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Peculiarities Of Changes Of Apelin-13 Concentration In Patients With Essential Hypertension And Extrasystole

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Changes of apelin-13 concentration in patients with essential hypertension and extrasystole
Short title: Apelin-13 concentration in patients with HT and extrasystole

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Abstract

Background: Hypertension is one of the leading causes of disability and mortality among cardiovascular diseases, so today new metabolic markers of cardiovascular risk are being actively studied. One of them is apelin-13.

The objective was to assess the concentration of apelin-13 in patients with essential hypertension and frequent extrasystoles.

Material and methods: One hundred fifty six patients with stage 2 essential hypertension were examined. One hundred twenty four of them had frequent symptomatic extrasystoles, 32 patients had no arrhythmias and were considered as the comparison group. Thirty apparently healthy normotensive persons were considered as the control group. All patients underwent a complete clinical and anthropometric examination, blood pressure measurement, automatic daily blood pressure monitoring, daily electrocardiogram monitoring, echocardiography and the assessment of serum apelin-13 concentration.

Results: It was found that the concentration of apelin-13 in patients with hypertension was significantly lower compared to the control group. Moreover, the average content of apelin-13 was significantly ($p = 0.02$) lower in patients with extrasystole than in those without arrhythmia. The lowest concentration of apelin-13 was noticed in patients with ventricular arrhythmias.

Conclusion: The results confirm the existing assumptions about the protective role of apelin-13 in preventing the progression of cardiovascular diseases due to counteracting the increase in blood pressure and life-threatening arrhythmias.
Key words: essential arterial hypertension; apelin-13; extrasystole; smoking; obesity

Introduction

Apelin-13 (AP13) is the most active form of pro-protein apelin, and it is considered adipokine as it is secreted by human adipocytes. Apelin receptors (namely the G-protein receptor of apelin, the old name — APG-receptor) were found in cardiomyocytes, endothelium, smooth muscle cells, brain, kidneys, and adrenal glands in high concentrations [1, 2].

The biological effects of apelin have been intensively studied over the last decade. Today, the weight of evidence supports the concept that apelin has a positive effect on the cardiovascular system because it counteracts the renin-angiotensin system, has an antihypertensive and positive inotropic effect. In addition, it has cardioprotective properties (reduces myocardial ischemia, improves heart contractility, and prevents myocardial hypertrophy) [3–5]. Further study of apelin and its receptors' properties has a great potential for the treatment of COVID-19, as the inhibition of angiotensin-converting enzyme production and angiotensin II production may reduce acute lung damage and thrombotic complications in COVID-19 [6].

Apelin concentration significantly decreases from the second day after acute myocardial infarction or ischemic stroke. In addition, the level of apelin is much lower in smokers compared to those who do not smoke [2, 7]. Additionally, the decrease in apelin levels promotes the arrhythmias progression, including life-threatening arrhythmias [8].

Apelin bears the potential of promoting obesity-related complications. However, its role in this matter remains unclear, as experimental data are inconsistent. In a study of young obese patients, plasma apelin levels were reduced compared to healthy patients. It can be partly explained by the progression of insulin resistance and its severity in obesity. Possible depletion of apelin's compensatory ability may be another explanation. However, another study showed that plasma apelin levels were significantly higher in obese children than in non-obese or overweight children [9, 10]. These controversial data can be explained by the differential expression of apelin in tissues, but certainly, this issue requires further careful study.

The aim of the study was to assess the changes of apelin-13 concentration in patients with essential hypertension and extrasystole.

Material and methods

The study included 156 patients with stage 2 essential hypertension (EH), including 124 with frequent symptomatic extrasystoles (aged 27 to 75 years). Another 32 patients with EH 2 (aged 32 to 72 years) had no cardiac arrhythmias and formed the comparison group. The study group consisted of 50 (40.3%) males and 74 (59.6%) females. The comparison group consisted of 15 (46.9%) men and 17 (53.1%) women. We also examined 30 healthy normotensive individuals (without cardiovascular disease or obesity), 16 (53.3%) men, and 14 (46.7%) women. There were no statistically significant differences between groups by age and sex ($p > 0.05$).

The criteria for inclusion of patients in the study were: 1) age from 25 to 75 years; 2) stage 2 EH; 3) frequent symptomatic premature beats (> 30 episodes of extrasystole per hour) verified by the data of the daily monitoring of the electrocardiogram; 4) absence of effective antiarrhythmic treatment at the time of inclusion; 5) consent of the patient to participate in the study.

Exclusion criteria were as follows: 1) age under 25 and over 75; 2) stage 1 or 3 hypertension; 3) diagnosed coronary heart disease, 4) heart failure greater than 2nd NYHA class and/or left ventricular ejection fraction < 40%; 5) the presence of prolonged episodes (> 20 s) of atrial fibrillation, persistent atrial fibrillation, or paroxysmal tachycardia; 6) diabetes7) alcohol or drug abuse; 8) severe neurological and mental disorders [11].

Frequent supraventricular extrasystoles (SVE) were registered in 74 (59.7%) and ventricular extrasystoles (VE) — in 50 (40.3%) patients of the main group. Arrhythmic history ranged from 1 to 27 years and the average was 8.06 ± 0.42 years.

All patients were examined and underwent clinical, laboratory, and additional tests at entry. General clinical and anthropometric examination, office blood pressure (BP) measurement, 12-lead ECG, daily BP monitoring, standard 12-lead ECG, and apelin-13 serum concentrations were performed in all patients who agreed to participate in the study.

The anthropometric examination included measurement of height and weight with the calculation of the body mass index (BMI), waist circumference (WC), and hip circumference (HC). BP was measured according to the current standard with Microlife device.

Daily BP monitoring (DBPM) and Holter ECG monitoring (HM) were performed using the hardware and software “DiaCard” (JSC “Solvaig”, Ukraine) according to the standard protocol.

The echocardiography in one- and two-dimensional modes with color, pulse, and continuous-wave Doppler imaging was used for the assessment of the structural-functional state of the heart (equipment My Lab 25, Italy).

The concentration of apelin-13 (AP13) in the serum was determined by enzyme-linked immunosorbent assay (ELISA) using Human AP13 ELISA kit (Elabscience, United States) according to the manufacturer's instructions.

Statistical processing was performed using the software “Statistica” v.12.0 (StatSoft). The results are presented as the mean (M) and the mean error (m) and the median with Q1 and Q3 where appropriate. In addition, χ^2, Kruskal-Wallis ANOVA test and median tests were employed [11].

All patients signed an informed consent, and the study was conducted in line with the Helsinki Declaration and the International Code of Medical Ethics.

Results

Clinical characteristic of analyzed subgroups is presented in Table 1. Stage 2 hypertension patients were more likely to be diagnosed with higher fasting glucose. Additionally, BMI in the study group was 31.40 ± 0.43 kg/m^2, compared to 30.21 ± 0.93 kg/m^2 in the reference **groups {???}** (p = 0.046). Higher rates of the abdominal obesity (60.5% vs. 37.5%, p = 0.02) was observed in the study group (Tab. 1).

The levels of AP13 in the general sample, in patients of different clinical groups, and healthy individuals are shown in Figures 1–4. In patients with essential hypertension, the concentration of AP13 was significantly lower (p <0.0001) compared with healthy individuals, both in patients with EH 2 and arrhythmias, and EH 2 without arrhythmias (Fig. 1). Furthermore, the average concentrations of AP13 in patients with hypertension without arrhythmias were significantly higher than in patients with hypertension and extrasystole (Fig. 2). The lowest concentration of AP13 was documented in patients with VE, which contrasted with concentrations seen in patients with SVE [814 (730–987) pg/mL *vs.* 947 (765–1227) pg/mL, respectively, p = 0.0006], and the patients with hypertension but without arrhythmias [814 (730–987) pg/mL *vs.* 1045 (823–1425) pg/mL, p < 0.0001]. In otherwise healthy smokers, the concentration of AP13 was significantly lower than in healthy individuals free of smoking habit [1347 (958–1458) pg/mL *vs.* 1046 (689–1254) pg/mL, p = 0.02] (Fig. 3). Patients with stage 2 HTN who were smokers had a tendency to a decreased AP13 level as compared with non-smoking patients [874 (688–1087) pg/mL *vs.* 934 (768–1184) pg/mL, p = 0.05) (Fig. 4).

Discussion

The main finding of our study is that average concentration of apelin-13 in patients with stage 2 hypertension was significantly lower as compared to healthy individuals (p < 0.0001).

The antihypertensive properties of apelin-13, which are associated with the apelin receptor of the APJ system that opposes actions of renin-angiotensin system, and its vasodilating effect is tied with nitric oxide — one of the main mediators of the apeline protective effect [2, 4, 7].

We have also documented that patients with stage 2 HTN and arrhythmias, had lower concentration of AP13 when compared to hypertensives free of cardiac arrhythmias. These data suggest that lower AP13 level is associated with more severe cardiac arrhythmias, namely frequent VE, and to some extent corresponds to previously published data [2]. The phenomenon of lowest AP13 concentrations supports the concept that failure in AP13 production may promote or mediate life-threatening arrhythmias [8, 11, 12].

Smokers were documented to have reduced levels of AP13, which may then translate to endothelial dysfunction [2, 7]. Our results support this phenomenon.

Interestingly, data on the relation between apelin levels and obesity-related morbidity progression were inconsistent [5, 9, 10]. Although our results did not support any of these concepts, yet it is mainly due to low statistical power. Nevertheless, one may speculate that other factors should be taken into account such as differential expression of apelin in tissues as well as the possible depletion of compensatory production of apelin in obese patients.

Conclusion

In patients with stage 2 hypertension, the concentration of apelin-13 is significantly lower when compared to healthy individuals. Furthermore, the concentrations of AP13 are different when more severe hypertension-mediated organ damage is evident, i.e., ventricular arrhythmias.

Conflict of interest

Not declared.

References

1. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020; 75(6): 1334–1357, doi: 10.1161/HYPERTENSIONAHA.120.15026, indexed in Pubmed: 32370572.

2. Tian Y, Chen R, Jiang Y, et al. The Protective Effects and Mechanisms of Apelin/APJ System on Ischemic Stroke: A Promising Therapeutic Target. Front Neurol. 2020; 11: 75, doi: 10.3389/fneur.2020.00075, indexed in Pubmed: 32194492.

3. Koguchi W, Kobayashi N, Takeshima H, et al. Cardioprotective effect of apelin-13 on cardiac performance and remodeling in end-stage heart failure. Circ J. 2012; 76(1): 137–144, doi: 10.1253/circj.cj-11-0689, indexed in Pubmed: 22082814.

4. Tycinska AM, Lisowska A, Musial WJ, et al. Apelin in acute myocardial infarction and heart failure induced by ischemia. Clin Chim Acta. 2012; 413(3-4): 406–410, doi: 10.1016/j.cca.2011.11.021, indexed in Pubmed: 22146598.

5. Hu G, Wang Z, Zhang R, et al. The Role of Apelin/Apelin Receptor in Energy Metabolism and Water Homeostasis: A Comprehensive Narrative Review. Front Physiol. 2021; 12: 632886, doi: 10.3389/fphys.2021.632886, indexed in Pubmed: 33679444.

6. Saravi SS, Beer J. Apelin-potential therapy for COVID-19? J Mol Cell Cardiol. 2020; 145: 84–87, doi: 10.1016/j.yjmcc.2020.06.007, indexed in Pubmed: 32562701.

7. Wang X, Tian X, Pei LL, et al. The Association Between Serum Apelin-13 and the Prognosis of Acute Ischemic Stroke. Transl Stroke Res. 2020; 11(4): 700–707, doi: 10.1007/s12975-019-00769-w, indexed in Pubmed: 31965512.

8. Falcone C, Buzzi MP, D'Angelo A, et al. Apelin plasma levels predict arrhythmia recurrence in patients with persistent atrial fibrillation. Int J Immunopathol Pharmacol. 2010; 23(3): 917–925, doi: 10.1177/039463201002300328, indexed in Pubmed: 20943064.

9. Wysocka MB, Pietraszek-Gremplewicz K, Nowak D. The Role of Apelin in Cardiovascular Diseases, Obesity and Cancer. Front Physiol. 2018; 9: 557, doi: 10.3389/fphys.2018.00557, indexed in Pubmed: 29875677.

10. El Wakeel MA, El-Kassas GM, Kamhawy AH, et al. Serum Apelin and Obesity-Related Complications in Egyptian Children. Open Access Maced J Med Sci. 2018; 6(8): 1354–1358, doi: 10.3889/oamjms.2018.312, indexed in Pubmed: 30159056.

11. Kuzminova NV, Ivankova AV, Lozinsky SE, et al. State of kidney function and features of metabolic status changes in patients with different forms of extrasystols. World Med Biol. 2019; 15(69): 083, doi: 10.26724/2079-8334-2019-3-69-83-89.

12. Hoogendijk MG, Géczy T, Yap SC, et al. Pathophysiological Mechanisms of Premature Ventricular Complexes. Front Physiol. 2020; 11: 406, doi: 10.3389/fphys.2020.00406, indexed in Pubmed: 32528299.

Table 1. Clinical characteristics of patients with stage 2 hypertension in the study group and comparison group

Features	Study group (n = 124)	Reference (n = 32)	p-value
Age (M > 55; W > 65 years)	71 (57.3%)	14 (43.8%)	0.17
PP > 60 mm Hg	58 (46.8%)	10 (31.3%)	0.11
Smoking	47 (37.9%)	11 (34.4%)	0.71
Dyslipidemia (TCL > 5 mmol/L or LDL-C > 3 mmol/L or TG > 1.7 mmol/L)	110 (88.7%)	27 (84.4 %)	0.50
Fasting glucose of 5.6–6.9 mmol/L	37 (29.8%)	4 (12.5%)	0.04
WC (M > 102; W > 88 cm)	92 (74.2%)	19 (59.4%)	0.09
Family history of CVD	91 (73.4%)	17 (53.1%)	0.03
The presence of AP in the CA pool	29 (23.4%)	8 (25.0%)	0.84
TIM > 0.9 mm	64 (51.6%)	17 (53.1%)	0.87
BMI, kg/m^2	31.93 ± 0.42	30.21 ± 0.93	0.046
NW (BMI 18.5–25.0 kg/m^2)	8 (6.5%)	8 (25.0%)	0.002
OW (BMI 25.1–30.0 kg/m^2)	41 (33.1%)	12 (37.5%)	0.64
Obesity (BMI > 30 kg/m^2)	75 (60.5%)	12 (37.5%)	0.02

M — men; W — women; PP — pulse pressure; TCL — total cholesterol; LDL-C — low density lipoprotein cholesterol; TG — triglycerides; WC — waist circumference; CV — cardiovascular; AP — atherosclerotic plaques; CA — carotid arteries; TIM — thickness of intima/media ratio; BMI — body mass index; NW — normal weight; OW — overweight

Intergroup significance of the difference between mean values calculated by t-test for independent samples, % — by χ^2 criterion

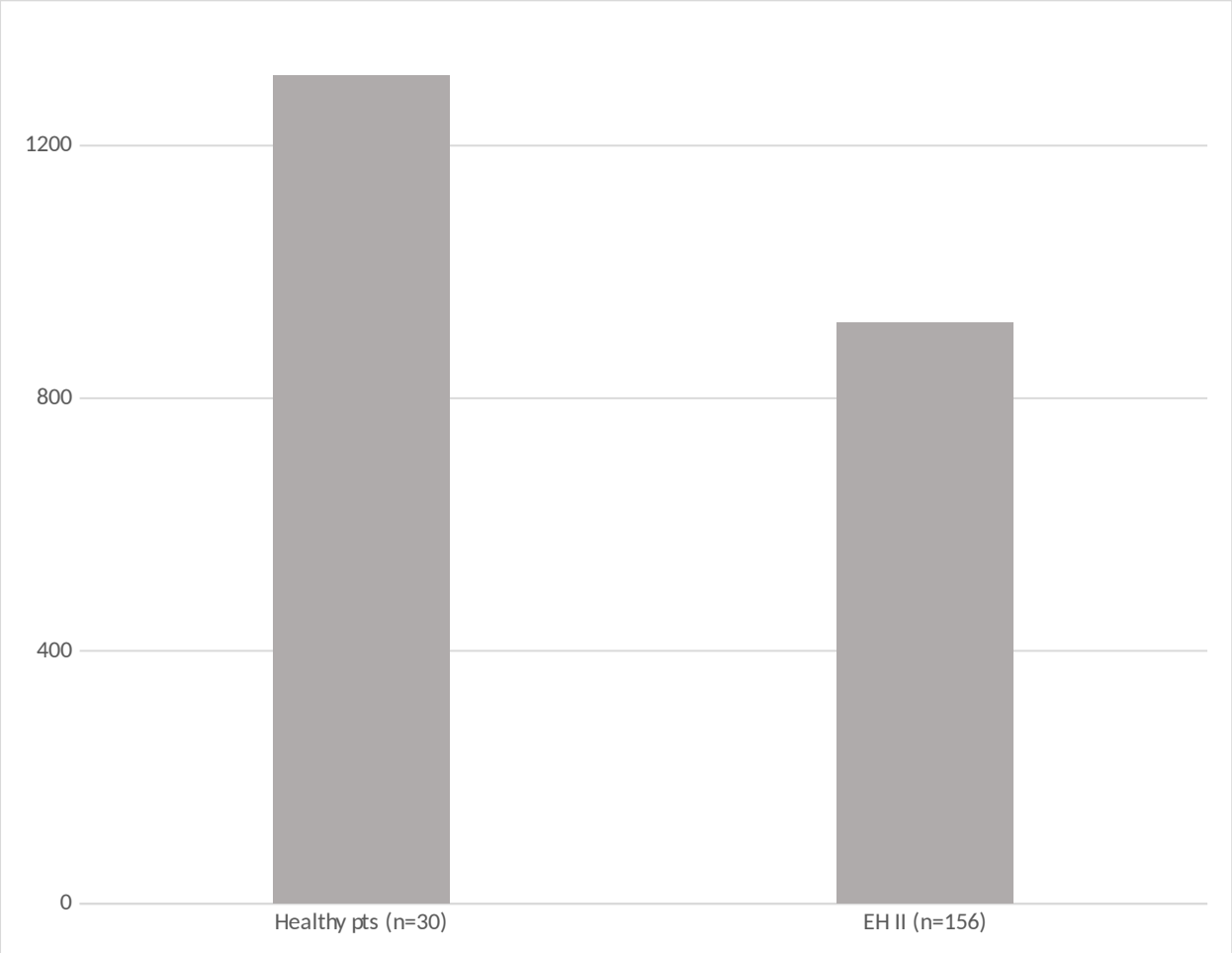

Figure 1. The concentration of apelin-13 in blood serum (pg/mL) in healthy patients and patients with stage 2 essential hypertension (EH)

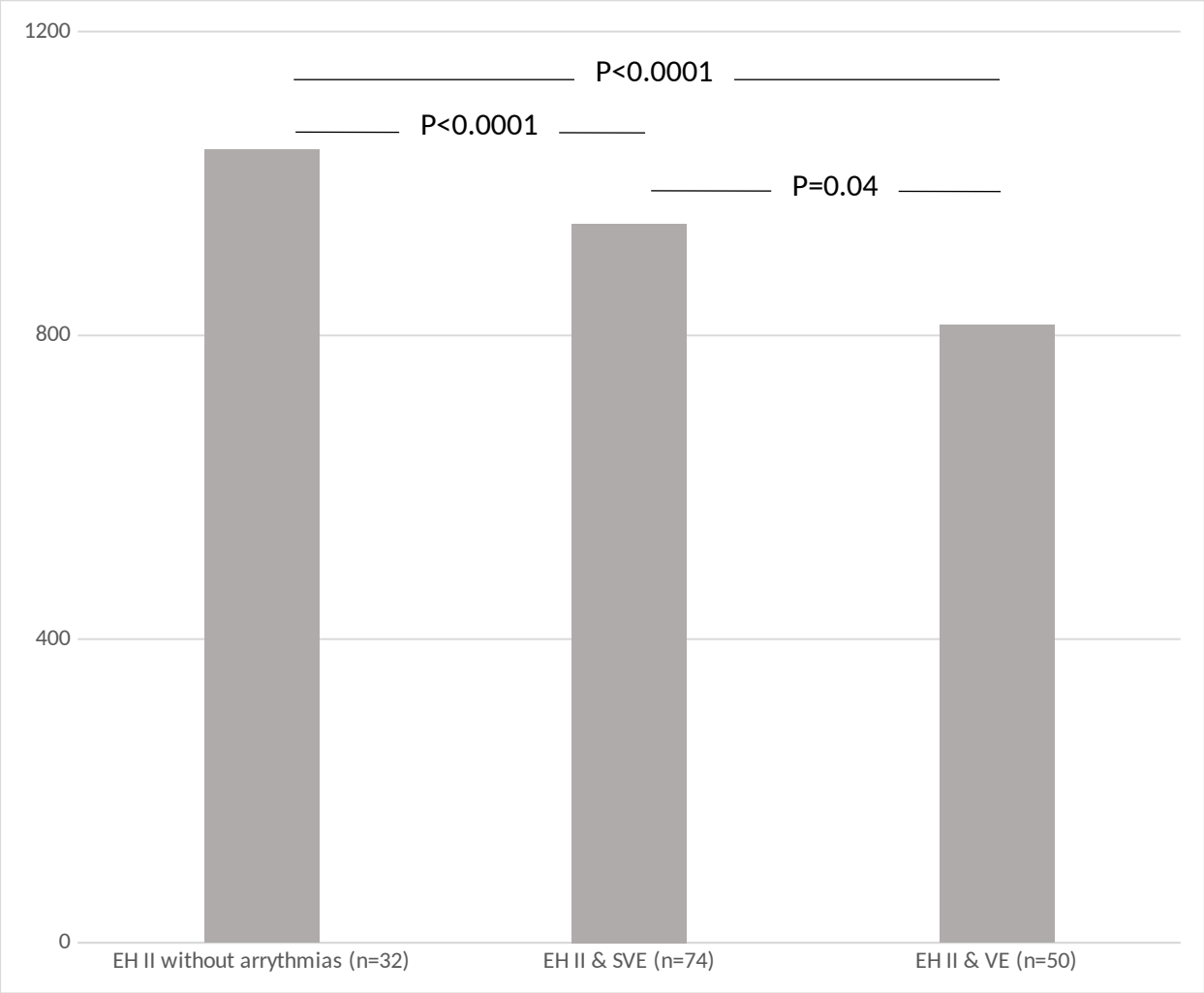

Figure 2. The concentration of apelin-13 in blood serum (pg/mL) in different clinical groups. EH — essential hypertension; SVE — supraventricular extrasystoles

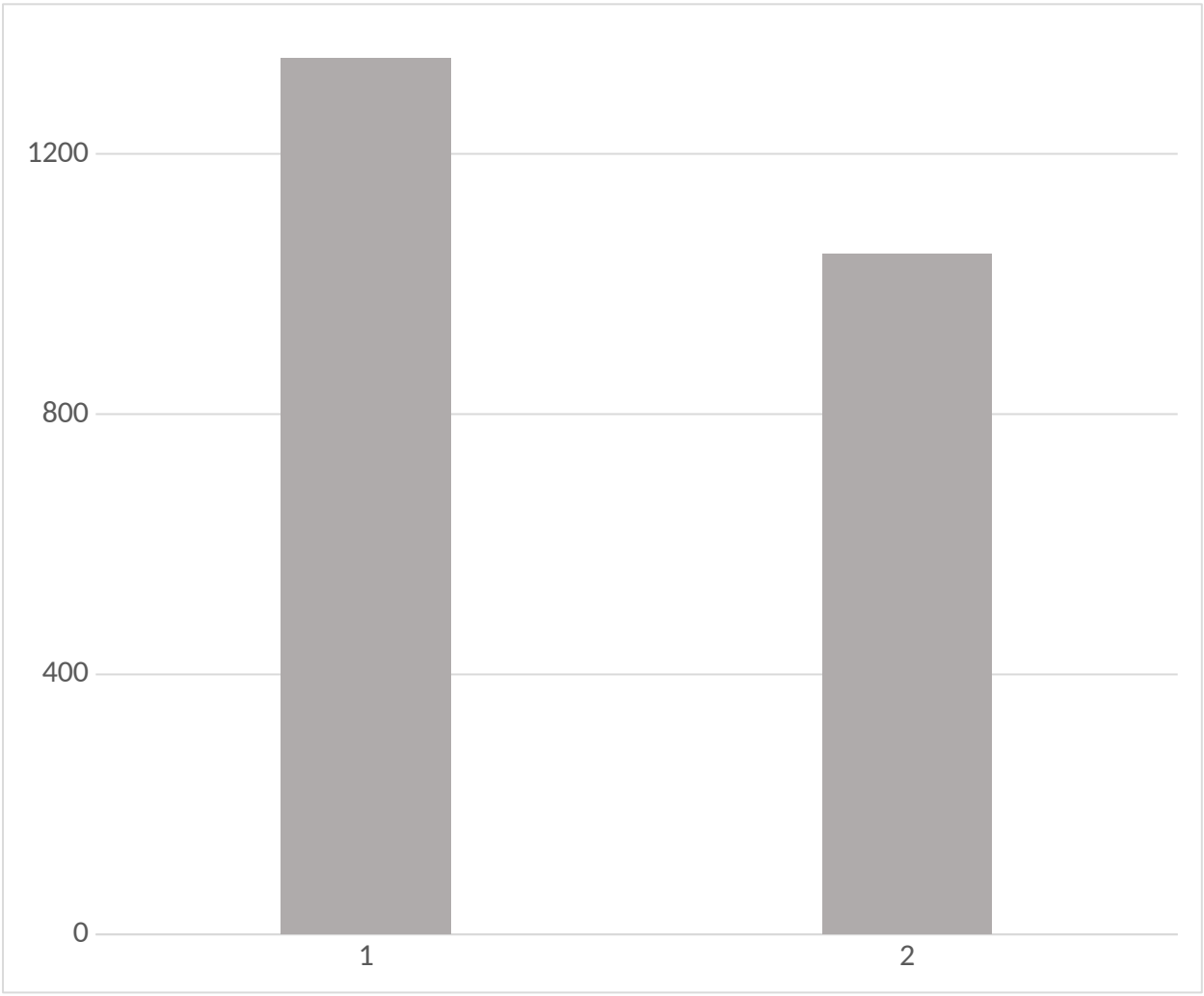

Figure 3. The concentration of apelin-13 in blood serum (pg/mL) in healthy smokers (1) and non-smokers (2)

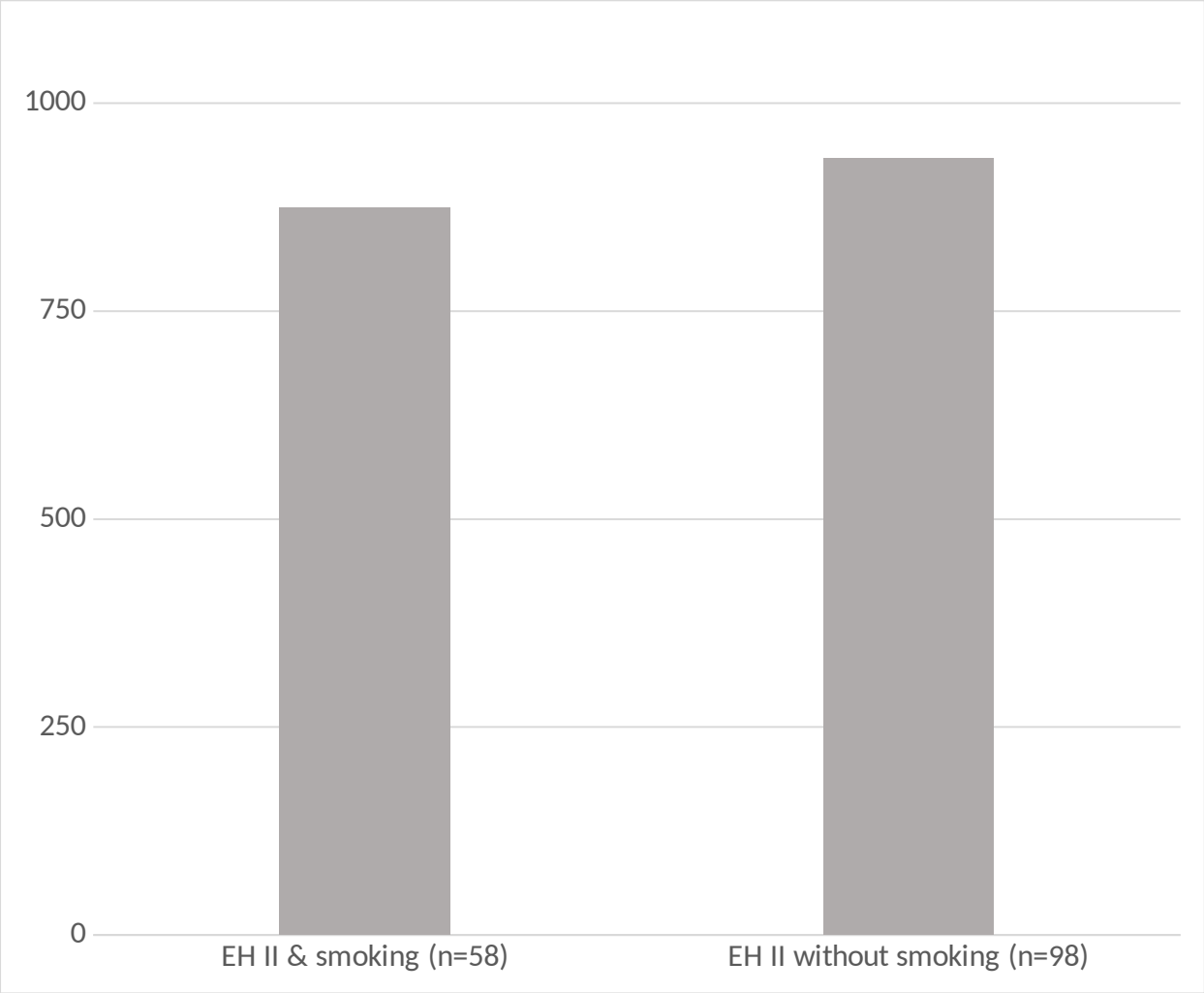

Figure 4. The concentration of apelin-13 in blood serum (pg/mL) in patients with essential hypertension (EH) 2 depending on smoking status