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Short communication

Parathyroid hormone-related protein is reduced in severe chronic heart failure

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ARTICLE INFO

Article history:
Received 14 December 2005
Received in revised form
10 January 2006
Accepted 11 January 2006
Published on line 28 February 2006

ABSTRACT

In the cardiovascular system, parathyroid hormone-related peptide (PTHrP) is expressed in various cells such as cardiac vascular smooth muscle cells, coronary endothelial cells and cardiomyocytes and acts as an autocrine/paracrine substance. We compared PTHrP levels in 35 consecutive patients with severe CHF (33 male, mean age 66.2 ± 8.9 years) with 26 normal controls (24 male, mean age 63.1 ± 8.6 years). PTHrP levels were reduced in severe CHF patients (11.10 ± 1.37 fmol/ml) compared with the controls (20.62 ± 3.30 fmol/ml, $p = 0.005$). PTHrP values decreased as a function of New York Heart Association classification. These results suggest that PTHrP levels decrease in proportion to the severity of heart failure and could potentially be used to monitor progression of disease non-invasively.

1. Introduction

The parathyroid hormone-related peptide (PTHrP) was originally discovered as a product of tumors associated with hypercalcemia [12]. In the cardiovascular system, PTHrP is expressed in various cells such as cardiac vascular smooth muscle cells, coronary endothelial cells and cardiomyocytes [5]. PTHrP affects mostly the cardiomyocytes and cardiac vascular smooth muscle cells by acting as an autocrine, paracrine, intracrine and endocrine bioactive substance. The myocardium, especially the atria, is a source of PTHrP [1]. The expression of the PTHrP gene in vascular smooth muscle cells is regulated by vasoconstrictors such as norepinephrin, endothellin-1, angiotensin-II, serotonin, bradykinin and thrombin and by mechanical stress, such as mechanical dissention of the vascular wall [13].

Recently Ogino et al. reported that PTHrP is produced in the myocardium and is increased in chronic heart failure (CHF) [8]. This was the only study that measured PTHrP levels in CHF and the authors concluded that PTHrP might be modulated by cardiac performance in patients with CHF and might serve as a new regulatory molecule, adding to the list of molecules, such as ANP and BNP, already recognized to have incremental prognostic power in the setting of heart failure. However, the majority of the patients in this study were in NYHA class II. Since in advanced CHF additional mechanisms may be

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0196-9781/$ – see front matter
doi:10.1016/j.peptides.2006.01.014

Table 1 – Demographic and clinical characteristics of CHF patients and normal controls

	Patients ($n = 35$)	Controls ($n = 26$)
Age (year)	66.2 ± 8.9	64.1 ± 8.6
Gender (male/female)	33/2	25/1
NYHA classification (III/IV)	23/12	–
Cardiac cachexia	6	–
Arterial hypertension	14	–
Diabetes mellitus	14	–
Hyperlipidemia	12	–
Current smoking	8	5
Serum creatinine (mg/dl)	1.18 ± 0.34	1.09 ± 0.32
Body mass index (kg/m^2)	25.4 ± 4.3	24.3 ± 4.2
Systolic blood pressure (mmHg)	116.2 ± 20.6	115.7 ± 19.4
Diastolic blood pressure (mmHg)	72.9 ± 11.9	73.2 ± 10.8
Heart rate (bpm)	78.7 ± 13.9	77.1 ± 11.8
Jugular vein distension	8	–
Edema	9	–
Third heart sound	12	–
Rales	7	–

activated, we evaluated the association of PTHrP levels and severe CHF (NYHA III/IV).

2. Materials and methods

We studied 35 consecutive patients with severe CHF (NYHA class III or IV) and 26 age- and sex-matched normal controls. CHF was due to an old myocardial infarction in 26 patients, to dilated cardiomyopathy in seven patients, to hypertension in one patient and to valvular heart disease in one patient. Twenty-four patients (68.6%) were treated with angiotensin-converting enzyme inhibitors, five (14.3%) with angiotensin II receptor blockers, 31 (88.6%) with furosemide, 28 (80%) with spironolactone, 21 (60%) with digitalis, and 24 (68.6%) with β-adrenergic blockers. Fifteen patients (42.8%) were receiving intermittent treatment with intravenous inotropes, especially levosimendan and dobutamine. Eleven patients (31.4%) with CHF were in atrial fibrillation. No CHF patients or control subjects had cancer, renal or liver dysfunction. Demographic and clinical characteristics of CHF patients and normal controls are shown in Table 1.

Fasting morning 5 ml blood samples were drawn from all subjects and allowed to clot for 90 min at 4 °C, serum was then separated by centrifugation in a clinical centrifuge and stored at −80 °C in the presence of protease inhibitors, apoprotin 500 U/ml, leupeptin 2.5 μg/ml and EDTA 100 mM. Serum concentration of PTHrP has been measured using a commercial two-site immunoradiometric assay (DSL-8100 Diagnostic Systems Laboratories Inc., Webster, TX, USA). PTHrP is recognized by an NH-terminal reactive antibody raised against PTHrP peptide (1–34). This antibody is immobilized on solid phase polystyrene tubes (capture antibody). The signal antibody is a COOH terminal reactive antibody raised against PTHrP peptide (47–86), labeled with iodine 125. Accordingly, the assay detects a sequence of PTHrP containing the major portion of the first 86 amino acids of the molecule, but will not detect NH-terminal or COOH-terminal fragments alone [6].

All patients underwent complete echocardiographic examinations (Vivid 7, Vingmed, GE, Norway). LV-end-diastolic and end-systolic volumes were determined from apical two- and four-chamber views by using the Simpson biplane formula according to the recommendations of the American Society of Echocardiography [11]. LV ejection fraction (LVEF) was calculated as (enddiastolic-endsystolic volume)/enddiastolic volume. LV systolic and diastolic dimensions and left atrial dimensions were measured from the M-mode echocardiogram, according to the recommendations of the American Society of Echocardiography [10]. The LV-diastolic indices were assessed from the transmittal flow velocity waveform from the apical four-chamber view by positioning a sized 2–4 mm sample volume at the tips of the mitral leaflets during diastole. The Doppler beam was aligned so as to be parallel to the blood flow vector (Table 2).

PTHrP values were normally distributed (Kolmogorov–Smirnov and P–P plot). Comparisons between groups for continuous variables were made using the Student's *t*-test. Correlations between PTHrP levels and clinical variables were evaluated by Spearman's rank correlation test. All the analyses were two-tailed. The SPSS statistical package (SPSS for Windows, statistical package, Release 11.0, standard version) was used for all analyses. A value of $P < 0.05$ was considered significant. Data are expressed as mean ± S.E.M.

3. Results

PTHrP levels were decreased in subjects with severe CHF compared with the normal controls (11.10 ± 1.37 fmol/ml versus 20.62 ± 3.30 fmol/ml, $p = 0.005$; Fig. 1). PTHrP measurements decreased according to NYHA class ($P = 0.04$), with those in NYHA class IV having levels of PTHrP (6.86 fmol/ml)

Table 2 – Echocardiographic findings of CHF patients and controls

	Patients	Controls
LVEF (%)	29.3 ± 6.4	66.07 ± 3.7
LVIDd (cm)	7.1 ± 0.8	5.32 ± 0.37
LVIDs (cm)	6.0 ± 0.8	3.08 ± 0.41
LVEDV (ml)	264.2 ± 66.5	108.4 ± 25.2
LVESV (ml)	184.9 ± 55.5	35.7 ± 18.4
Left atrial diameter (cm)	5.1 ± 0.6	3.36 ± 0.34
E (m/s)	0.8 ± 0.33	0.68 ± 0.14
E/A ratio	1.79 ± 0.24	0.41 ± 0.12
DT (s)	138.4 ± 40.2	192.3 ± 40.8
RV systolic pressure (mmHg)	45.5 ± 12.2	14.7 ± 4.3
LV diastolic function		
Normal	0	26
Impaired relaxation	7	
Pseudonormal	11	
Restrictive	17	

LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter at end diastole; LVIDs, left ventricular internal diameter at end systole; LVEDV, left ventricular volume at end diastole; LVESV, left ventricular volume at end systole; E, early diastolic filling velocity; DT, deceleration time of the early filling velocity.