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Authors: Anna Olasińska-Wiśniewska, Tomasz Urbanowicz, Piotr Kübler, Bartłomiej Perek, Marcin Misterski, Marek Grygier, Marcin Protasiewicz, Dominika Katarzyńska, Beata Begier-Krasińska, Marek Jemielity

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Increased parathyroid hormone concentration as a biomarker of atrial fibrillation in severe aortic stenosis

Short title: PTH as a biomarker of AF in aortic stenosis

Anna Olasińska-Wiśniewska[1], Tomasz Urbanowicz[1], Piotr Kübler[2], Bartłomiej Perek[1], Marcin Misterski[1], Marek Grygier[3], Marcin Protasiewicz[2], Dominika Katarzyńska[4], Beata Begier-Krasińska[5], Marek Jemielity[1]

[1]Department of Cardiac Surgery and Transplantology, Poznan University of Medical Sciences, Poznań, Poland
[2]Institute of Heart Diseases, Wroclaw Medical University, Wrocław, Poland
[3]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland
[4]Department of Pediatric Diabetes, Clinical Auxology and Obesity, Poznan University of Medical Sciences, Poznań, Poland
[5]Department of Hypertensiology, Angiology and Internal Medicine, Poznan University of Medical Sciences, Poznań, Poland

Correspondence to:
Assist. Prof. Anna Olasińska-Wiśniewska, MD, PhD,
Department of Cardiac Surgery and Transplantology,
Długa 1/2, 61–848 Poznań, Poland,
phone: +48 61 854 92 10,
e-mail: annaolasinska@ump.edu.pl

WHAT'S NEW?

Atrial fibrillation (AF) is a common arrhythmia in patients with aortic stenosis and heart failure. The novelty of the study is the phenomenon of an increased concentration of parathyroid hormone in patients with severe aortic stenosis presenting with AF compared with those with sinus rhythm. Patients with sinus rhythm and parathyroid hormone concentration over 84 pg/ml should be screened for paroxysmal AF.

ABSTRACT

Background: Atrial fibrillation (AF) is commonly observed in patients with aortic stenosis and comorbidities. Abnormal parathyroid hormone (PTH) concentration has been observed in heart failure.

Aim: To evaluate the potential association between increased concentration of PTH and AF in patients with severe aortic stenosis.

Material and methods: Patients with severe aortic stenosis and heart failure were included. Demographic, clinical, and laboratory data were collected. Patients were divided into the AF and the sinus rhythm groups.

Results: The study group comprised 106 consecutive patients (57 females [53.8%], median [interquartile range] age of 77 [72–82] years). All patients presented with severe aortic stenosis, with a median (interquartile range) peak transvalvular gradient of 86.5 (71–102.8) mm Hg. Left atrial diameter over 40 mm was revealed in 76 (71.7%) of them. A history of AF was revealed in 39 patients (36.8%). Patients with any form of AF were characterized by an increased concentration of PTH compared to patients with sinus rhythm (P = 0.03). Patients with and without impaired kidney function had different PTH concentrations (P <0.001). After adjustment of clinical and echocardiographic data, in the multivariable analysis, only PTH concentration (P = 0.02; OR, 1.02; 95% CI, 1.00–1.03) together with left atrial diameter (P = 0.008; OR, 1.13; 95% CI, 1.03–1.23), with area under the curve of 0.752, 43.3% sensitivity, 90% specificity, remained significant predictors of AF. The cut-off value for PTH concentration over 84.1 pg/ml was predictive of paroxysmal AF.

Conclusions: Increased PTH concentration may characterize patients with AF. Patients with aortic stenosis presenting with PTH concentration over 84 pg/ml should be screened for paroxysmal AF.

Key words: aortic stenosis, atrial fibrillation, parathyroid hormone

INTRODUCTION

Calcific aortic stenosis is the most common valvular pathology requiring intervention.

The risk factors for senile aortic degeneration result from a complex active process driven by inflammatory activation, lipid accumulation, and calcification [1–3]. It involves multifactorial pathological mechanisms that promote valvular calcification and processes that resemble bone formation [4, 5]. Among demographical and clinical factors related to the

progression of aortic valve degeneration, older age, arterial hypertension, hypercholesterolemia, diabetes mellitus, kidney failure, and obesity have been postulated as the most prominent.

Aortic stenosis is a progressive disease that causes compensatory mechanisms in the heart, including left ventricular hypertrophy and atrial augmentation. Atrial fibrillation (AF) related to valve pathology is believed to be a marker of advanced heart failure (HF) and a sign of a worse prognosis [6–8]. The compensatory mechanisms provoking atrial remodeling are the causative factors for supraventricular arrhythmias being diagnosed in 30% of patients with aortic stenosis [9] and represent one of the main risk factors of acute decompensation. Due to the negative impact of AF complications on the outcomes [10], predictors of its occurrence are essential in daily practice.

Parathyroid hormone (PTH) influence on HF development, including heart valve and muscle pathology, has been reported [11, 12]. The link between parathormone and the renin-angiotensin-aldosterone axis is claimed for its effects on the cardiovascular system [13]. The interplay between aldosterone, PTH, and fibroblast growth factor was found detrimental to endothelial dysfunction-provoking cardiovascular diseases [14]. Our previous study [15] showed the association between PTH concentration and inflammatory ratios, underlining the role of activated inflammatory response in aortic stenosis. Moreover, the mean aortic gradient correlated positively with PTH concentration, which proved the influences of parathyroid gland dysfunction on the progression of aortic stenosis. Therefore, PTH may serve as an additional marker of aortic stenosis severity. However, the significance of PTH concentration in the assessment of aortic stenosis consequences is less known.

Aim

The aim of the study was to find possible clinical implications of parathormone abnormalities in patients with severe aortic stenosis.

MATERIAL AND METHODS

Study group

The study group comprised 106 consecutive patients (49 males, 57 females, median [interquartile range, IQR] age of 77 [72–82] years) from 2 cardiac/cardiosurgical centers with severe aortic stenosis involved in the analysis between May 2021 and January 2022. Only patients with HF (New York Heart Association — stage II–IV) qualified for transcatheter aortic valve implantation were included. The analysis did not include patients with oncological and

inflammatory diseases and chronic renal replacement therapy or medication sufficiently influencing PTH concentration.

The study was approved by the Institutional Ethics Committee (No 272/2021 dated April 8, 2021) and respected the principles outlined in the Declaration of Helsinki. Patients provided written informed consent to participate in the study.

Clinical data

Demographic and clinical data were collected at the admission to the departments. The co-existence of AF was reported, and the differentiation into paroxysmal, and persistent or chronic stage was assessed. Transthoracic echocardiography was performed on each patient before the procedure by an experienced echocardiographer and according to current guidelines on aortic stenosis management [16]. The echocardiographic assessment included aortic stenosis severity, which was based on the peak and mean transvalvular gradient, aortic valve area, and an evaluation of left atrial diameter from the parasternal long axis, left ventricle ejection fraction (LVEF) and left ventricular hypertrophy. Electrocardiography was performed. HF was diagnosed based on current guidelines on its diagnosis and management [17].

Patients were divided into the AF group and the sinus rhythm group (SR).

Laboratory tests

Blood samples were collected for the simple whole blood analysis, serum creatinine, and N-terminal prohormone of brain natriuretic peptide. The glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease Study equation. Serum intact PTH concentrations were assessed by electrochemiluminescence immunoassay kit (Abbott Diagnostics, Abbott Park, IL, US) with normal ranges established at 15–68.3 pg/ml.

Statistical analysis

The Shapiro–Wilk test was used to characterize the data distribution. Normally distributed data were presented as mean and standard deviation, while those not normally distributed were expressed as median and interquartile range (IQR). Categorical variables were presented as numbers and percentages. Student T-test was used for normal, while the non-parametric Mann–Whitney test was for non-normally distributed, and count data were compared with χ^2 or Fisher exact test where applicable. Univariable and multivariable logistic regression with backward selection model was performed to analyze the data, which could predict AF. Demographical, clinical, echocardiographic, and laboratory data were included in the logistic regression model.

Statistical analysis was performed using JASP software (JASP Team; 2020. Version 0.13.1). The cut-off value was established using the Youden index in PQStat software (Version 1.8.6). *P* <0.05 was considered statistically significant.

RESULTS

All 106 patients presented with severe aortic stenosis, with a median (IQR) mean transvalvular gradient of 53.5 (43.4–65.4) mm Hg, median peak transvalvular velocity of 4.7 (4.2–5.1) m/s, median aortic valve area of 0.6 (0.6–0.7) cm^2, and median (IQR) LVEF of 56 (50–60)%. Fourteen patients presented with LVEF below 40%. Left atrial diameter over 40 mm was revealed in 76 (71.7%) of study group. History of AF, either paroxysmal (n = 23) or persistent/permanent (n = 16), was revealed in 39 patients (36.8%). Comorbidities were present in SR and AF subgroups, such as diabetes or impaired glucose tolerance, arterial hypertension, significant coronary artery disease or previous revascularization, and chronic obstructive pulmonary disease, and did not differ significantly between both subgroups (Table 1). Chronic kidney disease with GFR-Modification of Diet in Renal Disease was more common in the AF group (*P* = 0.05).

Patients with any form of AF presented an increased concentration of PTH compared to the SR group (*P* = 0.03). Those with paroxysmal and permanent AF did not differ significantly in PTH concentration (median [IQR] 62.8 pg/ml [46.2–103.7] vs. 77.5 pg/ml [61.9–106.5] in paroxysmal and permanent AF subgroups respectively; *P* = 0.41).

Patients with normal kidney function (GFR >90 ml/min) and those with at least mildly impaired kidney function (GFR <90 ml/min) did not differ in PTH concentration (median [IQR] 54.1 pg/ml [40.5–60] vs. 64.1 pg/ml [46.7–88.7]; *P* = 0.10). Obviously, patients with significantly impaired kidney function (GFR <60 ml/min) had different PTH concentrations (median [IQR] 72.5 pg/ml [58.9–94.2] vs. 54.7 pg/ml [39.9–75.5], in the group with GFR <60 ml/min vs. group with GFR >60 ml/min, respectively; *P* <0.001). Patients with GFR <60 ml/min more often were burdened with AF presence (24 [46.2%] vs. 15 [27.8%]; *P* = 0.05).

The univariable and multivariable logistic analyses were performed (Table 2). After adjustment of clinical and echocardiographic data, in the multivariable analysis only PTH concentration (*P* = 0.02; OR, 1.02; 95% CI, 1.00–1.03) together with left atrial diameter (*P* = 0.008; OR, 1.13; 95% CI, 1.03–1.23), with area under the curve of 0.752, 43.3% sensitivity and 90% specificity, remained significant predictors of AF (receiver operating characteristic curve analysis, Figure 1). In the further step, the cut-off value for PTH concentration predictive for paroxysmal AF was established as over 84.1 pg/ml.

DISCUSSION

Our study underlined the association between left atrial diameter, increased PTH concentration, and AF presence in patients with severe symptomatic aortic stenosis. The analysis was performed in patients with HF defined on the basis of clinical, laboratory and echocardiographic criteria according to current guidelines [17].

Atrial fibrillation is common in patients with HF in the course of cardiovascular disorders, including coronary artery disease and valvular disease. Differences between patients with SR and AF and management strategies have been profoundly investigated [18–21]. AF is a complex disorder with a heterogeneous background, which may be interpreted as an interplay between genetic factors and several comorbidities, such as cardiovascular, endocrine, pulmonary, and metabolic diseases [22]. The prevalence of AF is higher in patients with chronic kidney disease, particularly at the end-stage treated with renal replacement therapy [23], and more advanced kidney disease is associated to a higher thromboembolic and bleeding risk [24]. The presence of AF aggravates kidney dysfunction [25]. Inflammation is one of the important causative factors. Moreover, the burden of metabolic syndrome and its components, if untreated, may lead to the early development of atherosclerosis, adverse cardiac events [22], and a higher risk of AF [26]. Though thyroid gland disorders are commonly linked with supraventricular arrhythmias, the endocrine influence on the heart is far beyond thyroid diseases [27–29].

Increased PTH concentration in patients with HF has been presented [30]. Altay et al. [31] analyzed PTH concentration in patients with HF with reduced ejection fraction and suggested its value as a simple biomarker allowing rapid risk stratification and categorizing of patients with advanced HF. PTH concentration significantly increased with the New York Heart Association class increase. The authors proposed a cut-off value of PTH as 96.4 pg/ml to predict advanced HF. PTH concentrations correlated with worse echocardiographic, hemodynamic, and laboratory parameters. Several studies showed increased PTH concentration related to coronary artery calcifications [32], either with advanced chronic kidney disease or without kidney failure. Obviously, chronic kidney disease is associated with increased PTH concentration, which was confirmed in our patients' subgroup with GFR lower than 60 ml/min.

Phenomena that characterize HF, such as hyperaldosteronism, impaired other organs' function, mainly kidney disorders, and pharmacotherapy, including diuretics, change the body calcium and phosphate homeostasis, endorse plasma-ionized hypocalcemia and hypomagnesemia, and may be followed with secondary hyperparathyroidism. PTH may then

promote intracellular calcium overload, which leads to the induction of oxidative stress and functional degeneration of mitochondria, followed by cardiomyocyte necrosis and subsequent replacement fibrosis [33, 34]. Moreover, PTH stimulates aldosterone secretion [35, 36], the hormone which induces fibrosis [37]. In turn, there is a strong association between atrial fibrosis and AF occurrence [38, 39]. Moreover, atrial inflammatory infiltrates have been observed in patients with AF undergoing mitral valve surgery [40]. Ventricular fibrosis has also been linked to AF [40]. Both, fibrosis and inflammatory response are present in ventricular and atrial remodeling in patients with aortic stenosis. The presence of PTH in all heart chambers was reported and its atrial secretion overrides the ventricular para-endocrinal activity [41, 42].

Increased PTH and low vitamin D concentrations have been related to the incidence of AF in HF patients [43, 44]. Moreover, higher plasma concentrations of PTH were incrementally associated with an increased AF prevalence in patients with chronic kidney disease [45]. Trevisan et al. [46] reported the relation between AF and increased PTH levels in the older population, especially when associated with 25(OH)D deficiency. Rienstra et al. [47] demonstrated the elevated PTH level in patients with arterial hypertension and AF.

We aimed to explain our finding of the higher prevalence of AF in aortic stenosis patients with increased PTH concentration in accordance with the aforementioned studies. Indeed, many factors are engaged in the pathogenesis of AF in patients with aortic stenosis. Ventricular and atrial structural remodeling, increased intracardiac pressure overload, and fibrosis, which all occur in aortic stenosis, are prominent mechanisms. This phenomenon was related to our observation of left atrial diameter as a prognostic marker of AF. Left atrial diameter and function disturbances have been related to AF [48]. Changes in calcium concentration provoked by PTH concentration may probably influence electrical atrial remodeling [45]. Hara et al. [49] demonstrated enhanced cardiomyocytes' automaticity related to PTH, which may cause abnormal atrial electrical function. Resuming, we believe that AF occurrence in our study group is associated with structural remodeling in aortic stenosis and functional remodeling related to PTH influence. In turn, PTH concentration may be treated as a biomarker of AF prevalence. Patients with paroxysmal AF are a particularly difficult subpopulation due to difficulties in the diagnosis of arrhythmic episodes. We found that in patients with aortic stenosis, cut-off PTH concertation over 84 pg/ml may have an additional beneficial value in the prediction of paroxysmal AF. Thus, we suggest that patients with PTH over 84 pg/mL should be screened for paroxysmal AF even when presenting with SR.

Study limitations

We realize that PTH concentration in our analysis may be treated as a weak marker alone. However, plenty of factors may be related to AF occurrence, influencing structural and electrical remodeling. Therefore, we believe that PTH concentration is among those important ones. Moreover, PTH concentration remained a significant predictor of arrhythmia out of several other potential factors associated with AF, similar to the left atrial dimension, and the latter is a well-known feature of supraventricular arrhythmias. According to our analysis, patients with aortic stenosis presenting with PTH concertation over 84 pg/ml should be screened for paroxysmal AF, however, this observation needs further validation in larger population-based analyses. Secondly, left atrial dimension alone (as measured by transthoracic echocardiography) correlates poorly with left atrial volume measured by computed tomography in patients with AF [50]. Lack of more advanced measurements of left atrium morphology and function may be treated as a limitation.

CONCLUSION

Increased PTH concentration is characteristic for patients with AF, and those with aortic stenosis presenting with PTH concertation over 84 pg/ml should be screened for paroxysmal AF.

Article information

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Table 1. Baseline demographic and clinical data

Parameter	Study population (n = 106)	SR group (n = 67)	AF group (n = 39)	*P* (SR vs. AF)

Female, n (%)	57 (53.8)	40 (59.7)	17 (43.6)	0.11
Age, years (median, IQR)	77 (72–82)	77 (72–82)	80 (72–83)	0.44
BMI (mean, SD)	27.5 (4.8)	27.8 (5.2)	26.7 (3.8)	0.43
Diabetes or IGT, n (%)	48 (45.3)	31 (46.3)	17 (43.6)	0.79
Arterial hypertension, n (%)	85 (80.2)	51 (76.1)	34 (87.2)	0.17
COPD, n (%)	13 (12.3)	10 (14.9)	3 (7.7)	0.37
Coronary artery disease, n (%)	42 (39.6)	26 (38.8)	16 (41)	0.82
Atrial fibrillation paroxysmal, n (%)	23 (21.7)	0	23 (59)	<0.001
Atrial fibrillation permanent or chronic, n (%)	16 (15.1)	0	16 (41)	
Chronic kidney disease with GFR <60 ml/min/1.73 m^2, n (%)	52 (49.1)	28 (41.8)	24 (61.5)	0.05*
Previous myocardial infarction, n (%)	21 (19.8)	14 (20.9)	7 (18)	0.71
Previous stroke or TIA, n (%)	17 (16)	8 (11.9)	9 (23.1)	0.13
Pacemaker, n (%)	21 (19.8)	10 (14.9)	11 (28.2)	0.1
Previous CABG, n (%)	7 (6.6)	4 (6)	3 (7.7)	0.70
Previous PCI, n (%)	36 (34)	23 (34.3)	13 (33.3)	0.92
Peak aortic transvalvular gradient, mm Hg (median, IQR)	86.5 (71–102.8)	87.4 (72.9–102.6)	79 (66.9–101.3)	0.14
Mean aortic transvalvular gradient, mm Hg (median, IQR)	53.5 (43.4–65.4)	57 (44.2–68.2)	52 (41.4–60.9)	0.07

Left ventricular ejection fraction, % (median, IQR)	56 (50–60)	55 (50–60)	57 (50–60)	0.90
PASP, mm Hg (mean, SD)	43.4 (12.6)	42.5 (13.2)	44.9 (11.6)	0.38
Left atrial dimension, mm (mean, SD)	44.9 (6.1)	43.6 (5.6)	47.3 (6.3)	0.003*
NT-proBNP, pg/ml (median, IQR)	1980 (878.1–5098)	1111 (675.5–2665)	3408 (1197.1–8881.3)	0.03*
PTH, pg/ml (median, IQR)	62.3 (46.8–86.5)	60.1 (43.5–77.6)	66.6 (55.6–105.3)	0.03*
GFR, m/min/1.73 m^2 (median, IQR)	60.1 (46.1–73.3)	61.9 (48.4–77.1)	54.9 (39.5–64.8)	0.02*
Creatinine, umol/l (median, IQR)	97 (78.8–116)	91 (77–105.7)	102 (89.5–132.6)	0.008
Calcium, mmol/l (median, IQR)	2.4 (2.3–2.4)	2.3 (2.3–2.4)	2.3 (2.3–2.5)	0.91
Phosphates, mmol/l (median, IQR)	1.2 (1.1–1.2)	1.2 (1.1–1.2)	1.2 (1.1–1.2)	0.86

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; IGT, impaired glucose tolerance; MPG, mean transvalvular gradient; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; PPG, peak transvalvular gradient; PTH, parathyroid hormone; SD, standard deviation; SR, sinus rhythm; TIA, transient ischemic attack

Table 2. Uni and multivariable analysis for atrial fibrillation prediction

Parameter	Univariable			Multivariable		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.03	0.97–1.09	0.41	–		

Coronary artery disease	1.10	0.49–2.45	0.82	–		
PTH concentration	1.02	1.00–1.03	0.02	1.02	1.00–1.03	0.02
Chronic kidney disease with GFR <60 ml/min/1.73 m^2	2.23	0.99–5.00	0.05	–		
Male sex	1.92	0.86–4.26	0.11	–		
Diabetes or IGT	0.90	0.41–1.99	0.79	–		
Arterial hypertension	2.13	0.71–6.37	0.18	–		
COPD	0.48	0.12–1.84	0.28	–		
Peak transaortic gradient	0.98	0.97–1.00	0.08	–		
Left ventricular ejection fraction	1.00	0.96–1.04	0.97	–		
PASP	1.02	0.98–1.05	0.38	–		
Left atrial diameter	1.12	1.04–1.21	0.005	1.13	1.03–1.23	0.008
NT-proBNP	1.00	1.00–1.00	0.43	–		

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; IGT, impaired glucose tolerance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; PASP, pulmonary artery systolic pressure; PPG, peak transvalvular gradient; PTH, parathyroid hormone

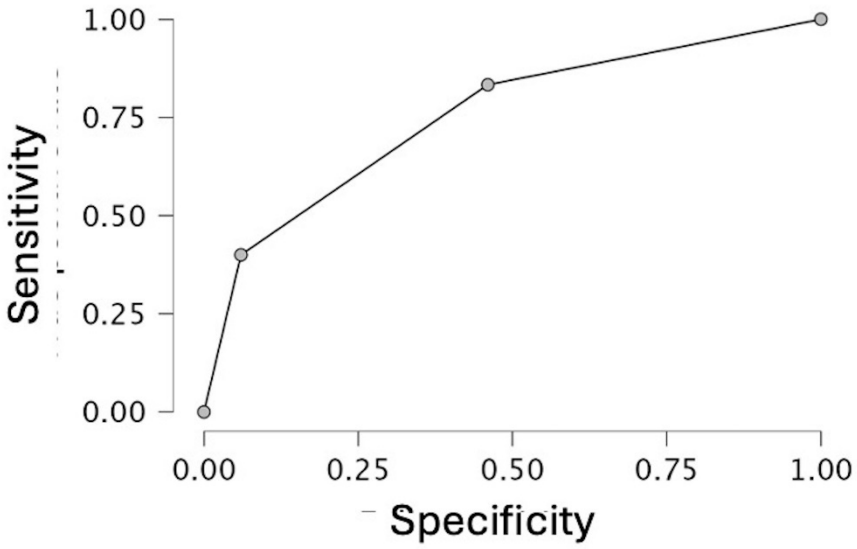

Figure 1. Receiver operating characteristic curve analysis for atrial fibrillation occurrence