Increased Body Mass Index is Associated with Device Detected Silent Atrial Fibrillation

Emrah Bozbeyoğlu[1], Göksel Çinier[2]

[1] İstanbul Dr. Siyami Ersek Cardiovascular Surgery Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
[2] Kaçkar State Hospital, Clinic of Cardiology, Rize, Turkey

ABSTRACT

Introduction: Atrial fibrillation (AF) is the most common cardiac rhythm disturbance in clinical practice. To prevent adverse outcomes associated with AF, it is necessary to identify and manage the modifiable risk factors. An increased body mass index (BMI) is strongly associated with the incidence of clinically symptomatic AF. However, the association of increased BMI with asymptomatic AF is unknown.

Patients and Methods: We prospectively evaluated 449 patients implanted with dual chamber pacemaker. Patients were divided into 3 groups according to their baseline BMI (normal weight: BMI 18-25 kg/m^2, overweight: BMI 25-30 kg/m^2, and obesity: BMI > 30 kg/m^2). Six months after the device implantation, pacemakers were interrogated to identify atrial high rate episodes (AHREs), which were defined as episodes faster than 220 bpm and longer than 5 minutes.

Results: AHRE was detected in 128 (28.5%) patients. Patients in the AHRE (+) group were older (65.51 ± 8.99 years vs. 70.84 ± 8.05 years, p< 0.01) and had greater BMI (26.84 ± 3.41 kg/m^2 vs. 28.65 ± 3.75 kg/m^2, p< 0.01) compared to those in the AHRE (-) group. Patients in the AHRE (+) group had significantly higher mean resting heart rate (84.03 ± 7.80 bpm vs. 74.76 ± 6.40 bpm, p< 0.01), greater left atrium antero-posterior (LA-AP) diameter (4.14 ± 0.33 cm vs. 3.90 ± 0.31 cm, p< 0.01), left atrium volume (31.92 ± 3.17 vs. 30.38 ± 3.15, p< 0.01), and CHA2DS2-VASc score (2.29 ± 0.83 vs. 1.81 ± 0.76, p< 0.01). On multivariate analysis, increased BMI, age, mean resting heart rate, LA-AP diameter, and CHA2DS2-VASc score were independently associated with the incidence of AHRE.

Conclusion: Increased BMI is not only associated with symptomatic AF but also with asymptomatic AF detected by cardiac implantable electronic devices.

Key Words: Silent atrial fibrillation; asymptomatic atrial fibrillation; atrial high rate episodes; obesity; increased body mass index

Artmış Vücut Kitle İndeksi Cihaz ile Saptanan Sessiz Atriyal Fibrilasyon Atakları ile İlişkilidir

ÖZET

Giriş: Atriyal fibrilasyon (AF) klinikte en sık karşılaşılan ritm bozukluğudur. AF ile ilişkili modifiye edilebilen risk faktörlerinin tedavi edilmesi AF'ye bağlı iskemik inme gibi katastrofik sonuçları engelleyebilmektedir. Artmış vücut kitle indeksi (VKİ) semptomatik AF atakları ile ilişkilendirilmiştir. Ancak VKİ ile asemptomatik AF arasındaki ilişki henüz ortaya çıkarılmamıştır.

Hastalar ve Yöntem: Daha önce çift odacıklı pacemaker takılmış 449 hasta çalışmaya dahil edilmiştir. Hastalar VKİ değerlerine göre üç gruba ayrılmıştır (normal VKİ: VKİ 18-25 kg/m^2, kilolu: VKİ 25-30 kg/m^2 ve obez: VKİ > 30 kg/m^2). Cihaz implantasyonundan 6 ay sonra yapılan kontrolde sessiz AF atakları yerine geçen atriyal yüksek hız epizodları (AYHE) tarandı. AYHE 5 dakikadan uzun ve 220/dakika'dan uzun epizodlar olarak tanımlandı.

Bulgular: Cihaz kontrolleri sonunda hastaların 128 (28.5%)'inde AYHE saptandı. AYHE (+) hastalar AYHE (-) hastalara göre daha yaşlı (65.51 ± 8.99 vs. 70.84 ± 8.05 p< 0.01) ve daha yüksek VKİ'ye (26.84 ± 3.41 kg/m^2 vs. 28.65 ± 3.75 kg/m^2 p< 0.01) sahip bulundu. AYHE (+) hastaların istirahat kalp hızları (84.03 ± 7.80 vs. 74.76 ± 6.40 vs. p< 0.01), sol atriyum antero-posterior çapları (LA-AP) (4.14 ± 0.33 vs. 3.90 ± 0.31, p< 0.01), sol atriyum volümleri (LAV) (31.92 ± 3.17 vs. 30.38 ± 3.15, p< 0.01) ve CHA2DS2-VASc skorları (2.29 ± 0.83 vs. 1.81 ± 0.76, p< 0.01) AYHE (-) hastalara göre daha yüksek bulundu. Yapılan çok değişkenli analizde artmış VKİ, istirahat kalp hızı, LA-AP ve CHA2DS2-VASc skorunun bağımsız olarak AYHE prediktörleri olduğu gösterildi.

Sonuç: Artmış VKİ sadece semptomatik AF ile değil aynı zamanda cihaz tarafından saptanan sessiz AF epizodları ile ilişkilidir.

Anahtar Kelimeler: Sessiz atriyal fibrilasyon; aseptomatik atriyal fibrilasyon; atriyal yüksek hız epizodları; obezite; artmış vücut kitle indeksi

Correspondence

Göksel Çinier

E-mail: cinierg@gmail.com
Submitted: 07.08.2018
Accepted: 13.10.2018

© Copyright 2018 by Koşuyolu Heart Journal. Available on-line at www.kosuyoluheartjournal.com

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac rhythm disorder in clinical practice and associated with significant morbidity and mortality, especially due to being the major cause of cardiac embolism(1). The age of the population and increase in the incidence of cardiac risk factors associated with AF, such as obesity and hypertension, are held responsible for this rising epidemic. Timely intervention to the modifiable risk factors and early detection of AF is of utmost importance since treatment strategies targeting the elimination of AF are limited and because recurrence rates following electrical/pharmacological cardioversion and pulmonary vein isolation are still considered to be high once AF develops.

Screening for asymptomatic AF is reasonable, particularly in patients with a high risk for developing AF, to prevent devastating adverse outcomes of undiagnosed AF. In a recent meta-analysis, electrocardiographic (ECG) monitoring detected previously undiagnosed AF in 11.5% stroke survivors(2). Technological advances in cardiac implantable electronic devices (CIED) enabled clinicians to identify atrial high rate episodes (AHRE), which are surrogates for asymptomatic AF during routine device interrogation. Subsequent studies demonstrated that patients with AHRE have a considerably high risk for developing clinical AF, ischemic stroke, and death(3-5). In the light of these findings, the recent European guidelines on AF management recommend that pacemakers (PM) and implantable cardiac defibrillators should be interrogated on a regular basis for AHRE and that patients with AHRE should undergo further ECG monitoring to document AF with class IB indication(6).

To identify patients who are more likely to develop AF is an important aspect for intervening modifiable risk factors associated with AF. Obesity has been demonstrated to be one such modifiable risk factor associated with an increased risk of incident AF in several studies(7,8). Progressive weight reduction was found to be associated with a reduction in AF burden and an increase in AF-free time interval in a long-term follow-up cohort(9). However, these studies have included only patients with clinically symptomatic AF. The association of increased body mass index (BMI) with silent AF remains unknown. In this report, we aimed to investigate the association between increased BMI with the occurrence of AHRE in patients with cardiac pacemaker.

PATIENTS and METHODS

Patients who underwent dual chamber PM implantation between January 2015 and February 2016 were included in this prospective study. In all cases, the choice of device manufacturer was left to the attending physician's discretion. Exclusion criteria were: BMI < 18 kg/m^2, previous history of atrial arrhythmias, renal failure, valvular heart disease more than mild degree, and previous valvuloplasty procedure or valve replacement operation. All patients provided written informed consent for participation to the study protocol. The study was approved by the institutional ethical committee.

Prior to PM implantation, demographical characteristics and medical history of study subjects were recorded. Patient's weight and height were measured and recorded using a standardized protocol. The BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Patients were divided into 3 groups according to their baseline BMI's as defined by World Health Organization guidelines: normal weight (BMI: 18-25 kg/m^2), overweight (BMI: 25-30 kg/m^2), and obese (BMI: > 30 kg/m^2)(10). Hypertension was defined as systolic blood pressure ≥ 140 mm/Hg, diastolic blood pressure ≥ 90 mm/Hg, or use of anti-hypertensive medical therapy. The criteria for the diagnosis of diabetes mellitus were fasting glucose level ≥ 126 mg/dL (7.0 mmol/L), random glucose level ≥ 200 mg/dL (11.1 mmol/L), or use of oral anti-diabetics/insulin injections to treat hyperglycemia. Patients were categorized as current smoker if they smoked ≥ 1 cigarette per day and current alcohol consumer if they consumed ≥ 1 drink per day. The CHA2DS2-VASc score was calculated for each patient by assigning 2 points for the history of stroke/transient ischemic attack or age ≥ 75 years and 1 point for each of the following parameters: age ≥ 65 years, history of congestive heart failure, hypertension, diabetes mellitus, female sex, and vascular diseases.

Transthoracic echocardiography (Vivid 7, GE healthcare, Horten, Norway) was performed for all patients by an expert on cardiovascular imaging. Left atrial antero-posterior (LA-AP), left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters, and left atrium volume (LAV) were measured and recorded as outlined by the current guidelines of chamber quantification by the American Society of Echocardiography(11). Left ventricular ejection fraction was calculated using the modified Simpson's method.

All patients were implanted dual chamber PM, which was programmed to the DDDR mode. The atrial tachycardia detection mode was enabled, and the AF suppression feature was programmed off by performing atrial overdrive pacing. Bipolar atrial leads sensitivity and post ventricular atrial blanking period was interrogated properly to reduce P-wave sensitivity and far-field R-wave over-sensing to identify atrial activities and prevent ventricular Rwave sensing during AHRE detection.

Six months after the PM implantation, devices were interrogated to detect and categorize the patients on the basis of occurrence of AHRE. AHRE was defined as atrial high rates faster than 220 bpm and lasting longer than 5 minutes based on previous studies indicating its significance concerning the increased rate of stroke and to exclude slower atrial tachycardias and Rwave over-sensing episodes that were identified frequently at periods shorter than 5 minutes(12,13). The onset detection number of consecutive beats was 10, and the termination of AHRE was defined as occurrence of 20 consecutive beats below the AHRE detection rate to exclude short episodes of atrial premature beats. Patients were divided into 2 groups on the basis of presence (AHRE [+]) or absence (AHRE [-]) of AHRE at the time of device interrogation.

All data were evaluated using the Number Cruncher Statistical System (NCSS, Kaysville, Utah, USA). Mean and standard deviations were used for quantitative variables. Student T test was used for normally distributed variables in both groups and Mann-Whitney U test was used for variables that were not normally distributed. Qualitative variables were evaluated using the Pearson Chi-square and Continuity (Yates) correction. The backward stepwise logistic regression analysis was used for multivariate analysis to identify risk factors for the occurrence of AHRE. A p value of < 0.05 was accepted statistically significant.

RESULTS

A total of 535 patients were enrolled in the study between January 2015 and February 2016. Of these, 3 patients had BMI < 18 kg/m^2, 27 patients had previous diagnosis of atrial arrhythmias, 39 patients had more than mild valvular heart disease, 18 patients had a previous valve replacement operation or valvuloplasty procedure. The final cohort consisted of 449 (mean age: 67.0 ± 9.0, men: 61.7%, mean BMI: 27.36 ± 3.60 kg/m^2) patients. There were 117 patients with BMI in the range 18-25 kg/m^2 group, 230 patients with BMI in the range 25-30 kg/m^2 group, and 102 patients with BMI > 30 kg/m^2 group. AHRE was detected in 128 (28.5%) patients during the device interrogation at clinical visit 6 months after implantation. Baseline demographic and clinical characteristics of the study population according to presence of AHRE are listed in Table 1.

Patients in the AHRE (+) group were older (65.5 ± 8.9 years vs 70.8 ± 8.1 years, p< 0.01) and had greater BMI (26.84 ± 3.41 kg/m^2 vs 28.65 ± 3.75 kg/m^2, p< 0.01) compared to patients in the AHRE (-) group. When adjusted to BMI groups, patients in the BMI 18-25 kg/m^2 group were less likely to have AHRE (96 [29.9%] vs. 21 [16.4%], p= 0.03). In contrast, there was no difference in terms of AHRE detection in patients with BMI 25-30 kg/m^2 (166 [52.0%] vs. 64 [50.0%], p= 0.75). Patients with BMI > 30 kg/m^2 were more likely to have AHRE (58 [18.1%] vs 43 [33.6%], p< 0.01). In addition, patients in the AHRE (+) group had significantly higher mean resting heart rate (74.8 ± 6.4 bpm vs. 84.0 ± 7.8 bpm, p< 0.01), greater LA-AP diameter (4.14 ± 0.33 cm vs 3.90 ± 0.31 cm, p< 0.01), LAV (31.92 ± 3.17 mL vs. 30.38 ± 3.15 mL, p< 0.01), and CHA2DS2-VASc score (2.29 ± 0.83 vs. 1.81 ± 0.76, p< 0.01).

The multivariable logistic regression analysis results are shown in Table 2. Overall, BMI remained significant in predicting the occurrence of AHRE. Among different BMI groups, only the BMI > 30 kg/m^2 group remained independently associated with the incidence of AHRE (odds ratio [OR]: 2.47, 95% confidence interval [CI]: 1.112-5.47, p= 0.03). Other independent risk factors for AHRE were age (OR: 1.06, 95% CI: 1.02-1.10, p= 0.002), mean resting heart rate (OR: 1.23, 95% CI: 1.17-1.29, p= 0.001), LA-AP diameter (OR: 5.8, 95% CI: 2.36-14.33, p= 0.001) and CHA2DS2-VASc score (OR: 1.62, 95% CI: 1.10-2.38, p= 0.015).

DISCUSSION

The major findings of the present study were as follows: First, patients with higher BMI had a higher incidence of AHRE during their device interrogation. There was no significant difference in terms of AHRE detection in overweight (BMI > 25-30 kg/m^2) patients. In contrast, patients with BMI > 30 kg/m^2 were more likely to have AHRE during their device interrogation. Second, patients with AHRE had higher mean resting heart rate, LA-AP diameter, LAV, and CHA2DS2-VASc score.

Despite significant progress in the management of patients with AF, the common arrhythmia is still considered to be one of major causes of stroke and heart failure. This can be partly attributed to increased prevalence and associated comorbid conditions of AF in the aging population and relatively high recurrence rates following contemporary medical and ablation therapies once AF develops. Recently, advances in the diagnosing techniques for asymptomatic AF particularly in patients with CIEDs led to the emergence of the term "silent AF". Technological advances in CIED systems allowed clinicians to detect and store AHRE. Several studies have identified AHRE as a harbinger of future atrial arrhythmias, stroke, and death[3,5]. In the MOST trial, authors concluded that AF is a progressive condition (AF begets AF) and has an intermediate stage during which AF recurs and may be permanent. Multiple non-sustained AF episodes are prior to this stage and have independent clinical outcomes[3]. The incidence of AHRE in the MOST trial was 51%, which is significantly higher than our finding (28.5%). This can be associated with a longer follow-up duration in the MOST trial and the inclusion of the population with different baseline characteristics.

The solid evidence related to adverse outcomes of even asymptomatic AF necessitated researchers to identify and manage the modifiable risk factors to prevent AF. Obesity is not only an independent risk factor for AF, but also contributes to the progression of paroxysmal AF to permanent AF[7,8,14]. However, patients with only symptomatic AF were included in these studies. Our data demonstrated that increased BMI is an independent risk factor for asymptomatic AF as well.

Several studies have investigated the effect of risk factor management on the incidence, symptom burden, and outcome of AF with both short- and longterm follow-up[9,15-17]. Among these, goaldirected, long-term, sustained weight loss was associated with a reduction in AF severity and burden in the

Table 1. Comparison of demographic and clinical parameters of patients with and without AHRE

		AHRE (-)	AHRE (+)	p
Parameters				
Age (years)		65.51 ± 8.99	70.84 ± 8.05	< 0.01
Weight (kg)		77.81 ± 8.60	85.30 ± 10.41	< 0.01
BMI (kg/m^2)		26.84 ± 3.41	28.65 ± 3.75	< 0.01
		Number (%)	**Number (%)**	
Gender	Female	118 (36.8)	54 (31.4)	0.33
	Male	203 (63.2)	74 (57.8)	
BMI (kg/m^2)	18-25	96 (29.9)	21 (16.4)	0.03
	25-30	166 (52.0)	64 (50.0)	0.754
	> 30	58 (18.1)	43 (33.6)	< 0.01
Current smoking (+)		100 (31.2)	42 (32.8)	0.80
Current alcohol consumption (+)		89 (27.7)	37 (28.9)	0.73
Hypertension (+)		135 (42.1)	57 (44.5)	0.63
Diabetes mellitus (+)		126 (39.3)	59 (46.1)	0.18
		Mean ± SD	**Mean ± SD**	
Mean resting heart rate (bpm)		74.76 ± 6.40	84.03 ± 7.80	< 0.01
Sodium (mmol/L)		138.18 ± 2.99	138.23 ± 2.21	0.84
Potassium (mmol/L)		4.12 ± 0.54	4.20 ± 0.55	0.16
Calcium (mmol/L)		9.18 ± 0.54	9.25 ± 0.65	0.23
LA-AP diameter (cm)		3.90 ± 0.31	4.14 ± 0.33	< 0.01
LVEDD (cm)		4.61 ± 0.38	4.61 ± 0.40	0.89
LVESD (cm)		2.66 ± 0.35	2.66 ± 0.42	0.37
EF (%)		60.36 ± 5.09	60.59 ± 5.12	0.59
Hemoglobin level (g/dL)		13.22 ± 1.38	13.01 ± 0.87	0.06
CHA2DS2-VASC score		1.81 ± 0.76	2.29 ± 0.83	< 0.01
LAV (mL)		30.38 ± 3.15	31.92 ± 3.17	< 0.01
		Number (%)	**Number (%)**	
ACE inhibitor (+)		176 (55.8)	75 (58.6)	0.60
Beta-blocker (+)		175 (54.5)	77 (60.2)	0.29
Statin (+)		137 (42.7)	63 (49.2)	0.24

AHRE: Atrial high rate episodes, ACE: Angiotensin converting enzyme, SD: Standard deviation, BMI: Body mass index, LA-AP: Left atrium antero-posterior, LVEDD: Left ventricle end-diastolic diameter, LVESD: Left ventricle endsystolic diameter, EF: Ejection fraction, LAV: Left atrium volume.

Table 2. Multivariate logistic regression analysis of parameters associated with AHRE

	95% CI	OR	p
Parameters			
Age (years)	1.028-1.109	1.68	0.001
BMI 25-30 (kg/m^2)	0.757-3.017	1.51	0.242
BMI 30-35 (kg/m^2)	1.117-5.473	2.47	0.026
Mean resting hear rate (bpm)	1.169-1.289	1.22	0.001
LA-AP diameter (cm)	2.342-14.036	5.73	0.001
CHA2DS2-VASc	1.118-2.417	1.64	0.012
Hemoglobin level (g/dL)	0.636-1.007	0.80	0.057

AHREs: Atrial high rate episodes, CI: Confidence interval, BMI: Body mass index, LA-AP: Left atrial antero-posterior diameter, OR: Odds ratio.

LEGACY trial. The maintenance of sinus rhythm was facilitated by weight management during the 5-year follow-up period.

There was no previous study reporting the direct relation between mean resting heart rate and AF. However, mean resting heart rate often coexists with comorbid conditions associated with AF, including hypertension, atherosclerosis, and diabetes mellitus[18]. In hypertensive patients, increased resting heart rate in sinus rhythm was a predictor of newonset AF independent from the effect of arterial pressure lowering treatment. This finding was attributed to the increased effect of sympathetic activity, which promotes AF through several pathways[19].

In conclusion, patients with higher BMI (30 kg/m^2) are more likely to have asymptomatic AF episodes. The results of the present study highlight the importance of screening high-risk patients (such as obese and physically inactive patients) for AF and to intervene necessary lifestyle habits before AF develops to prevent detrimental adverse outcomes including stroke and heart failure.

Study Limitations

The present study has several inherent limitations. First, this is a singlecenter study with a limited number of patients. Second, there are several diagnostic criteria for defining AHRE in literature. We adopted AHRE faster than 220 bpm and longer than 5 minutes. Using different criteria for AHRE would lead results different from those of the present study. Third, other diagnostic tools including long-term ECG and Holter monitoring can be used for detecting silent AF. Among those tools, we included only AHRE detection by cardiac PM. Different results can be obtained by using a variety of diagnostic methods for the detection of silent AF.

CONFLICT of INTEREST

The authors declare that they have no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: EB, GÇ
Analysis/Interpretation: EB
Data Acquisition: GÇ
Writting: GÇ
Critical Revision: EB
Final Approval: All of authors

REFERENCES

1. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text. Europace 2006;8:651-745.
2. Sposato LA, Cipriano LE, Saposnik G, Vargas ER, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2015;14:377-87.
3. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). Circulation 2003;107:1614-9.
4. Gonzalez M, Keating RJ, Markowitz SM, Liu CF, Thomas G, Ip JE, et al. Newly detected atrial high rate episodes predict long-term mortality outcomes in patients with permanent pacemakers. Heart Rhythm 2014;11:2214-21.
5. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012;366:120-9.
6. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). Eur J Cardiothorac Surg 2016:ezw313.
7. Wang TJ, Parise H, Levy D, D'Agostino RB, Wolf PA, Vasan RS, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA 2004;292:2471-7.
8. Tedrow UB, Conen D, Ridker PM, Cook NR, Koplan BA, Manson JE, et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study). J Am Coll Cardiol 2010;55:2319-27.
9. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: A Long-Term Follow-Up Study (LEGACY). J Am Coll Cardiol 2015;65:2159-69.
10. Pi-Sunyer FX, Becker DM, Bouchard C, Carleton R, Colditz G, Dietz W, et al. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Am J Clin Nutr 1998;68:899-917.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39. e14.
12. Jorgensen H, Nakayama H, Reith J, Raaschou H, Olsen TS. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. Neurology 1997;48:891-5.
13. Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett E. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. Circulation 1994;89:224-7.
14. Tsang TS, Barnes ME, Miyasaka Y, Cha SS, Bailey KR, Verzosa GC, et al. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. Eur Heart J 2008;29:2227-33.
15. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. J Am Coll Cardiol 2015;66:985-96.
16. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol 2014;64:2222-31.

17. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA 2013;310:2050-60.

18. Palatini P, Julius S. The physiological determinants and risk correlations of elevated heart rate. Am J Hypertens 1999;12:3S-8S.

19. Okin PM, Wachtell K, Kjeldsen SE, Julius S, Lindholm LH, Dahlof B, et al. Incidence of atrial fibrillation in relation to changing heart rate over time in hypertensive patients: the LIFE study. Circ Arrhythm Electrophysiol 2008;1:337-43.