ORIGINAL ARTICLE

Biomarkers of left atrial overload in obese and nonobese patients with atrial fibrillation qualified for electrical cardioversion

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ABSTRACT

BACKGROUND Biomarkers of left atrial (LA) overload are considered factors affecting the efficacy of atrial fibrillation (AF) treatment. Increasing obesity rates contribute to a growing number of obese patients qualified for electrical cardioversion (CVE).

AIMS The aim of the study was to evaluate serum concentrations of biomarkers of LA overload and their impact on the efficacy of CVE.

METHODS A total of 82 patients with persistent AF who underwent successful CVE were prospectively enrolled in the study. The study population was divided into the obese group (OG) and the nonobese group (NOG). The serum levels of the following biomarkers were measured on the day of admission and at follow-up: high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-B-type natriuretic peptide, copeptin, galectin 3, growth differentiation factor 15 (GDF-15), and renalase.

RESULTS Baseline and follow-up hs-CRP levels were increased in the OG compared with the NOG. Four-week CVE efficacy was 38.8% in the OG and 60.6% in the NOG. Time of the observation, allocation to the groups, and CVE outcomes showed no associations with most LA biomarkers during follow-up. Baseline concentrations of 2 biomarkers of LA overload were associated with clinical characteristics of the study group, that is, $\log_{10}$ serum GDF-15 and $\log_{10}$ serum renalase levels correlated positively with the CHA_2DS_2-VASc score.

CONCLUSIONS Although obesity modifies the long-term efficacy of CVE, the OG and NOG did not differ significantly in most biomarkers of LA overload, except hs-CRP. The efficacy of CVE seems to be independent of the levels of biomarkers. A favorable procedure outcome did not affect their blood concentrations.

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INTRODUCTION Biomarkers of left atrial (LA) overload are a heterogenous group of proteins, serum levels of which increase in some cardiovascular conditions such as atrial fibrillation (AF). Natriuretic peptides, markers of myocardial fibrosis and inflammation as well as biomarkers of hemodynamic stress are the main proteins related to LA overload. Their increased serum levels are supposed to affect not only the prevalence of arrhythmia but also the efficacy of AF treatment.[1-3]

The prevalence of obesity increases every year; therefore, those with an increased body mass index (BMI) constitute a large group of patients with AF.[4] Some studies suggest that obesity could be related to an increase in biomarkers of LA overload. That observation could have an impact on sinus rhythm restoration outcomes in this population.[5]

Taking into account the increasing number of obese patients with AF, the aim of the study was

WHAT'S NEW?

In our study, obese patients had higher serum levels of high-sensitivity C-reactive protein compared with nonobese individuals, both at baseline and at follow-up. The efficacy of electrical cardioversion seems to be independent of the biomarkers of left atrial overload—a favorable procedure outcome does not affect their blood concentrations. Serum levels of growth differentiation factor 15 and renalase reflect thromboembolic risk in patients with atrial fibrillation.

TABLE 1 Measurement of serum concentrations of biomarkers of left atrial overload by enzyme-linked immunosorbent assays: the laboratory method

Variable	Sensitivity	Intra-assay CV, %	Interassay CV, %
hs-CRP, µg/ml	0.001	5.75	12.7
NT-proBNP, ng/ml	0.01	<10	<12
Copeptin, pg/ml	10	<10	<12
Galectin 3, ng/ml	0.29	7.5	5.4
GDF-15, pg/ml	20	6.75	4.25
Renalase, ng/ml	1.31	<10	<12

Abbreviations: CV, coefficient of variation; GDF-15, growth differentiation factor 15; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide

to evaluate serum concentrations of biomarkers of LA overload and their impact on the efficacy of electrical cardioversion (CVE) in obese and nonobese patients.

METHODS

A total of 82 patients (30 women and 52 men; mean [SD] age, 65 [10] years) with persistent symptomatic AF hospitalized at the 1st Department of Cardiology, Medical University of Silesia in Katowice, Poland between 2017 and 2019 after a successful CVE were prospectively enrolled in the study. Exclusion criteria included: active inflammatory disease, antiarrhythmic treatment with amiodarone, chronic kidney disease with estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73 m^2, severe valvular heart disease, left ventricular (LV) ejection fraction of less than 40%, cardiomyopathy, diabetes mellitus treated with insulin therapy, and morbid obesity (BMI ≥40 kg/m^2).

On the day of CVE, patients underwent clinical examination including measurements of anthropometric parameters, electrocardiography (ECG), and echocardiography. In addition, venous blood samples (10 ml) were drawn in the morning, after an overnight fast on admission and at 4-week follow-up. Serum and plasma samples (collected according to the recommendation of the manufacturer of the kits) were stored frozen at –70 °C.

Body mass index, which was the discriminating factor for the study groups, was 30 kg/m^2 or greater in the obesity group (OG) and less than 30 kg/m^2 in the nonobese group (NOG).

The study was approved by the Bioethical Committee of Medical University of Silesia (no. KNW/022/KB1/159/16/17; January 31, 2017) and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. Patients qualified for the study gave their informed consent prior to their inclusion.

Anthropometric measurements Body mass morning measurements in light clothing using a balance beam scale, height measurements using a stadiometer, and waist circumference using a measuring tape were performed on the day of CVE. Body mass index was calculated by dividing patients' body mass in kilograms by their height in meters squared. Body surface area was calculated with the Mosteller formula.

Biochemical measurements Patients underwent basic laboratory testing including complete blood count, electrolyte and creatinine levels as well as concentrations of lipids and glucose prior to CVE.

The following biomarkers of LA overload, including high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), copeptin, galectin 3, growth differentiation factor 15 (GDF-15), and renalase, were measured in samples collected on the day of admission to CVE and at 4-week follow-up. Serum concentrations of biomarkers of LA overload were obtained by enzyme-linked immunosorbent assays (ELISA). The method sensitivity, intra-assay coefficient of variation, and interassay coefficient of variation are presented in TABLE 1.

Echocardiography Transthoracic echocardiography was performed on the day of admission by a single experienced investigator using Epiq 7G (Philips, Andover, Massachusetts, United States) with a 2.5-MHz probe in 2D, M, and Doppler modes.

Data analysis Nutritional status was assessed based on the World Health Organization criteria: obesity was defined as BMI of 30 kg/m^2 or greater, overweight as BMI from 25 to 29.9 kg/m^2, and normal weight as BMI from 18.5 to 24.9 kg/m^2. According to these definitions, patients were divided into 2 groups: those diagnosed with obesity (OG) and those with overweight and normal weight (NOG).

Persistent AF was defined as arrythmia with a typical pattern of irregular R-R intervals and no discernible, distinct P waves observed on ECG, lasting more than 7 days. Arterial hypertension was defined as newly recognized hypertension based on 2 separate measurements that exceeded 140/90 mm Hg during the hospitalization, a previous hypertension diagnosis, or the use of any antihypertensive drug. Diabetes mellitus was defined as fasting blood glucose levels greater

TABLE 2 Demographic and baseline clinical characteristics of the obese and nonobese groups

Variable		OG (n = 49)	NOG (n = 33)	*P* value
Age, y		64 (10)	66 (10)	0.2
Sex, n (%)	Female	21 (43)	9 (27)	0.15
	Male	28 (57)	24 (73)	
Weight, kg		97 (89–108)	80 (69–85)	<0.001
Height, cm		169 (10)	170 (8)	0.02
BMI, kg/cm^2		33.4 (31.9–36.8)	27.1 (24.2–28.7)	<0.001
BSA, m^2		2.26 (0.25)	1.91 (0.17)	<0.001
Waist circumference, cm		113.2 (12.7)	96.3 (11.6)	<0.001
CHA_2DS_2-VASc, points		3 (1–4)	3 (1–4)	0.94
EHRA score		2 (2–2)	2 (2–2)	0.77
Basic laboratory test				
Platelet count, × 1000/mm^3		217.5 (59.1)	224.7 (47.1)	0.69
Hemoglobin concentration, g/dl		14.3 (1.3)	14.6 (1.6)	0.35
White blood cells, × 1000/mm^3		7.1 (1.9)	6.9 (1.8)	0.69
Serum creatinine concentration, mg/dl		0.98 (0.18)	0.94 (0.15)	0.35
eGFR, ml/min/1.73 m^2		75.4 (11.4)	78.8 (9.4)	0.16
Glucose, mg/dl		108 (98–124.8)	100 (92–114)	0.06
Total cholesterol, mg/dl		163.8 (44.9)	176.6 (43.5)	0.21
Low-density lipoprotein cholesterol, mg/dl		86.4 (39.1)	96.2 (38.3)	0.28
High-density lipoprotein cholesterol, mg/dl		50.7 (15)	54.2 (15.7)	0.32
Triglycerides, mg/dl		129 (100–151)	109 (83–157)	0.88
Transthoracic echocardiography				
LA anteroposterior diameter, mm		44.8 (4.9)	42.4 (5.2)	<0.05
LA area, cm^2		26.1 (4.2)	24.2 (4.1)	<0.05
LA volume, ml		83.9 (18.1)	75.2 (20.9)	<0.05
LV ejection fraction, %		54.8 (5.4)	57.7 (5.8)	<0.05
LV end-diastolic diameter, mm		51.9 (5.4)	48.9 (4.4)	<0.01
LV end-systolic diameter, mm		33.2 (5.7)	30.4 (4.5)	<0.05
LV end-diastolic volume, ml		133.8 (36.5)	110.3 (27.5)	<0.01
LV end-systolic volume, ml		60.1 (19.9)	47.5 (14.8)	<0.01
Rate control and nonamiodarone antiarrhythmic therapy before CVE				
β-Blocker therapy, n (%)		42 (85.7)	23 (69.7)	0.09
Sotalol therapy, n (%)		2 (4.8)	5 (15)	0.1
Propafenone therapy, n (%)		2 (4.1)	3 (9.1)	0.39
CVE efficacy at 4-week follow-up, n (%)		19 (38.8)	20 (60.6)	<0.05

Data are presented as mean (SD) or median (interquartile range) unless indicated otherwise.

Abbreviations: BMI, body mass index; BSA, body surface area; CVE, electrical cardioversion; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; LA, left atrial; LV, left ventricular, NOG, nonobese group; OG, obese group

than 125 mg/dl in 2 separate measurements or the use of hypoglycemic agents. Impaired fasting glucose and impaired glucose tolerance were analyzed jointly with diabetes mellitus. The Cockcroft-Gault formula was used to calculate eGFR.

Electrical cardioversion procedure Patients who were referred for CVE had received a vitamin K agonist with adequate anticoagulation confirmed by laboratory testing or a new oral anticoagulant (NOAC) for at least 3 weeks. The procedure was performed under short-acting intravenous anesthesia. The anterolateral position of paddles was used both in the first and in subsequent shocks with no change to the anteroposterior position after an unsuccessful shock. The performing physician decided on the energy of subsequent shocks considering patient clinical characteristics (BMI, FA duration). If CVE was not successful after 3 attempts, the procedure was ended.

In order to limit the potent influence of amiodarone on the efficacy of CVE, patients on antiarrhythmic therapy with that drug were excluded from the study. Antiarrhythmic therapy with amiodarone was not implemented in any of the patients after CVE. In patients treated with nonamiodarone antiarrhythmic drugs (sotalol, propafenone), the therapy was maintained.

Statistical analysis Statistical analysis was performed by the Statistica 13.0 (TIBCO Software Inc., Palo Alto, California, United States) and StataSE 13.0 (StataCorp LP, College Station, Texas, United States) software. Statistical significance was set at a *P* value below 0.05. All tests were 2-tailed. Variables were presented as means (SD) in case of a normal data distribution, or medians and interquartile ranges for other distributions, or numbers and percentages for data in a nominal and ordinal scale. The distribution of variables was evaluated by the Anderson–Darling test and the quantile-quantile (Q-Q) plot. The homogeneity of variances was assessed by the Levene test. The *t* test was done to compare 2 independent groups (according to BMI ≥30 kg/m^2 and BMI <30 kg/m^2) for normally distributed data, and in case of nonnormal distribution, the Mann–Whitney test was used. One-way and 2-way analysis of variance (ANOVA) with repeated measurements were done to assess the influence of obesity, CVE insufficiency, and time (follow-up) on serum levels of biomarkers. In case of skewed data, the logarithmic transformation of data was done. For nonparametric data, the χ^2 test was used. Multivariable linear regression with stepwise, backward method was used to assess factors influencing serum levels of the biomarkers.

RESULTS

Clinical characteristics of the study groups The demographic and clinical characteristics are listed in TABLE 2. There were no differences in mean age and gender distribution

TABLE 3 Serum levels of biomarkers of left atrial overload in the obese group and the nonobese group at baseline and 4-week follow-up

Variable	OG	NOG
Baseline		
hs-CRP, µg/ml	3.75 (19.1–82.4)	1.78 (0.96–3.15)
NT-proBNP, ng/ml	38.48 (21.41–93.91)	42.3 (29.33–97.9)
Copeptin, pg/ml	621.9 (302.5–923.9)	601.5 (278.3–902.3)
Galectin 3, ng/ml	18.02 (14.40–24.90)	15.84 (10.33–27.92)
GDF-15, pg/ml	1616 (919–2 214)	1491 (1104–3233)
Renalase, ng/ml	9549 (8 520–11 326)	9434 (8855–12 117)
4-week follow-up		
hs-CRP, µg/ml	3.93 (2.43–9.1)	1.95 (0.68–4.74)
NT-proBNP, ng/ml	31.38 (22.2–88.6)	29.75 (21.3–50.83)
Copeptin, pg/ml	584.1 (290.9–923.9)	302.5 (212.5–868.2)
Galectin 3, ng/ml	14.4 (8.99–16.56)	15.02 (10.39–21.87)
GDF-15, pg/ml	1605 (1123–2468)	1750 (1172–3308)
Renalase, ng/ml	9549 (8520–11 326)	9665 (8838–10 828)

Data are presented as median (interquartile range).

Abbreviations: see TABLES 1 and 2

between the study groups. Patients in both the OG and NOG were symptomatic (median EHRA score, 2 in the OG and NOG), with high risk of thromboembolism (median CHA_2DS_2-VASc score, 3 in the OG and NOG), and with no differences in the most common comorbidities and used medicaments. Anticoagulant therapy was administered according to the European Society of Cardiology guidelines[6]: dabigatran was used in 40%, rivaroxaban in 34%, acenocoumarol in 20%, warfarin in 3%, and apixaban in 3% of patients. The frequency of concomitant diseases was as follows: 92% of included patients had atrial hypertension, 52%, hyperlipidemia, 33%, diabetes mellitus, and 28%, coronary artery disease. Nearly 14% of patients had already experienced stroke or transient ischemic attack. In the study population, 9% of patients were smokers and 1% self-reported alcohol abuse.

There were no significant differences in basic laboratory measurements between the groups, including complete blood count, electrolytes and glucose levels as well as in the lipid profile. On echocardiography, patients from the OG had greater left heart dimensions (LV end-diastolic and -systolic diameter, LV end-diastolic and -systolic volumes, LA anteroposterior diameter, LA area, and LA volume). Moreover, statistically significant lower LV ejection fraction was observed in the OG compared with the NOG (TABLE 2).

Biomarkers of left atrial overload: the obese group and the nonobese group At baseline and at 4-week follow-up, patients from the OG had higher hs-CRP levels compared with the NOG. The differences in other evaluated biomarkers were not significant (TABLE 3).

Biomarkers of left atrial overload: electrical cardioversion efficacy, ANOVA analysis Only 47.5% of patient after a successful sinus rhythm restoration were free of arrhythmia at 4-week follow-up. The efficacy of CVE reached 38.8% in the OG and 60.6% in the NOG (P <0.05) (TABLE 2). The time of the observation (baseline vs 4-week follow-up), allocation to the groups (OG vs NOG), and CVE outcomes (efficient vs inefficient) did not have an impact on the concentration of most biomarkers of LA overload (TABLE 4).

A significant reduction in the galectin 3 level after CVE (mean [SD], 23.29 [20.15] pg/ml vs 14.59 [7] pg/ml; P <0.001) was observed in the whole population enrolled in the study (TABLE 4). The analysis in the sex-divided subgroups revealed significant differences in serum galectin 3 concentrations between baseline and follow-up measurements in the male subpopulation (P <0.01). A lower galectin 3 concentration at follow-up was found in men, independently

TABLE 4 Biomarkers of left atrial overload in patients undergoing CVE: the analysis of variance

Variable	ANOVA at baseline			ANOVA with repeated measurements			
	OG vs NOG	CVE efficacy	*P* for interaction	Time	Time / OG vs NOG	Time / CVE efficacy	*P* for interaction
hs-CRP, µg/ml	<0.001	0.86	0.08	0.63	0.68	0.36	0.53
NT-proBNP, ng/ml	0.89	0.09	0.52	0.35	0.33	0.93	0.77
Copeptin, pg/ml	0.3	0.5	0.31	0.11	0.2	0.18	0.54
Galectin 3, ng/ml	0.72	0.16	0.19	<0.001	0.09	0.54	0.86
GDF-15, pg/ml	0.49	0.41	<0.05	0.17	0.69	0.64	0.51
Renalase, ng/ml	0.51	0.48	<0.05	0.15	0.72	0.97	0.84

Abbreviations: see TABLES 1 and 2

from the efficacy of CVE (P <0.05). There were no statistically significant relations in the female subpopulation.

Biomarkers of left atrial overload: regression analysis For each biomarker, the multivariable backward stepwise linear regression was done. The baseline model included: gender, age, BMI, EHRA, and CHA_2DS_2-VAS score, LA anteroposterior diameter, LA volume index (LAVI), LV ejection fraction, LV end-diastolic and end-systolic diameters, hemoglobin concentrations, white blood cell and platelet counts, eGFR, levels of glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides.

Increased serum hs-CRP levels were associated with BMI, LAVI, and decreased, with female sex, LA anteroposterior diameter, and hemoglobin concentration. Our results revealed that increased serum NT-proBNP concentrations were associated with female sex and eGFR, and decreased, with platelet count. Increased serum GDF-15 concentrations were associated with female sex and CHA_2DS_2-VAS score (P <0.01), and decreased with BMI and LAVI. Serum renalase levels increased with CHA_2DS_2-VAS and decreased with ESD. None of the analyzed factors were in a statistically significant relation with serum galectin 3 concentrations (TABLE 5).

DISCUSSION

This study showed that obese patients with AF undergoing CVE had higher serum hs-CRP levels compared with nonobese participants without significant differences in other evaluated biomarkers. In our study, the 4-week CVE efficacy was relatively low with worse procedure outcomes in the OG. However, no significant differences were observed in serum levels of the LA biomarkers measured between patients with efficient and inefficient procedures either at baseline or 4-week follow-up. Moreover, the analysis did not reveal significant differences in the change of biomarkers between the patients with efficient CVE compared with patients with AF recurrence. Serum concentrations of biomarkers corresponded to different clinical variables; however, the most important finding seems to be the positive correlation between GDF-15 and renalase levels and thromboembolic risk in the CHA_2DS_2-VASc score.

In our study, the most commonly used anticoagulant was dabigatran, which confirms the dominant role of NOACs in the management of patients with AF. According to the study by Janion-Sadowska et al[7] NOACs are increasingly used instead of vitamin K antagonists.

The observation regarding higher serum hs-CRP levels in patients with BMI of 30 kg/m^2 or greater compared with nonobese individuals confirms previous outcomes.[8-10] Most data suggest that obesity is the major factor associated with elevated C-reactive protein. In the population-based cross-sectional study by Aronson et al,[11] a total of 1929 patients underwent laboratory testing, which revealed significantly higher serum C-reactive protein concentrations in obese patients with metabolic syndrome.

In our study, the efficacy of CVE was not related to serum hs-CRP concentrations. This observation does not correspond with previous studies. A meta-analysis by Yo et al[12] including 347 patients revealed that hs-CRP levels greater than the cutoff point were an independent risk factor of AF recurrence after CVE. Moreover, a high preablation hs-CRP level could be a marker for AF recurrence after pulmonary vein isolation.[13] It should be noted that inflammation was an exclusion criterion in our study, which may explain our results.

Some studies suggested that elevated NT-proBNP levels, which is a peptide taking part in fluid homeostasis, could be a predictor of AF recurrence after restoring sinus rhythm. In a study by Zografos et al,[14] low preprocedural NT-proBNP levels were associated with long-term CVE efficacy. In the randomized trial by Andersson et al[1] including 199 patients qualified for CVE, the NT-proBNP cutoff of 500 ng/l predicted AF recurrence in 30 days after restoring sinus rhythm. In our study, an elevated serum concentration of NT-proBNP was observed in the OG and the NOG at baseline as well as at 4-week follow-up. Despite those observations, CVE efficacy did not affect serum NT-proBNP levels.

Taking into account previous data, the study evaluated serum levels of copeptin, a stable fragment of provasopressin. In the study by Yildrim et al,[15] copeptin was an independent predictor of some cardiovascular complications such as contrast-induced nephropathy observed in patients after percutaneous coronary intervention in ST-segment elevation myocardial infarction. Moreover, copeptin seems to predict adverse cardiac events not only in coronary artery disease but also in heart failure.[16,17] Nevertheless, its role in AF is uncertain. In our study, the serum copeptin concentration was not related to obesity nor to CVE inefficacy.

Galectin 3, one of the most explored markers of myocardial fibrosis, could be used to detect paroxysmal AF. A study by Selcoki et al[18] showed that serum galectin 3 levels were significantly elevated in patients with arrhythmia. In a study by Kocyigit et al[19] including 65 patients with AF, galectin 3 was proved as a predictor of thrombogenicity. In our study, serum galectin 3 levels measured 4 weeks after CVE were significantly lower compared with baseline, irrespective of the obesity status or success of CVE.

GDF-15, a stress-responsive cytokine, which plays an important role in regulating inflammatory pathways and is involved in the apoptosis process, cell repair, and cell growth, is considered

TABLE 5 Results of linear stepwise, backward linear regression: factors affecting concentrations of biomarkers of left atrial overload

Variable	log_{10} hs-CRP		log_{10} NT-proBNP		log_{10} copeptin		log_{10} GDF-15		log_{10} renalase	
	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value	β coefficient (95% CI)	*P* value
Female sex	–0.32 (–0.63 to –0.01)	<0.05	0.36 (0.06–0.66)	0.05	–	–	0.18 (0.02–0.34)	0.05	–	–
BMI, kg/cm^2	0.06 (0.03–0.09)	<0.01	–	–	–	–	–0.01 (–0.03 to –0.001)	0.05	–	–
EHRA ≥3	0.3 (–0.04 to 0.64)	0.08	–	–	–	–	–	–	–	–
CHA_2DS_2-VASc, points	–	–	–	–	–	–	0.09 (0.03–0.15)	<0.01	0.04 (0.02–0.06)	<0.001
LA anteroposterior diameter, mm	–0.04 (–0.07 to –0.004)	0.05	–	–	–	–	0.01 (–0.0003 to 0.03)	0.05	–	–
LAVI, ml/m^2	0.02 (0.003–0.03)	0.05	–	–	–	–	–0.01 (–0.02 to –0.003)	<0.05	–	–
LV end-diastolic diameter, mm	–	–	–	–	0.03 (0.0002–0.05)	<0.05	–	–	–	–
LV end-systolic diameter, mm	–	–	–	–	–0.03 (–0.05 to –0.003)	<0.05	–	–	–0.004 (–0.01 to 0.01)	0.09
Hemoglobin concentration, g/dl	–0.11 (–0.22 to –0.004)	0.05	–	–	–	–	–	–	–	–
Platelet count, × 1000/mm^3	–	–	–0.002 (–0.003 to –0.0002)	0.05	–	–	–	–	–	–
eGFR, ml/min/1.73 m^2	–	–	0.15 (0.01–0.29)	<0.05	–	–	–	–	–	–
Glucose, mg/dl	–	–	–0.003 (–0.006 to 0.0001)	0.06	0.003 (–0.0001 to 0.005)	0.06	–	–	–	–
Triglycerides, mg/dl	–	–	0.003 (–0.0001 to 0.005)	0.05	–	–	–	–	–	–
R^2	0.35		0.19		0.09		0.28		0.29	

Abbreviations: LAVI, left atrial volume index; others, see TABLES 1 and 2

a prognostic risk factor for cardiovascular complications.[20] In a study by Hu et al[21] including 894 patients with nonvalvular AF without anticoagulation, elevated serum GDF-15 levels were associated with a higher risk of LA appendage thrombus. In logistic regression analysis, after adjusting for potential clinical characteristics, GDF-15 was an independent risk factor for LA appendage thrombus, with the cutoff value reaching 809.9 ng/l. On the other hand, elevated serum GDF-15 levels remained significantly associated with major bleeding and all-cause mortality, but not stroke in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial.[22] Considering the abovementioned studies, it seems that the correlation of high serum GDF-15 concentrations with an increased thromboembolism risk in the CHA_2DS_2-VASc score is of importance in our analysis. On the other hand, CVE outcomes did not have significant impact on serum GDF-15 levels. High concentrations of serum GDF-15 exceeding the cutoff value of 809.9 ng/l suggested as a predictor of LA appendage thrombus were observed both in the OG and NOG.

According to the new promising studies, low serum levels of renalase, an enzyme that is involved in catecholamine metabolism, correlates with an increased risk of AF recurrence after pulmonary vein isolation. Its impact on CVE outcomes was not evaluated previously.[23] In our study, the relation between serum renalase concentrations and sinus rhythm maintenance was not confirmed; however, high renalase levels correlated with an increased thromboembolic risk.

Besides the biomarkers of LA overload, adipokines, which are a group of cytokines secreted by adipose tissue, are also related to an elevated arrhythmic risk. A constant low-grade inflammation and fibrosis of LA mediated by adipokines secreted mostly by visceral adipose tissue play an important role in AF pathogenesis. Based on previous research,[24] adipokines and irisin, a myokine involved in energy expenditure and glucose tolerance, exert a significant but weak effect on echocardiographic parameters and affect the risk of AF. Anaszewicz et al[24] analyzed the association of the levels of leptin, adiponectin, tumor necrosis factor α (TNF-α), and irisin with AF. The study revealed that patients with AF had higher serum leptin levels and lower levels of adiponectin and TNF-α. After indexation to the body surface area, fat mass, and visceral obesity, the serum irisin concentration was also lower in patients with arrhythmia (OR, 1.02; 95% CI, 1.01–1.03; P <0.01). The risk of AF was related to serum leptin concentrations with stronger correlation after indexation to fat mass (OR, 1.34; 95% CI, 1.01–1.81; P <0.05). Both irisin and adipokine levels were dependent on echocardiographic parameters, but the correlation with irisin was the strongest.

Limitations A limited number of enrolled patients was the main limitation of the study. Other clinical situations affecting serum biomarkers concentration, except obvious inflammation, could confound the interpretation of the results.

Using BMI as the only measure to determinate obesity is not faultless. It does not account for the overall body composition as well as exact body fat content and its distribution. The discussed index is unreliable in individuals with extensive muscle mass or in patients with severe edema. Recent studies suggest that individuals with the same BMI could significantly differ in fat tissue content which results in their cardiovascular risk heterogeneity.

Although the World Health Organization definition of obesity is based on BMI, other anthropometric parameters should also be considered. It has been proven that waist circumference and waist-to-hip ratio have an even stronger correlation with cardiovascular risk than BMI. Waist circumference and waist-to-hip ratio are substantially dependent on the content of visceral fat tissue, which is a highly metabolically active tissue responsible for increased risk of cardiovascular complications.[25]

Summary Although obesity modifies the long-term nonsatisfied efficacy of CVE, patients with BMI of 30 kg/m^2 or greater did not significantly differ in most of the LA biomarkers from the patients without obesity. The efficacy of CVE seems to be independent of levels of biomarkers of LA overload. Moreover, a favorable procedure outcome does not affect their blood concentration. Elevated serum GDF-15 and renalase concentrations in patients with AF reflect higher thromboembolic risk in CHA_2DS_2-VASc score.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT KM-S and MC conceived the idea of the study and contributed to the design of the research. AO and RM analyzed the data. All authors were involved in data collection. All authors edited and approved the final version of the manuscript.

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REFERENCES

1 Andersson J, Rosenqvist M, Tornvall P, Boman K. NT-proBNP predicts maintenance of sinus rhythm after electrical cardioversion. Thromb Res. 2015; 135: 289-291.

2 Kawamura M, Munetsugu Y. Type III procollagen-N-peptide as a predictor of persistent atrial fibrillation recurrence after cardioversion. Europace. 2012; 14: 1719-1725.

3 Kallergis EM, Goudis CA, Kanoupakis EM, et al. Sinus rhythm restoration affects collagen turnover in patients with persistent atrial fibrillation. Europace. 2014; 16: 1726-1730.

4 Guglin M, Maradia K, Chen R, Curtis A. Relation of obesity to recurrence rate and burden of atrial fibrillation. Am J Cardiol. 2011; 107: 579-582.

5 Lubbers ER, Price MV, Mohler PJ. Arrhythmogenic substrates for atrial fibrillation in obesity. Front Physiol. 2018; 9: 1482.

6 Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021. 42: 373-498.

7 Janion-Sadowska A, Sadowski M, Konieczyńska M, et al. Polish regional differences in patient knowledge on atrial fibrillation and its management as well as in patterns of oral anticoagulant prescription. Kardiol Pol. 2019; 77: 437-444.

8 Potpara TS, Mujovic N. Integrating multiple aspects of care for better management of atrial fibrillation: teamwork between physicians and patients. Kardiol Pol. 2019; 77: 415-416.

9 Visser M, Bouter LM, McQuillan GM, et al. Elevated C-reactive protein levels in overweight and obese adults. JAMA. 1999; 282: 2131-2135.

10 Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease. Circulation. 2003; 107: 499-511.

11 Aronson D, Bartha P, Zinder O, et al. Obesity is the major determinant of elevated C-reactive protein in subjects with the metabolic syndrome. Int J Obes Relat Metab Disord. 2004; 28: 674-679.

12 Yo CH, Lee SH, Chang SS, et al. Value of high-sensitivity C-reactive protein assays in predicting atrial fibrillation recurrence: a systematic review and meta-analysis. BMJ Open. 2014; 4: e004418.

13 Carballo D, Noble S, Carballo S, et al. Biomarkers and arrhythmia recurrence following radiofrequency ablation of atrial fibrillation. J Int Med Res. 2018; 46: 5183-5194.

14 Zografos T, Maniotis C, Katsivas A, Katrisis D. Relationship between brain natriuretic peptides and recurrence of atrial fibrillation after successful direct current cardioversion: a meta-analysis. Pacing Clin Electrophysiol. 2014; 37: 1530-1537.

15 Yildrim E, Cabbar AT. Association between copeptin and contrast-induced nephropathy in patients with ST-elevation myocardial infarction. Rev Port Cardiol. 2019; 38: 873-879.

16 Choi HJ, Kim MC, Sim DS, et al. Serum copeptin levels predict clinical outcomes after successful percutaneous coronary intervention in patients with acute myocardial infarction. Ann Lab Med. 2018; 38: 538-544.

17 Molvin J, Jujic A, Bachus E, et al. Cardiovascular biomarkers predict post-discharge re-hospitalization risk and mortality among Swedish heart failure patients. ESC Heart Fail. 2019; 6: 992-999.

18 Selcoki Y, Aydin HI, Celik TH, et al. Galectin-3: a biochemical marker to detect paroxysmal atrial fibrillation? Clin Invest Med. 2016; 39: 27528.

19 Kocyigit D, Gurses KM, Yalcin MU, et al. Serum galectin-3 level as a marker of thrombogenicity in atrial fibrillation. J Clin Lab Anal. 2017; 31: 22120.

20 Tzikas S, Palapies L, Bakogiannis C, et al. GDF-15 predicts cardiovascular events in acute chest pain patients. PLoS One. 2017; 12: e0182314.

21 Hu XF, Zhan R, Xu S, et al. Growth differentiation factor 15 is associated with left atrial / left atrial appendage thrombus in patients with nonvalvular atrial fibrillation. Clin Cardiol. 2018; 41: 34-38.

22 Hijazi Z, Oldgren J, Andersson U, et al. Growth-differentiation factor 15 and risk of major bleeding in atrial fibrillation: insights from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Am Heart J. 2017; 190: 94-103.

23 Wybraniec M, Wieczorek J, Woźniak-Skowerska I, et al. Renalase is associated with adverse left atrial remodeling and disease burden in patients with atrial fibrillation undergoing pulmonary vein isolation. Kardiol Pol. 2018; 76: 1232-1241.

24 Anaszewicz M, Wawrzeńczyk A, Czerniak B, et al. Leptin, adiponectin, tumor necrosis factor α, and irisin concentrations as factors linking obesity with the risk of atrial fibrillation among inpatients with cardiovascular diseases. Kardiol Pol. 2019; 77: 1055-1061.

25 Bjorntorp P. Classification of obese patients and complications related to the distribution of surplus fat. Am J Clin Nutr. 1987; 45: 1120-1125.