SHORT COMMUNICATION

The elevated serum parathyroid hormone level is associated with the occurrence of atrial fibrillation in patients with advanced heart failure

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Introduction   In the past decade, the role of calcium and phosphate metabolism in the pathogenesis of cardiovascular disease attracted growing scientific interest, which has resulted in an increasing number of studies on this issue. Numerous authors have investigated the link between vitamin D and parathormone (PTH) status and the risk of atrial fibrillation (AF) in the general population. Although a meta-analysis by Zhang et al[1] has shown that vitamin D deficiency can be associated with the incidence of AF, the results of a recent large observational study[2] have implied that PTH is a better predictor of a new AF onset. Moreover, both vitamin D deficiency and increased parathormone levels are thought to be related to disease severity and to predict worse prognosis in patients with heart failure (HF).[3]

Considering that AF is the most common arrhythmia in patients with HF and the fact that there is no sufficient data on the relationship between PTH / vitamin D imbalance and AF in this group of patients, we decided to analyze the parameters of calcium–phosphate metabolism in relation to cardiac rhythm in patients with advanced HF.

Methods   The study group consisted of 138 clinically stable patients (83% men, 17% women) admitted to the Department of Heart Failure and Transplantology due to chronic HF with reduced ejection fraction. The study patients were divided into 2 groups according to the type of cardiac rhythm, as confirmed by an electrocardiogram on admission: sinus rhythm or AF. All patients in the AF group presented with permanent arrhythmia. Five patients had undergone ablation for AF, a single patient for atrial flutter, and 4 of those patients maintained sinus rhythm during the study. Exclusion criteria were as follows: a creatinine level above 2.5 mg/dl, primary hyperparathyroidism, vitamin D and calcium supplementation, cancer (active, present in a medical history, or suspected), and treatment for osteoporosis. Serum concentrations of 25-hydroxyvitamin D, PTH, calcium, and phosphorus were measured during the first days of hospitalization. The study was approved by the local ethics committee and all patients provided informed consent prior to enrollment.

Statistical analysis   The Shapiro–Wilk test was used to verify the null hypothesis of normal data distribution. Continuous variables were expressed as mean (SD) in the case of values representing normal distribution or median (interquartile range) in the case of values with non-normal distribution. Differences between the study groups were tested using the t, Mann–Whitney, or χ^2 tests (with the Yates correction for continuity where needed), as appropriate. The relationship between continuous variables was evaluated by the Spearman correlation test. Logistic regression analysis was performed in order to identify the independent predictors of AF incidence. The multivariable model included variables identified as significant in the univariate model. A P value less than 0.05 was considered significant. Statistical analysis was conducted using the Statistica PL 12.0 software (StatSoft Inc., Palo Alto, California, United States).

Results and discussion   Atrial fibrillation was diagnosed in 26 patients (19%). The baseline characteristics of the study patients and

TABLE 1 Baseline characteristics and test results of the study population

Characteristics		All patients (n = 138)	AF (+) (n = 26)	AF (–) (n = 112)	P value
Clinical characteristics					
Age, y, median (IQR)		52.3 (42.7–58.5)	58.6 (43.7–64.4)	50 (42–57.4)	0.002
Male sex		114 (83)	21 (81)	119 (83)	0.99
BMI, kg/m^2, mean (SD)		27.7 (3.9)	28.7 (3.3)	27.5 (4.1)	0.13
Coronary artery disease		45 (33)	5 (19)	40 (36)	0.11
DCM		93 (67)	21 (81)	72 (64)	0.11
Hypertension		39 (28)	9 (35)	30 (27)	0.43
Diabetes		29 (21)	3 (12)	26 (23)	0.19
NYHA class	II	97 (70)	18 (69)	79 (70.5)	0.9
	III	41 (30)	8 (31)	33 (29)	
Echocardiographic parameters					
LVEF, %, median (IQR)		28 (21–35)	25 (20–35)	28.5 (22–35)	0.94
LAA, cm^2, median (IQR)		28 (22.5–36)	36.3 (28–34)	26 (22–32.9)	<0.001
Mitral regurgitation[a]		35 (25)	9 (35)	26 (23)	0.23
Tricuspid regurgitation[a]		11 (80)	4 (15)	7(6)	0.25
Laboratory test results					
NT-proBNP, pg/ml, median (IQR)		915 (410–1860)	1273 (911–2290)	789 (353–1650)	0.008
eGFR, ml/min/1.73 m^2, mean (SD)		104 (30)	94 (25)	106 (31)	0.05
Ca, mmol/l, mean (SD)		2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	0.83
P, mmol/l, mean (SD)		1.1 (0.2)	1.1 (0.1)	1.2 (0.2)	0.31
Vitamin D, ng/ml, median (IQR)		14.8 (10.1–21.9)	18.6 (13.4–23.5)	14 (9.7–20.6)	0.04
PTH, pg/ml, median (IQR)		46.9 (36.9–66.6)	69.5 (56–93)	43.8 (35.1–58.5)	<0.001
Medication					
β-Blockers		137 (99)	26 (100)	111 (99)	0.42
ACEI / ARB		136 (99)	26 (100)	110 (98)	0.82
Spironolactone / eplerenone		125 (91)	23 (88)	102 (91)	0.97
Loop diuretics		114 (83)	22 (85)	92 (82)	0.99
Amiodarone		16 (12)	3 (12)	13 (12)	0.74
Digoxin		24 (17)	7 (27)	17 (15)	0.26
Exercise capacity test results					
6-minute walk test, m, median (IQR)		470 (400–520) (n = 132)	420 (340–480) (n = 23)	480 (410–530) (n = 109)	0.01
Peak VO$_2$ during CPX, ml/kg/min, median (IQR)		16 (12.4–19) (n = 114)	12.1 (10–16.5) (n = 19)	16 (13–19.9) (n = 95)	0.008

Data are presented as the number (percentage) of patients unless otherwise indicated.

a At least moderate regurgitation

SI conversion factors: to convert vitamin D to nmol/l, multiply by 2.5, and parathormone to pmol/l, by 0.106.

Abbreviations: –, absent; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CPX, cardiopulmonary exercise testing; DCM, dilated cardiomyopathy; IQR, interquartile range; LAA, left atrial area; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; NYHA, New York Heart Association; VO$_2$, oxygen uptake; +, present

differences in relation to this arrhythmia are presented in TABLE 1.

The parameters listed in TABLE 1 were analyzed by means of univariate regression analyses, except the results of exercise capacity tests. Advanced age, an enlarged left atrial area, and elevated PTH levels were identified as the predictors of AF. All of the following factors remained significant when included in the multivariable regression analysis model: age (odds ratio [OR],

1.06 [per 1 year]; 95% CI, 1–1.11; P = 0.04), left atrial area (OR, 1.09 [per 1 cm^2]; 95% CI, 1.03–1.15; P = 0.001), and the PTH level (OR, 1.02 [per 1 pg/ml]; 95% CI, 1.01–1.04; P = 0.002).

Certain processes occurring in the course of HF, such as increased aldosterone activity and diuretic-induced calcium loss, lead to the development of secondary hyperparathyroidism. Moreover, in the cases complicated by renal dysfunction, phosphorus retention and disturbances in 25-hydroxyvitamin D synthesis are observed. On the other hand, several mechanisms suggest that the imbalanced regulation of calcium–phosphate metabolism plays a role in the pathophysiology of HF progression.[4] Receptors for both vitamin D and PTH are expressed in a wide range of tissues, including the myocardium and vessel walls.[4,5] The reported effects of vitamin D deficiency and elevated PTH levels on the cardiovascular system include the stimulation of the renin–angiotensin–aldosterone system, exacerbating tissue inflammation, and endothelial dysfunction.[4] Additionally, PTH can induce myocardial hypertrophy and fibrosis as well as increase the heart rate.[4] All those actions may also promote the electrical and structural remodeling of the atrium leading to AF development.

To date, the results of studies on the correlation among AF, HF, and calcium–phosphate metabolism have been equivocal, and there is insufficient evidence to draw firm conclusions. While Schierback et al[3] did not find any differences with regard to AF incidence in terms of PTH levels, Belen et al[6] reported that both vitamin D and PTH levels changed (decreased and elevated, respectively) in patients with HF and AF compared with those with sinus rhythm. Since vitamin D deficiency is the predominant cause of secondary hyperparathyroidism, it may be expected that low vitamin D and high PTH concentrations would be responsible for similar effects. Our study in patients with HF showed a relationship between AF and the elevated PTH level yet not with other parameters of calcium–phosphate metabolism (vitamin D, calcium and phosphorus concentration). However, increased PTH levels correlated with the low levels of vitamin D (R = −0.3, P <0.001). It may suggest that the pleiotropic effects of PTH are seen before evident calcium and phosphate homeostasis disturbances become apparent and remain consistent with changes in vitamin D levels. Furthermore, similar to Altay et al,[7] we observed that both AF (TABLE 1) and elevated PTH levels were associated with HF progression (PTH levels correlated with higher N-terminal fragment of the prohormone brain natriuretic peptide levels [R = 0.3, P <0.001] and with poorer results of exercise tests [6-minute walk test: R = −0.2, P = 0.02; cardiopulmonary exercise test: R = −0.4, P <0.001]). In the light of the above observations, the relationship between PTH levels

and AF seems to be more pronounced in patients with advanced HF.

The discussion of the abovementioned selected mechanisms is a contribution to the ongoing research, with numerous questions still to be explored. In addition to the fact that there is a link among AF, PTH levels, and HF, it should be emphasized that PTH is the main regulator of the serum calcium concentration. Therefore, it may be suspected that it also influences cardiac electrophysiology. Recently, a clinical study has demonstrated that adolescents with vitamin D deficiency were more prone to ventricular repolarization anomalies.[8] Although it is tempting to apply the analogy to atrial arrhythmias, unfortunately, there have been no studies demonstrating the direct impact of PTH levels on the electrical activity of atrial myocytes.

Study limitations   Patients included in our study were significantly younger and presented with more advanced HF (higher N-terminal fragment of the prohormone brain natriuretic peptide levels and lower left ventricular ejection fraction) than populations usually enrolled in such observational studies. Moreover, the measurements of vitamin D levels were not adjusted for the season.

Conclusions   In our study, elevated PTH levels predicted the incidence of AF. Nevertheless, it remains controversial whether this metabolic disorder directly contributes to arrhythmia or there is just a coincidence of both pathologies in the clinical settings of advanced HF. However, if we consider the fact that the PTH level remained to be a significant predictor of AF, in addition to well-supported clinical risk factors such as advanced age and an enlarged left atrium, its potential role in the pathophysiology of atrial arrhythmia cannot be neglected.

ARTICLE INFORMATION

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