

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

Artmış Vücut Kitle İndeksi Cihaz ile Saptanan Sessiz Atriyal Fibrillasyon Atakları ile İlişkilidir.

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ABSTRACT

Introduction: Atrial fibrillation (AF) is the most common cardiac rhythm disturbance in clinical practice. Identifying and managing modifiable risk factors is important to prevent adverse outcomes associated with AF. Increased body mass index is strongly associated with the incidence of clinically symptomatic AF. However, the association of increased body mass index with asymptomatic AF is unknown.

Materials and Methods: We prospectively evaluated 449 patients implanted with dual chamber pacemaker. Patients were divided into 3 groups according to their baseline body mass index (BMI) (normal weight: BMI 18-25 kg/m², overweight: BMI 25-30 kg/m² and obesity: BMI > 30 kg/m²). Six months after the device implantation, pacemakers were interrogated to identify atrial high rate episodes. AHRE was defined as episodes faster than 220 bpm and longer than 5 minutes.

Results: AHRE was detected in 128 (28.5%) patients. Patients in AHRE (+) group were older (65.51±8.99 vs 70.84±8.05 P <0.01) and had greater BMI (26.84±3.41 kg/m² vs 28.65±3.75 kg/m² P <0.01) compared to patients in AHRE (-) group. Patients in AHRE (+) group had significantly higher mean resting heart rate (84.03±7.80 vs 74.76±6.40 vs, P <0.01), greater left atrium antero-posterior diameter (4.14±0.33 vs 3.90±0.31, 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 incidence of AHRE.

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

Keywords: Silent atrial fibrillation; asymptomatic atrial fibrillation; atrial high rate episodes; obesity; increased body mass index.

ÖZET

Giriş: Atriyalfibrillasyon (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.

Materyal ve Metodlar: Daha önce çift odacıklı pacemaker takılmış 449 hasta çalışmaya dahil edilmiştir. Hastalar VKİ değerlerine göre 3 gruba ayrılmıştır (Normal VKİ: BMI 18-25 kg/m², kilolu: BMI 25-30 kg/m² ve obez: BMI > 30 kg/m²). Cihaz implantasyonundan 6 ay sonra yapılan kontrolde sessiz AF atakları yerine geçen atriyal yüksek hız epizodları (AYHE) tarandı. AYHE 5 dakikadan uzun ve 220/dk'dan uzun epizodlar olarak tanımlandı.

Bulgular: Cihaz kontrolleri sonunda hastaların 128'inde (28.5%) 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/m²vs 28.65±3.75 kg/m² P <0.01)sahip bulundu. AYHE (+) hastaların istirahat kalp hızları (84.03±7.80 vs 74.76±6.40 vs, P <0.01), sol atriyanterio-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 sözcükler: Sessiz atriyalfibrillasyon, asemptomatikatriyalfibrillasyon, atriyal yüksek hız epizodları, obezite, artmış vücut kitle indeksi.

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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 embolism¹. Aging of the population and increasing 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 modifiable risk factors and early detection of AF is of utmost importance since treatment strategies targeting the elimination of AF are limited and recurrence rates following electrical/pharmacological cardio-version and pulmonary vein isolation are still considered to be high once AF develops.

Screening for asymptomatic AF is reasonable especially in patients with high risk for developing AF in order to prevent devastating adverse outcomes of undiagnosed AF. Electrocardiographic (ECG) monitoring detected previously undiagnosed AF in 11.5% stroke survivors in a recent meta-analysis². 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 considerably high risk for developing clinical AF, ischemic stroke and death³⁻⁵. In the light of these findings, recent European guideline on AF management recommends to interrogate pacemakers (PM) and implantable cardiac defibrillators (ICD) on a regular basis for AHRE and patients with AHRE should undergo further ECG monitoring to document AF with class IB indication⁶.

To identify patients who are more likely to develop AF is an important aspect in order to intervene modifiable risk factors associated with AF. Obesity was demonstrated to be such a 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 cohort⁹. However, these studies included only patients with clinically symptomatic AF. The association of increased body mass index (BMI) with silent AF remained to be unknown. In this report, we aimed to investigate the association between increased BMI with occurrence of AHRE in patients with cardiac pacemaker.

METHODS

Patients who were implanted dual chamber PM 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/m², 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 to the study protocol. The study was approved by the institutional ethical committee.

Prior to PM implantation, demographical characteristics and medical history of study objects were recorded. Patient's weight and height were measured using a standardized protocol and recorded. 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 guideline; 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. 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 smoking ≥ 1 cigarette per day and current alcohol consumer if drinking ≥ 1 drink per day. CHA₂DS₂-VASc score was calculated for each patient by assigning 2 points for history of stroke/transient ischemic attack or age ≥ 75 and 1 point for each parameter; age ≥ 65 , history of congestive heart failure, hypertension, diabetes mellitus, female sex and vascular diseases.

Transthoracic echocardiography (TTE) (Vivid 7, GE healthcare, Horten, Norway) was performed to all patients by an expert on cardiovascular imaging. Left atrial antero-posterior (LA-AP), left ventricular end-diastolic (LVEDD), end-systolic (LVESD) diameter and left atrium volume (LAV) were measured and recorded as outlined by current guideline of chamber quantification by American Society of Echocardiography¹¹. Left ventricular ejection fraction was calculated by using modified Simpson's method.

All patients were implanted dual chamber PM, which was programmed to DDDR mode. The atrial tachycardia detection mode was enabled and AF suppression feature by performing atrial overdrive pacing was programmed off. 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 in order to identify atrial activities and prevent ventricular R wave sensing during detection of AHRE.

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 R wave 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 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 two groups on the basis of presence [(AHRE(+)] or absence [(AHRE(-)] of AHRE at the time of device interrogation.

All data were evaluated by using NCSS (Number Cruncher Statistical System, 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 which were not normally distributed. Qualitative variables were evaluated by Pearson Chi-square and Continuity (Yates) correction. 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

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

Patients in AHRE (+) group were older (65.5 ± 8.9 vs 70.8 ± 8.1 , $P < 0.01$) and had greater BMI ($26.84\pm 3.41\text{kg/m}^2$ vs $28.65\pm 3.75\text{kg/m}^2$, $P < 0.01$) compared to patients in AHRE (-) group. When adjusted to BMI groups, patients in BMI $18\text{-}25\text{kg/m}^2$ group had 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 $25\text{-}30\text{kg/m}^2$ [166 (52.0%) vs 64 (50.0%), $P = 0.75$]. Patients with BMI $> 30\text{kg/m}^2$ were more likely to have AHRE [58 (18.1%) vs 43 (33.6%), $P < 0.01$]. In addition, patients in AHRE (+) group had significantly higher mean resting heart rate (74.8 ± 6.4 vs 84.0 ± 7.8 , $P < 0.01$), greater LA-AP diameter (4.14 ± 0.33 vs 3.90 ± 0.31 , $P < 0.01$), LAV (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 , $P < 0.01$).

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 BMI $>30\text{kg/m}^2$ group remained independently associated with incidence of AHRE (OR: 2.47, 95% 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 greater incidence of AHRE during their device interrogation. There was no significant difference in terms of AHRE detection in overweight (BMI > 25 - 30 kg/m²) patients. In contrast patients with BMI > 30 kg/m² 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 were made in the management of patients with AF, this 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 aging population and relatively high recurrence rates following contemporary medical and ablation therapies once AF develops. Recently, advances in diagnosing techniques for asymptomatic AF particularly in patients with CIED's led the emergence of the term "silent AF". Technological advances in CIED systems allowed clinicians to detect and store AHRE. Several studies identified AHRE as a harbinger of future atrial arrhythmias, stroke and death^{3,5}. In MOST trial, authors concluded 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 outcomes³. The incidence of AHRE in MOST trial was 51%, which is significantly higher than our finding (28.5%). This can be associated with longer follow-up duration in MOST trial and including 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 just an independent risk factor for AF^{7,8} but also contributes to the progression of paroxysmal AF to permanent AF¹⁴. 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 investigated the effect of risk factor management on incidence, symptom burden and outcome of AF with both short- and long term follow-up^{9,15-17}. Among these, in LEGACY trial, goal directed long-term sustained weight loss was associated with reduction in AF severity and burden. The maintenance of sinus rhythm was facilitated by weight management during the 5 years follow-up period.

There was no previous study reporting the direct relation between mean resting heart rate and AF. However, mean resting heart rate is often coexists with comorbid conditions associated with AF including hypertension, atherosclerosis and diabetes mellitus¹⁸. In hypertensive patients, increased resting heart rate in sinus rhythm was a predictor of new-onset AF independent from the effect of arterial pressure lowering

treatment. This finding was attributed to increased effect of sympathetic activity, which promotes AF through several pathways.¹⁹

In conclusion, patients with higher BMI (30 kg/m^2) were 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 in order to prevent detrimental adverse outcomes including stroke and heart failure.

STUDY LIMITATIONS

Present study has several inherent limitations. First, this is a single center study with 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 different results from our 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 pacemakers. Different results can be obtained by using variety of diagnostic methods for the detection of silent AF.

Conflict of interest statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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

Parameters		AHRE (-)	AHRE (+)	P value
Age (years)		65.51±8.99	70.84±8.05	<0.01
Weight (kilograms)		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 (Na) (mmol/L)		138.18±2.99	138.23±2.21	0.84
Potassium (K) (mmol/L)		4.12±0.54	4.20±0.55	0.16
Calcium (Ca) (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
LVDD (cm)		4.61±0.38	4.61±0.40	0.89
LVSD (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
CHA ₂ DS ₂ -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

SD: standard deviation. BMI: body mass index. LA-AP: left atrium antero-posterior. LVDD: left ventricle diastolic diameter. LVSD: left ventricle systolic diameter. EF: ejection fraction. LAV: left atrium volume

Table 3: Multivariate logistic regression analysis of parameters associated with AHRE

	95% CI	ODDS Ratio	P value
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
CHA ₂ DS ₂ -VASc	1.118 – 2.417	1.64	0.012
Hemoglobin level (g/dL)	0.636 – 1.007	0.80	0.057

AHRE: atrial high rate episodes, CI: confidence interval, BMI: body mass index, LA-AP: left atrial antero-posterior diameter