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EVIDENCE FOR NATRIURETIC PEPTIDES A AND B AS NON-INVASIVE MARKERS IN CONGENITAL AND VALVULAR HEART DISEASE

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Aim. The aim of this study was to evaluate the diagnostic utility of natriuretic peptides of type A and B as non-invasive markers in the diagnosis and treatment of congenital and valvular heart disease.

Methods. Blood samples from 82 patients with various congenital and valvular heart diseases were measured for A and B natriuretic peptide levels and levels compared with those in a reference group of blood donors. Electrochemiluminiscence immunoassay and immunoluminometric essay were used for quantification of natriuretic peptides A and B. Particular reference values in serum or plasma of blood donors were adapted from literature.

Results. Natriuretic peptide levels in cardiac patients were significantly higher than reference levels. The levels of both peptides in blood serum or plasma showed positive correlation with age, gender and disease severity.

Conclusions. Natriuretic peptides are efficient, non-invasive cardiac markers for facilitating diagnosis, management and treatment of valvular heart disease.

INTRODUCTION

Valvular heart disease is any disease process involving one or more of the valves of the heart (the aortic and mitral valves on the left and the pulmonary and tricuspid valves on the right). Valve problems may be congenital (inborn) or acquired (due to another cause later in life).

Heart valve dysplasia is an error in the development of any of the heart valves, and a common cause of congenital heart defects in humans as well as animals; tetralogy of Fallot is a congenital heart defect with four abnormalities, one of which is stenosis of the pulmonary valve. Ebstein's anomaly is an abnormality of the tricuspid valve. Valvular heart disease is commonly caused by damage to the heart muscle as a result of rheumatic fever or a congenital abnormality. Valvular heart problems can be corrected surgically, by direct repair of the valve, replacement of the damaged valve with an artificial valve, or by a non-surgical technique called balloon valvuloplasty. Patients with valvular heart disease are also at risk for bacterial endocarditis. Cardiac auscultation and various non-invasive and invasive cardiac tests are necessary to establish a firm diagnosis which is the basis for rational treatment of the underlying disorder. Two-dimensional and Doppler echocardiography is particularly useful in this regard[1]. This study provides evidence for the natriuretic peptides (NT-proBNP-N-terminal pro-brain natriuretic peptide and atrial natriuretic peptide -proANP) as non-invasive cardiac markers in establishing diagnosis, management and treatment of congenital and valvular heart diseases.

MATERIALS AND METHODS

Patients

Eighty two samples of both blood serum or blood plasma from patients (36 males, mean age of 46 years, range 22–75 years and 46 females, mean age of 45 years, range 22–79 years) with various types of valvular heart diseases were collected for investigation of serum NT-proBNP levels and plasma mid-regional proANP levels. Consecutive ambulatory patients were previously examined in a specialized Cardiology Department. Clinically relevant indices (hypertension, history of acute myocardial infarction, treatment by angiotensin converting enzyme (ACE) inhibitors and angiotensin antagonists, beta blockers and diuretics, left ventricular ejection fraction, systolic and diastolic pressure and kidney function expressed as S-creatinine levels) were investigated. Echocardiography was used to determine the degree of severity of the heart diseases.

Patient characteristic are listed in Table 1.

Methods

Blood samples were collected by venipuncture into tubes (Sarstedt, Vacutainer) containing EDTA as an anticoagulant. Immediately after the collection were samples transported in laboratory and after centrifugation (4000 g at 4°C and 10 min) the aliquots of serum and plasma were frozen immediately and kept at –20°C until proANP and NT-proBNP were analyzed. Serum levels of NT-proBNP were measured using a commercially available electrochemiluminescence sandwich immunoassay (ECLIA, Roche, Germany) on Elecsys System 2010. Plasma mid-re-

Table 1. Characteristic of the patients.

	Males	Females	**Total**
N	36	46	82
LVEF (Mean ± SD) (%)	49.2 ± 18.2	60.2± 14.3	55.0 ± 16.9
N-MID-proANP (mean ± SEM) (pmol/l)	191.0 ± 39	120.7 ± 25.5	154.6 ± 23.5
NT-proBNP (mean ± SEM) (pg/ml)	2051.6 ± 657.2	795.4 ± 118.5	1360.0 ± 298.4
Hypertension (%)	19 (53)	22 (48)	41 (50)
Systolic pressure [mm Hg] (mean ± SD) Diastolic pressure [mm Hg] (mean ± SD)	129.1 ± 19.4 78.7 ± 10.7	123.3 ± 18.3 75.3 ± 12.4	125.8 ± 18.8 76.8 ± 11.7
Creatinine [µmol/l] (mean ± SD)	101.8 ± 33.3	77.9 ± 13.1	89.4 ± 27.4
History of AMI (%)	14 (38)	13 (28)	27 (33)
ACE inhibitors (%) Angiotensin antagonists (%) Beta blockers (%) Diuretics (%)	10 (28) 2 (6) 14 (39) 14 (39)	13 (28) 0 13 (28) 13 (28)	23 (28) 2 (2) 27 (33) 27 (33)
Atrial stenosis	1	1	2
Atrial septal defect	8	15	23
Atrial regurgitation	2	0	2
Atrioventricular septal defect	0	2	2
Transposition and corrected transposition of great arteries	7	5	12
Tricuspidal atresia	2	1	3
Ventricular septal defect	2	6	8
Ebstein anomaly	2	5	7
Tricuspidal and atrial regurgitation	0	1	1
Mitral valve prolapse	0	1	1
Tetralogy of Fallot	3	1	4
Dilated cardiomyopathy	1	0	1
Eisenmenger syndrome and heavy pulmonal hypertension	1	4	5
Pulmonary valve stenosis	1	1	2
Mitral regurgitation	1	1	2
Coronary artery bypass graft and mitral regurgitation	4	0	4
Coarctation of the aorta	1	1	2
Patent ductus arteriosus	0	1	1

gional proANP levels were measured by using a sandwich immunoluminometric assay for mid-regional proANP (amino acids 53–90) (BRAHMS SERISTRA, BRAHMS AG, Germany) as previously described in Morgenthaler et al[2].

Statistical analysis

Differences between the medians for reference values of both natriuretic peptides and the medians in patients with valvular heart diseases were tested for statistical significance by the Wilcoxon Signed rank test. $P < 0.05$ was considered as statistically significant difference.

RESULTS

Blood serum and plasma concentrations of both natriuretic peptides were significantly elevated in patients with congenital and valvular heart disease as compared with reference values. Both peptides showed positive correlation with age and gender. A summary of the results is shown in Table 2.

The non significant differences in the group of males over 60 years for NT-proBNP, and in females over 56 years for N-MID-proANP may have been due to large variability and range of results (males over 60years: NT-pro BNP range 60–16071 pg/ml; females over 56 years: N-MID-proANP range 83–280 pmol/l). Serum levels of NT-proBNP in patients were significantly elevated above the cut off values (100 pg/ml for males, 150 pg/ml for

Table 2. Correlation of natriuretic peptides with age gender and reference values in patiens with congenital and valvular heart diseases adpated from[2, 16, 20].

Natriuretic peptides	Reference values – Blood donors (Median)	Patients values (Median)	P value (Significance)
NT-proBNP (age, gender)	Males 18–54 years: 20.8pg/ml Males 54–64 years: 29.7 pg/ml Males > 64 years: 117.5 pg/ml Females 18–54 years: 46.3 pg/ml Females 54–64 years: 67.5 pg/ml Females > 64 years: 138.1 pg/ml	Males 18–54 years: 310.8 pg/ml Males 54–64 years: 1913 pg/ml Males > 64 years: 500.8 pg/ml Females 18–54 years: 334.3 pg/ml Females 54–64 years: 239.9 pg/ml Females > 64 years: 760.3 pg/ml	p < 0.0001 (S) p = 0.0156 (S) p = 0.1250 (NS) p < 0.0001 (S) p = 0.0117 (S) p = 0.0033 (S)
N-MID-proANP	Whole group: 45 pmol/l Males: 45.3 pmol/l Females 45 pmol/l	Whole group: 106 pmol/l Males: 212 pmol/l Females: 85.8 pmol/l	p < 0.0001 (S) p = 0.0012 (S) p = 0.0002 (S)
N-MID-proANP (age, gender)	Males 18–25 years: 35 pmol/l Males 26–35 years: 31.7 pmol/l Males 36–45 years: 44 pmol/l Males 46–55 years: 57.4 pmol/l Males 56–65 years: 64.8 pmol/l Females 18–25 years: 43.3 pmol/l Females 26–35 years: 45.1 pmol/l Females 36–45 years: 41.1 pmol/l Females 46–55 years: 41.4 pmol/l Females 56–65 years: 68.6 pmol/l	Males 18–25 years: 71.5 pmol/l Males 26–35 years: 141.6 pmol/l Males 36–45 years: 68.1 pmol/l Males 46–55 years: 225 pmol/l Males 56–65 years: 212 pmol/l Females 18–25 years: 61.6 pmol/l Females 26–35 years: 238.5 pmol/l Females 36–45 years: 48.8 pmol/l Females 46–55 years: 83 pmol/l Females 56–65 years: 115.5 pmol/l	p = 0.0005 (S) p = 0.0002 (S) p = 0.0012 (S) p = 0.0081 (S) p = 0.0081 (S) p = 0.0002 (S) p = 0.0002 (S) p = 0.0002 (S) p = 0.0002 (S) p = 0.058 (NS)

Reference values of both natriuretic peptides were calculated from the group of healthy blood donors and were previously published in[2, 16, 20]. Wilcoxon Signed rank test was used to test the statistical significance between medians of reference group and patients with congenital and valvular heart disease. Value of $p < 0.05$ was considered as significant difference.
S- significant, NS- non-significant

females and 125 pg/ml for all patients) approved for the NT-proBNP assay. The blood serum and plasma levels of both natriuretic peptides correlate well with the measured cardiological parameters (diastolic blood pressure and systolic blood pressure, left ventricular ejection fraction (LVEF), history of acute myocardial infarction (AMI)).

DISCUSSION

The presented study shows the complex approach to investigation of valvular heart diseases with biochemical and cardiovascular surveillance of patients.

To date, several studies show the relevance of natriuretic peptides in valvular and congenital heart diseases. The present results confirm the findings of other studies showing significantly elevated levels of natriuretic peptides in various types of congenital and valvular heart diseases[3–5]. Other studies have shown a relationship between concentrations of natriuretic peptides and severity of heart failure[6–12]. In agreement with previous publications[6–12], the levels of both natriuretic peptides increased with severity of the heart impairment. The highly significant relationship to age and gender for both natriuretic peptides found, accords with other studies[13–18]. Diuretics, ACE inhibitors, angiotensin receptor antagonists, beta-blockers and renal impairment have been shown to decrease levels of natriuretic peptides[19]. In the present study, 27 of 82 patients were treated by drugs but only three of these patients showed significantly lower values of NT-proBNP and NT-proANP. Nevertheless, these results correlated with increase of the left ventricular ejection fraction (over 60%) resulting in less severe heart impairment. Values of S-creatinine were investigated as a marker of renal impairment. In 80 of 82 patients, the results show normal levels of S-creatinine according to the age and gender. One patient had mildly elevated levels of S-creatinine (130 μmol/l) and one patient had significantly elevated level of S-creatinine (200 μmol/l). In both patients, the levels of natriuretic peptides were significantly higher than reference values (1st patient: S-creatinine: 130 μmol/l, NT-proBNP -1040 pg/ml, N-MID-proANP 78 pg/ml; 2nd patient: – S-creatinine: 200 μmol/l, NT-proBNP -16071 pg/ml, N-MID-proANP 504 pg/ml) In both cases, levels of natriuretic peptides correlated with the severity of heart impairment (LVEF = 35% and 10% respectively).

In conclusion, the results of the present study indicate that the natriuretic peptides (NT-proBNP and N-MID-proANP) are well appropriate as non-invasive cardiac biochemical markers in establishing diagnosis, as well as in management and treatment of valvular and congenital heart diseases.

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