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N-Terminal Pro-B-Type Natriuretic Peptide and Its Relationship With Cardiac Function in Adults With Congenital Heart Disease

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Objectives The aim of this study was to determine the value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in adults with congenital heart disease (CHD) and investigate its relationship with ventricular function and exercise capacity.

Background NT-proBNP may detect early deterioration in cardiac function.

Methods In this cross-sectional study, extensive echocardiography, exercise testing, and NT-proBNP measurements were performed on the same day in consecutive adult patients with CHD.

Results In total, 475 patients were included in this study (mean age of 34 ± 12 years, 57% male, 90% New York Heart Association class I). The median NT-proBNP level was 15.1 pmol/l (interquartile range [IQR]: 7.1 to 31.3 pmol/l), and the NT-proBNP level was >14 pmol/l in 53% of patients. The highest NT-proBNP levels were observed in patients with Fontan circulation (36.1 pmol/l [IQR: 14.4 to 103.8 pmol/l]) and a systemic right ventricle (RV) (31.1 pmol/l [IQR: 21.8 to 56.0 pmol/l]), and the lowest values were seen in patients with aortic coarctation (7.3 pmol/l [IQR: 2.8 to 19.5 pmol/l]). NT-proBNP levels correlated with age ($r = 0.39$, $p < 0.001$) and were higher in women (median of 21.7 vs. 10.4 pmol/l; $p < 0.001$). In patients with aortic stenosis or aortic coarctation, NT-proBNP levels correlated with diastolic function parameters of E/E′ ratio ($r = 0.40$, $p < 0.001$) and left atrial dimension ($r = 0.36$, $p < 0.001$). In patients with a systemic RV, NT-proBNP levels correlated with RV annulus diameter ($r = 0.31$, $p = 0.024$). In patients with tetralogy of Fallot, the strongest correlations were observed with left atrial dimension ($r = 0.46$, $p < 0.001$) and left ventricular ejection fraction ($r = 0.37$, $p < 0.001$). NT-proBNP levels were associated with exercise capacity ($n = 198$) (maximum workload: $\beta = -0.08$, $p = 0.021$) and peak oxygen uptake ($\beta = -0.012$, $p = 0.011$) in a multivariable regression model adjusted for age and sex.

Conclusions NT-proBNP levels in adults with CHD clearly differ by diagnosis and are related to echocardiographic parameters and exercise capacity. Disease-specific correlations contribute to the understanding of the main hemodynamic problems per diagnosis. Follow-up data are needed to elucidate the additional prognostic value. (J Am Coll Cardiol 2013;62:1203–12) © 2013 by the American College of Cardiology Foundation

The remarkable improvement in survival due to the success of cardiac surgery, anesthesia, intensive care, and specialist (pediatric) cardiological care has caused a rapid increase in the number of adults with congenital heart disease (CHD) (1,2). As a result of this success, late complications are more often encountered, such as ventricular dysfunction, need for reintervention, arrhythmias, and sudden death. These adverse effects have important consequences for patients' prognosis and quality of life (3). Therefore, early detection of deterioration in ventricular function and adequate timing of (re)interventions is crucial.

N-terminal pro-B-type natriuretic peptide (NT-proBNP), known as the inactive fragment of prohormone of brain natriuretic peptide, is primary secreted by cardiac myocytes in response to abnormal ventricular wall stress and loading conditions (4). NT-proBNP is a well-known marker of ventricular dysfunction and heart failure in patients with acquired heart disease (5). The additional use of NT-proBNP as a marker for ventricular dysfunction in patients with CHD has been suggested (6). However, NT-proBNP has

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Abbreviations and Acronyms

AoS = aortic valvular stenosis

ASO = arterial switch operation

CHD = congenital heart disease

CoA = aortic coarctation

FAC = fractional area change

IQR = interquartile range

LV = left ventricle

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

RV = right ventricle

TGA = transposition of the great arteries

ToF = tetralogy of Fallot

Vo_{2max} = maximal oxygen uptake

$workload_{max}$ = maximal exercise capacity

only been studied in a small number of patients with a specific type of congenital cardiac lesion, and the relationship between NT-proBNP level and cardiac function has not been assessed at all (7). The wide spectrum of congenital heart lesions, each with their own degree of complexity and complications, suggests that disease-specific use of the marker might be required (8). Furthermore, not all diagnostic and treatment options that are beneficial in patients with acquired heart disease can be extrapolated to patients with CHD, as has been shown with medical treatment of heart failure (9).

The aim of this study was to evaluate the value of NT-proBNP in adults with CHD and investigate its relationship with cardiac function and exercise capacity.

Methods

Study sample. Patients were recruited consecutively at the adult CHD outpatient clinic of the Erasmus Medical Center between May 2010 and October 2012. The following congenital cardiac diagnoses were included: aortic valvular stenosis (AoS), aortic coarctation (CoA), atrial septal defect, tetralogy of Fallot (ToF) (also including patients with pulmonary atresia and ventricular septal defect), transposition of the great arteries (TGA) corrected by arterial switch operation (ASO), systemic right ventricle (RV) (TGA corrected by Mustard procedure or congenitally corrected TGA), and Fontan circulation. Of all eligible patients, 95% agreed to participate. Exclusion criteria were defined as renal impairment (serum creatinine level >200 μmol/l) and age younger than 18 years.

Medical ethics and quality of data. The local medical ethics committee approved the study protocol. Written informed consent was obtained from all study participants. Several measures were taken to ensure optimal data quality. When patient enrollment was completed, one investigator compared the data entered in the electronic case report form with hospital records of 30 randomly selected study patients (6%), which were all in accordance. Before further analyses were conducted, manual edit checks were performed by the investigators to search for missing data, contradictory data entries, and values that were out of the specified normal range.

Clinical characteristics. On the day of inclusion in the study, all 475 patients underwent detailed 2-dimensional transthoracic echocardiography, 12-lead electrocardiography, and laboratory testing. A total of 198 patients also underwent bicycle ergometry on the same day. The following patient characteristics were recorded: age, sex, type of congenital heart defect, history of prior interventions, body mass index, New York Heart Association (NYHA) functional class, blood pressure, heart rate, and oxygen saturation.

Echocardiography. Two-dimensional transthoracic echocardiography was performed by experienced sonographers using a commercially available system (iE33, Philips, Best, the Netherlands). Dimensions of the left ventricle (LV) (end-diastolic and end-systolic endocardial diameter), RV (annulus and apex-base distance), left atrium (4-chamber longitudinal and transversal diameter as well as parasternal long axis diameter), and right atrium (4-chamber longitudinal and transversal diameter) were measured. All ventricular measures were indexed for body surface area. Left ventricular systolic function was assessed by left ventricular ejection fraction using the biplane modified Simpson rule (10). Right ventricular function was assessed by measurement of right ventricular fractional area change (FAC) and tricuspid annulus plane systolic excursion. In patients with an RV supporting the systemic circulation, right ventricular FAC and tricuspid annulus plane systolic excursion were used as systemic ventricle function measures. Furthermore, diastolic function was assessed using pulsed wave Doppler signals of the mitral or tricuspid valve inflow (E, A, E/A ratio, and deceleration time) and septal tissue Doppler imaging (E′). For the measured dimensions and function parameters, approximately 95% of the images were of sufficient quality.

Exercise test. Maximal exercise capacity ($workload_{max}$) and maximal oxygen uptake (Vo_{2max}) were assessed by bicycle ergometry. Exercise test results were only obtained in patients undergoing bicycle ergometry for routine clinical follow-up (n = 198). Workload was increased stepwise with 10 to 20 W/min. The results of exercise capacity were compared with the results of healthy subjects adjusted for age, sex, and body height and weight. $Workload_{max}$ and Vo_{2max} were considered decreased when <85% of the predicted value was achieved. Performance was considered maximal when a respiratory quotient of ≥1.1 was reached.

Laboratory testing. Peripheral venous blood samples were obtained from all participants after they had rested for at least 30 minutes. Plasma and serum were separated immediately after collection of blood samples, and NT-proBNP, creatinine, and hemoglobin levels were measured. NT-proBNP levels were determined using the Elecsys system (Roche Diagnostics, Basel, Switzerland). The cutoff value of normal in our hospital is ≤14 pmol/l.

Statistical analysis. Categorical variables are summarized as frequencies and percentages, and continuous variables with a normal distribution are reported as mean ± SD. We report median values with interquartile range (IQR) in case of a non-normal distribution. Differences between cardiac diagnoses were compared using the Student unpaired *t* test or Wilcoxon rank sum test. Differences between more than