Serum intact parathyroid hormone levels predict hospitalisation for heart failure

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ABSTRACT

Objective: To assess whether circulating levels of intact parathyroid hormone (intact PTH) in outpatients predict hospitalisation for heart failure (HF).

Methods: Eighty-eight consecutive outpatients with HF were enrolled in the study. The independent association between intact PTH and hospitalisation for HF was assessed using Cox regression analysis.

Results: Mean (SD) serum intact PTH levels significantly increased as New York Heart Association classes increased (I: 40 (21), II: 55 (24), III: 76 (46), IV: 131 (45) pg/ml). The receiver operating characteristic (ROC) curves showed intact PTH levels ⩾47 pg/ml to be the optimal cut-off points for hospitalisation for HF, with sensitivity 87%, specificity 71% and area under the ROC curve 0.82 (95% CI 0.72 to 0.91). After adjustment for variables accepted to be predictors for hospitalisation due to HF (age, gender, hypertension, diabetes mellitus, atrial fibrillation, ischaemic heart disease, left ventricular ejection fraction, B-type natriuretic peptide, estimated glomerular filtration rate and cardiac drugs), intact PTH levels ⩾47 pg/ml were associated with a hazard ratio of 7.13 for hospitalisation for HF (95% CI 1.79 to 28.4).

Conclusion: Serum intact PTH levels obtained in outpatients with HF were shown to be an independent predictor of hospitalisation for HF.

Advances in medical treatment have improved the symptoms, quality of life and survival of patients with heart failure (HF), but the number of annual hospitalisations for HF and mortality rates among patients admitted to hospital with HF remain high.[1–3] B-type natriuretic peptide (BNP) has been used as a biomarker to define diagnosis and prognosis.[4–6] BNP levels predict long-term mortality in patients with non-cardiac and cardiac causes of acute dyspnoea.[7]

Parathyroid hormone (PTH) is secreted by the parathyroid glands as a polypeptide containing 84 amino acids. PTH and PTH-related proteins directly affect cardiac function, increasing heart rate and coronary blood flow and altering the automaticity of the heart.[8–10] Recent experimental and clinical studies have suggested that hyperparathyroidism is associated with HF in patients with primary and secondary aldosteronism.[11–15] It has also been reported that secondary hyperparathyroidism may contribute to the systemic illness that accompanies HF.[13 14] Raised serum intact PTH levels are thought to be related to the systemic induction of oxidative stress[11–13] that leads to tissue injury and contributes to the pathophysiology of HF.[16 17] However, the association of serum intact PTH levels with severity and prognosis of HF remains unknown. This prospective study was conducted to determine whether circulating levels of intact PTH in outpatients predict hospitalisation for HF.

PATIENTS AND METHODS

Study group

In this prospective cohort study, we evaluated 88 consecutive, stable outpatients from 231 patients who attended Matsusaka Chuo General Hospital between 1 June 2006 and 1 September 2007, for the evaluation and/or treatment of HF (defined as the symptoms and signs secondary to abnormal cardiac function and established by trained cardiologists). Written informed consent was obtained and the protocol was approved for use by the Human Studies Subcommittee of Matsusaka Chuo General Hospital. Patients who presented to the emergency room and were admitted to hospital on the same day, who planned an elective admission to examine the aetiology of HF and/or to treat HF, who had coronary artery stenosis as a candidate for coronary intervention, who had collagen diseases, cancer, sepsis, severe hepatic disease or end-stage renal disease undergoing dialysis treatment and who did not agree with our protocol were excluded. Demographic measures, medical history and vital signs were determined, and 12-lead ECG, laboratory tests and two-dimensional echocardiography were carried out routinely. Dilated cardiomyopathy was defined by coronary angiography and cardiac biopsy. Diastolic HF was defined as (*a*) the clinical syndrome of HF; (*b*) a preserved left ventricular ejection fraction (⩾0.50); (*c*) left ventricular diastolic dysfunction by two-dimensional echocardiography and (*d*) the absence of major valve disease.

Measurement of serum intact parathyroid hormone

After enrolment, blood samples were collected for intact PTH measurement. Serum intact PTH levels were obtained in the clinic for outpatients using an electrochemiluminescence immunoassay kit (Modular Analytics E 170, Roche, Mannheim, Germany). Assays were performed by a laboratory technician blinded to the patient's clinical data. The established normal range for this assay was 10–65 pg/ml. The interassay coefficient of variation was 3.8% at 36 pg/ml, 3.8% at 90 pg/ml and 2.7% at 189 pg/ml. The intra-assay coefficient of variation was 2.4% at 39 pg/ml, 2.3% at 92 pg/ml and 4.3% at 190 pg/ml. Plasma was immediately separated from the blood element by centrifugation at 4°C for the measurement of BNP using a

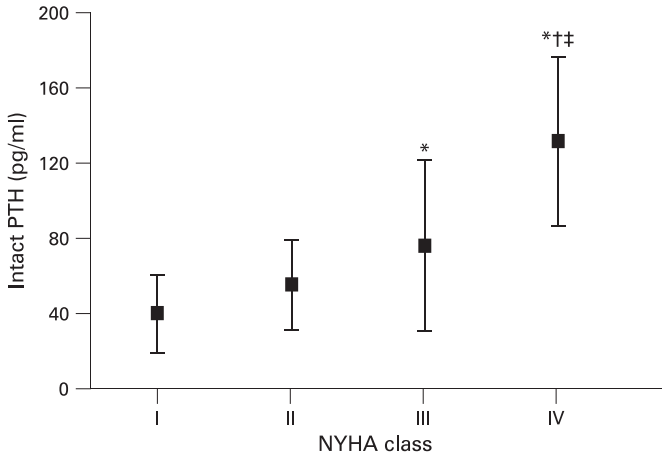

Figure 1 Outpatient data comparing the New York Heart Association (NYHA) class and intact parathyroid hormone (intact PTH) levels taken in clinics or emergency rooms. *p<0.05 vs NYHA I; †p<0.05 vs NYHA II; ‡p<0.05 vs NYHA III.

specific immunoradiometric assay for human BNP (Shionoria, Shionogi and Co, Osaka, Japan). The minimum detectable quantity of human BNP is 2 pg/ml. The established normal range for this assay was 19 pg/ml. The intra-assay and interassay coefficients of variation were 5.2% and 6.1%, respectively.

End point

The study end points were hospitalisation or death due to the exacerbation of HF. End point data were collected during follow-up visits.

Statistical analysis

Continuous variables were presented as mean (SD) and compared using the Student *t* test or the Mann–Whitney U test. Categorical variables were presented as percentage frequencies and differences between proportions were compared using χ^2 test. Group differences were compared using analysis of variance; post hoc multiple group comparisons were assessed with the Scheffé method. To compare the predictive value of intact PTH with that of BNP for hospitalisation for HF, a receiver operating characteristic (ROC) curve analysis was performed and the area under the curve was calculated. The optimal cut-off value of intact PTH for hospitalisation for HF was determined and was defined as the intact PTH value providing the maximal sum of sensitivity and specificity. Age, gender, hypertension, diabetes mellitus, atrial fibrillation, ischaemic heart disease, left ventricular ejection fraction, BNP values (dichotomised according to the optimal cut-off value for hospitalisation for HF), estimated glomerular filtration rate (eGFR), cardiac drugs (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, β blockers) and intact PTH values (dichotomised according to the optimal cut-off value for hospitalisation for HF) were then entered in a multivariable Cox hazard regression model to identify independent predictors of hospitalisation for HF. Hazard ratios are given with 95% confidence intervals (CI). For all tests, a p value of <0.05 (two sided) was considered significant. Data were analysed using standard statistical software (SPSS, version 11.5).

Table 1 Baseline characteristics

Characteristics	Intact PTH (pg/ml) <47 pg/ml (n = 41)	Intact PTH (pg/ml) ⩾47 pg/ml (n = 47)	p Value
Demographic and medical history			
Age (years)	69 (15)	72 (14)	0.31
Male sex, n (%)	21 (51)	14 (30)	0.042
Hypertension, n (%)	28 (68)	41 (87)	0.032
Diabetes mellitus, n (%)	13 (32)	11 (23)	0.39
Atrial fibrillation, n (%)	7 (17)	13 (28)	0.17
NYHA class III/IV, n (%)	5 (12)	25 (53)	<0.001
Heart rate (bpm)	76 (18)	88 (26)	0.010
Systolic blood pressure (mm Hg)	133 (25)	147 (30)	0.022
Diastolic blood pressure (mm Hg)	73 (15)	83 (18)	0.01
Aetiology of heart failure			
Ischaemic heart disease, n (%)	14 (34)	17 (36)	0.84
Diastolic heart failure, n (%)	22 (54)	19 (40)	0.22
Dilated cardiomyopathy, n (%)	1 (2)	4 (9)	0.22
Valvular heart disease, n (%)	4 (10)	7 (15)	0.47
Drugs			
ACE inhibitors/ARB, n (%)	27 (66)	29 (62)	0.69
β Blockers, n (%)	7 (17)	10 (21)	0.62
Calcium channel blockers, n (%)	12 (29)	20 (43)	0.21
Diuretics, n (%)	7 (17)	15 (32)	0.11
Laboratory measurements			
B-type natriuretic peptide (pg/ml)	226 (438)	638 (914)	0.012
Estimated GFR (ml/min/1.73 m^2)	74 (27)	59 (24)	0.009
Corrected calcium (mmol/l)	2.33 (0.13)	2.33 (0.13)	0.79
Inorganic phosphate (mmol/l)	1.13 (0.19)	1.13 (0.26)	0.83
Magnesium (mmol/l)	0.91 (0.16)	0.82 (0.08)	0.18
Haemoglobin (g/l)	129 (23)	120 (26)	0.12
Haemoglobin A1c	0.061 (0.014)	0.059 (0.009)	0.49
Echocardiography			
LA diameter (mm)	42 (9)	44 (10)	0.51
LV end-diastolic diameter (mm)	53 (9)	54 (8)	0.49
LV end-systolic diameter (mm)	35 (10)	39 (11)	0.085
LV fractional shortening (%)	35 (10)	30 (10)	0.019
LV ejection fraction (%)	63 (13)	54 (16)	0.012

Values are given as mean (SD) unless stated otherwise.
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; GFR, glomerular filtration rate; LV, left ventricular; NYHA, New York Heart Association; PTH, parathyroid hormone.

RESULTS

Baseline characteristics

The study group comprised 88 patients (40% male) with a mean age of 70.6 (14.5) years. The median (range) length of follow-up was 138 (1–473) days. The intact PTH levels ranged from 11 to 230 pg/ml, with a mean of 62.2 (40.6) pg/ml, a median of 49.0 pg/ml and 25th and 75th centile values of 35.5 and 75.5, respectively. Mean (SD) serum intact PTH levels significantly increased as New York Heart Association (NYHA) classes increased (I: 40 (21), II: 55 (24), III: 76 (46), IV: 131 (45) pg/ml) (fig 1). Table 1 presents the clinical characteristics of the patients, divided according to an intact PTH level of 47 pg/ml (optimal cut-off value to predict hospitalisation for HF).

The proportion of female patients with hypertension and an NYHA class of III/IV was higher in patients with intact PTH levels ⩾47 pg/ml than patients with intact PTH levels <47 pg/ml. Heart rate, systolic blood pressure, diastolic blood pressure and BNP levels were significantly higher, while eGFR

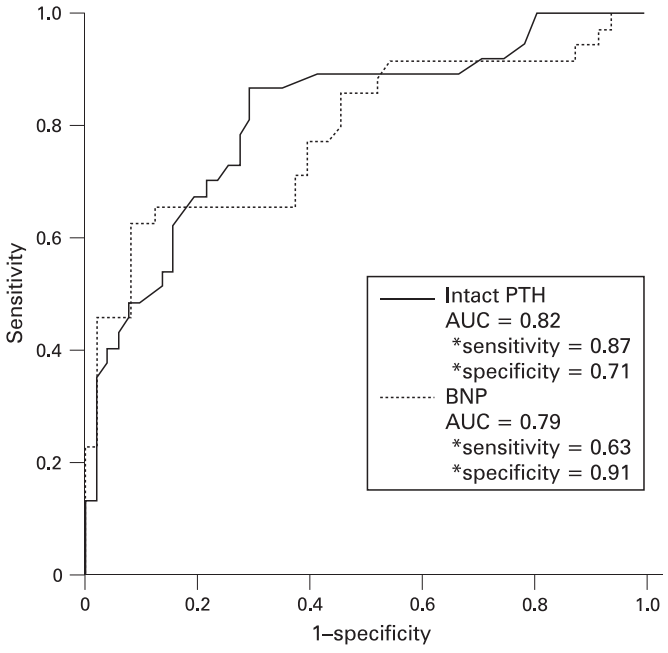

Figure 2 Receiver operating characteristic curves of serum intact parathyroid hormone (intact PTH) and B-type natriuretic peptide (BNP) against hospitalisation for heart failure. *These values obtained using the optimal cut-off value. AUC, area under the curve.

levels, left ventricular fractional shortening and left ventricular ejection fractions were lower in patients with intact PTH levels ⩾47 pg/ml.

Outcome and ROC curve analysis

During follow-up, 35 (39.8%) patients were admitted to hospital for HF and five (5.7%) deaths occurred after hospitalisation for HF, including two non-cardiac deaths. The ROC curves demonstrated intact PTH levels ⩾47 pg/ml to be the optimal cut-off point for hospitalisation for HF with 87% sensitivity, 71% specificity and the area under the ROC curve = 0.82 (95% CI 0.72 to 0.91). The area under the ROC curve was greater for intact PTH than for BNP (area under the curve = 0.79 (95% CI 0.68 to 0.89)) (fig 2).

Prognostic value of intact PTH

Kaplan–Meier survival curves demonstrate that patients with intact PTH levels of ⩾47 pg/ml had lower survival than patients with intact PTH levels of <47 pg/ml (fig 3). Independent predictors of hospitalisation for HF were identified by Cox hazard regression analysis, which demonstrated that intact PTH was the strongest predictor for hospitalisation for HF (fig 4). The adjusted hazard ratio for hospitalisation due to HF in patients with baseline intact PTH levels of ⩾47 pg/ml was 7.13 (95% CI 1.79 to 28.4).

DISCUSSION

This study demonstrated that a single measurement of intact PTH, obtained in patients with HF, significantly increased as NYHA classes increased and was an accurate predictor of hospitalisation for HF. This association persists even after adjustments for variables conventionally accepted to be risk factors for HF.[2 18]

Low or falling serum calcium levels act within seconds to stimulate PTH secretion. A slower regulation of PTH occurs

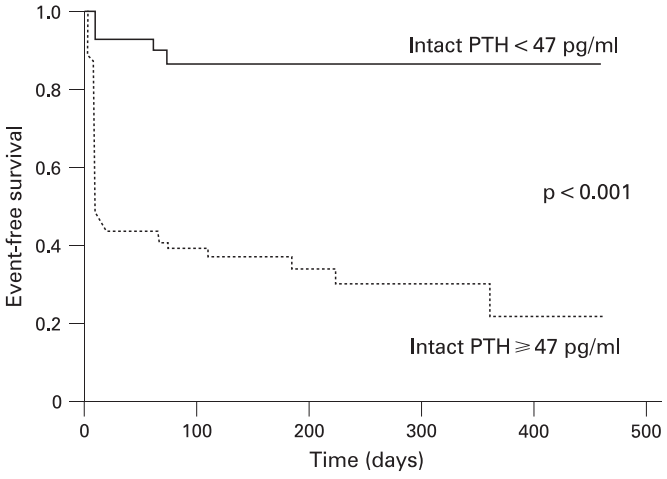

Figure 3 Kaplan–Meier curve showing hospitalisation for heart failure free survival, according to intact parathyroid hormone (intact PTH) levels.

within hours as a result of cellular changes in PTH messenger RNA. Hypocalcaemia from any cause stimulates PTH secretion and chronic hypocalcaemia also stimulates the growth of the parathyroid glands.[19]

Primary hyperparathyroidism has been reported to be associated with hypertension, disturbances in the renin–angiotensin–aldosterone system and structural and functional alterations in the vascular wall, leading to an increase in cardiovascular death.[15] It has recently been recognised that urinary and fecal excretion of Ca^{2+} and Mg^{2+} that accompany aldosteronism leads to secondary hyperparathyroidism, and the attendant Ca^{2+} paradox of hyperparathyroidism leads to adverse cardiovascular event.[13 20 21] The underlying mechanism for this association cannot be determined from this study. However, our data are consistent with previous data showing that serum levels of PTH increase in NYHA class IV patients with

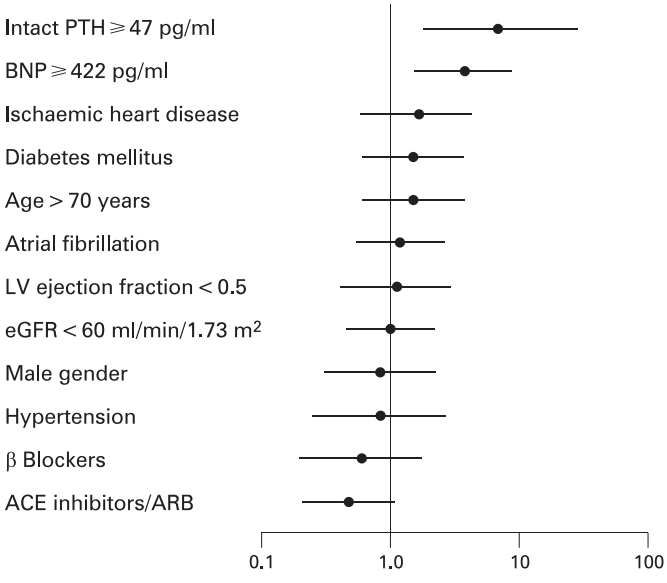

Figure 4 Multivariate Cox regression model showing independent predictors of hospitalisation for heart failure. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LV, left ventricular; PTH, parathyroid hormone.

ischaemic heart disease,[22] and suggest that serum levels of PTH are associated with the severity of HF. Several mechanisms suggest that secondary hyperparathyroidism is a covariant of HF. Aberrations in minerals and micronutrient homoeostasis that includes Ca^{2+}, Mg^{2+}, vitamin D, zinc and selenium may cause secondary hyperparathyroidism HF.[13 23–25] The long-term use of a loop diuretic with its attendant urinary wasting of Ca^{2+} and Mg^{2+} may predispose patients with HF to secondary hyperparathyroidism.[13 26]

BNP has been used as a biomarker to define diagnosis and prognosis in patients with stable ambulatory HF, decompensated HF[4–6] and acute dyspnoea presenting to the emergency department.[7] Our data are consistent in showing that serum BNP levels independently associated with increased hospitalisation for HF.

In this study, the area under the ROC curve for hospitalisation for HF was greater for intact PTH than for BNP. This result suggests that intact PTH is also a useful biomarker to define the prognosis of HF. The prognostic significance of PTH in HF is unknown, but a previous report has shown that serum PTH levels are related to the severity and mortality of illness in patients in the emergency department, especially with acute myocardial infarction or congestive HF.[27]

Intact PTH levels are modified by several factors. Many studies have reported that PTH levels are higher in the elderly than in young adults. Contributing to the higher PTH levels in elderly people are several factors that are intrinsic to ageing, such as decreased renal function, less efficient intestinal absorption of calcium, resistance to the calcaemic action of PTH, a greater prevalence of vitamin D insufficiency, lactose intolerance and the acidotic tendency of old age. Phosphorus loading, a deficiency of calcitriol and renal failure increase PTH levels in an effort to maintain the same serum calcium concentration.[6]

In this study, eGFR was significantly lower in patients with intact PTH levels $\geq$47 pg/ml than <47 pg/ml. However, mild renal insufficiency was not a significant risk factor of hospitalisation for HF. Although the mechanism responsible for the association between mild renal insufficiency and cardiovascular mortality remains unknown,[28] our results suggest that by raising intact PTH concentration, mild renal insufficiency may be associated with cardiovascular events.

Study limitations

Certain limitations need to be considered in the interpretation of these findings. Because this was a single-centre study with a relatively small number of enrolled patients, who exhibited severe HF (NYHA III/IV), and because serum levels of intact PTH were determined only once at baseline, our cut-off points cannot be extrapolated and more studies are needed to identify the best cut-off points and percentage variation. However, our results are in accordance with previous observations.[14 27] A relationship between intact PTH and hospitalisation for HF may be applicable to the HF population in general. Our preliminary results need to be supported by further studies assessing the predictive value of intact PTH in cardiovascular outcomes.

We excluded patients who presented to the emergency room and were admitted to hospital on the same day and who had narrow coronary arteries and were candidates for coronary intervention. Therefore, the aetiology of HF might not match that of the general population.

CONCLUSION

Serum intact PTH levels obtained in outpatients with a diagnosis of HF significantly increased as NYHA classes increased and were independently associated with increased hospitalisation for HF.

Competing interests: None.

Ethics approval: Ethics committee approval obtained.

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Heart

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