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Mitral Regurgitation and Serum N-Terminal Pro-Brain Natriuretic Peptide Levels in Children: A Modification of Adult Criteria

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Mitral regurgitation can result from congenital heart disease, rheumatic valve disease, or other congenital malformations of the mitral valve. Faulty valves require surgical repair or replacement. However, echocardiographic and biochemical parameters that inform surgical decision-making for adults may not be appropriate for children. To investigate whether adult parameters can be used in children, we correlated echocardiographic parameters with serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in children with chronic mitral regurgitation.

Our sample comprised 45 patients and 38 healthy children. M-mode measurements, left atrial and left ventricular volumes, and Doppler and tissue Doppler echocardiograms were collected. We graded mitral regurgitation according to European Association of Echocardiography recommendations and indexed effective regurgitant area, vena contracta, and regurgitant volume to body surface area. Patients were grouped by regurgitation severity (mild vs moderate or severe) and left ventricular end-systolic dimension (normal vs enlarged).

The NT-proBNP level was higher in patients than in controls (P=0.003), higher in patients with moderate or severe regurgitation (P=0.02), and higher in patients with an enlarged left ventricle (P=0.003). Serum NT-proBNP levels correlated with effective regurgitant area (r=0.47; P=0.002), vena contracta width (r=0.46; P=0.003), regurgitant volume (r=0.32; P=0.04), left ventricular end-systolic diameter (r=0.58; P <0.001), and left atrial diameter (r=0.62; P <0.001). An NT-proBNP value of 66 pg/mL differentiated the mild regurgitation group from the moderate or severe regurgitation group.

Our results correlating NT-proBNP and echocardiographic parameters indexed to body surface area indicate that these adult criteria can be used in children to grade mitral regurgitation and inform surgical decision-making. ***(Tex Heart Inst J 2022;49(4):e207285)***

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Isolated mitral regurgitation (MR) can be caused by congenital heart disease, rheumatic valve disease, or other congenital malformations of the mitral valve (MV). Treatment for MR involves surgical repair or replacement of the faulty MV. However, MV replacement is not an attractive option for children because of their smaller body size and the possible need for reoperation or anticoagulation. Moreover, the timing of MV surgery is a major consideration in the pediatric population. Clinical evaluation of MR is a vital component of treatment decision-making.

Certain echocardiographic parameters used to assess MR severity and the timing of surgical intervention in adults are also feasible for use in children.[1-4] However, whether parameters that inform surgical decision-making in adults can be applied to children as well is not clear. Cutoff values for various echocardiographic measurements that would indicate surgery have been established for adults but have not yet been validated for pediatric patients. The associations between clinical and biochemical parameters and echocardiographic indices also have not been investigated.

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a neurohormone produced after cleavage of BNP secreted by the myocardium under myocardial wall stress and is a biochemical parameter known to correlate the severity of heart failure with volume overload.[5] In this study, we examined the association between echocardiographic

parameters (including 2-dimensional, Doppler, and tissue Doppler echocardiographic parameters) and serum NT-proBNP levels in children and adolescents with chronic MR due to rheumatic fever or MV prolapse.

Patients and Methods

Patients

This prospective study compared patients with chronic MR (MR group) and healthy subjects (control group). The MR group included patients with chronic MR due to MV prolapse or rheumatic valvular disease. Exclusion criteria included a diagnosis of MR with MV cleft or mitral stenosis, any other valvular regurgitation or stenosis, and additional congenital heart defects or systemic disease. Patients who had recovered from acute rheumatic fever within the last 6 months were also excluded. The control group had no valvular disease, congenital heart disease, or systemic disorder. All participants were required to be 18 years of age or younger.

All study participants underwent a thorough medical history, physical examination, 12-lead electrocardiography, and echocardiography in resting condition. Serum NT-proBNP levels were obtained with use of an Elecsys analyzer and a chemiluminescent immunoassay kit (Roche Diagnostics). Serum samples were drawn from an antecubital vein on the same day as the echocardiographic evaluation. All clinical measurements, echocardiographic evaluations, and blood tests were obtained during routine follow-up visits.

The study was approved by the local ethics committee of the Marmara University Hospital, Istanbul, Turkey (protocol number: 09.2014.0205). Participants and their parents were informed about the study, and written and oral consents were obtained.

Mitral Regurgitation Severity

European Association of Echocardiography criteria for evaluating MR in adults[2] were modified for use in children and adolescents to enable differentiation between patients with mild versus moderate or severe MR. Mitral regurgitation severity was graded semiquantitatively (vena contracta [VC] width and mitral/aortic time velocity integral [VTI] ratio) and quantitatively (effective regurgitant orifice area [EROA] and regurgitant volume [RVol]).

Because these parameters were originally intended for use with adults, we adjusted VC, EROA, and RVol for each participant according to his or her body surface area (BSA, expressed in m^2).[2] For instance, adjusted VC width = (measured VC × 1.72)/BSA; adjusted EROA = (measured EROA × 1.72)/BSA; and adjusted RVol = (measured RVol × 1.72)/BSA. After this adjustment, MR severity was classified as mild if VC <3 mm, EROA <20 mm^2, RVol <30 mL, and mitral/aortic VTI <1; moderate if VC=3 to 6 mm, EROA=20 to 39 mm^2, RVol=30 to 59 mL, and mitral/aortic VTI=1 to 1.4; or severe if VC ≥7 mm, EROA ≥40 mm^2, RVol ≥60 mL, and mitral/aortic VTI >1.4.

Left Ventricular Size

In adult patients with flail MR, a left ventricular end-systolic diameter (LVESD) ≥22 mm/m^2 (ie, adjusted for BSA) has been shown to be associated with increased mortality; surgery is recommended for these patients.[6] We therefore classified patients into 2 subgroups according to LV size, adjusted for BSA: normal (LVESD <22 mm/m^2) or enlarged (LVESD ≥22 mm/m^2). As defined, an enlarged LV is an indication for surgical intervention.

Echocardiography

Echocardiography was performed with use of a Philips IE33 echocardiography machine (Philips Medical Systems) equipped with a 5-MHz transducer. Echocardiographic examinations for all study participants included LVESD, LV end-diastolic diameter (LVEDD), interventricular septal diameter (IVSD), LV end-diastolic posterior wall thickness (LVPWD), left atrial diameter (LAD), and pulmonary artery pressure. Pulmonary hypertension was also estimated by using the Bernoulli formula applied to the velocity of tricuspid regurgitation flow. Ejection fraction (EF) and shortening fraction (SF) were calculated from M-mode echocardiographic measurements in the parasternal long-axis view. Mitral annulus diameter (MAD) was measured at systole in the parasternal long-axis view, MV area (MVA) was calculated planimetrically in the parasternal short-axis view, left ventricular end-diastolic and end-systolic volumes were calculated with use of the biplane Simpson method in the 4-chamber view, and left atrial volume was calculated with use of the biplane area-length method in the 4-chamber view. All measurements were adjusted according to BSA, as described above.

To assess LV diastolic functions, mitral inflow parameters (mitral E and mitral A wave velocities, isovolumetric relaxation time, and deceleration time) were measured with use of pulse-wave Doppler echocardiography. The myocardial performance index was calculated with use of tissue Doppler echocardiography. For MR evaluation and analysis, the type of regurgitation jet (central or eccentric) was defined, VC width was measured with use of color-Doppler echocardiography, EROA and RVol were calculated with use of a flow convergence method at a Nyquist limit of 50 to 60 cm/s, and the mitral/aortic VTI ratio was calculated with use of pulse-wave Doppler echocardiography.

Echocardiographic values and NT-proBNP levels were compared between the MR and control groups, between patients with mild MR versus moderate or severe MR, and between patients with normal versus enlarged LVs.

Statistical Analysis

Statistical analysis was performed with use of SPSS for Windows version 22.0 (IBM Corporation). Data were presented as mean ± SD for continuous variables and as number and percentage or median and range for noncontinuous variables. For comparisons between groups, Student *t* tests, χ^2 tests, and Mann-Whitney U tests were used, as appropriate. P <0.05 was considered statistically significant.

Regression analyses were performed to investigate correlations between echocardiographic values and NT-proBNP levels and to determine cutoff values that would differentiate between patients with MR and healthy control subjects, patients with mild versus moderate or severe MR, and patients with normal versus enlarged LVs. Correlations between nonparametric variables were expressed in terms of the Spearman rank correlation coefficient; correlations between parametric variables were expressed in terms of the Pearson correlation coefficient. As a validity check, a multivariate regression analysis was performed, controlled for patients' age, weight, and systolic blood pressure.

Receiver operating characteristic (ROC) curves for NT-proBNP were calculated for MR diagnosis (yes vs no), LVESD (normal vs enlarged), and MR severity (mild vs moderate or severe).

Results

The study sample included 45 patients with chronic MR (mean age, 11.7 ± 3.2 yr; median,12 yr; range, 5–18 yr) and 38 healthy control subjects (mean age, 11.0 ± 3.0 yr; median, 11 yr; range, 5–17 yr). The MR group comprised 31 patients with rheumatic MV disease and 14 patients with MV prolapse.

The MR and control groups were similar in terms of age, height, weight, BSA, and systolic and diastolic blood pressures. Most of the participants in each group were girls, and both groups had statistically similar proportions of girls and boys (P=0.59) (Table I).

Of the 45 patients in the MR group, 27 had mild MR, and 18 had moderate (n=12) or severe (n=6) MR; 27 had a normal-sized LV, and 18 had an enlarged LV. Whether differentiated by MR severity or by LV size, the subgroups were comparable in terms of age, height, weight, and BSA. No patient had pulmonary hypertension, as determined either clinically or by Bernoulli estimation.

Echocardiography

M-mode measurements of the LV, including IVSD/BSA, LVEDD/BSA, LVESD/BSA, and LVPWD/BSA, were similar between MR patients and the control group (Table II). The LAD/BSA was significantly larger in the MR group than in the control group (P=0.02). In comparisons of 2-dimensional echocardiographic measurements, LVEDV/BSA (P=0.02) and MVA/BSA (P=0.001) were also significantly larger in the MR group.

Using Doppler and tissue Doppler echocardiography, we found significantly higher mitral/aortic VTI (P=0.01) and S′ wave velocity (P=0.001) in the MR group than in the control group (Table II). As expected, the mitral E/A ratio was significantly higher in the MR group than in the control group (P=0.03).

In subgroup comparisons of patients with mild versus moderate or severe MR (Table II), LVEDD/BSA (P=0.005), LVESD/BSA (P=0.003), LAD/BSA (P=0.02), and MAD/BSA (P=0.03) were significantly larger in the moderate or severe MR subgroup. Mitral E was significantly higher in the moderate/severe MR subgroup (P=0.008).

In subgroup comparisons of patients with an enlarged versus normal LV, MAD/BSA (2.69 ± 0.69 mm vs 2.03 ± 0.34 mm; P=0.03) and LAD/BSA (2.69 ± 0.62 mm vs 2.09 ± 0.33 mm; P=0.02) were significantly greater in patients with an enlarged LV. Furthermore, VC/BSA

TABLE I. Demographic and Clinical Characteristics of 45 Children With Mitral Regurgitation and 38 Healthy Children as Controls

Characteristics	MR Group (n=45)	Control Group (n=38)	*P* Value
Age (yr)	11.7 ± 3.2	11.0 ± 3.0	0.24
Female	32 (71)	27 (71)	0.59
Weight (kg)	39 ± 15.2	37.5 ± 12.2	0.54
Height (cm)	143.6 ± 13.8	141.0 ± 15.4	0.20
BSA (m^2)	1.23 ± 0.31	1.19 ± 0.30	0.28
Systolic blood pressure (mmHg)	110.0 ± 13.4	104.5 ± 12.0	0.08
Diastolic blood pressure (mmHg)	62.8 ± 8.6	62.6 ± 9.9	0.60

BSA = body surface area; MR = mitral regurgitation

Data are presented as mean ± SD or as number and percentage. P <0.05 was considered statistically significant.

TABLE II. Comparison of Echocardiographic Parameters in 45 Children With Mitral Regurgitation and 38 Healthy Children as Controls

	All Participants			Patients With MR		
Variable	MR Group (n=45)	Control Group (n=38)	*P* Value	Mild Group (n=27)	Moderate/ Severe Group (n=18)	*P* Value
LVESV/BSA (mL/m^2)	26.33 ± 8.70	22.87 ± 5.7	0.11	24.8 ± 7.6	27.5 ± 9.4	0.71
LVEDV/BSA (mL/m^2)	67.96 ± 17.57	57.38 ± 10.1	0.02	66 ± 17.2	69 ± 18.1	0.83
MAD/BSA (mm/m^2)	2.25 ± 0.58	2.09 ± 0.3	0.08	2.00 ± 0.48	2.41 ± 0.62	0.03
MVA/BSA (cm^2/m^2)	3.79 ± 0.91	3.08 ± 0.51	0.001	3.54 ± 0.59	3.99 ± 1.08	0.28
IVSD/BSA (mm/m^2)	5.8 ± 0.46	6.01 ± 0.11	0.55	5.9 ± 0.64	6.1 ± 0.18	0.52
LVEDD/BSA (mm/m^2)	3.82 ± 1.04	3.52 ± 0.55	0.14	3.26 ± 0.60	4.10 ± 1.12	0.005
LVESD/BSA (mm/m^2)	2.32 ± 0.67	2.23 ± 0.38	0.50	1.93 ± 0.47	2.55 ± 0.67	0.003
LVPWD/BSA (mm/m^2)	5.7 ± 0.37	5.3 ± 0.92	0.23	5.5 ± 0.72	5.4 ± 0.44	0.43
LAD/BSA (mm/m^2)	2.37 ± 0.67	2.31 ± 0.41	0.02	2.00 ± 0.36	2.48 ± 0.74	0.02
Mitral E (cm/s)	1.10 ± 0.20	1.04 ± 0.25	0.13	0.92 ± 0.20	1.10 ± 0.26	0.008
Mitral A (cm/s)	0.62 ± 0.19	0.65 ± 0.17	0.95	0.59 ± 0.12	0.65 ± 0.19	0.17
Mitral E/A (cm/s)	1.99 ± 1.17	1.66 ± 0.30	0.03	1.57 ± 0.28	1.72 ± 0.30	0.28
TDI E′ (cm/s)	18.18 ± 4.47	18 ± 2.52	0.54	17.5 ± 3.24	18.5 ± 5.15	0.61
TDI A′ (cm/s)	8.3 ± 2.19	7.8 ± 1.97	0.33	8.8 ± 1.8	7.9 ± 2.3	0.33
TDI S′ (cm/s)	12.2 ± 3.17	9.6 ± 1.94	0.001	12.1 ± 3.2	12.2 ± 3.1	0.61
Mitral E/TDI E′ (cm/s)	0.05 ± 0.017	0.06 ± 0.01	0.60	0.05 ± 0.01	0.06 ± 0.01	0.18
MPI	0.66 ± 0.13	0.67 ± 0.13	0.77	0.69 ± 0.17	0.65 ± 0.09	0.29
Mitral/AoVTI	0.97 ± 0.18	0.85 ± 0.14	0.01	0.90 ± 0.11	1.01 ± 0.21	0.10

BSA = body surface area; IVSD = interventricular septal diameter; LAD = left atrial diameter; LVEDD = left ventricular diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; LVPWD = left ventricular end-diastolic posterior wall thickness; MAD = mitral annulus diameter; Mitral A = mitral peak late wave velocity; Mitral/AoVTI = mitral/aortic velocity time integral; Mitral E = mitral peak early wave velocity; MPI = myocardial performance index; MR = mitral regurgitation; MVA = mitral valve area; TDI A′ = tissue Doppler imaging septal annular velocity during atrial contraction; TDI E′ = tissue Doppler imaging mitral early diastolic septal annular velocity during atrial contraction; TDI S′ = tissue Doppler imaging systolic annular velocity

Data are expressed as mean ± SD. *P* <0.05 was considered statistically significant.

(8.49 ± 4.9 mm vs 4.72 ± 1.13 mm), median EROA/BSA (45.6 vs 24.2 mm^2), and median RVol/BSA (49.2 vs 30.0 mL) were also significantly greater in those with an enlarged LV (all *P*=0.001).

N-Terminal Pro-Brain Natriuretic Peptide

Serum NT-proBNP levels were higher in the MR group than in the control group (*P*=0.003). Because NT-proBNP levels change with age, we performed a subanalysis of patients by age (5–11 yr vs 12–18 yr). In both age groups, serum NT-proBNP levels were higher in MR patients than in the control group (5–11 yr, *P*=0.001; 12–18 yr, *P*=0.01) (Fig. 1A–B).

Serum NT-proBNP levels were also significantly higher in patients with moderate or severe MR (mean, 140.4 ± 15.7 pg/mL; median, 83 pg/mL; range, 10–112 pg/mL) than in those with mild MR (mean, 49.8 ± 24.2 pg/mL; median, 51 pg/mL; range, 24–780 pg/mL) (*P*=0.02) (Fig. 1C). Patients with an enlarged LV had higher NT-proBNP levels (median, 89.5 pg/mL; range, 31–780 pg/mL) than did those with a smaller LV (median, 64.0 pg/mL; range, 10–232 pg/mL) (*P*=0.003).

In univariate analysis of the MR group, serum NT-proBNP levels correlated with VC/BSA (*r*=0.46; *P*=0.003), EROA/BSA (*r*=0.47; *P*=0.002), RVol/BSA (*r*=0.32; *P*=0.04), LVESD/BSA (*r*=0.58; *P* <0.001), LAD/BSA (*r*=0.62; *P* <0.001), and MAD/BSA (r=0.44; *P*=0.004) (Table III). In subsequent multivariate linear regression analysis, all 6 parameters were independent predictors of NT-proBNP after controlling for age, weight, and systolic blood pressure, in accordance with the univariate analyses (Table III). In the control group, serum NT-proBNP level correlated with LAD/BSA in both univariate analysis (r=0.48; *P*=0.02) and multivari-

ate analysis (β=18.83, standard error [SE]=8.69; *t*=2.17; *P*=0.04).

The NT-proBNP cutoff value that best differentiated patients with MR from healthy control subjects was 62 pg/mL, resulting in 89.2% specificity and 59.5% sensitivity for the presence of MR. The NT-proBNP cutoff value that best differentiated patients with mild MR from those with moderate or severe MR was 66 pg/mL, resulting in 93.3% specificity and 70.4% sensitivity. The NT-proBNP cutoff value that best differentiated patients with enlarged LVs from those with normal LVs was 82 pg/mL, resulting in 83.3% specificity and 61.1% sensitivity.

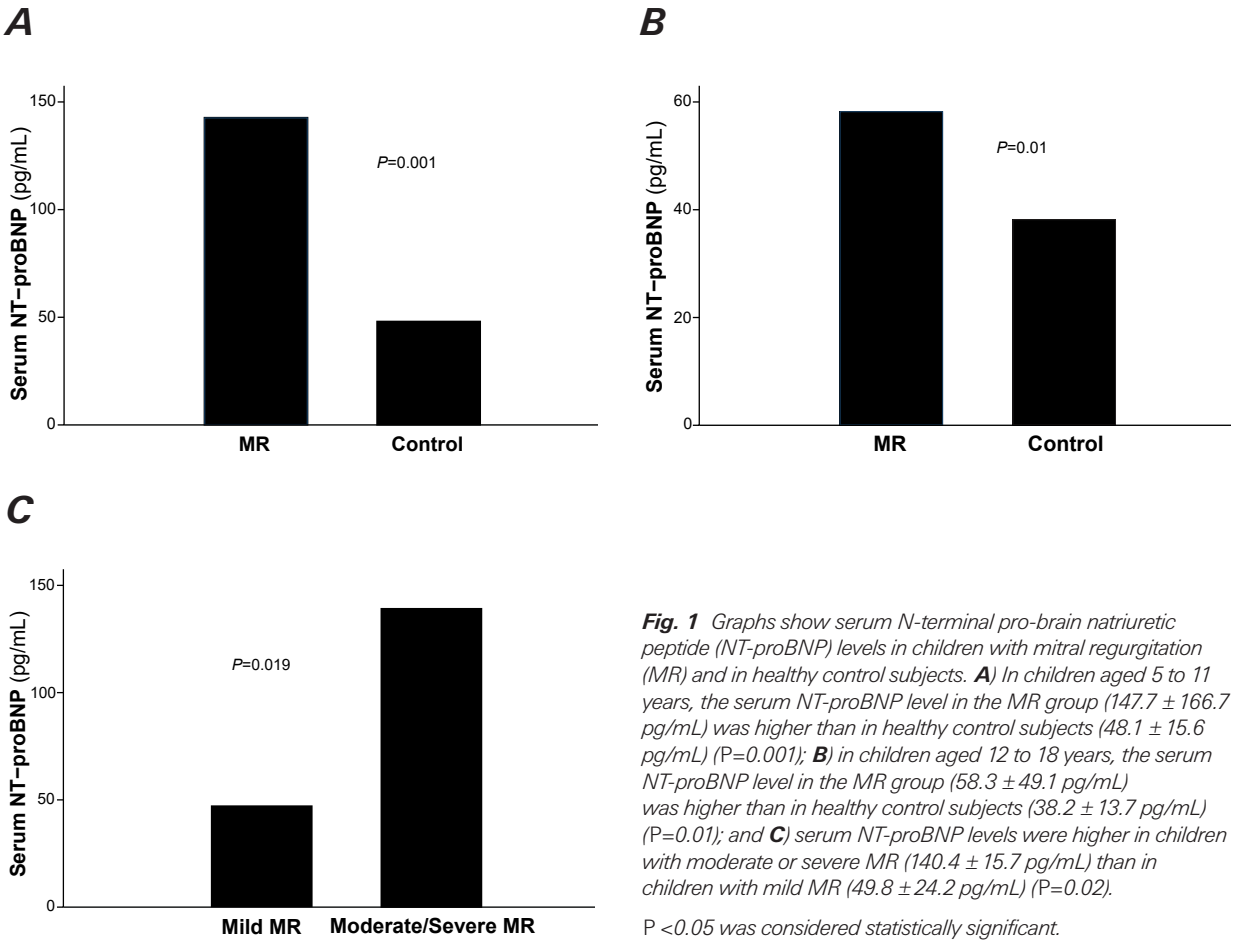

Fig. 1 *Graphs show serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in children with mitral regurgitation (MR) and in healthy control subjects.* ***A****) In children aged 5 to 11 years, the serum NT-proBNP level in the MR group (147.7 ± 166.7 pg/mL) was higher than in healthy control subjects (48.1 ± 15.6 pg/mL) (P=0.001);* ***B****) in children aged 12 to 18 years, the serum NT-proBNP level in the MR group (58.3 ± 49.1 pg/mL) was higher than in healthy control subjects (38.2 ± 13.7 pg/mL) (P=0.01); and* ***C****) serum NT-proBNP levels were higher in children with moderate or severe MR (140.4 ± 15.7 pg/mL) than in children with mild MR (49.8 ± 24.2 pg/mL) (P=0.02).*

P *<0.05 was considered statistically significant.*

TABLE III. Univariate Correlation and Multivariate Linear Regression Analyses of N-Terminal Pro-Brain Natriuretic Peptide with Quantitative and Semiquantitative Parameters for Grading Mitral Regurgitation and Left Ventricular and Left Atrial Diameters

	Univariate		Multivariate			
Variable	***r***	***P* Value**	**β**	**SE**	***t***	***P* Value**
VC/BSA	0.46	0.003	15.97	6.61	2.42	0.02
EROA/BSA	0.47	0.002	1.86	0.84	2.23	0.03
RVol/BSA	0.32	0.04	1.31	0.53	2.48	0.02
LVESD/BSA	0.58	<0.001	97.67	42.3	2.31	0.03
LAD/BSA	0.62	<0.001	100	32.8	3.05	0.004
MAD/BSA	0.44	0.004	175.4	40	4.39	0.001

BSA = body surface area; EROA = effective regurgitant orifice area; LAD = left atrial diameter; LVESD = left ventricular end-systolic diameter; MAD = mitral annulus diameter; MR = mitral regurgitation; NT-proBNP = N-terminal pro-brain natriuretic peptide; RVol = regurgitant volume; SE = standard error; VC = vena contracta

P <0.05 was considered statistically significant.

The areas under the ROC curves for NT-proBNP were as follows: for a diagnosis of MR (yes vs no), 0.732 (SE=0.06); for LV diameter (normal vs enlarged), 0.700 (SE=0.09); for the severity of valve insufficiency (mild vs moderate or severe), 0.781 (SE=0.07).

Follow-up Data

Data collected during routine follow-up visits indicated that only 2 patients (one 12-yr-old and one 10-yr-old) underwent subsequent MV repair for severe MR. This low repair rate was probably related to the patients' young age and the absence of symptoms. Serum NT-proBNP levels had declined from 381 pg/mL to 120 pg/mL in the 12-year-old patient and from 780 pg/mL to 223 pg/mL in the 10-year-old patient. Left ventricular dimensions and volumes decreased in both patients. In another patient with rheumatic MR, MR severity decreased from moderate or severe to mild or moderate, and NT-proBNP levels decreased from 228 pg/mL to 87 pg/mL.

Discussion

Chronic MR is a common health problem during childhood.[7] In underdeveloped or developing countries, chronic MR is most likely related to the high prevalence of rheumatic heart disease. In contrast, in industrialized countries, chronic MR is more typically caused by congenital malformations of the MV or by MV prolapse, a progressive disease that starts at an early age. Mild to moderate MR may go unnoticed for a long period of time, and affected individuals may be asymptomatic until severe LV dysfunction causes clinical deterioration. Moreover, conventional LV systolic function indices, such as SF and EF, are not reliable in the presence of MR because of the LV's systolic emptying and excessive use of compensational mechanisms. Decline in SF and systolic function is usually a terminal sign that indicates a poor prognosis after surgery.[8,9]

The European Association of Echocardiography has established echocardiographic criteria for grading MR in adults, and the American College of Cardiology and American Heart Association have published recommendations for the timing of surgery.[2,10] However, whether these criteria can be applied to children has not been extensively studied. Even if a child with severe MR meets the criteria for surgical intervention as defined for adults, the age or body size of the child can necessitate repeated intervention after early valve replacement.

In this study, we found that the echocardiographic criteria defined by the European Association of Echocardiography reliably identified children with moderate or severe MR. As expected, we found increased left atrial dimensions and LV volumes in patients with MR, despite normal systolic function. This increase was more prominent in patients with moderate or severe MR.

Left-sided heart chamber enlargement correlated significantly with NT-proBNP level in this study. We used NT-proBNP as an indicator of volume overload, because in serum NT-proBNP is more stable than its precursor, BNP.[11] Furthermore, NT-proBNP correlates well with symptoms of heart failure in both adults and children and differentiates between pulmonary and cardiac causes of dyspnea.[5] One previous study identified cutoff points in NT-proBNP levels in children with heart failure (according to the Ross classification).[12] The NT-proBNP levels in our study were lower than the levels reported for children in previous studies. However, investigators in those studies assessed BNP and NT-proBNP levels in children with heart failure due to congenital heart disease or cardiomyopathy; volume and pressure overload in such patients are much higher than they would be in the patients in our study, who had only valvular heart disease.[12-14] To our knowledge, only one study has evaluated NT-proBNP levels in children with rheumatic valvular heart disease.[15] In that study, the median NT-proBNP level was 154.4 pg/mL in children with moderate MR and 220.3 pg/mL in children with severe MR. This suggests that the lower NT-proBNP results in our study may be related to the higher proportion of patients with moderate MR to patients with severe MR.

Age-stratified analyses of NT-proBNP levels have been performed in children with heart failure and in healthy children.[13,14,16,17] Variations in population age among those studies may have caused differences in metabolic clearance of NT-proBNP, which in turn may have caused differences in peptide levels. Similarly, the assays used in those studies to obtain NT-proBNP levels in healthy children were not consistent. For instance, in our study, we used an Elecsys analyzer and an chemiluminescent immunoassay kit; in contrast, Soldin and colleagues[17] used the Dade RxL Dimension method, while Lin and associates[12] used yet another method. The differences in antibody specificity and cross-reactivity among these various assays may have caused differences in the NTproBNP levels that were identified.[17,18]

In addition, BNP and NT-proBNP levels may be higher in hospitalized patients, for various reasons. In the study by Soldin's group,[17] blood samples were obtained from leftover specimens from a mixture of inpatients and outpatients; in contrast, the healthy children who formed our control group were referred to our clinic because of innocent murmur or noncardiac chest pain.

The good correlation between NT-proBNP levels and echocardiographic parameters in our study and others indicates its usefulness as a parameter for monitoring. Studies in adult patients have shown that serum NT-proBNP levels and MR severity are associated.[19-21] In addition, those studies found that NT-proBNP correlated with symptoms, New York Heart Association (NYHA) classification, and echocardiographic indices

like left atrial volume adjusted to BSA, LV end-systolic volume adjusted to BSA, atrial fibrillation, and pulmonary artery pressure. After MV replacement, decline in NT-proBNP levels correlated with improvement in NYHA classification and EF and reduction in LAD and LVESD.[21] In concordance with findings by Ribiero and associates,[15] we found that NT-proBNP level correlated with LAD/BSA and LVESD/BSA, highlighting the hemodynamic consequences of MR. Heart failure symptoms in pediatric patients after the infant and toddler periods may be subtle. This emphasizes the need for the measurement of reliable parameters in the follow-up monitoring of these patients.

In our study, serum NT-proBNP levels were higher in both younger and older patients with MR than they were in healthy control subjects; they were also higher in patients with moderate or severe MR than in patients with mild MR and healthy control subjects. Levels of NT-proBNP have been shown to be highly sensitive and specific for severe asymptomatic MR.[19] In our study, however, serum NT-proBNP levels had generally high specificity but low sensitivity in differentiating patients from control subjects at a cutoff value of 62 pg/mL (specificity, 89.2%; sensitivity, 59.5%), differentiating patients with moderate or severe MR from those with mild MR at a cutoff value of 66 pg/mL (specificity, 93.3%; sensitivity, 70.4%), and differentiating patients with an enlarged LV (>22 mm/BSA)—as an indication for surgery—from those who did not with a value of 82 pg/mL (specificity, 83.3%; sensitivity, 61.1%). Given that we had no criterion standard other than NT-pro BNP level and echocardiography to use, new parameters specifically for children may be needed to increase the sensitivity of the NT-proBNP parameter.

The European Association of Echocardiography uses VC, RVol, and EROA as the most reliable criteria for determining the severity of MR.[1] However, these criteria were established for adult patients, and few studies have evaluated their use in children.[3,4] Interpreting these constant values in children with MR is complicated by the widely varying ages and body sizes of such a population. Either Z scores or BSA adjustment can be used to adapt these criteria for use with children. For example, in one pediatric study, VC, RVol, and EROA were adjusted to BSA and were found to correlate with the regurgitant fraction calculated by magnetic resonance.[22] In our study, we also used a formula that included adjustment for BSA. When we then applied European Association of Echocardiography criteria, NT-proBNP levels differed significantly between mild and moderate/severe MR groups, therefore showing the potential usefulness of this method in identifying MR severity. Moreover, VC, RVol, and EROA correlated well with NT-proBNP levels.

Precise criteria for surgical intervention are available for adults with chronic and severe MR. Surgery is recommended for asymptomatic adults with severe chronic MR and preserved LV function (EF, >60%; LVESD, <40 mm) (class IIa indication) or mild to moderate LV dysfunction (EF, 30–60%; LVEDD, ≥40 mm) (class I indication).[2] Surgery is feasible before onset of symptoms in adult patients with chronic MR; however, identifying the right time for surgery in children with chronic MR is difficult, because no precise cutoff values for that purpose have been established echocardiographically in children. Some studies investigated preoperative Z scores for LV dimensions and SF in order to set prognostic values. A preoperative LVEDD Z score ≥5 and SF ≤33% were found to be predictors of late LV dysfunction in children.[23] In contrast, another study showed that age, preoperative EF, and LVEDD Z score were not associated with late LV dysfunction, whereas preoperative SF >34% had a negative predictive value.[24] In adults with flail MV leaflets, an LVESD of 45 mm (or ≥40 mm or 22 mm/BSA) indicates appropriate timing for MV surgery.[6] When we divided our patients according to normal versus enlarged LVESD, NT-proBNP levels were significantly higher (P <0.003) in those with an enlarged LVESD.

Another criterion indicating surgery in adults with asymptomatic severe MR is pulmonary hypertension (pulmonary artery systolic pressure >50 mmHg at rest or >60 mmHg with exercise).[10] We measured pulmonary artery pressure noninvasively in this study by using echocardiography rather than through cardiac catheterization. None of our patients had pulmonary hypertension, whether determined clinically or estimated by applying the Bernoulli formula to the velocity of tricuspid regurgitation flow.

Another issue related to surgical decision-making in children with MR caused by rheumatic valvular disease is the continuous healing process even after the acute phase of the disease has ended. We observed that the grade of MR decreased from moderate or severe to mild in one patient.

Even with echocardiographic criteria and NT-pro BNP data (an objective criterion for evaluating heart failure), age and clinical status remain important in deciding whether to perform surgery. As in our cohort, only 2 patients in the severe MR group eventually underwent surgery; in both cases, the decision was based on the clinical situation and relatively older age. This suggests that more criteria are needed to support the evaluation of MR and surgical decision-making.

Limitations

Our study population was small, especially the group of patients with severe MR. A longitudinal study of serial NT-proBNP levels and changes in echocardiographic parameters in a larger study population with valvular heart disease would help gain insights into improving patient follow-up and timing of intervention.

Conclusion

The echocardiographic criteria defined by European Society of Echocardiography for adult patients can be used in pediatric patients with chronic MR when indexed to BSA. Routine measurement of NT-proBNP levels may increase the reliability of these criteria.

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