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RESEARCH ARTICLE

Usefulness of parathyroid hormone as a predictor of heart failure with preserved ejection fraction

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Abstract

Objective: To investigate the relation between parathyroid hormone (PTH) and heart failure with preserved ejection fraction (HF-PEF) in outpatients.

Methods: One hundred consecutive patients who had preserved left ventricular (LV) ejection fraction and heart failure (HF) symptoms, were enrolled. Echocardiography, assessing the diastolic functions was performed. Blood samples were collected for intact PTH and brain natriuretic peptide (BNP).

Results: Significant correlations between PTH level and predictors of advanced HF-PEF were found ($p < 0.05$). PTH level and left atrium diameter were found to be independent predictors of DHF.

Conclusion: Measurement of serum PTH provides complementary information for the diagnosis and prognosis of HF-PEF.

Keywords: Parathyroid hormone, heart failure with preserved ejection fraction

Introduction

Diastolic heart failure, or with its newer name, heart failure with preserved ejection fraction (HF-PEF), is a clinical syndrome, defined by the presence of symptoms and signs of HF, preserved EF, and abnormal left ventricular (LV) diastolic function (Zile & Brutsaert 2002). It is estimated that approximately half of all patients with HF suffer from HF-PEF (Zile et al. 2010). On the other hand, morbidity, hospitalization rates and health-care costs per patient, are quite similar between patients with systolic HF and HF-PEF (Hogg et al. 2004). Despite this fact, there is still lack of robust and widely accepted diagnostic criteria. Signs of congestion, especially in the outpatient setting may be absent, echocardiography is not always available and natriuretic peptides are imperfect. This investigation may identify potential opportunity to identify a novel marker. Ultimately, it is an exploratory trial.

Recent data support a causal role for PTH in the underlying pathology leading to HF-PEF. It has been reported that elevated PTH levels cause accumulation of calcium in vascular smooth muscle cells promoting atherosclerosis and ischemia (Rashid et al. 2007). It was also suggested that accumulation of calcium in myocardium produce myocardial calcification and hence diastolic stiffness (Stefenelli et al. 1997). Other possible mechanisms may be explained by direct effects of PTH on myocardial myocytes and interstitial fibroblasts, inducing myocardial hypertrophy and fibrosis (Liu et al. 2008; Amann et al. 1994). The present study was conducted to examine the association of HF-PEF and elevated intact PTH, and to evaluate the use of PTH as a biomarker in diagnosis and stratification of patients with HF-PEF.

Methods

A total of 180 consecutive patients with de novo HF symptoms (all had dyspnea on exertion and/or ortopnea and/or paroxysmal nocturnal dypnea

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at admission) visited our outpatient clinic between January and April 2011 (Figure 1). Of note, none of the patients had previous diagnosis of HF, hence, we planned to consider patients with initial diagnosis of HF. All patients were referred to transthoracic echocardiography. Eighty patients who were determined to have LVEF <50% were excluded. Remaning patients (n = 100) who had normal LV systolic function (LVEF > 50%) were enrolled in the present study after obtaining informed consent from each participant. Then, detailed echocardiographic examination was performed in order to assess the diastolic functions and to evaluate the LV mass index (LVMI). Other exclusion criteria included presence of previous history of HF, creatinine clearance <60 ml/min/m^2, previous history of moderate to severe valvular heart disease, moderate to severe anemia, hypertrophic or restrictive cardiomyopathy, pericardial diseases, significant pulmonary disease, primary hyperparathyroidism, chronic alcoholism and pancreatitis.

Optimal cut-off point of PTH (at which sensitivity and specificity would be maximal) for the prediction of HF-PEF was defined with ROC curve analysis. Patients were classified according to this cut-off value of PTH. Group I consisted of patients with PTH ≤ 68.4 pg/ml (n = 54) and Group II consisted of patients with PTH >68.4 pg/ml (n = 46). Patients were also classified into groups based upon their NYHA functional class. Consensus of two experienced clinicians, blinded to each other, was required for classification of functional classes. In case of disagreement, a third opinion was obtained from an expert physician.

Anemia was defined as hemoglobin levels <13 g/dl in men and <12 g/dl in women in accordance with World Health Organization criteria (World Health Organization 1968). Hypertension was defined as blood pressure >140/90 mmHg on >2 occasions during office measurements or being on antihypertensive treatment. Diabetes mellitus was defined as fasting blood glucose >126 mg/dl or use of antidiabetic treatment. Hyperlipidemia was defined as serum low-density lipoprotein cholesterol >160 mg/dl or total cholesterol >240 mg/dl or triglyceride >200 mg/dl or high-density lipoprotein cholesterol <40 mg/dl or use of lipid-lowering drugs (Adult Treatment Panel III 2001). Coronary artery disease was recorded as present in the presence of a clinical history of coronary artery disease, abnormal stress test results with evidence of ischemia, or documented coronary stenosis >50%. Those who continued smoking during the index admission were considered current smokers. Body mass index (BMI) was calculated via dividing weight in kilograms by squared height in meters. We used the Sokolow–Lyon index [S in V1 + R in V5 or V6 (whichever is larger) ≥35

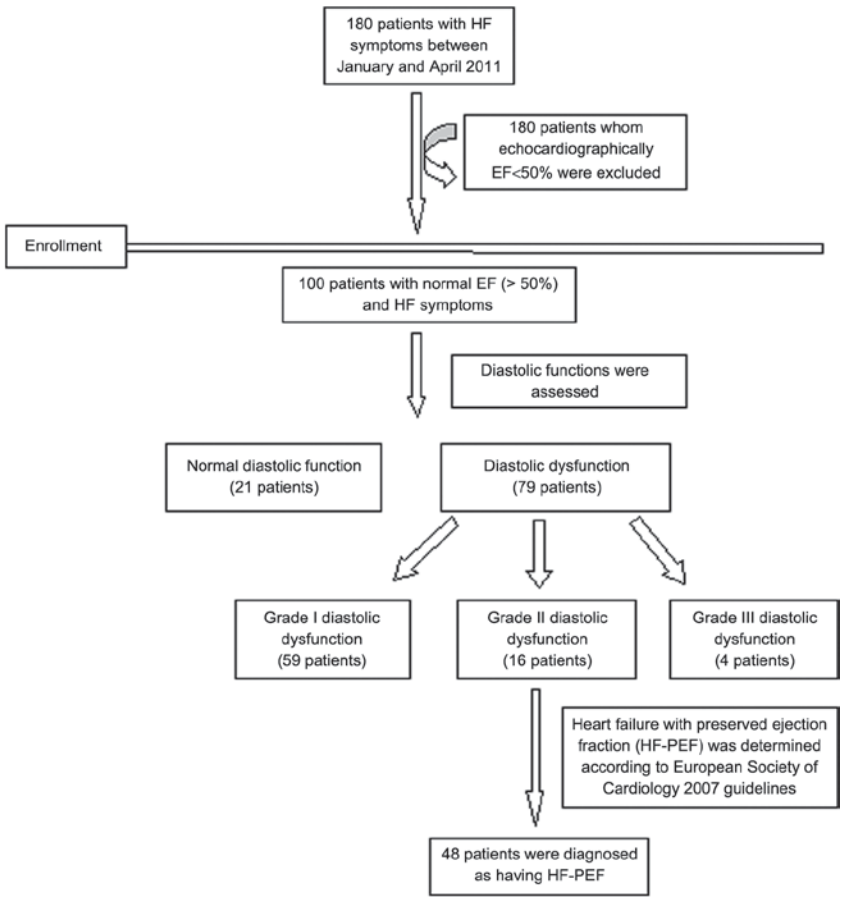

Figure 1. Patient flow-chart.

mm] to establish left ventricular hypertrophy (LVH) by electrocardiography (ECG) (Sokolow & Lyon 2001).

Blood samples were collected for intact PTH and brain natriuretic peptide (BNP) measurements just after echocardiographic examinations. Serum intact PTH levels were obtained at an outpatient clinic using an Immulite intact PTH assay (Diagnostics Product Corporation, 2000, Los Angeles, CA, USA). The established normal range for this assay was 10–65 pg/ml.

Echocardiography was performed via the Vivid 7 system (GE Healthcare, Wauwatosa, Wisconsin) with 2.5- to 5-MHz probes and measurements were made by standard two-dimensional protocols according to guidelines of the American Society of Echocardiography (Lang et al. 2005). Left ventricular mass was calculated by using Devereux's formula, and then, LVMI was calculated by dividing LV mass by body surface area (Devereux et al. 1986). Echocardiographic diagnosis of LVH was made when LVMI was >88 g/m^2 for women and >102 g/m^2 for men (Devereux et al. 1986). Transmitral diastolic flow was obtained by pulsed-wave Doppler from an apical four-chamber view, with the pulsed Doppler sample volume placed perpendicular to the inflow jet previously identified with the use of color Doppler. Mitral early and late diastolic inflow velocities were designated as E and A, respectively. Two-dimensionally guided pulsed-tissue Doppler imaging sample volume was placed at the level of the lateral mitral valve annulus, measuring the mitral annular early diastolic velocity, designated as E'. Patients were classified into 4 groups, namely, normal (21%), grade I diastolic dysfunction (59%), grade II diastolic dysfunction (16%) and grade III diastolic dysfunction (4%). Left ventricle filling pressure was estimated using the ratio of mitral inflow, E, to early diastolic annular velocity, E (Nagueh et al. 1997).

Diagnosis of HF-PEF was made if the patient met the following criteria besides having signs or symptoms of HF and LVEF greater than 50%, proposed by the European Society of Cardiology (ESC) 2007 guidelines: i) If E/E' ratio is greater than 15, no other criteria is needed ii) If E/E' ratio is between 8 and 15, other additional criteria are needed such as BNP greater than 200 pg/ml or LVMI greater than 122 g/m^2 in female or greater than 149 g/m^2 in male (Paulus et al. 2007). Out of the study population, 48 (48%) patients met these criteria and accepted to have HF-PEF (Figure 1).

Continuous variables were expressed as mean ± SD or median (interquartile range) in the presence of abnormal distribution, and categorical variables as percentages. Receiver operator characteristic curve analysis was performed to identify the optimal cut-off point of PTH and BNP (at which sensitivity and specificity would be maximal) for the prediction of HF-PEF. Areas under the curve (AUC) were calculated as measures of the accuracy of the tests. We compared the AUC with use of the Z test. Patients were categorized into two as normal (Group I) or high (Group II) PTH according to this cut off value. Comparisons between groups of patients were made by use of a χ^2-test for categorical variables, independent samples t test for normally distributed continuous variables, and Mann–Whitney *U* test when the distribution was skewed. Correlations were evaluated either via Pearson or Spearman correlation tests. We used univariate cox proportional-hazards analysis to quantify the association of variables with HF-PEF. Variables found to be statistically significant in univariate analysis were used in a multivariable logistic regression model with forward stepwise method in order to determine the independent predictors of HF-PEF. All statistical procedures were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL). A p value of 0.05 was considered as statistically significant.

Results

Considering the whole cohort, mean age of patients was 62 ± 9 years (44% male, 56% female). Mean PTH level was 67 ± 26 pg/ml. HF-PEF and presence of LV diastolic dysfunction (all subtypes) was observed in 48 (48%) and 79 (79%) patients, respectively.

Receiver operator characteristic curve analyses of PTH and BNP were shown in Figure 2. According to the ROC curve analyses: optimal cut-off value of PTH to predict HF-PEF was found as >68.4 pg/ml, with 91.7% sensitivity and 96.2% specificity (AUC = 0.979, 95% confidence interval = 0.928–0.997). A threshold of >168 pg/ml for BNP to predict HF-PEF was shown to have 56.2% sensitivity and 100% specificity (AUC = 0.796, 95% confidence interval = 0.703–0.870), respectively.

Comparisons of two subgroups of patients with HF symptoms along with baseline characteristics, hemodynamic, electrocardiography, echocardiography and laboratory findings are listed in Table 1. BMI, the proportion of patients with echocardiographic and electrocardiographic hypertrophy criteria, left atrium diameter, E/E' ratio, interventricular septal wall thickness, posterior wall thickness, LVMI, BNP levels and diuretic use were significantly higher in those with high PTH levels (Group II). Fourty-eight patients were shown to have HF-PEF. Of these 48 patients, 4 (7%) patients in group I, 44 (93%) patients were in group II ($p < 0.001$). Furthermore, 79 patients were shown to have varying grades of LV diastolic dysfunction. Of these 79 patients, 33 (61%) patients were in group I, 46 (100%) patients were in group II ($p < 0.001$).

Serum intact PTH levels were correlated with NYHA functional class, LV diastolic function, E/E' ratio, BNP levels, left atrium diameter, LVMI, and diuretic use. Serum PTH levels significantly increased as NYHA functional class increased (NYHA I = 49 ± 13.2 pg/ml, NYHA II = 78.6 ± 10.2 pg/ml, NYHA III = 120 ± 28.5 pg/ml, Figure 3). Serum PTH level was the lowest when LV diastolic function was shown to be normal (43.7 ± 13.4 pg/ml), and it increased as severity of LV diastolic dysfunction increased (Grade I = 66.3 ± 19.9 pg/ml, Grade II = 91.6 ± 19.9 pg/ml, Grade III = 117.3 ± 44.8 pg/ml, Figure 3).

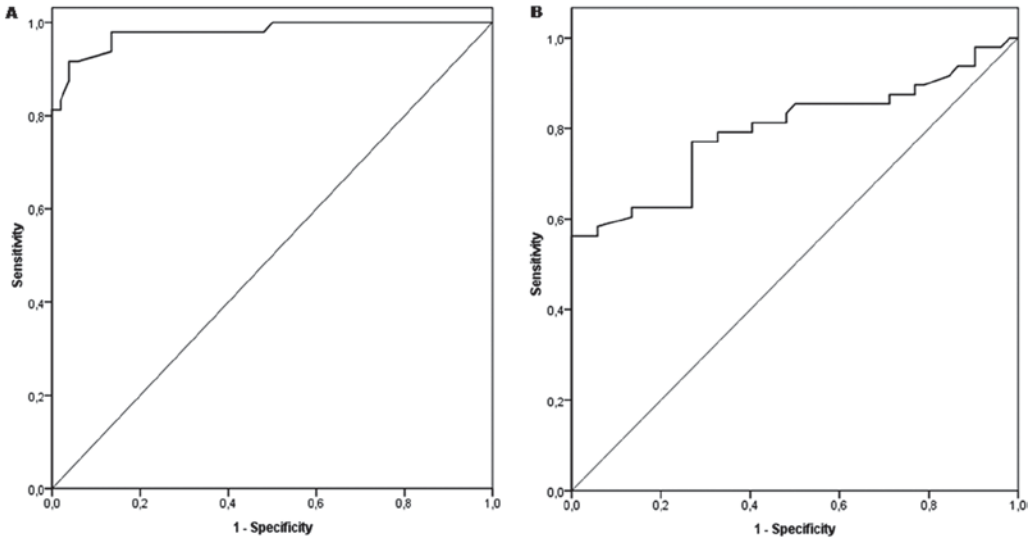

Figure 2. ROC Curve for Parathyroid hormone (AUC = 0.979 , 95% CI = 0.928–0.997) (A), and Brain natriuretic peptide (AUC = 0.796, 95% CI = 0.703–0.870) (B).

Parathyroid hormone, BNP, E/E' ratio, presence of LV hypertrophy, left atrium diameter, LVMI, presence of hypertension, BMI, age, gender, and diuretic use were associated with HF-PEF in univariate analysis. In multivariate logistic regression model, PTH level (Odds ratio = 1.300, $p = 0.001$) and left atrium diameter (Odds ratio = 1.351, $p = 0.033$) were found to be independent predictors of HF-PEF (Table 2).

Discussion

This study, to the best of our knowledge for the first time in the literature, demonstrated that a single measurement of PTH, obtained from patients, admitted to the outpatient clinic with symptoms of HF, designated NYHA functional class and severity of diastolic dysfunction and LV filling pressures. Serum PTH level was correlated with demographic, echocardiographic and laboratory parameters, known to be associated with HF-PEF. After controlling for these parameters, PTH level and left atrial size were found to be independent predictors of HF-PEF.

Parathyroid hormone has been linked to HF, with levels of PTH being predictive for hospitalization (Sugimoto et al. 2009) and mortality (Schierbeck et al. 2011) in patients with HF. Recently, our group has shown the association of serum PTH levels with severity of systolic HF (Altay et al. 2011). As in systolic HF, preclinical and clinical evidence suggest activation of the renin-angiotensin-aldosterone system (RAAS) as a contributing factor for the development of HF-PEF, principally through the trophic effects of angiotensin II on the vasculature and myocardium, but perhaps also through myocardial fibrosis mediated by aldosterone (Yamamoto et al. 2000). From this perspective of view, we hypothesized the potential relation of serum PTH level to the diagnosis and/or severity of HF-PEF and/or diastolic dysfunction. We found a strong positive correlation with serum PTH level and NYHA functional class, concordant with our hypothesis. We also found that PTH levels increased as the grade of LV diastolic dysfunction and LV filling pressure, estimated by E/E' ratio increased. PTH was related to diuretic use as well, though, it was rare. Of note, all patients with hypertension were taking antihypertensive medication with different classes of drugs, and in rare occasions, diuretics were accompanying medications. Diuretics may aid PTH release via the excretion of calcium and magnesium in urine and feces (Alsafwah et al. 2007). On the other hand, utilization of antihypertensive medications might have confounded the verification of diagnosis of HF-PEF via the criteria of guidelines despite higher prevalence of diastolic dysfunction in this cohort.

Left ventricular hypertrophy and increased LVMI, both of which are essential components of HF-PEF are well known cardiovascular prognostic predictors (Levy et al. 1990). According to previous literature, in primary hyperparathyroidism, increased PTH and serum calcium can affect cardiomyocytes, vascular endothelial cells and vascular smooth muscle cells (Andersson et al. 2004). PTH acts on cardiomyocytes by binding to the PTH related Peptide receptor, thereby inducing a rise in the intracellular levels of calcium (Smogorzewski et al. 1993). Increased calcium levels activate protein kinase C and mediate hypertrophic as well as metabolic effects on the cardiomyocyte. Activation of the protein kinase C cascade subsequently activates hypertrophic processes inside the cell (Schluter et al. 1995). Furthermore, secondary hyperparathyroidism, in patients with kidney disease, has been linked to cardiovascular disease, hypertension, left ventricular hypertrophy, and valvular calcification (Horl 2004). *In vitro*, PTH has been shown to have a direct hypertrophic effect on cardiomyocytes (Schluter et al. 1995). These findings both in primary and secondary hyperparathyroidism suggest that the pathophysiological concept, derived from PTH excess,

Table 1. Baseline characteristics of study patients.

	All patients (n:100)	Parathyroid hormone ≤68.4 pg/ml (n:54)	Parathyroid hormone >68.4 pg/ml (n:46)	*p*
Baseline characteristics				
Mean age (years)	62 ± 9	60 ± 11	64 ± 7	0.070
Women	56 (56%)	29 (54%)	27 (59%)	0.616
Body mass index (kg/m^2)	31 ± 5	30 ± 5	32 ± 6	0.044
Hypertension	75 (75%)	36 (67%)	39 (85%)	0.064
Diabetes mellitus	28 (28%)	14 (26%)	14 (30%)	0.782
Coronary artery disease	33 (33%)	14 (26%)	19 (41%)	0.157
Smoking	24 (24%)	13 (24%)	11 (24%)	0.985
Hyperlipidemia	44 (44%)	24 (44%)	20 (43%)	0.923
Hemodynamic findings				
NYHA Functional Class				
I	51 (51%)	49 (91%)	2 (4%)	<0.001
II	39 (39%)	5 (9%)	34 (74%)	<0.001
III	10 (10%)	0 (0%)	10 (22%)	<0.001
Echocardiography parameters				
Presence of HF-PEF	48 (48%)	4 (7%)	44 (96%)	<0.001
Presence of LV diastolic dysfunction	79 (79%)	33 (61%)	46 (100%)	<0.001
LV Diastolic dysfunction (Grade)				
I	59 (59%)	32 (59%)	27 (58%)	0.954
II	16 (16%)	1 (2%)	15 (33%)	<0.001
III	4 (4%)	0 (0%)	4 (9%)	0.042
II-III	20 (20%)	1 (2%)	19 (41%)	<0.001
LV diastolic diameter, (mm)	4.6 ± 0.4	4.6 ± 0.3	4.6 ± 0.5	0.420
Left atrium size (mm)	39.7 ± 5.3	37 ± 4.6	43 ± 4.0	<0.001
E/E' Ratio	9.5 ± 4.6 (5.9–12)	7.0 ± 2.6 (5.3–8.6)	12.4 ± 4.7 (8.6–16)	<0.001
Interventricular septal wall thickness (mm)	1.3 ± 0.3	1.2 ± 0.2	1.5 ± 0.2	<0.001
Posterior wall thickness (mm)	1.2 ± 0.2	1.1 ± 0.1	1.4 ± 0.1	<0.001
Presence of LV hypertrophy	67 (67%)	25 (46%)	42 (91%)	<0.001
LV mass index	143 ± 41	125 ± 38	164 ± 34	<0.001
Electrocardiography parameters				
Atrial fibrillation	11 (11%)	6 (11%)	5 (11%)	1.000
Presence of LV hypertrophy criterion	69 (69%)	18 (41%)	51 (91%)	<0.001
Laboratory findings				
Parathyroid hormone (pg/ml)	67 ± 26	49 ± 13	89 ± 22	<0.001
Brain natriuretic peptide (pg/ml)	142 ± 150 (38–212)	70 ± 45 (834–111)	227 ± 183 (89–303)	<0.001
Creatinine clearance (ml/min/m^2)	107 ± 30	107 ± 29	106 ± 32	0.908
Hemoglobin (g/dl)	13 ± 1.2	13.4 ± 1.2	13.1 ± 1.1	0.225
Presence of mild anemia	15 (15%)	8 (15%)	7 (15%)	0.955
Medication				
Beta-blockers	25 (25%)	12 (22%)	13 (28%)	0.643
ACE inhibitors/ARB	32 (32%)	15 (28%)	17 (37%)	0.444
Calcium chanel blockers	10 (10%)	6 (11%)	4 (9%)	0.750
Diuretics	10 (10%)	1 (2%)	9 (19.6%)	0.005

LV, left ventricle, ACE, angiotensin–converting enzyme, ARB, angiotensin receptor blocker, HF-PEF, heart failure with preserved ejection fraction.

can potentially be applied to the relationship between hyperparathyroidism and HF-PEF. In our study, serum PTH level was related to both electrocardiographic and echocardiographic LVH criteria and LVMI in patients with normal kidney function and no known primary hyperparathyroidism. As this study considered patients without a well-established history of HF, solely the symptoms of breathlessness without physical signs suggestive of HF and Doppler echocardiographic index of abnormal LV relaxation and filling would not be enough for the diagnosis of HF-PEF. That is why the evidence of LVH had important contribution to the accurate diagnosis of HF-PEF in our study when Doppler echocardiography yielded non-conclusive results.

Older age, another essential component of HF-PEF, is associated with lower circulating concentrations of

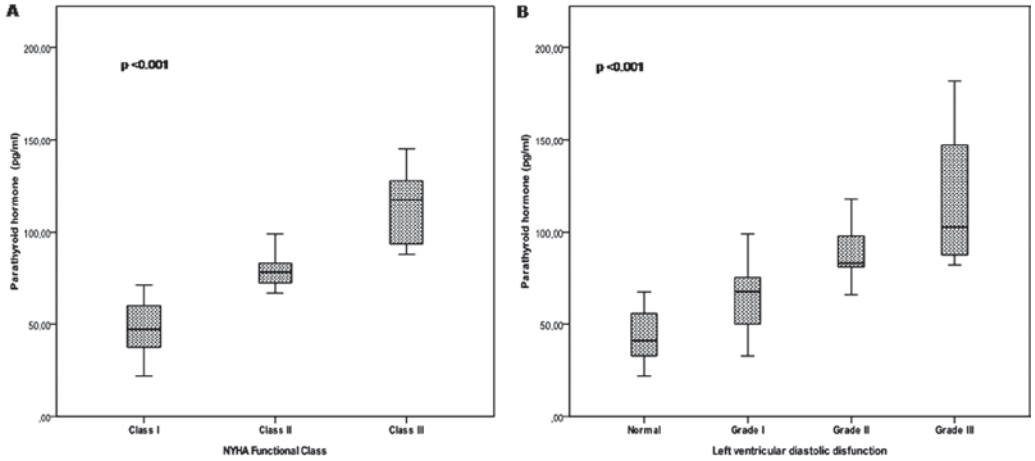

Figure 3. Parathyroid hormone levels according to NYHA Functional Classes (A) and left venticular diastolic dysfunction (B).

Table 2. Univariate and multivariate analysis for predicting heart failure with preserved ejection fraction.

	Univariate			Multivariate		
Variable	*p*	OR	(95% CI)	*p*	OR	(95% CI)
Laboratory findings						
Parathyroid hormone (pg/ml)	<0.001	1.341	1.152–1.561	0.001	1.300	1.110–1.522
Brain natriuretic peptide (pg/ml)	<0.001	1.016	1.009–1.023			
Echocardiography parameters						
E/E′	<0.001	1.510	1.270–1.796			
Presence of LV hypertrophy	<0.001	20.455	5.621–74.434			
Left atrium diameter (mm)	<0.001	1.537	1.303–1.814	0.033	1.351	1.025–1.780
LV mass index	<0.001	1.040	1.023–1.057			
Electrocardiography parameters						
Presence of LV hypertrophy criterion	<0.001	29.000	6.357–132.303			
Baseline characteristics						
Body mass index (kg/m^2)	0.018	1.101	1.017–1.192			
Hypertension	0.069	2.429	0.935–6.311			
Age (years)	0.028	1.051	1.005–1.099			
Gender	0.098	1.969	0.882–4.399			
Diuretic usage	0.022	11.769	1.430–96.846			

All the variables from Table 1 were examined and only those significant at $p < 0.1$ level are shown in univarite analysis.
Multivariable logistic regression model including all the variables in univariate analysis with forward stepwise method.
CI, confidence interval; OR, odds ratio, LV, left ventricle, ACE, angiotensin–converting enzyme, ARB, angiotensin receptor blocker, HF-PEF, heart failure with preserved ejection fraction.

25-hydroxyvitamin D, impaired vitamin D activation within the kidney, and a rise in serum PTH concentrations (Brunette et al. 1978). We found a positive, but weak, correlation between PTH and age. Plus, BMI was slightly higher in those with high PTH levels. The association of PTH and obesity which is a frequent accompany in patients with HF-PEF, was shown before (Kamycheva et al. 2004).

The BNP also increases in diastolic HF, but to a lesser extent than systolic HF due to less distinct wall tension in HF-PEF (Maisel et al. 2003). In the present study, the cut-off value for BNP to predict HF-PEF was found to be as 168 pg/ml with 56.2% sensitivity and 100% specificity. This value was lower than the standart threshold value of 200 pg/ml proposed currently in European recommendations (Paulus et al. 2007) but higher than the other studies published previously which reported unexpectedly lower BNP concentrations (<100 pg/ml) (Mottram et al. 2003). The low sensitivity and high specifity of BNP for the diagnosis of HF-PEF in the present study were more or less consistent with the literature which caused the European guideline to state that BNP should therefore be recommended for exclusion of HF-PEF, not for diagnosis (Paulus et al. 2007). As the cut-off point for BNP becomes lower, the sensitivity of BNP for diagnosing HF-PEF increases. Reciever operating characteristic analysis showed that BNP level was significant predictor of HF-PEF with AUC value >0.75 which has been comparable to other studies (Grewal et al. 2008). In our study, we found a larger ROC curve area for PTH than BNP for predicting HF-PEF. However, we still think that it might not be true to conclude with a single study that as a biomarker, PTH is superior to BNP for diagnosis and stratification HF-PEF, though, this finding can add an

explanation for lesser utility of BNP in the management of diastolic HF. On the other hand, PTH threshold of 68.4 pg/ml seems promising as a rule in test.

Our study has limitations. Because of the relatively small number of enrolled patients, cut-off points can not be extrapolated, and more studies are needed to identify the best threshold for diagnosis of HF-PEF. Objective evidence of reduced exercise capacity was not provided for the patients with exertional dyspnea. Modified Framingham criteria for diagnosis of HF was not used as well. Because of that, its difficult to exclude completely other etiologies of dyspnea on exertion in this patient group who were especially obese and elderly. Considerable amount of patients were already on angiotensin converting enzyme inhibitor/angiotensin receptor blocker treatment which can have confounding influence on the results. Of note, almost all patients with the diagnosis of HF-PEF were prescribed diuretics after the index outpatient visit, and hence, diagnostic performance of PTH in the presence of chronic diuretic therapy might be another challenge.

Conclusion

Despite significant advances in our understanding of systolic HF, at present the epidemiology, pathohysiology and therapy of HF-PEF is poorly understood, in large part because of the robust and widely accepted diagnostic criteria. However, the prevelance of HF-PEF is increasing with similar morbidity and mortality rates as systolic HF. Therefore, the ability to better identify patients with HF-PEF at an early stage during initial outpatient visit could be critically important. This study extends the previous reports of an association of PTH with systolic HF to diastolic HF designating that PTH is strongly associated with HF-PEF. It also seems to be a promising novel biomarker for predicting prognosis in this patient group. This is an explarotory study at best. Whether PTH levels might be used in clinical practice as a test for diagnosis and prognosis of HF-PEF is a question that merits further studies.

Declaration of interest

The authors declared no conflict of interest.

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