ORIGINAL ARTICLE

Leptin, adiponectin, tumor necrosis factor α, and irisin concentrations as factors linking obesity with the risk of atrial fibrillation among inpatients with cardiovascular diseases

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KEY WORDS
adiponectin, atrial fibrillation, irisin, leptin, tumor necrosis factor α

ABSTRACT

BACKGROUND The endocrine function of adipose tissue and skeletal muscles mediates the risk of cardiovascular complications of obesity.

AIMS The aim of this study was to determine the associations of leptin, adiponectin (ADA), tumor necrosis factor α (TNF-α), and irisin levels with the diagnosis of atrial fibrillation (AF) on admission to the hospital as well as parameters of transthoracic echocardiography among inpatients with cardiovascular diseases (CVDs).

METHODS The study included 80 consecutive patients hospitalized due to paroxysmal or persistent AF and a control group of 165 age- and sex-matched individuals admitted due to exacerbation of chronic CVD. In all participants, we assessed serum leptin, ADA, TNF-α, and irisin concentrations, body composition determined by bioelectrical impedance analysis, and transthoracic echocardiographic parameters.

RESULTS Compared with controls, patients with AF had greater fat mass (FM), higher serum leptin levels and lower levels of ADA, TNF-α, and irisin when indexed to body surface area, FM, and visceral adiposity. Hyperleptinemia slightly increased the risk of AF (odds ratio [OR], 1.02; 95% CI, 1.01–1.03; P <0.01). The correlation was stronger after indexation to FM (OR, 1.34; 95% CI, 1.01–1.81; P <0.05). The coefficients of significant correlations with echocardiographic parameters were stronger for irisin than for adipocytokines: 0.16 to 0.35 and 0.12 to 0.22, respectively.

CONCLUSIONS Adipocytokines and irisin exert a significant but weak effect on heart chamber size and affect the risk of AF occurrence. Their blood concentrations do not seem to be related simply to body composition but probably depend on individual variations in adipocytokine and myokine secretion as a result of numerous factors.

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INTRODUCTION There is evidence for an association between nutritional status and an increased risk of cardiovascular disease (CVD), including atrial fibrillation (AF).[1-6] However, among patients with CVD, overweight and class 1 obesity (BMI ≤30; <35 kg/m^2) are also related to better prognosis, which is referred to as the "obesity paradox" or "lean paradox."[1-3] Recently discussed issues concerning the relationships between nutritional status and the risk of CVD include the limitations of body mass index (BMI) for cardiometabolic risk stratification, the importance of individual variance in adipose tissue distribution, and the concepts of

WHAT'S NEW?

Blood concentrations of adipocytokines, hormones secreted by adipose tissue, are considered to link obesity with cardiovascular disease (CVD). However, in our study, they were only weakly related to the risk of atrial fibrillation (AF). We also found only weak correlations between blood adipocytokine concentrations and both the body composition and echocardiographic parameters. Circulating irisin, a substance secreted by skeletal muscles, showed a stronger correlation with the risk of AF and echocardiographic parameters than the adipocytokines. The weak correlations between the parameters of body composition and circulating adipocytokines and irisin suggest the presence of disturbances in the regulation of their secretion among patients with AF and other CVDs.

"metabolically healthy obesity" and the "fat but fit" phenomenon.[1-4,7] A potential pathomechanism linking body composition with CVD risk is inflammation[1-5,8,9] as well as an imbalance in the secretion of various adipocytokines and myokines produced in adipose tissue and skeletal muscles, respectively.[10,11] However, studies reported thus far in the literature provide ambiguous conclusions concerning the role of the endocrine function of adipose tissue and skeletal muscles in relation to AF risk.[4-30] For example, adiponectin (ADP) has been shown to have antidiabetic, antiatherogenic, and anti-inflammatory properties in experimental studies.[11-15] Nevertheless, the outcomes of clinical studies concerning the relationship between blood ADP concentrations and CVD risk are ambiguous.[13-18] Leptin exerts proinflammatory and profibrotic activities,[19,21,24] which can affect AF risk by causing electrical and structural heart remodeling and disturbances in cardiac and vascular function.[10,19,21,30,31] However, not all studies confirm these effects of leptin.[20,21,24,25] Similarly, there is currently no evidence on cardiovascular effects of increased blood levels of tumor necrosis factor α (TNF-α), a cytokine with proinflammatory and profibrotic activity that is secreted mainly through adipose tissue.[19,22] Irisin, a myokine, potentially exerts a favorable effect on the cardiovascular system,[9,23] but data concerning its relationships with CVD and AF risk are scarce.

In this study, we aimed to determine the associations between blood concentrations of selected adipocytokines (leptin, ADP, and TNF-α) as well as a myokine (irisin) and the diagnosis of AF on admission to the hospital, body composition, and transthoracic echocardiographic parameters. We also evaluated the risk of AF on admission associated with blood leptin, ADP, TNF-α, and irisin concentrations among patients with CVD.

METHODS

Patients This observational study included 80 consecutive patients hospitalized due to paroxysmal or persistent AF. The control group consisted of 165 consecutive inpatients with no history of AF and no indication of AF on admission electrocardiogram (ECG), who were hospitalized for exacerbation of several forms of CVD, such as a shortening of claudication distance, angina pectoris, and hypertension. The exclusion criteria for both groups were a history or clinical signs of inflammatory processes or malignancy, lack of informed consent for participation in the study, and an implanted mechanical valve, cardioverter, or cardiostimulator. At least 1 year following discharge, all participants (or their relatives) took part in a standardized telephone interview conducted by the same physician.

Determination of adipocytokine and irisin levels Serum leptin, ADP, TNF-α, and irisin levels were measured using enzyme-linked immunosorbent assay kits (leptin, cat. no. 11-LEPHU-E01, ALPCO, Salem, Massachusetts, United States; ADP, cat. no. 80-ADPHU-E01, ALPCO; TNF-α, cat. no. CSB-E04740h, CUSABIO, Houston, Texas, United States; irisin, cat. no. RAG018R, BioVendor, Brno, Czech Republic). All parameters were determined in accordance with the manufacturers' instructions and indexed to adjust for the effect of differences in body composition between the AF and control groups (TABLE 1).

Parameters of nutritional status assessment Nutritional status was assessed for all study participants. Body composition was determined using a bioelectrical impedance analysis (BIA) and a TANITA BC-420 MA device (TANITA Corporation, Tokyo, Japan). The following BIA parameters were analyzed: fat mass (FM) (%, kg); visceral adipose tissue (VAT) score (range, 1–59); fat-free mass (kg); and skeletal muscle mass (%, kg).

Parameters of transthoracic echocardiography Echocardiography was performed in all participants on admission by the same experienced cardiologist, using an Aplio transthoracic ultrasound device (TOSHIBA, Canon, Tustin, California, United States) and a 2- to 5-MHz radial probe. The following echocardiographic parameters were analyzed: left ventricular end-diastolic dimension (LVEDD), interventricular septum thickness (IVST) at end diastole, posterior wall thickness (PWT), left ventricular ejection fraction (LVEF), left ventricular mass (LVM), as well as left atrial area (LAA) and left atrial volume (LAV) in the apical 4- and 2-chamber views (LAA4, LAV4 and LAA2, LAV2, respectively). The LVM, LAA2, LAA4, LAV2, and LAV4 were indexed to body surface area (BSA) to obtain the LVM, LAA, and LAV indices. The biplane 2-dimensional method of disks (modified Simpson's rule) in apical 4- and 2-chamber views was used

TABLE 1 Clinical characteristics of patients with atrial fibrillation and controls

Parameter	Atrial fibrillation (n = 80)	Control group (n = 165)	*P* value[c]
Age, y, median (SD)	69.50 (8.87)	69.21 (9.29)	0.81
Male sex, n (%)	41 (51.3)	88 (53.33)	0.88
Smoking, past / current, n (%)	8 (10.0) / 30 (37.5)	56 (33.94) / 77 (46.67)	<0.01
Diabetes mellitus, n (%)	30 (37.5)	72 (43.64)	0.58
Dyslipidemia, n (%)	70 (87.5)	146 (88.48)	0.82
Hypertension, n (%)	68 (85)	141 (85.45)	0.92
History of myocardial infarction, n (%)	8 (10)	50 (30.3)	0.02
CHA_2DS_2VASc score[a], median (SD)	3.16 (1.56)	4.09 (1.61)	<0.01
BMI, kg/m^2, median (SD)	31.26 (6.07)	27.32 (4.91)	<0.01
BMI range[b], <18.5 / 18.5–24.99 / 25–29.99 / >30 kg/m^2, n (%)	0 / 10 (12.5) / 25 (31.25) / 45 (56.25)	0 / 45 (27.27) / 79 (47.88) / 41 (24.85)	<0.01
Central adiposity in reference to WHtR, n (%)	54 (67.50)	80 (48.48)	<0.01
FM, %, median (SD)	36.20 (9.56)	30.55 (9.37)	<0.01
FM, kg, median (SD)	32.59 (12.46)	23.65 (10.02)	<0.01
SMM, kg, median (SD)	36.15 (5.34)	39.40 (5.44)	<0.01
VAT score, median (SD)	15.43 (4.87)	12.25 (3.82)	<0.01
LVEDD, mm, median (SD)	50.65 (7.34)	46.61 (9.50)	<0.01
IVST at end diastole, mm, median (SD)	12.01 (1.82)	11.19 (1.81)	<0.01
LVEF, %, median (SD)	53.44 (10.42)	59.77 (10.15)	<0.01
LAV4, mm^3, median (SD)	106.16 (36.02)	70.86 (24.94)	<0.01
LAVI, mm^3/m^2, median (SD)	52.86 (19.45)	37.78 (12.2)	<0.01
LVM, g, median (SD)	246.50 (81.27)	196.09 (69.29)	<0.01
LVMI, g/m^2, median (SD)	121.22 (35.54)	104.51 (32.43)	<0.01
ACEIs, n (%)	49 (61.25)	112 (67.88)	0.67
β-Blockers, n (%)	71 (88.75)	125 (75.76)	<0.01
Statins, n (%)	52 (65)	165 (100)	<0.01
Anticoagulants, VKAs / NOACs, n (%)	42 (52.5) / 38 (47.5)	1 (0.61) / 2 (1.21)	<0.01

a Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke or thromboembolism, vascular disease, age 65–74 years, female sex

b According to World Health Organization

c Mann–Whitney test or 2-tailed χ^2 test

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; BMI, body mass index; FM, fat mass; IVST, interventricular septum thickness; LAV4, left atrial volume calculated in 4-chamber view; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMI, left ventricular mass index; NOAC, non–vitamin K antagonist oral anticoagulant; SMM, skeletal muscle mass; VAT, visceral adipose tissue; WHO, World Health Organization; WHtR, waist-to-height ratio; VKA, vitamin K antagonist

to assess LVEF. Left ventricular mass was calculated using the following formula: LVM (g) = 0.8 × {1.04 × ([LVEDD + IVST + PWT]^3 – LVEDD^3)} + 0.6. Body surface area was calculated using the following formula: BSA (m^2) = 0.01666667 × height$^{0.5}$ × body mass$^{0.5}$.

Ethical approval The study was conducted in compliance with the Declaration of Helsinki for medical research, after receiving permission from the local bioethics committee (No. 389/2015). Each patient gave written consent to participate in the study.

Statistical analysis Statistical analysis was conducted using a licensed version of the STATISTICA software, version 13.1 (TIBCO Softwares, Palo Alto, California, United States). The normal distribution of the study variables was checked using the Shapiro–Wilk test. The results were mainly presented as the mean (SD), median (interquartile range), or number (percentage). The significance of differences between groups was verified using the *t* test, Mann–Whitney test, and 2-tailed χ^2 test. A logit model using the Generalized Linear/Nonlinear Models module was used to determine the odds ratios (ORs) and 95% CI as parameters of the risk of AF occurrence associated with unitary changes (eg, per 1 pg/ml) in blood adipocytokine and myokine concentrations. Spearman correlations were assessed to determine the relationships between adipocytokine and irisin levels and the parameters of transthoracic echocardiography and body composition. The significance level was set at a *P* value of less than 0.05.

RESULTS

Clinical characteristics Compared with the control group, patients with AF significantly less often were smokers, less often had coronary artery disease, and more often had obesity, especially in terms of abdominal adiposity (increased waist-to-height ratio). They also had a higher FM and VAT score as well as lower skeletal muscle mass (TABLE 1). Moreover, they had a greater LVEDD, IVST, LAV, LAV index (calculated as the ratio of LAV to BSA), LVM, LVM index, and lower LVEF (TABLE 1). Finally, they significantly more often used β-blockers and anticoagulants and less often took statins compared with controls.

Parameters of endocrine function of adipose tissue and skeletal muscle Compared with the control group, patients with AF had higher blood levels of leptin and of leptin adjusted for BSA (TABLE 2). They also had lower ratios of ADP to leptin levels and ADP to C-reactive protein (CRP) levels. Finally, they had lower ADP and TNF-α levels indexed to BSA, FM, and VAT score.

TABLE 2 Blood adipocytokine and irisin concentrations and their selected indexed values in patients with atrial fibrillation and controls

Parameter	Atrial fibrillation (n = 80)	Control group (n = 165)	*P* value[a]
Leptin, pg/ml	36.94 (18.26–86.61)	18.34 (8.84–45.22)	<0.01
Leptin-to-BSA ratio	19.20 (8.78–40.86)	9.77 (5.00–24.75)	<0.01
Leptin-to-FM ratio	1.17 (0.64–2.1)	0.91 (0.48–1.91)	0.88
Leptin-to-VAT ratio	2.57 (1.12–5.61)	1.51 (0.76–4.4)	0.14
ADP, pg/ml	4.86 (1.60–12.64)	5.76 (3.16–10.95)	0.18
ADP-to-BSA ratio	2.29 (0.85–6.12)	3.03 (1.67–5.47)	0.11
ADP-to-leptin ratio	0.11 (0.03–0.30)	0.28 (0.10–0.71)	0.01
ADP-to-CRP ratio	1.29 (0.21–5.63)	2.17 (0.65–6.75)	0.02
ADP-to-FM ratio	0.15 (0.05–0.39)	0.25 (0.14–0.53)	0.04
ADP-to-VAT ratio	0.29 (0.10–0.85)	0.49 (0.26–0.93)	0.03
TNF-α, pg/ml	22.61 (6.04–45.71)	30.83 (7.57–63.72)	0.77
TNF-α-to-FM ratio	0.72 (0.21–1.64)	1.31 (0.47–2.84)	0.01
TNF-α-to-VAT ratio	1.52 (0.44–3.6)	2.57 (0.83–4.9)	0.04
Irisin, μg/ml	10.92 (7.90–13.86)	11.15 (7.38–16.82)	0.17
Irisin-to-BSA ratio	5.43 (3.85–7.24)	6.05 (3.94–8.82)	0.02
Irisin-to-FM ratio	0.35 (0.24–0.48)	0.54 (0.33–0.81)	0.01
Irisin-to-VAT ratio	0.79 (0.47–0.98)	0.93 (0.60–1.51)	<0.01
Irisin-to-SMM ratio	0.34 (0.24–0.48)	0.40 (0.26–0.61)	0.03

Data are presented as median (interquartile range).

a Mann–Whitney test

Abbreviations: ADP, adiponectin; BSA, body surface area; CRP, C-reactive protein; TNF-α, tumor necrosis factor α; others, see TABLE 1

Adipocytokines, irisin, body composition, and echocardiographic parameters We found significant correlations of blood adipocytokine and irisin concentrations, both in relation to their crude and adjusted values, with parameters of transthoracic echocardiography and body composition (data not shown). The correlations were mostly positive for blood leptin concentrations and negative for ADA, irisin, and TNF-α, expressed as crude values and as values indexed to BSA and FM. However, the blood concentrations of the adipocytokines and irisin explained no more than 12.3% of the variance in the echocardiographic parameters (the correlation coefficients were 0.12 to 0.22 for adipocytokines and 0.16 to 0.35 for irisin). The strongest correlations among the indexed values were observed for leptin and TNF-α indexed to BSA as well as for irisin indexed to FM. However, the parameters of body composition explained only 25% on average of the variance in the adipocytokine and myokine levels.

Adipocytokines, irisin, and the risk of atrial fibrillation Using a logistic regression model, we confirmed significant associations between the risk of AF on admission and leptin, ADA, TNF-α, and irisin levels (FIGURE 1). The AF risk increased with increasing blood leptin concentrations (by 2%), blood leptin concentrations indexed to BSA (by 2%), and blood leptin concentrations indexed to FM expressed as a percentage of whole body mass (by 34%). A significant reduction in the risk of AF on admission was linked with increased ratios of ADP to leptin (by 61%), ADP to CRP (by 4%), ADP to FM expressed in kg (by 50%), and ADP to VAT score (by 28%). However, these associations were weaker than the relationships between the risk of AF and the indexed values of irisin. The risk of AF decreased with an increase in the ratio of blood irisin levels to FM expressed in kg (by 81%) and irisin to VAT (by 67%). No significant relationship was found between the crude value of TNF-α concentrations and AF risk, but the ratios of TNF-α to FM and TNF-α to VAT score appear to have a significant inverse relationship with AF risk (FIGURE 1).

DISCUSSION Our prospective observational study was conducted in a cohort of consecutive inpatients with AF and a high prevalence of cardiometabolic risk factors (TABLE 1), who were matched for age and sex with individuals with mild nonarrhythmic cardiovascular disorders. Compared with controls, we found that individuals with AF had significantly higher FM, blood leptin concentrations, and leptin-to-BSA ratio. Although an increase in crude blood leptin concentrations by 1 pg/ml increased AF risk by 2% on average, indexing blood leptin concentrations to FM expressed as a percentage of whole body mass increased the risk of AF by 34% on average. This may suggest that the proarrhythmic effect of obesity[4-6,32] does not simply depend on body composition and adipocytokine levels but mainly on individual differences in imbalance in the secretive activity of adipose tissue and skeletal muscles (eg, 1 kg of FM produced more leptin and less ADA in patients with AF than in controls). These variations may be related to genetic factors (eg, gene polymorphism), physical activity, adipose distribution (eg, higher VAT score), sensitivity of adipocytokine receptors, and insulin resistance, the latter being an important factor leading to hyperleptinemia and a cross-talk between the adipose tissue, skeletal muscles, and liver.[1-4,9,23,32] We did not confirm the importance of adipose tissue distribution on the proarrhythmic effect of visceral obesity because the measured adipocytokines and irisin indexed to VAT were not associated with the risk of AF on admission (leptin) or were associated with a lower reduction in this risk (ADP, TNF-α, irisin) than the same parameters indexed to FM. Nonetheless, our results suggest that higher blood leptin concentrations and lower ADP and irisin levels indexed to FM and VAT may be

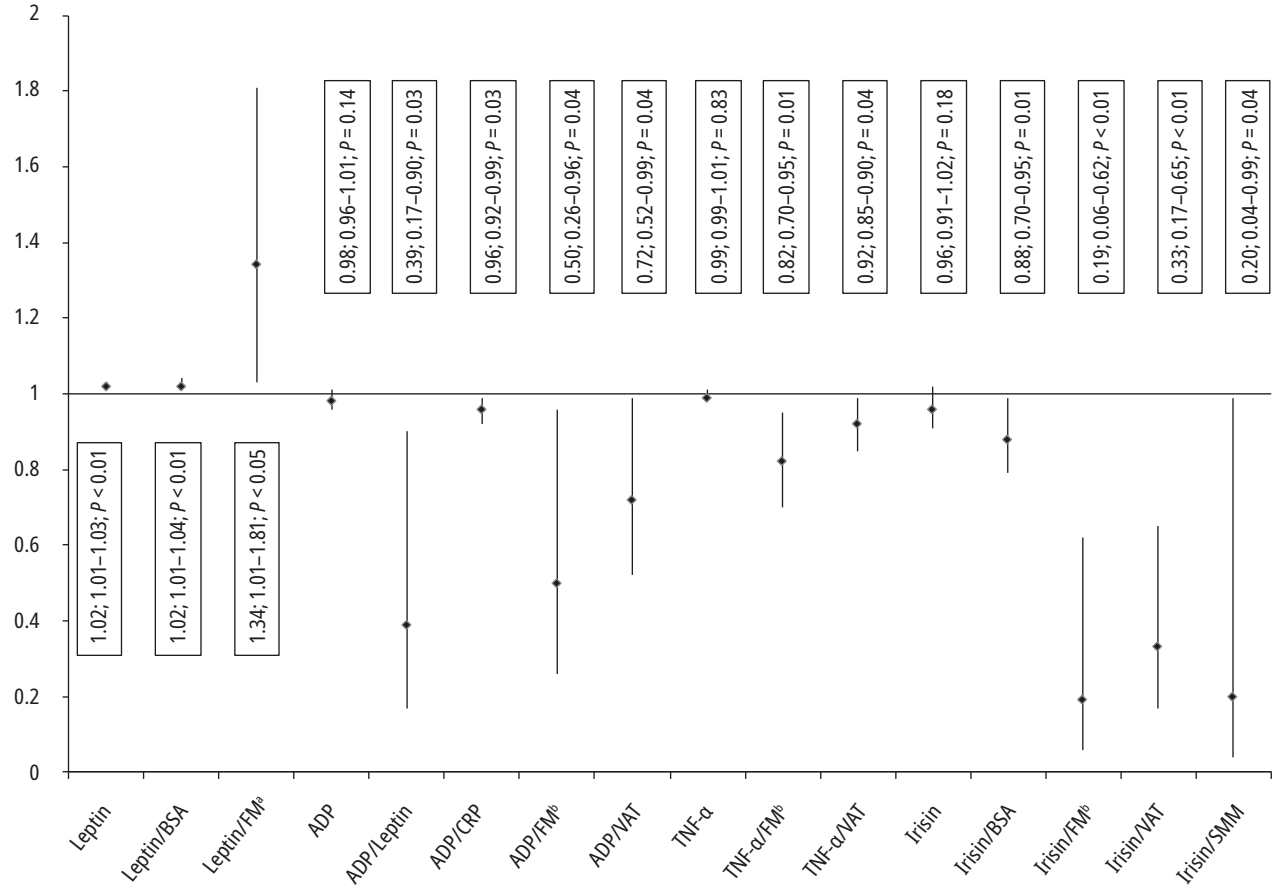

FIGURE 1 Association between the risk of atrial fibrillation on admission and selected crude and indexed blood adipocytokine and irisin concentrations. Fat mass expressed in percentage (**a**) or kilogram (**b**). Data are presented as odds ratio and 95% CI for changes per one unit.

Abbreviations: see TABLES 1 and 2

recognized as markers of a proarrhythmic effect of obesity and an imbalance in the endocrine function of adipose tissue and skeletal muscles. This is in line with the results reported by other investigators, although they did not analyze indexed values of adipocytokines.[1-6,10,11,16-18,21,23-33] On the other hand, in the studies by Kim et al,[13] Kawada,[12] Macheret et al,[15] and Barnett and Piccini,[27] high circulating ADA levels were independently associated with an increased risk of AF. In addition, Ermakov et al[30] did not find any significant associations between plasma leptin and ADA concentrations and the risk of AF.

Our study showed that the adipocytokines and irisin were weakly correlated with heart enlargement and body composition. This finding indirectly corroborates the outcomes of other authors. For example, in a rabbit model, after incubation of isolated left atrial myocytes, Lin et al[31] found that leptin modulates electrophysiological characteristics and isoproterenol-induced arrhythmogenesis in atrial myocytes, which suggests that hyperleptinemia may favor AF occurrence. Similarly, it was reported that leptin may take part in the pathogenesis of atrial fibrosis in ob/ob mice[24] and Sprague–Dawley rats.[25] However, in contrast to the results of our study, Kamimura et al[34] found that higher blood leptin concentrations were associated with lower LVM. In addition, in a study by Shimano et al,[17] ADA exerted beneficial effects on ventricular and atrial remodeling in patients with AF, and Ybarra et al[35] found an inverse relationship between ADA and left atrial size independent of age, sex, insulin resistance, and LVM.

Limitations Although numerous associations shown in our study reached significance, we were unable to avoid limitations that could reduce the strength of our results. First, our control group did not include healthy individuals as in the majority of studies on the effect of nutritional status on cardiovascular risk. However, in our study, we tested the hypothesis that patients with AF differ from those with other CVDs with regard to the severity of inflammation status mediated by adipocytokines (leptin, ADP, TNF-α) and myokine (irisin).

Second, patients with AF and the control group differed with regard to potential confounding factors (TABLE 1). We enrolled consecutive

patients with a diagnosis AF on admission to the hospital, and despite subject matching, differences between the groups were impossible to avoid. To reduce the effect of these differences, we not only assessed crude values but also the indexed values of the studied parameters.

Third, we only determined blood irisin concentrations in patients after a night's rest, but it is known that myokines are secreted after exercise. Moreover, physical activity was not assessed in our study, while it is a more significant predictor of a patient's prognosis than an increased BMI value.[1-4,33]

Fourth, patients were included to the control group based on the lack of history of AF and a diagnosis of sinus rhythm on ECG on enrollment, without the exclusion of silent AF cases that would be possible with long-term ECG monitoring prior to the patient allocation to the study groups.[36] This may be the source of an important bias because it is well known that AF may include clinically occult arrhythmia and that the incidence of AF increases with age and comorbidities, such as smoking and a history of myocardial infarction, which were more prevalent in the control group.

Conclusions Compared with patients without arrhythmia, patients with AF were more often obese, had higher crude and indexed blood leptin concentrations, and lower indexed values of ADA, TNF-α, and irisin. These parameters were significantly associated with an increased risk of arrhythmia. Leptin, ADA, TNF-α, and irisin were significant but weak mediators of the obesity effect on heart remodeling in patients with CVD. As blood adipocytokine and irisin concentrations were only weakly related to body composition, the individual variance in their secretion seems to be a potential pathomechanism explaining the heterogeneous proarrhythmic effect of obesity.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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