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Associations between N-terminal pro-B-type natriuretic peptide and cardiac function in adults with corrected tetralogy of Fallot

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ABSTRACT

Background: Amino-terminal B-type natriuretic peptide (NT-proBNP) may detect early cardiac dysfunction in adults with tetralogy of Fallot (ToF) late after corrective surgery. We aimed to determine the value of NT-proBNP in adults with ToF and establish its relationship with echocardiography and exercise capacity.

Methods and results: NT-proBNP measurement, electrocardiography and detailed 2D-echocardiography were performed on the same day in 177 consecutive adults with ToF (mean age 34.6 ± 11.8 years, 58% male, 89% NYHA I, 29.3 ± 8.5 years after surgical correction). Thirty-eight percent of the patients also underwent a cardiopulmonary-exercise test. Median NT-proBNP was 16 [IQR 6.7–33.6] pmol/L, and was elevated in 55%. NT-proBNP correlated with right ventricular (RV) dilatation ($r = 0.271$, $p < 0.001$) and RV systolic dysfunction ($r = -0.195$, $p = 0.022$), but more strongly with LV systolic dysfunction ($r = -0.367$, $p < 0.001$), which was present in 69 patients (39%). Moderate or severe pulmonary regurgitation was not associated with higher NT-proBNP. Tricuspid and pulmonary regurgitation peak velocities correlated with NT-proBNP ($r = 0.305$, $p < 0.001$ and $r = 0.186$, $p = 0.045$, respectively). LV twist was measured with speckle-tracking echocardiography in 71 patients. An abnormal LV twist (20 patients, 28%) was associated with elevated NT-proBNP ($p = 0.030$). No relationship between NT-proBNP and exercise capacity was found.

Conclusions: 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.

1. Introduction

Tetralogy of Fallot (ToF) is the most common form of cyanotic congenital heart disease (ConHD), with a birth prevalence of approximately 3–4 per 10,000 live births [1]. The survival of patients with ToF has improved considerably since Lillehei reported the first successful corrective surgery in 1954 [2]. Despite satisfactory survival results of over 90%, 30 years after corrective surgery [3,4], an increasing number of late complications are encountered such as pulmonary regurgitation with the need for reintervention, right and left ventricular dysfunction, aortic root dilatation and arrhythmias. Although no clear data on very long-term outcomes are available yet, life expectancy is presumed to be diminished [3].

Nearly all adults with ToF have some degree of residual pulmonary regurgitation (PR) due to repair of the right ventricular (RV) outflow tract during corrective surgery. Pulmonary regurgitation causes volume overload of the RV, which can lead to RV dilatation and dysfunction [5]. The progression of RV dysfunction may also affect the left ventricle (LV), whereas both ventricles are known to interact [6,7]. Up to 20% of all adults with ToF develop LV dysfunction [8]. Early detection of deterioration in ventricular function is crucial, as both RV and LV dysfunction can lead to heart failure and life-threatening ventricular arrhythmias, which are both associated with increased morbidity and mortality [9].

Exercise capacity in adults with ToF is often diminished [10], and a worse cardiopulmonary-exercise test is known to be predictive for adverse outcome in these patients [11].

Another diagnostic tool that may be used to detect early changes in ventricular function and exercise capacity is the well-established heart failure biomarker N-terminal probrain natriuretic peptide (NT-proBNP). NT-proBNP is released from the cardiac myocytes in response to pressure and volume overload, and is a marker of increased myocardial-wall stress. While natriuretic peptides have proven to be of adjuvant diagnostic

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and prognostic value in patients with acquired heart failure [12], less is known about the usefulness of NT-proBNP in ToF. A recent article demonstrated that even though the vast majority of adults with ToF are asymptomatic, they have elevated NT-proBNP levels [13]. The significance of this observation is unknown, and therefore the potential diagnostic and prognostic value of NT-proBNP remains to be determined. We established NT-proBNP levels in adult patients with ToF and assessed the echocardiographic and exercise-related determinants of elevated NT-proBNP.

2. Methods

2.1. Patient inclusion

Patients diagnosed with ToF were recruited consecutively at the adult ConHD outpatient clinic at Erasmus Medical Center between May 2010 and March 2013. All patients had to be 18 years of age or older.

2.2. Clinical assessment

All patients underwent an extensive 2D-transthoracic echocardiogram (TTE) with speckle-tracking echocardiography, electrocardiogram, laboratory testing and were seen by a cardiologist on the same day. A subgroup of patients also underwent a cardiopulmonary-exercise test with maximum oxygen uptake (VO_2max). Exercise tests were not performed in all patients due to logistical reasons, and exercise results were only included in this study when the test was performed in the same week. The following patient characteristics were obtained: age, gender, surgical history, New York Heart Association (NYHA) functional class, body mass index (BMI), blood pressure, heart rate, and oxygen saturation.

2.3. Echocardiography

Two-dimensional echocardiography was performed by experienced sonographers with use of the commercially available system iE33 (Philips, Best, The Netherlands). Measured dimensions included the left ventricle (LV) end-diastolic and end-systolic endocardial diameter; right ventricle (RV) end-diastolic annulus and apex-base diameter; left atrium (LA) four chamber longitudinal diameter and area at the end of the ventricular systole. As quantitative measurement of the right atrium (RA) was not possible in all patients, we assessed RA size visually, which was then graded as no, mild or severe dilation [14,15]. Chamber dimensions were indexed for body surface area (BSA). Left ventricular systolic function was assessed on the basis of LV ejection fraction (LVEF) with use of the biplane modified Simpson's rule [14]. Right ventricular systolic function was assessed using tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (RV FAC) and systolic excursion of the lateral tricuspid annulus (S′) using tissue Doppler imaging (TDI). Diastolic LV function was assessed using pulsed wave Doppler of the mitral valve inflow (E, A, E/A-ratio and deceleration time) and septal TDI (E′). For the assessment of valvular regurgitation and stenosis, we used the recommendations of the European Association of Echocardiography [16–18].

2.4. Speckle-tracking echocardiography

Speckle-tracking echocardiography (STE) was used to evaluate LV twist. For optimal STE, images of the apical and basal short-axis were obtained with a frame rate of ≥60 frames/s. Images were transferred to a QLAB workstation to perform offline analysis (Philips Medical Systems). The images were analysed"" with QLAB software version 9.0. LV twist was defined as the maximal value of simultaneous systolic apical rotation minus basal rotation. Twist patterns of ToF patients were compared with twist patterns of healthy individuals, who were defined as normal. A normal twist pattern is characterized by an end-systolic clockwise basal rotation and end-systolic counter-clockwise apical rotation [19]. Other twist patterns were defined as abnormal. Excellent intra-observer and inter-observer reproducibility for LV twist measurements using QLAB software has been described for our lab [20].

2.5. Cardiopulmonary-exercise test

Maximal exercise capacity ($workload_{max}$) and maximal oxygen uptake during exercise (VO_{2max}) were assessed using bicycle ergometry. Workload was increased gradually by 10–20 ""watts per minute. Exercise capacity results were compared with reference values that were adjusted for age, gender, body height and weight. Performance was considered maximal when a respiratory exchange ratio (RER) of >1.0 was reached.

2.6. Laboratory testing

Peripheral venous blood samples were obtained from all patients after at least 15 min of rest. Creatinine levels were assessed since renal dysfunction is known to influence NT-proBNP levels. Renal dysfunction was defined as a creatinine level of ≥200 μmol/L. Plasma NT-proBNP levels were measured using an enzyme immunoassay (Elecsys, Roche Diagnostics, Basel, Switzerland). The cut-off value of normal in our laboratory is ≤14 pmol/L.

2.7. Statistical analysis

Continuous variables were reported as mean ± standard deviation when normally distributed, or median and interquartile ranges (IQR) were reported when not normally distributed. Categorical variables were presented as frequencies and percentages. Differences in continuous variables between two groups were compared using Student's unpaired *t*-test when normally distributed or Wilcoxon rank sum test when data distribution was skewed. Differences in continuous variables with normal distribution between more than two groups were investigated with one-way ANOVA, or when not normally distributed investigated with the Kruskal–Wallis test. Baseline characteristics were compared between patients with normal and elevated NT-proBNP levels. To compare categorical data, the Chi-square test or when applicable, Fisher's exact test was used. Correlation analyses between NT-proBNP and patient characteristics were performed using the Pearson correlation test or the Spearman correlation test when data was skewed. Linear regression modelling was performed to evaluate the relationship between NT-proBNP and echocardiographic and bicycle ergometry parameters. We adjusted for baseline characteristics that were significantly associated with NT-proBNP, including age, gender and NYHA class which are known factors that influence NT-proBNP levels [21]. As NT-proBNP is non-parametric, the variable was log-transformed which created a normal distribution for further statistical analyses. All statistical tests were two-sided and a p-value of <0.05 was considered statistically significant. The Statistical Package for Social Sciences, version 21.0 (SPSS, Chicago, Illinois) was used for all statistical analyses.

2.8. Medical ethics and data quality

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local medical ethics committee. Written informed consent was obtained from all patients. Several measures were taken to ensure optimal data quality. Before the statistical analyses, manual edit checks were performed by the investigators to search for missing data, contradictory data entries and for values that were out of the specified normal range. Data of a random sample of 15 participants (8%) was checked by an independent investigator; no discrepancies were observed between data in medical records and in the database used for statistical analyses.

3. Results

A total of 177 ToF patients were included in the study, 28 of whom had a diagnosis of ToF with pulmonary valve atresia (ToF/PA). Baseline characteristics of all study participants are summarized in Table 1. Median NT-proBNP level was 15.6 [IQR 6.7–33.6] pmol/L. In 55% of the patients the NT-proBNP level was above the reference value of normal (>14 pmol/L). None of the patients had renal dysfunction (median creatinine level 75 [IQR 65–83.5] μmol/L). In Table 1 the baseline characteristics are presented for all patients together, and specified for patients with normal or elevated NT-proBNP levels. NT-proBNP levels were significantly higher in women than in men (23.9 [IQR 13.8–41.3] pmol/L versus 9.6 [IQR 4.8–21.4] pmol/L, $p < 0.001$). Median NT-proBNP levels increased with NYHA class ""(NYHA I 14.5 [IQR 6.3–29.4] pmol/L, NYHA II 29.7 [IQR 16.7–135.3] pmol/L, NYHA III ($n = 1$) 169.6 pmol/L, $p < 0.001$. Patients with elevated NT-proBNP had undergone corrective surgery at older age, and more often had a prior palliative shunt. In patients with normal NT-proBNP levels a transannular or RVOT patch was used more often during corrective surgery. NT-proBNP levels did not differ between patients with or without prior pulmonary valve replacement.

3.1. Electrocardiography

The majority of patients were in sinus rhythm (n = 146, 83%), and had a right bundle branch block (n = 118, 91%) (Table 2). In 22 patients (12%) QRS duration was ≥180 milliseconds. Mean QRS duration was longer in patients with an elevated NT-proBNP level. NT-proBNP levels were significantly higher in patients in atrial fibrillation (101.3 [IQR 40.5-661] pmol/L) than in patients in sinus rhythm (13.9 [IQR 6.3-26.9] pmol/L) or pacemaker rhythm (24.6 [IQR 14.3-43.8] pmol/L), $p < 0.001$.

3.2. Echocardiography

Based on annulus and apex-base diameter, more than 50% of the patients had a dilated RV (Table 3). RV function (i.e. RV fractional area change < 35%, TAPSE < 16 and/or S' < 10) was diminished in one-third