

Plasma N-Terminal Pro-Brain Natriuretic Peptide as a Marker of Right Ventricular Dysfunction in Patients With Tetralogy of Fallot After Surgical Repair*

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Objective: Chronic heart failure is associated with neurohormonal activation that is not only related to outcome but is also a therapeutic target. We have attempted to demonstrate whether a similar pattern of neurohormonal activation exists in adult congenital heart disease (ACHD) and, if so, whether it relates to disease severity determined by cardiopulmonary exercise testing. **Methods and results:** Concentrations of N-terminal pro-atrial natriuretic peptide, N-terminal pro-brain natriuretic peptide (NT-proBNP), endothelin (ET)-1, renin, aldosterone, adrenalin, and noradrenalin were determined in 50 adults (mean age, 27.8 ± 1.7 years [\pm SEM]; 26 women) with tetralogy of Fallot (TOF) after surgical repair (New York Heart Association functional class 1.1 ± 0.1). One hundred age- and sex-matched healthy blood donors served as a control group for NT-proBNP determination. Dimensions of ventricles, left ventricular pump function, and estimated right ventricular (RV) systolic pressure were determined by echocardiography. Maximum oxygen uptake ($\dot{V}O_{2\max}$) was measured in all patients using spiroergometry. TOF patients had elevated levels of NT-proBNP compared with healthy individuals: NT-proBNP (women: 180 pg/mL vs 43 pg/mL, and men: 147 pg/mL vs 32 pg/mL; $p < 0.0001$) and ET-1 (2.5 fmol/L vs 0.7 fmol/L). There was a significant correlation of NT-proBNP to dimension and estimated peak systolic pressure of the RV as well as impairment of $\dot{V}O_{2\max}$. **Conclusions:** RV dysfunction detected by echocardiography and plasma NT-proBNP determination in asymptomatic or minimally symptomatic TOF patients correlates well with their cardiopulmonary exercise capacity. Thus, these simple and noninvasive screening methods can be used additionally to stratify ACHD patients with impaired cardiac function before they become clinically symptomatic. (CHEST 2005; 128:2563–2570)

Key words: cardiopulmonary exercise test; congenital heart disease; natriuretic peptides; right ventricular dysfunction; tetralogy of Fallot

Abbreviations: ACHD = adult congenital heart disease; BNP = brain natriuretic peptide; CI = confidence interval; ET = endothelin; FS = fractional shortening; LV = left ventricle/ventricular; LVed = left ventricular end-diastolic dimension; NT-proANP = N-terminal pro-atrial natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PR = pulmonary regurgitation; RBBB = right bundle-branch block; RV = right ventricle/ventricular; RVed = right ventricular end-diastolic dimension; TAP = transannular patch; TIVmax = tricuspid valve regurgitation; TOF = tetralogy of Fallot; $\dot{V}O_{2\max}$ = maximum oxygen uptake

The number of patients with adult congenital heart disease (ACHD) is growing, and their follow-up, medical treatment, and/or late complications are increasingly important. The most common cause of cyanotic ACHD worldwide is the tetralogy of Fallot (TOF).¹ Follow-up investigations^{1,2} of sur-

gical intervention have documented a favorable long-term outcome in these patients. Despite the very good life expectancy, many patients are faced with multiple residua and sequelae. Residual pulmonary artery stenosis and suboptimal relief of the obstructed right ventricular (RV) outflow tract lead to a state of chronic pressure overload. Additionally, various degrees of pulmonary regurgitation (PR) may create volume overload and eventual dilation of the

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RV.³ Due to the hemodynamic burden, heart failure develops in the long-term as an important determinant of morbidity and mortality.⁴

It is important to establish diagnostic tools and methods that are sensitive enough to detect and evaluate developing heart failure at an early stage in patients after corrective surgery. Clinical examinations, including the subjective New York Heart Association (NYHA) functional classification, allow only a rough impression and general estimation of the current status in asymptomatic or minimally symptomatic patients, but they will not be able to reveal a latent cardiac failure as a rule.

Echocardiography can allow objective criteria in determining pump function of the left ventricle (LV). However, in patients with TOF, the systolic function of the LV usually appears to be normal. In these cases, the RV is affected, so that echocardiography is only of limited value.

Brain natriuretic peptide (BNP) is a well-established marker for diagnosis, prognosis, and risk stratification in patients with congestive heart failure.⁵⁻⁸ The N-terminal pro-BNP (NT-proBNP) represents the N-terminal fragment of pro-BNP, the precursor of the biologically active BNP. Unlike BNP, NT-proBNP circulates at considerable concentrations in human plasma, is stable at room temperature, can easily be detected, and is quantified by immunoassay.^{9,10}

Studies¹¹⁻¹⁴ in adults with congestive heart failure clearly indicate that blood levels of NT-proBNP and the maximal oxygen uptake ($\dot{V}O_2\text{max}$) index measured by cardiopulmonary exercise testing can be used for objective assessment of heart failure and risk stratification. Little is known about the role of these variables and their interrelationship with respect to the long-term effects of abnormal RV loading conditions in adult TOF patients > 2 decades after surgical repair. Therefore, the purpose of our present study was to measure various clinical parameters in asymptomatic or minimally symptomatic patients with chronic RV pressure and/or volume overload due to operated-on TOF, to investigate the relationship between these variables and clinical status, and finally to propose an efficient usage of these clinical markers.

MATERIALS AND METHODS

Study Population

We performed a prospectively designed detailed assessment of clinical and neurohormonal variables in 50 adult patients with TOF (26 women and 24 men) > 20 years after surgical repair. Patients were consecutively recruited from the specialized ACHD outpatient clinic of the Georg-August-University of Göt-

tingen between January 2001 and September 2003. All the tests for each patient were carried out on the same day. One hundred age- and sex-matched healthy blood donors served as a control group for NT-proBNP levels.

Exclusion Criteria

Exclusion criteria were symptomatic heart failure, acute infection, chronic lung disease, severe mental retardation, and medication, *ie*, converting enzyme inhibitors and β -blockers.

Clinical Investigation

In addition to a thorough clinical examination, all patients underwent two-dimensional and M-mode echocardiography via a transthoracic approach (Sonos 2000 Diagnostic Ultrasound System; Hewlett-Packard; Andover, MA) interfaced with a multifrequency transducer. LV end-diastolic dimension (LVed) and RV end-diastolic dimension (RVed) were determined by echocardiography from a short-axis view by M-mode. Fractional shortening (FS) was used as a parameter of systolic pump function of the LV. Velocities of tricuspid valve regurgitation (TIV_{max}) and antegrade pulmonary valve flow were measured by continuous-wave Doppler echocardiography and served to estimate RV systolic pressure and the gradient in the RV outflow tract. Standard 12-lead ECG was recorded to analyze the cardiac rhythm and to determine the width of the QRS complex.

Exercise Testing

Cardiopulmonary exercise testing was performed in all patients on a bicycle ergometer starting with a workload of 35 W, and increasing by 30 W every 3 min. Subjects maintained a pedaling rate from 45 to 65 revolutions per minute. Oxygen consumption was measured using the breath-by-breath technique (Oxycon Pro; Jaeger; Hoechberg, Germany). Exercise was carried out until each subject reached the $\dot{V}O_2\text{max}$. During exercise, cardiac status was monitored with standard ECG leads and arterial pressure was measured every 3 min. Heart rate was derived from the ECG.

Neurohormonal Assessment

Peripheral venous blood samples were obtained from all participants after they had rested for at least 15 min before exercise testing. Blood samples were immediately placed on ice and centrifuged at 5,000 revolutions per minute for 10 min. Plasma and serum aliquots were stored at -80°C until analysis. N-terminal pro-atrial natriuretic peptide (NT-proANP) and endothelin (ET)-1 were determined by enzyme immunoassays. NT-proBNP was measured using immunoassay (Elecsys 2010; Roche Diagnostics; Mannheim, Germany). Aldosterone and active renin were determined by radioimmunoassay. Adrenalin and noradrenalin concentrations were measured using high-performance liquid chromatography with electrochemical detection.

Informed Consent

After adequate explanation of the purpose of the study, informed consent was obtained from all patients. The study protocol was approved by the local ethical committee.

Statistical Analysis

The data were analyzed on a personal computer using the statistical software (Excel 2000; Microsoft; Redmond, WA; and

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