogy of Fallot (ToF) is the most common form of cyanotic congenital heart anomaly, with a prevalence of 0.27 per 10,000 live births (2.5% of all congenital heart anomalies (1). With an increasing number of survivors after primary surgery for Tetralogy of Fallot, treatment of possible surgical sequelae, such as chronic pulmonary valvular insufficiency and dysfunction. This topic is of increasing clinical interest, proving the fact that pulmonary valve replacement due to pulmonary valvular insufficiency is today the most common procedure that is repeated in the population of adult patients with congenital heart anomalies (GUCH- Grown Up Congenital Heart) (2).

Even within the morphological definition, there are no two identical hearts with Tetralogy of Fallot (3,4).Right ventricular failure with cavity dilatation, systolic dysfunction and myocardial fibrosis, leading to volume retention and symptoms of congestive heart failure have been reported in a growing population of surviving adults with surgically corrected ToF (5-8). Little is known about the mechanism responsible for the remodeling of the overloaded right ventricle. Limited evidence suggests that these mechanisms may differ from the well-established pathway described in left ventricular failure.

Right ventricular function and adaptation to adverse loading conditions after ToF repair have been the focus of increasing research in the past decade. Various factors can affect long-term right ventricular performance, with a wide range of right ventricular remodeling.

In addition to poor myocardial preservation at the time of initial repair, large ventriculotomy, and chronic cyanosis before the procedure, patients with corrected ToF are faced with an unfavorable burden imposed by chronic pulmonary and tricuspid regurgitation, progressive myocardial fibrosis and scarring, right-left ventricular dyssynchrony, cardiopulmonary bypass, and pressor overload. load on the right ventricle. Considering that pulmonary valve replacement is an available option for the correction of the anomaly, a large number of medical studies are trying to define the benefit and optimal timing of such an intervention, weighing the preservation of the right ventricle against the risk and consequences of this surgical procedure. Multiple retrospective studies have attempted to define the benefit of pulmonary valve replacement for promoting right ventricular remodeling after surgery, reducing arrhythmic burden, improving exercise tolerance, and reducing adverse outcomes (9-11). Although MRI of the heart and 3D echocardiographic analysis represent the "golden diagnostic standard", both methods do not have wide practical availability, and 2D, M mode-, pulse and tissue Doppler analysis, in combination with cardiac biomarkers, represent the first and probably the only choice in the assessment of cardiac function.

2. Hypothesis

Research Hypothesis: The value of NTproBNP in patients after surgical correction of Tetralogy of Fallot correlates with the dimensions of the right heart chambers, the volume load of the right heart chamber and the severity of pulmonary regurgitation

Research Aim: To examine the relationship of the serum NTproBNP value in patients after surgical correction of Tetralogy of Fallot with the dimensions of the right heart chambers, the volume load of the right heart chamber and the severity of pulmonary regurgitation

3. Materials and Methods

3.1 Design Type Research

The research will be designed as a cohort, observational, prospective study, which include patients with surgically corrected congenital cardiac anomaly of the Fallot tetralogy type at the Pediatric Clinic of CCU Sarajevo.

The research include 39 patients aged 1-17 years, 1±17 years after the primary surgical correction of a congenital heart anomaly of the tetralogy of Fallot type, divided into two groups:

Group I: patients who underwent surgical correction less than 10 years ago beginning of the study

Group II: patients who underwent operative correction in a period longer than 10 years before beginning of the study

3.2 Criteria for Exclusion from the Research

Patients with conditions that interfere with serum natriuretic protein values will be excluded from the study: febrile condition two weeks before the examination, inflammatory diseases, severe infections, renal failure, invasive procedures, which were performed two months before the examination, lung diseases, endocrine metabolic disorders, cirrhosis of the liver with ascites, use of cardiotoxic drugs, anemia, adiposity, cardiac trauma.

3.3 Research Methods

The treatment procedure for patients and subjects include: age and type of reparative procedure, duration of follow-up after the procedure, history of arrhythmias, current therapy, anthropometric data - body mass, height, body mass index (BMI), eating habits, respiratory rate, heart rate, capillary filling time and liver palpation in order to determine the functional status for the pediatric population - Ross class, duration of the QRS complex on the ECG record.

3.4 Laboratory Tests

Serum concentration of NT-pro BNP was determined for all subjects. The reference value for the pediatric population is less than 450 pg/ml. Blood samples for the laboratory determination of NT-proBNP levels in the serum, after venipuncture, according to the standard procedure and ultrasound examination of the subjects, were analyzed in a certified laboratory (Roche).

3.5 Echocardiographic Examination

The transthoracic ultrasound examination was performed using a GE Vivid S5 ultrasound machine, by the same examiner-sonographer, with three, repeated measurements of each individual ultrasound parameter, using two-dimensional, M mode, pulsed and Tissue Doppler imaging (TDI):

1. mean pulmonary arterial pressure (mPAP)
2. pulmonary arterial acceleration time (PA acceleration time-PAAT)
3. the relationship between the volume of tricuspid regurgitation and the right ventricular outflow tract (TRV/RVOT VTI ratio) and pulmonary vascular resistance (PVR)
4. Tricuspid annular plane systolic excursion (TAPSE)
5. Fractional shortening of the RVOT (FS-RVOT)
6. RV fractional area (RV FAC)
7. Systolic-to-diastolic duration ratio (S/D ratio)
8. Right ventricular myocardial performance index (RVMPI) – TAI index
9. LV eccentricity index (LEI index)
10. Tissue Doppler velocities (s', e', a')

Considering that the echocardiographic analysis of the right heart will precede the taking of the blood sample, the examiner-sonographer was not aware of the serum concentrations of NT pro BNP - "blind analysis".

3.6 Statistical Processing of Research Results

All results were analyzed in the statistical program SPSS for Windows, using adequate procedures of descriptive and inferential statistics. The mean, standard deviation (SD), minimum, maximum and range will be calculated for all quantitative variables. Quantitative data were examined with the Kolmogrov Smirnov test for normality.

The obtained results were analyzed with a t-test for comparison between the examined groups if the conditions for their application were met, or with appropriate non-parametric tests (Mann-Whitney test) if an irregular distribution of variables was determined. Chi square (x 2) test was used to study the association between NT-Pro BNP and different variables in disease groups.

The correlation between NT-proBNP and different echocardiographic variables in the diseased groups was determined using the Pearson correlation test. Comparison between different echocardiographic variables was performed on the basis of diseased groups, and also on the basis of elevated NT-proBNP level, using Student's independent t test. Values of $p<0.05$ will be considered statistically significant. The research results will be presented in appropriate tables and graphs.

4. Research Results

39 patients participated in the study, with an average age of 9.1±4.63 years, and a range of 1 to 17 years. Of the mentioned number of patients, 20 (51.3%) underwent surgery less than 10 years ago, on average 4.85 years ago, while 19 (48.7%) respondents underwent surgery more than 10 years ago, on average 11.74 years ago.

In relation to the gender distribution of the respondents, it was determined that in the group of respondents

who underwent surgery within 10 years, 18 (90%) respondents were female. In the group of respondents who underwent surgery more than 10 years ago, 11 (57.9%) respondents were female. It was found that there is a significant statistical difference in gender representation between the two investigated groups (x2=5.267; p=0.022). Of the 20 subjects who were operated on within 10 years, 7 of them (35%) use some form of therapy, while among the subjects who were operated on 10 years or more ago, 2 of them (10.5%) use some form of therapy. No significant statistical difference was found in the frequency of therapy consumption (x2=3.288; p=0.070). Dysrhythmias were not found in any patient. Pericardial effusion was also not found in any patient. The analysis of monitored variables is presented in Table 1.

Table 1. *Tested variables*

	<10 years since surgery			≥10 years since surgery			t	p
	Mean	Min	Max	Mean	Min	Max		
QRS (ms)	6.20	0.06	110.00	7.14	0.06	120.00	-0.102	0.92
NTproBNP	846.6	78.0	7217.0	129.2	20.0	432.0	1.737	0.091
mPAP	23.2	7.4	34.9	22.3	9.2	35.0	0.353	0.726
PAAT(ms)	125	98	192	124	78	192	0.064	0.949
PVR	1.67	0.98	2.12	1.91	1.45	2.87	-2.393	0.022
TAPSE(mm)	16.5	9.8	22.0	17.1	11.2	28.0	-0.585	0.562
FS-RVOT(%)	37	22	55	45	32	62	-2.766	0.009
RVOT-SE(mm)	0.63	0.42	0.78	0.71	0.57	0.85	-2.646	0.012
RV-FAC(%)	41	28	65	43	30	62	-0.833	0.41
S/D	1.08	0.70	1.44	1.07	0.53	1.79	0.163	0.871
IVA	2.44	1.69	3.28	2.46	1.45	3.30	-0.118	0.907
TAI index	0.55	0.30	0.67	0.60	0.43	0.71	-1.919	0.063
LEI index	1.02	1.00	1.20	1.01	1.00	1.12	0.678	0.502
E"/A"	1.12	0.68	2.20	1.14	0.77	1.85	-0.197	0.845
S"	0.10	0.08	0.12	0.10	0.07	0.15	-0.662	0.512

In relation to the elapsed time since the operation, significantly higher values of PVR were found in subjects who had the operation performed ten or more years ago (p=0.022). Significantly higher values of FS-RVOT (%) (p=0.009) and significantly higher values of RV-FAC (%) were also determined; p=0.012. No significant differences were found in other examined variables.

Observed in relation to the reference values, no significant differences were found in the distribution of respondents in relation to the presence/absence of the reference values of the investigated variables.

Table 2. *Distribution of respondents in relation to referral values and elapsed time since surgery*

Variable	Referal	<10 years since surgery		≥10 years since surgery		x^2	p
		N	%	N	%		
QRS blok	Absent	18	90.0%	17	89.5%	0.003	0.957
	Present	2	10.0%	2	10.5%		
NTproBNP	Referal	13	65.0%	15	78.9%	0.936	0.333
	Out of referal area	7	35.0%	4	21.1%		
mPAP referal	Referal	20	100.0%	18	94.7%	1.08	0.299
	Out of referal area	0	0.0%	1	5.3%		
PAAT referal	Referal	18	90.0%	16	84.2%	0.292	0.589
	Out of referal area	2	10.0%	3	15.8%		
PVR referal	Referal	20	100.0%	19	100.0%		
	Out of referal area	0	0.0%	0	0.0%		
TAPSE referal	Referal	14	70.0%	14	73.7%	0.065	0.798
	Out of referal area	6	30.0%	5	26.3%		

FS-RVOT(%) referal	Referal	13	65.0%	17	89.5%	3.288	0.07
	Out of referal area	7	35.0%	2	10.5%		
RVOT-SE(mm) referal	Referal	18	90.0%	17	89.5%	0.003	0.957
	Out of referal area	2	10.0%	2	10.5%		
RV-FAC(%) referal	Referal	17	85.0%	18	94.7%	1.004	0.316
	Out of referal area	3	15.0%	1	5.3%		
IVA referal	Referal	20	100.0%	19	100.0%		
	Out of referal area	0	0.0%	0	0.0%		
TA Iindex referal	Referal	13	65.0%	16	84.2%	1.886	0.17
	Out of referal area	7	35.0%	3	15.8%		
Lei Index=1	Referal	18	90.0%	18	94.7%	0.308	0.579
	Out of referal area	2	10.0%	1	5.3%		
E/A referal	Referal	17	85.0%	17	89.5%	0.174	0.676
	Out of referal area	3	15.0%	2	10.5%		
S referal	Referal	11	55.0%	13	68.4%	0.742	0.389
	Out of referal area	9	45.0%	6	31.6%		

Table 3. *Analysis of examined variables in individual groups in relation to NTpro BNP referral values*

Group	**<10 years since surgery**					**≥10 years since surgery**				
Variable	**NtproBNP referal area**		**NTproBNP outside referal area**		**p**	**NtproBNP referal area**		**NTproBNP outside referal area**		**p**
	Mean	Min-Max	Mean	Min-Max		Mean	Min-Max	Mean	Min-Max	
QRS (ms)	0.09	0.06-0.12	15.79	0.07-110	0.220	8.08	0.06-120	0.08	0.08-0.08	0.727
mPAP	21.8	7.4-34.9	25.6	14.6-34.8	0.361	21.5	9.2-35	25.0	16.6-31.7	0.414
PAAT(ms)	125	98-192	125	98-142	0.995	126	78-192	119	98-142	0.64
PVR	1.61	1.1-1.92	1.78	0.98-2.12	0.262	1.94	1.45-2.87	1.80	1.69-1.91	0.463
TAPSE(mm)	16.1	13.7-22	17.2	9.8-22	0.467	17.3	11.2-28	16.7	14.2-19	0.794
FS-RVOT(%)	39	26-55	35	22-43	0.290	46	32-62	41	32-55	0.313
RVOT-SE	0.64	0.42-0.78	0.61	0.43-0.75	0.485	0.72	0.63-0.85	0.65	0.57-0.73	0.073
RV-FAC(%)	41	28-65	40	31-54	0.981	43	38-62	43	30-59	0.933
S/D	1.09	0.89-1.44	1.06	0.7-1.44	0.712	1.10	0.53-1.79	0.94	0.87-1.11	0.3
IVA	2.57	1.78-3.28	2.20	1.69-3.11	0.114	2.36	1.45-3.3	2.83	2.49-3.21	0.116
TAI index	0.56	0.33-0.67	0.52	0.3-0.59	0.386	0.60	0.43-0.71	0.62	0.56-0.68	0.716
LEI index	1.01	1-1.1	1.03	1-1.2	0.377	1.01	1-1.12	1.00	1-1	0.62
E'/A'	1.12	0.87-2	1.13	0.68-2.2	0.936	1.16	0.79-1.85	1.09	0.77-1.34	0.676
S'	0.10	0.08-0.12	0.10	0.09-0.11	0.291	0.11	0.07-0.15	0.10	0.09-0.11	0.283

Table 4. *Analysis of examined variables in relation to therapy*

		<10 years since surgery					≥10 years since surgery				
Varijabla	Referal	With therapy		Without therapy		Fishers exact	With therapy		Without therapy		Fishers exact
		N	%	N	%		N	%	N	%	
QRS blok	Yes	11	84.6%	7	100.0%	0.274	15	88.2%	2	100.0%	0.608
	No	2	15.4%	0	0.0%		2	11.8%	0	0.0%	
NTproBNP	Yes	10	76.9%	3	42.9%	0.128	13	76.5%	2	100.0%	0.440
	No	3	23.1%	4	57.1%		4	23.5%	0	0.0%	
mPAP	Yes	13	100.0%	7	100.0%	x	16	94.1%	2	100.0%	0.725
	No	0	0.0%	0	0.0%		1	5.9%	0	0.0%	

PAAT	Yes	12	92.3%	6	85.7%	0.639	14	82.4%	2	100.0%	0.517
	No	1	7.7%	1	14.3%		3	17.6%	0	0.0%	
PVR	Yes	13	100.0%	7	100.0%	x	17	100.0%	2	100.0%	x
	No	0	0.0%	0	0.0%		0	0.0%	0	0.0%	
TAPSE	Yes	10	76.9%	4	57.1%	0.357	13	76.5%	1	50.0%	0.421
	No	3	23.1%	3	42.9%		4	23.5%	1	50.0%	
FS-RVOT(%)	Yes	10	76.9%	3	42.9%	0.128	15	88.2%	2	100.0%	0.608
	Ne	3	23.1%	4	57.1%		2	11.8%	0	0.0%	
RVOT-SE(mm)	Yes	13	100.0%	5	71.4%	0.040	15	88.2%	2	100.0%	0.608
	N	0	0.0%	2	28.6%		2	11.8%	0	0.0%	
RV-FAC(%)	Yes	12	92.3%	5	71.4%	0.212	16	94.1%	2	100.0%	0.725
	No	1	7.7%	2	28.6%		1	5.9%	0	0.0%	
IVA	Yes	13	100.0%	7	100.0%	x	17	100.0%	2	100.0%	x
	No	0	0.0%	0	0.0%		0	0.0%	0	0.0%	
TAI index	Yes	9	69.2%	4	57.1%	0.589	14	82.4%	2	100.0%	0.517
	No	4	30.8%	3	42.9%		3	17.6%	0	0.0%	
Lei Index=1	Yes	12	92.3%	6	85.7%	0.639	16	94.1%	2	100.0%	0.725
	No	1	7.7%	1	14.3%		1	5.9%	0	0.0%	
E/A	Yes	13	100.0%	4	57.1%	0.011	15	88.2%	2	100.0%	0.608
	No	0	0.0%	3	42.9%		2	11.8%	0	0.0%	
S’	Yes	7	53.8%	4	57.1%	0.888	11	64.7%	2	100.0%	0.310
	No	6	46.2%	3	42.9%		6	35.3%	0	0.0%	

Table 5. *Correlation matrix of the tested variable NTproNBP and other variables*

Groups	<10 years since surgery		≥10 years since surgery	
Variables	NTproBNP		NTproBNP	
	r	p	r	p
mPAP	-0.077	0.748	0.234	0.335
PAAT(ms)	-0.004	0.986	-0.217	0.371
PVR	-0.291	0.213	-0.065	0.792
TAPSE(mm)	0.151	0.526	-0.076	0.756
FS-RVOT(%)	-0.216	0.360	-0.149	0.544
RVOT-SE(mm)	-0.284	0.225	-0.164	0.503
RV-FAC(%)	-0.212	0.368	0.138	0.574
S/D	0.294	0.209	-0.139	0.570
IVA	-0.401	0.079	0.374	0.115
TAI index	-0.254	0.279	0.127	0.603
LEI index	0.382	0.096	0.000	0.999
E’/A’	0.468*	0.037	-0.215	0.376
S’	0.075	0.755	-0.172	0.482

A significant correlation between the value of NTproBNP and the E”/A” index was determined, r=0.468; p=0.037. The relationship was evaluated as a medium-strong relationship, with a positive sign, which indicates that an increase in the value of one variable can be expected to increase the other variable as well.

5. Discussion

It is the first study in our country related to echocardiographic functional testing of the right heart in pediatric patients after operative correction of tetralogy of Fallot in combination with determination serum level of cardiac biomarkers and its relationship.

This study showed a direct proportionality between the value of NTproBNP and the E"/A" index (r=0.468; p=0.037), indicating that an increase in the value of one variable can be expected to increase the other variable as well. In relation to the elapsed time since the operation, significantly higher values of pulmonary vascular resistance were found in subjects who had the operation performed ten or more years ago (p=0.022). Significantly higher values of FS-RVOT (%) (p=0.009) and significantly higher values of RV-FAC (%) were also determined; p=0.012. No significant differences were found in other examined variables.

A study by Tatani et al showed that proBNP increased in 53% of patients after surgical correction of TOF (12). In the mentioned study, proBNP levels showed a significant correlation with the dimensions of the right heart chamber and with the severity of pulmonary regurgitation by univariate analysis, but no correlation was proven with the indices of systolic and diastolic function of the right ventricle. These results may suggest that the increased proBNP levels in these patients reflect right ventricular myocardial fiber stretching possibly due to volume overload secondary to pulmonary regurgitation.

The absence of correlation between proBNP levels and indices of right ventricular systolic function, even preload-dependent defects such as the tricuspid annular S-wave, may be explained. In left ventricular dysfunction, levels of this peptide mostly correlate with functional class, while patients with clinically compensated ventricular dysfunction may have proBNP levels closer to reference values (13). Therefore, it is not surprising that there was no correlation of proBNP level with indices of systolic function of the right ventricle, because most patients showed no or few symptoms.

It is known that NT-proBNP is elevated in asymptomatic patients with repaired TOF compared to other types of congenital heart disease, however, clear data on diagnostic and prognostic utility in this population are not yet available (14-17). NT-proBNP concentrations correlated with structural and volumetric changes of the right ventricle in most studies and meta-analyses (18). Our results revealed a moderate association between NT-proBNP levels and right ventricular structural and volumetric changes.

Furthermore, Wiese et al showed that isometric contraction of the fiber had no effect on BNP expression, while excessive diastolic stretch led to the release of natriuretic peptide, from which it follows that diastolic stress appears to be the most important mechanical factor in the expression of natriuretic peptides (19). Similar findings in chronic left ventricular dysfunction by Iwanaga et al. also suggest that BNP correlates more with diastolic ventricular wall stress than with ventricular filling pressure (20). An increase in proBNP serum levels in these patients, with still preserved right ventricular systolic function, could indicate an intensification of the compensatory mechanism for maintaining hemodynamic balance.

This study compares quantitative parameters of pulmonary regurgitation by echocardiography with serum levels of NTproBNP. Echocardiography is still the most commonly used technique for quantifying regurgitant valvular lesions.

Due to the difficulty in visualizing the pulmonary valve and the low frequency of pathological pulmonary regurgitation in the pediatric population, only a few studies have analyzed the quantification of pulmonary regurgitation by echocardiography and Doppler technique. Currently, the recommended methods are based on the required time interval for the equalization of diastolic flow between the right ventricle and the pulmonary artery: a more severe degree of pulmonary regurgitation has a shorter pressure half-time (PHT), a longer deceleration time, and shorter pulmonary regurgitation indices (21, 22).

In addition, there are no parameters that would define the severity of the lesion. Studies by Li et al. and Silversides et al. analyzing patients with repaired TOF showed that the pulmonary regurgitation index and pressure half-time (PRi and PHT) show a good correlation with the pulmonary regurgitant fraction obtained by magnetic resonance. pulmonary regurgitation and suggest the activation of compensatory mechanisms to maintain hemodynamic balance in patients after surgically corrected tetralogy of Fallot without or with few symptoms. Further studies would be necessary to analyze the importance of this finding in the follow-up of these patients (22, 23).

In a study of adult patients after surgical correction of ToF, systolic and diastolic dysfunction of the right ventricle was proven in patients compared to controls, which is manifested by statistically significantly lower tissue velocity (s", e", a"), but the older age of the subjects, with significantly more severe pulmonary regurgitation, was emphasized (mean age 21.4 ± 3.8 years vs age 1.4 ± 0.5 SD compared to 4.1 ± 1.5 SD)

(24-26). In the conclusions of the study by Eindhoven et al it is stated that NT-proBNP levels are elevated in more than 50% of adults with corrected ToF, while they are in stable clinical condition. Higher NT-proBNP is most strongly associated with elevated pulmonary pressures, and with LV dysfunction rather than RV dysfunction. NT-proBNP has the potential to become routine examination in patients with ToF to monitor ventricular function and may be used for timely detection of clinical deterioration (27).

In pulmonary valve replacement (PVR) after tetralogy of Fallot (TOF) repair, the right ventricular end-diastolic and end-systolic volume index (RVEDVI and RVESVI) of cardiac magnetic resonance imaging (cMRI) are often used as indicators of the RV volume. Sugiura et al.

examined the utility of QRS duration, cardiothoracic ratio (CTR), and plasma brain natriuretic peptide (BNP) as indicators of the appropriate timing of cMRI to assess the RV volume and function before pulmonary valve replacement. A prolonged QRS duration is a useful marker of RVEDVI and RVESVI enlargement after TOF repair.

We recommend performing cMRI before the QRS duration reaches 160 ms due to normalization of the RV volume after pulmonary valve replacement (28). Pulmonary valve replacement in asymptomatic repaired tetralogy of Fallot patients is appropriate and effective in reducing right ventricular size and preserving right ventricular function.

The recommended criterion of RV end-systolic volume index for pulmonary valve replacement is 120 mL/m^2 (29).Ambulatory determination of NT-proBNP might be an easy, readily available and cost-effective alternative for MRI follow-up evaluation of these patients according to the conclusions of the Paolino study (30).

Echocardiography and cardiac magnetic resonance imaging are the central modalities to assess repaired tetralogy of Fallot patients and have complementary and overlapping roles, contribute to our understanding of its pathophysiology and management (31).

6. Conclusion

Echocardiographic assessment of right heart function is challenging due to the limitations inherent in the right ventricle, as well as the lack of normative data in children. Nevertheless, quantification of right heart function is possible and should be routinely performed using a combination of different parameters. Evidence supports the use of natriuretic peptides as an additional tool in the integrated screening, diagnosis, treatment and follow-up of children with heart lesions.

Future prospective studies will need to investigate the use of index and sequential NT-proBNP measurements to predict adverse outcomes and facilitate clinical decision making in this population. This synergy, which leads to mutual completion and improvement of individual diagnostic methods, confirms the fact that the best diagnostic and therapeutic strategy should be based on multiparametric analysis and correlation of clinical, imaging and biochemical test data.

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