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The Relationship Between Atrial Fibrillation and Parathyroid Hormone in Heart Failure Outpatients

Background	Atrial fibrillation (AF) is a common arrhythmia in heart failure (HF). Plasma concentrations of parathyroid hormone (PTH) have been shown to increase in HF. The relationship between PTH concentrations and the presence of AF in HF is, however, unknown. This study analyzed the relationship between plasma PHT concentrations and AF in patients with systolic HF.
Material and methods	131 consecutive, stable HF patients, who were admitted to the HF outpatient clinic, were included in this prospective, observational study. Patients were classified as those with AF (n = 36) and those in sinus rhythm (SR, n = 95).
Results	PTH concentrations were markedly higher in patients with AF compared to the patients in SR [85 (15-320) vs. 112 (30-326) U/ml, p=0.007]. PTH, creatinine clearance, hemoglobin, creatinine, age, and left ventricular ejection fraction were found to be related to AF by univariate analysis; though, multivariate logistic regression analysis showed that only PTH concentration was independently related to AF.
Conclusion	PTH concentrations can be used to indicate AF in patients with systolic HF.
Keywords	Heart failure; atrial fibrillation; parathyroid hormone
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1. Introduction

The most common cardiac arrhythmia in heart failure (HF) patients is atrial fibrillation (AF), and AF is an independent risk factor for mortality and morbidity. AF is highly prevalent in HF, and its prevalence is reported to be over 30% [1–4]. Atrial stress, inflammation, increase in neurohumoral activity, and electrophysiological and structural remodeling are believed to cause AF in HF patients [5–7]. The pathogenesis of AF is, however, not fully understood.

Parathyroid hormone (PTH) is vital for calcium hemostasis. Previous studies have shown that PTH also affects, directly and indirectly, the cardiovascular system via G proteins on endothelial and myocardial cells [8]. Disorder of PTH causes an increase in the incidence of hypertension, left ventricular hypertrophy, heart failure, and arrhythmia [8].

PTH concentrations increase in patients with HF along with increased mortality [9]. Recent studies showed that plasma PTH is associated with AF [10–13]. This study examined whether PTH concentrations could independently identify AF in patients with HF.

2. Material and methods

2.1. Patients

This prospective, observational study included 131 consecutive, stable, adult (>18 yrs of age) patients who had no exclusion criteria (see below). These subjects were admitted to the HF outpatient clinic with a left ventricular ejection fraction (EF) of less than 40%, i.e., HF with reduced ejection fraction (HFrEF). Exclusion criteria were: liver or renal dysfunction, hospitalization for acute, decompensated HF or with recent decompensation (within 6 mos), a history of acute coronary syndrome within the previous month, uncontrolled hypertension, severe chronic obstructive pulmonary disease (COPD), hyper/hypothyroidism, advanced coronary artery disease who were not revascularized or could not be revascularized, recent diagnosis of oncological disease, recent chemotherapy, less than a year life expectancy, pacemaker rhythm, AF secondary to severe valvular disease, HF due to severe valvular disease, or with known serious osteoporosis.

At admission, plasma PTH concentrations were measured, and ECGs were obtained. The patients were classified into two groups based on the presence or absence of AF on the

admission ECG. Echocardiographic variables, cardiovascular risk factors, laboratory data, medication use, comorbid conditions, and cardiovascular risk factors were compared between the two groups. Hypertension (HT) was defined as a blood pressure greater than 140/90 mmHg during two visit measurements or undergoing antihypertensive treatment. Diabetes mellitus (DM) was defined as a fasting glucose of 126 mg/dl or patients receiving antidiabetic treatment. Coronary artery disease (CAD) was defined as having a history of CAD, abnormal test results indicating coronary ischemia, or coronary stenosis of more than 50%. Anemia was defined as hemoglobin concentrations of less than 13 g/dl in males and less than 12 g/dl in females [14].

Power analysis was applied to determine the number of cases required in each group. This analysis showed that a minimum 30 patients in each group was required for an error of 0.05 and a power of 0.80.

The study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee (25.03.2011–74). Informed consent was obtained from all participants.

2.2. Standard Echocardiography

Transthoracic echocardiographic examinations with a Vivid 7® cardiac ultrasonography system (GE VingMed Ultrasound AS; Horten, Norway) using 2.5- to 5-MHz probes was performed by a cardiologist who was blinded to the study plan. The images were obtained in the left lateral decubitus position from standard acoustic views (parasternal, apical, and subcostal) and evaluated according to the recommendations of the European Society of Echocardiography guidelines [15].

2.3. Parathyroid hormone assay

A 7 ml blood sample was obtained at admission from a peripheral vein into tubes containing EDTA. The samples were centrifuged at 2,500 rpm, and the plasma was extracted, aliquoted, and stored at −80° C prior to analysis. Plasma PTH concentrations were determined with an enzyme immuno-assay (Diagnostics Product Corporation, 2000, Los Angeles, CA, USA) according to the manufacturer's instructions. The normal range established for this assay was 10 to 65 pg/ml.

2.4. Statistical analysis

Parametric data are expressed as mean±standard deviation (SD) or as median (minimum-maximum), and categorical data are expressed as numbers (percentages). Independent parameters were compared with independent sample t tests, and data with non-normal distributions were compared with Mann–Whitney U tests. Correlations were assessed by the Pearson test for normally distributed

Table 1. Baseline characteristics of patients

Variable	Patients with SR (n=95)	Patients with AF (n=36)	p
Mean age (yrs)	66±10	70±7	0.016
Women	26 (27)	14(39)	0.287
Body mass index (kg/m²)	26.5±4	26.3±4	0.795
Hypertension	51 (54)	21 (58)	0.762
Diabetes mellitus	25 (26)	9 (25)	0.173
CAD	55 (58)	28 (78)	0.057
Currenting smoking	35 (37)	19 (54)	0.112
Hyperlipidemia	28 (30)	7 (19)	0.349
Systolic blood pressure (mm Hg)	120 (80-200)	120 (90-170)	0.881
Diastolic blood pressure (mm Hg)	80 (50-100)	70 (50-90)	0.107
Medications			
Antiplatelet agents	64 (67)	29 (81)	0.204
Beta-blockers	66 (70)	24 (67)	0.922
ACE inhibitor / Angiotensin receptor blocker	64 (64)	25 (69)	0.721
Statins	27 (28)	11 (31)	0.980
Diuretics	73 (77)	31 (86)	0.353

Data are number (%), mean±SD, or median (minimum-maximum). CAD, coronary artery disease

Table 2. Laboratory and echocardiographic findings

Variable	Patients with SR (n=95)	Patients with AF (n=36)	p
Laboratory findings			
PTH (pg/ml)	85 (15-320)	112 (30-326)	0.007
Brain natriuretic peptide (pg/ml)	663 (51-6400)	952 (110-5364)	0.117
Brain natriuretic peptide >500 pg/ml	40 (64)	15 (79)	0.328
Creatinine clearance (ml/min)	79.5 (46-88)	69 (50-84)	0.011
ALT (IU/l)	21 (10 -158)	20.5 (6-95)	0.799
Hemoglobin (gr/dl)	13.3±1.6	12.5±1.6	0.012
Anemia	28 (30)	14 (39)	0.412
Fasting glucose (mg/dl)	105 (68-378)	107 (57-354)	0.256
Creatinine (mg/dl)	1.0±0.3	1.2±0.3	0.009
TSH (mg/dl)	1.3 (0.1-13)	1.3 (0.1-5.7)	0.971
Sodium (mmol/l)	137±4	136±6	0.186
Potassium (mmol/l)	4.3±0.5	4.5±0.8	0.326
Calcium (mg/dl)	9±0.5	9±0.5	0.172
Echocardiographic findings			
Left ventricular, EF(%)	30 (10-40)	25 (8-40)	0.034
Left atrial diameter (cm)	4.7±0.5	4.9±0.5	0.077
Left ventricular diameter (cm)	5.9±0.9	6.2±0.7	0.115
Systolic pulmonary artery pressure (mm Hg)	42 (20-65)	45 (30-85)	0.129

Data are number (%), mean±SD, or median (minimum-maximum).

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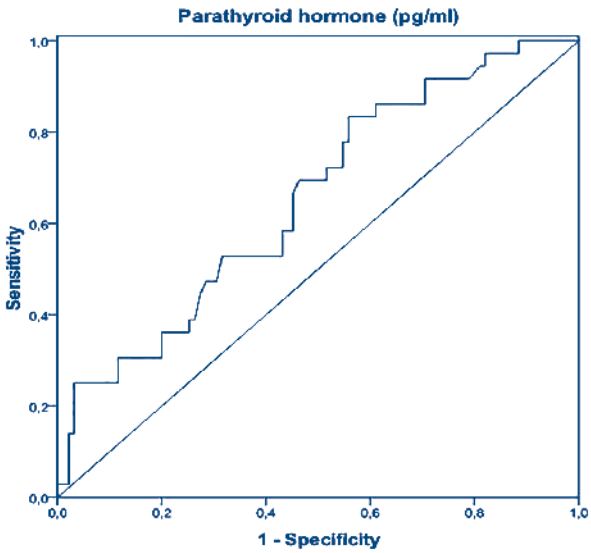
Table 3. Correlation coefficients for PTH

Variables correlated with PTH	r	p
Brain natriuretic peptide >500 pg/ml	0.546	< 0.001
Left ventricular, EF	-0.448	< 0.001
Left atrial diameter	0.402	< 0.001
Creatinine	0.319	< 0.001
Creatinine clearance	-0.275	0.013
Diuretics usage	0.267	0.002
Hemoglobin	-0.238	0.009

Figure 1. OC curve for parathyroid hormone prediction of AF



variables and by the Spearman test for non-normally distributed variables. Categorical data were evaluated by a chi square test. The MedCalc receiver operator characteristic (ROC) curve analysis (v12.7.8) was used to determine the optimal cut-off point for PTH prediction of AF. This was accomplished by determining the area under the curve (AUC) with a 95% confidence interval. The best cutoff value for PTH was determined by calculating the highest sum of sensitivity and specificity-1. Univariate analysis was used to quantify the association of AF variables. Statistically significant variables in the univariate analysis and potential other confounders were used in a multivariate, logistic regression model with forward stepwise method to determine independent, prognostic factors for AF. All statistical analysis was performed using SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA). A p value of 0.05 was considered statistically significant.

3. Results

At admission there were two groups of patients, one with AF (n=36) and the other with sinus rhythm (SR, n=95). Baseline characteristics and laboratory and echocardiographic data are shown in Tables 1 and 2. Age was significantly greater in the AF group, whereas EF was markedly lower in the AF group (66±10 vs 70±7 yrs, p=0.016; 30 (10-40) vs 25 (8-40) %, p=0.034; respectively). Plasma creatinine and PTH concentrations were significantly higher (1.0±0.3 vs 1.2±0.3 mg/dl, p=0.009; 85 (15-320) vs 112 (30-326) pg/ml, p=0.007; respectively), while creatinine clearance and hemoglobin concentrations were significantly lower in the AF group compared to the SR group (79.5 (46-98) vs 69 (50-94) ml/min, p=0.011; 13.3±1.6 vs. 12.5±1.6 g/dl, p=0.012; respectively). Other basal characteristics, laboratory values, and echocardiographic parameters were similar between the groups.

Of note, PTH concentrations were positively correlated with brain natriuretic peptide (BNP) concentrations, left atrial diameter, use of diuretics and negatively correlated with left ventricular EF, hemoglobin concentration, and creatinine clearance (Table 3).

Univariate and multivariate logistic regression analyses for AF are presented in Table 4. In the univariate analysis, PTH, age, creatinine clearance, hemoglobin, left ventricular ejection fraction, and creatinine were found to be associated with the presence of AF. However, the PTH concentration (OR=1.012, 95% CI=1.002–1.022, p=0.016) remained linked to the presence of AF in the multivariate logistic regression model after adjustment for statistically significant variables in the univariate analysis and adjustment for variables correlated with PTH concentration.

Based on the ROC curve analysis, the PTH optimal cut-off concentration to designate AF was ≥ 69 (pg/ml), with a sensitivity of 44.2% and a specificity of 83.3% (AUC=0.654, 95% CI=0.551–0.756, p=0.007, Figure 1).

4. Discussion

In this study, increased concentrations of plasma PTH were found to be an independent risk factor for AF in HFrEF outpatients. Heart failure and AF are often jointly observed. Many risk factors for HF such as HT, CAD, DM, and heart valve disease are also risk factors for AF. Similarly, most echocardiographic findings, such as left atrial enlargement in HF, decreased left ventricular fractional shortening, and increased left ventricular wall thickness, create AF development liability [16, 17]. These two diseases with common risk factors are closely related, due to their complex mechanisms, such as inflammatory, neurohumoral, structural and electrophysiological changes [2, 7]. Atrial and ventricular wall tension and inflammatory markers have been shown in many studies to be closely related to AF in HF patients [18, 19].

Liquid restriction and use of potent loop diuretic by patients with HF decreases intravascular volume and, thus, reduces renal perfusion. Decreased renal perfusion results in secondary hyperaldosteronism by activation

Table 4. Univariate and multivariate regression analyses for predicting AF.

Variable	Univariate analysis			Multivariate analysis		
	p	OR	95% CI	p	OR	95% CI
Statistically significant variables						
PTH (pg/ml)	0.006	1.009	1.002-1.015	0.016	1.012	1.002-1.022
Ccr (ml/min)	0.010	0.950	0.913-0.988	0.073	0.960	0.918-1.004
Age (yrs)	0.041	1.047	1.002-1.094	0.472	1.028	0.953-1.109
LVEF (%)	0.028	0.950	0.907-0.995	0.636	0.981	0.906-1.062
Hemoglobin (g/dl)	0.015	0.709	0.537-0.935	0.149	0.741	0.493-1.113
Creatinine (mg/dl)	0.011	6.064	1.507-24.405	0.974	1.063	0.270-41.541
Variables that correlated with PTH						
BNP > 500 pg/ml	0.216	2.156	0.639-7.277	0.505	0.577	0115-2.904
Diuretics usage	0.216	1.868	0.649-5.383	0.768	0.733	0.094-5.748
Left atrial diameter	0.080	2.151	0.912-5.085	0.750	1.376	0.193-9.809

All the variables from Table 1 were examined, and only those significant at $p<0.05$ and correlated with PTH are shown in the univariate analysis. The multivariate logistic regression model included all the variables in the univariate analysis with forward stepwise method. BNP, brain natriuretic peptide; CI, confidence interval; Ccr, creatinine clearance; LVEF, left ventricular ejection fraction; OR, odds ratio; PTH, parathyroid hormone.

of the renin-angiotensin-aldosterone system. Secondary hyperaldosteronism and increased diuretic use brings about secondary hyperparathyroidism. Increased PTH leads to excessive calcium elevation in cells and mitochondria, which may lead to cardiomyocyte necrosis and structural remodeling [20]. These neurohumoral changes, caused by increased PTH, may explain the PTH and AF relationship in HF. Plasma PTH might also increase, secondarily to the hemodynamic and structural consequences of AF. PTH-related protein messenger RNA expression increases due to increased atrial or ventricular distention or overload [21]. Decreased atrial systole function during AF leads to increased atrial volume and pressure overload, which causes atrial stretch. AF pathophysiology includes atrial ischemia, inflammation, and infiltration, which in turn stimulates PTH release [22]. Studies have shown a relationship between PTH and HF risk and severity [9, 12]. The relationship between plasma PTH concentrations and AF prevalence, regardless of HF, has been shown previously [13]. In accordance with the literature, univariate and multivariate analyses of the current study found that PTH is an independent predictor of AF in HFrEF outpatients.

The limitations of this study include the inclusion of patients from a single center and the relatively small sample size. Furthermore, we did not measure magnesium or ionized calcium, which are the key determinants of PTH secretion. Patients who were admitted to the emergency room and/or to the hospital due to acute cardiac decompensation were excluded. Hence, the current findings are solely limited to stable HFrEF outpatients. Hence, atrial stretch, i.e., atrial size, might not be critically important in the absence of acute hemodynamic loading, as in the case of acute decompensation. The etiology of HF might not reflect the overall HF population or other HF phenotypes, as there were several exclusions. However, this study was a reasonable pathway to determine a relationship between intact PTH and AF in HFrEF outpatients. Intact-PTH assay measures not only full-length biologically active PTH with 84 amino acids, but also some PTH fragments such as (7-84) PTH, whole-PTH assay is a new method believed to react only with (1-84) PTH [23]. Therefore our preliminary results should be externally validated with further studies assessing the predictive value of intact PTH in cardiovascular outcomes.

5. Conclusion

PTH acts as a cardiac hormone in addition to its key role in calcium metabolism, due to its effects on blood pressure regulation and smooth muscle proliferation. In vivo studies show that PTH is involved in HF pathogenesis with its role in collagen synthesis and organization. PTH, at the same time, seems to be independently associated with AF among outpatients with HFrEF, since it potentially increases intracellular calcium. Based on this, the PHT concentration may be an important determinant of AF in heart failure patients.

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REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021;42(36):3599–726. DOI: 10.1093/eurheartj/ehab368
2. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. The American Journal of Cardiology. 2003;91(6A):2D-8D. DOI: 10.1016/S0002-9149(02)03373-8
3. Kawabata M, Hirao K, Hachiya H, Higuchi K, Tanaka Y, Yagishita A et al. Role of oral amiodarone in patients with atrial fibrillation and congestive heart failure. Journal of Cardiology. 2011;58(2):108–15. DOI: 10.1016/j.jjcc.2011.06.005
4. Hohendanner F, Heinzel FR, Blaschke F, Pieske BM, Haverkamp W, Boldt HL et al. Pathophysiological and therapeutic implications in patients with atrial fibrillation and heart failure. Heart Failure Reviews. 2018;23(1):27–36. DOI: 10.1007/s10741-017-9657-9
5. Shelton RJ, Clark AL, Goode K, Rigby AS, Houghton T, Kaye GC et al. A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CAFE-II Study). Heart. 2009;95(11):924–30. DOI: 10.1136/hrt.2008.158931
6. Raitt MH, Kusumoto W, Giraud G, Mcanulty JH. Reversal of Electrical Remodeling After Cardioversion of Persistent Atrial Fibrillation. Journal of Cardiovascular Electrophysiology. 2004;15(5):507–12. DOI: 10.1046/j.1540-8167.2004.03217.x
7. Nikolaidou T, Cai XJ, Stephenson RS, Yanni J, Lowe T, Atkinson AJ et al. Congestive Heart Failure Leads to Prolongation of the PR Interval and Atrioventricular Junction Enlargement and Ion Channel Remodelling in the Rabbit. PLOS ONE. 2015;10(10):e0141452. DOI: 10.1371/journal.pone.0141452
8. Brown SJ, Ruppe MD, Tabatabai LS. The Parathyroid Gland and Heart Disease. Methodist DeBakey Cardiovascular Journal. 2017;13(2):49–54. DOI: 10.14797/mdcj-13-2-49
9. Altay H, Zorlu A, Binici S, Bilgi M, Yilmaz MB, Colkesen Y et al. Relation of Serum Parathyroid Hormone Level to Severity of Heart Failure. The American Journal of Cardiology. 2012;109(2):252–6. DOI: 10.1016/j.amjcard.2011.08.039
10. Rienstra M, Lubitz SA, Zhang ML, Cooper RR, Ellinor PT. Elevation of Parathyroid Hormone Levels in Atrial Fibrillation. Journal of the American College of Cardiology. 2011;57(25):2542–3. DOI: 10.1016/j.jacc.2011.01.041
11. Shor R, Tilis Y, Boaz M, Matas Z, Fux A, Halabe A. Serum parathyroid hormone--related protein levels before and after paroxysmal atrial fibrillation. The American Journal of Emergency Medicine. 2008;26(3):361–3. DOI: 10.1016/j.ajem.2007.08.005
12. Wannamethee SG, Welsh P, Papacosta O, Lennon L, Whincup PH, Sattar N. Elevated parathyroid hormone, but not vitamin D deficiency, is associated with increased risk of heart failure in older men with and without cardiovascular disease. Circulation. Heart Failure. 2014;7(5):732–9. DOI: 10.1161/CIRCHEARTFAILURE.114.001272
13. Lee KH, Shin M-H, Park HW, Cho JG, Kweon S-S, Lee Y-H. Association between Serum Parathyroid Hormone Levels and the Prevalence of Atrial Fibrillation: the Dong-gu Study. Korean Circulation Journal. 2018;48(2):159–67. DOI: 10.4070/kcj.2017.0187
14. Arora H, Sawhney JPS, Mehta A, Mohanty A. Anemia profile in patients with congestive heart failure a hospital based observational study. Indian Heart Journal. 2018;70:S101–4. DOI: 10.1016/j.ihj.2018.06.017
15. Lang R, Bierig M, Devereux R, Flachskampf F, Foster E, Pellikka P et al. Recommendations for chamber quantification. European Journal of Echocardiography. 2006;7(2):79–108. DOI: 10.1016/j.euje.2005.12.014
16. Hulme OL, Khurshid S, Weng L-C, Anderson CD, Wang EY, Ashburner JM et al. Development and Validation of a Prediction Model for Atrial Fibrillation Using Electronic Health Records. JACC: Clinical Electrophysiology. 2019;5(11):1331–41. DOI: 10.1016/j.jacep.2019.07.016
17. Higashiyama A, Kokubo Y, Watanabe M, Nakao YM, Okamura T, Okayama A et al. Echocardiographic Parameters and the Risk of Incident Atrial Fibrillation: The Suita Study. Journal of Epidemiology. 2020;30(4):183–7. DOI: 10.2188/jea.JE20180251
18. Cullington D, Goode KM, Zhang J, Cleland JGF, Clark AL. Is heart rate important for patients with heart failure in atrial fibrillation? JACC. Heart failure. 2014;2(3):213–20. DOI: 10.1016/j.jchf.2014.01.005
19. Kaya H, Zorlu A, Yucel H, Tatlisu MA, Kivrak T, Coskun A et al. Higher cancer antigen 125 level is associated with the presence of permanent atrial fibrillation in systolic heart failure patients. Acta Cardiologica. 2016;71(1):61–6. DOI: 10.1080/AC.71.1.3132099
20. Zia AA, Kamalov G, Newman KP, McGee JE, Bhattacharya SK, Ahokas RA et al. From aldosteronism to oxidative stress: the role of excessive intracellular calcium accumulation. Hypertension Research. 2010;33(11):1091–101. DOI: 10.1038/hr.2010.159
21. Ross G, Schluter K. Cardiac-specific effects of parathyroid hormone-related peptide: Modification by aging and hypertension. Cardiovascular Research. 2005;66(2):334–44. DOI: 10.1016/j.cardiores.2005.02.001
22. Watson T, Shantsila E, Lip GYH. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. The Lancet. 2009;373(9658):155–66. DOI: 10.1016/S0140-6736(09)60040-4
23. Ito N, Fukumoto S. Significance of a new PTH assay (the comparison between whole-PTH and intact-PTH assay). Clinical Calcium. 2004;14(9):55–6. PMID: 15577110