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Comparison of Patients With Atrial Fibrillation Without Structural Heart Disease and Normal Population in Terms of Urine Catecholamines

Yapısal Kalp Hastalığı Olmayan Atriyal Fibrilasyonlu Hastalar ile Normal Popülasyonun İdrar Katekolaminleri Açısından Karşılaştırılması

ABSTRACT

Objective: This study aimed to compare the sympathetic nervous system activity of atrial fibrillation patients without structural heart disease and the normal population in terms of urinary metanephrine levels.

Methods: Our study was conducted with 40 paroxysmal or persistent patients without structural heart disease and CHA2DS2VASc score of 0 or 1 and 40 healthy controls. Laboratory parameters, demographic characteristics, and 24-hour urine metanephrine levels were compared between the 2 groups included in the study.

Results: Metanephrine value in urine was found to be significantly higher in the atrial fibrillation group (atrial fibrillation group 97.50 ± 17.19 μg/day vs. control group 74.27 ± 15.55 μg/day; $P < 0.001$). The body mass index of the atrial fibrillation group was found to be significantly higher than the control group (atrial fibrillation group 27.26 ± 2.97 kg/m^2 vs. control group 24.05 ± 2.24 kg/m^2; $P < 0.001$). In multivariate linear regression analysis, body mass index (beta: 0.266, $P = .02$) and urinary metanephrine level (beta: 0.522, $P = 0.002$) were found to be independent risk factors. According to receiver operating characteristic analysis, it was determined that urinary metanephrine value (area under the curve = 0.834, $P < 0.001$) and body mass index (area under the curve = 0.803, $P < 0.001$) predicted the development of atrial fibrillation.

Conclusion: Our study found that urinary metanephrine levels were higher in patients with atrial fibrillation without structural heart disease than those without atrial fibrillation, and metanephrine values predicted the development of atrial fibrillation.

Keywords: Atrial fibrillation, urinary catecholamines, sympathetic nervous system

ÖZET

Amaç: Bu çalışmada yapısal kalp hastalığı olmayan atriyal fibrilasyon (AF) hastaları ile normal popülasyonun sempatik sinir sistemi aktivitesinin üriner metanefrin düzeyleri açısından karşılaştırılması amaçlandı.

Yöntemler: Çalışmamız yapısal kalp hastalığı olmayan, CHA2DS2VASc skoru 0 veya 1 olan paroksismal veya persistan 40 hasta ve 40 sağlıklı kontrol ile gerçekleştirildi. Çalışmaya alınan iki grup arasında laboratuvar parametreleri, demografik özellikler ve 24 saatlik idrar metanefrin düzeyleri karşılaştırıldı.

Bulgular: İdrardaki metanefrin değeri AF grubunda anlamlı olarak yüksek bulundu (AF grubu 97,50 ± 17,19 μgr / gün, kontrol grubu 74,27 ± 15,55 μgr / gün; p < 0,001). AF grubunun vücut kitle indeksi (VKİ) kontrol grubuna göre anlamlı olarak yüksek bulundu (AF grubu 27,26 ± 2,97 kg/m^2, kontrol grubu 24,05 ± 2,24 kg/m^2; p < 0,001). Çok değişkenli lineer regresyon analizinde VKİ (Beta: 0.266, p = 0.02) ve idrar metanefrin düzeyi (Beta: 0.522, p = 0.002) bağımsız risk faktörleri olarak bulundu. ROC analizine göre idrar metanefrin değeri (AUC = 0.834, p < 0.001) ve VKİ'nin (AUC = 0.803, p < 0.001) AF gelişimini öngördüğü belirlendi.

Sonuç: Çalışmamızda yapısal kalp hastalığı olmayan AF'li hastalarda idrar metanefrin düzeylerinin AF'si olmayanlara göre daha yüksek olduğu ve metanefrin değerlerinin AF gelişimini öngördüğü bulundu.

Anahtar Kelimeler: Atrial fibrilasyon, idar katekolaminleri, sempatik sinir sistemi

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Atrial fibrillation (AF) is the most common supraventricular arrhythmia in clinical practice, characterized by irregular ventricular rhythm, uncoordinated activation, and insufficient atrial contraction. There are several classifications for AF. Classifications are generally made on the temporal continuity of AF.[1] About 10% of patients with AF have no structural heart disease. This condition, especially in the young population, can cause severe clinical pictures such as cardiomyopathy and cerebrovascular events if not treated.[2] Although focal inducers and multiple waves are essential in the onset and maintenance of AF, electrical and structural remodeling that develops over time in the atrium perpetuates AF.[3]

Activation of the sympathetic system is considered one of the causes of cardiac arrhythmias. Autonomic nervous system activation can electrophysiologically induce atrial tachyarrhythmias, including atrial tachycardia and AF. Spontaneous or induced atrial arrhythmias are reduced by methods or drugs that reduce the output of autonomic innervation. In other words, it is known that neuromodulation can be effective in treating common tachyarrhythmias such as AF.[4-7] In a study by Nguyen et al.[8] a significant increase was observed in atrial sympathetic nerve densities in patients with chronic AF. Yoshida et al[9] compared the plasma catecholamine levels in paroxysmal and persistent patients with AF without structural heart disease and determined that it was higher in the persistent group. According to AF types, there are other studies on the effect of catecholamines on AF and the levels of plasma catecholamines.[10] There is no comparison of sympathetic nervous system activity in AF patients with the normal population in the early stages of AF, where structural heart disease has not yet been documented.

In some patients with a structurally normal heart, vagal tone predominates in the minutes before the onset of AF. In contrast, in some patients, there is a shift toward a predominance of sympathetic tone.[11,12] According to clinical studies, the preferred screening tests for catecholamine metabolism are to evaluate metanephrine and normetanephrine in the plasma or urine.[13,14] In addition, the metanephrine level in the urine is the catecholamine screening that is least affected by food.

A single triggering factor or mechanism cannot explain the occurrence of AF. Added comorbidities and triggers contribute to the formation and progression of AF. In this study, we sought the answer to the question: Are catecholamine levels higher in AF patients with the least comorbidity and triggers compared to the normal population? In our study, we selected CHA2DS2VASc 0 or 1 AF patients with minimal risk and trigger factors and who had not been previously compared with the normal population in terms of catecholamine levels. We used the 24-hour urinary catecholamine level, which is reliable because it can be collected easily and shows the 24-hour mean level. Thus, it does not reflect changes in urine and serum levels during the day.

MAIN POINTS

- The study aims to analyze the relationship between the risk of developing atrial fibrillation and the sympathetic system.
- Atrial fibrillation patients without structural heart disease and the normal population were compared for urinary catecholamines.
- In our study, urinary metanephrine levels and obesity were higher in patients with atrial fibrillation.

Materials and Methods

Study Population

The study was initiated after the ethics committee's approval, dated May 27, 2020, and protocol code 2011-KAEK-25 2020/05-01. It was conducted with 40 patients who were found to have AF without structural heart disease and CHA2DS2VASc 0 or 1, and 40 healthy control groups with no history of AF and structural heart disease, and CHA2DS2VASc 0 or 1 as a result of routine examinations in the cardiology outpatient clinic between June 1, 2020, and December 1, 2020. Moderate to severe valve disease left ventricular systolic dysfunction (ejection fraction < 50%), left ventricular hypertrophy (interventricular septum thickness ≥12 mm), and left ventricular diastolic dysfunction (due to *e´*, *E/e´* ratio, left atrial volume index, and peak tricuspid regurgitation velocity) were determined as structural heart disease. Since the female gender was evaluated as 1 point, there were no additional factors accompanying the CHA2DS2VASc score in females. In male patients, only patients with a CHA2DS2VASc score of 0 were included in the study. The flowchart of the study is shown in Figure 1.

Patients were included in the study by signing an informed consent form. Transthoracic echocardiography (TTE), 12-lead

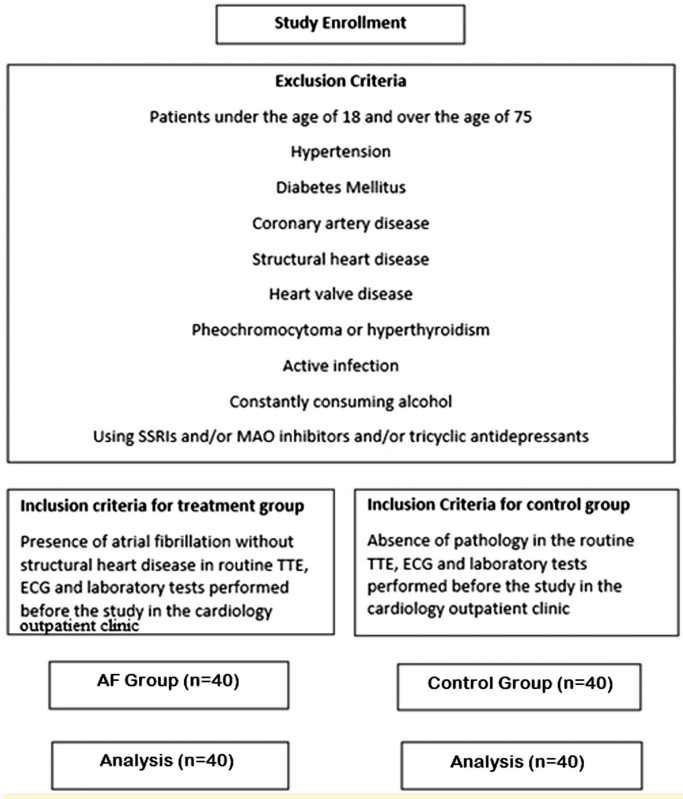


Figure 1. Inclusion criteria, exclusion criteria, and study flowchart.

electrocardiography (ECG), hemogram, liver, kidney, thyroid function tests, and infection parameters were evaluated in all patients. Demographic and clinical data were recorded prospectively. Height and weight measurements were made, and body mass indexes (BMI) were calculated. Electrocardiography recording, rhythm Holter recording, or AF lasting at least 30 seconds in monitoring were sought to recruit patients to the AF group. When choosing the patients, the patients with blood pressure below 140/90 mmHg in at least 2 measurements and who did not use antihypertensive drugs were accepted as normotensive and included in the study. History of coronary artery disease, moderate or severe valve stenosis/insufficiency, low ejection fraction (EF) or left ventricular hypertrophy, high C-reactive protein or white blood cell (WBC), evidence of infection, alcohol consumption more significant than 10 g per day, and abnormal thyroid function tests were accepted as exclusion criteria. In addition, the study did not include patients who used sympatholytic or sympathomimetic drugs that would affect the test result. Beta-blockers were discontinued at least 5 days before the urine test. Patients using amiodarone were not included in the study due to the long half-life of amiodarone. The female/male ratio was chosen as equal in the AF and control groups. Thirty patients in the AF group have paroxysmal, and 10 have persistent AF.

Sample Collection for Urine Metanephrine Level

Participants stopped taking alcohol, coffee, tea, chocolate, and vanilla food 3 days before the test. Smoking was banned 1 day before. Urine catecholamine samples from patients other than the control group were collected only if AF was shown in the 12-lead ECG on the day of sample collection. Before collecting the urine samples, 10 mL of preserving acid (6N HCl) was added to each urine collection cup. The container in which urine samples will be collected was wrapped with a black light-proof bag and given to the participants so that the sample would not see the light. After the first urine out after getting up in the morning, the urines made until the following day were collected for 24 hours. The catecholamine metabolite metanephrine (by ELISA method) was measured in urine samples. The upper limit of the kit used for the urinary metanephrine level was 312 µg/day for the healthy population. These metanephrine levels were compared between the AF group and the control group. Since the total level of metanephrine in the urine will be measured, the hydrolysis stage was first applied. After 10 µL of standard and urine samples were placed in the hydrolysis tubes, 40 µL of 0.1 M HCl was added. After the tubes were closed and hydrolyzed at 90° for 1 hour, they were left to cool at room temperature. After adding 100 µL of indicator buffer, 20 µL of acylation reagent was added. After capping the tubes and waiting for 15 minutes at room temperature, 1 ml of assay buffer was added to each tube. Fifty microliters of acylated standard and urine samples were placed in a 96-well plate, and 50 µL of metanephrine biotin and metanephrine antiserum were pipetted into the wells. The plate was covered with adhesive foil and incubated in an orbital shaker (circular shaker) device at 500 rpm for 1 hour at room temperature. The optical density in the plates was read in an ELISA reader at a wavelength of 405 nm.

Statistical Analysis

A statistical study was performed using Statistical Package for Social Sciences version 23 (SPSS Inc., Chicago, Ill, USA) package program. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequency and percentage (%). Comparisons between groups were made with Student's *t*-test for normally distributed numerical variables and non-normally distributed numerical variables with Mann–Whitney *U* test. Chi-square or Fisher's exact tests were used to compare categorical data. Spearman correlation analysis was used to determine the correlation between 2 continuous variables. Multivariable linear regression analysis was used to identify independent predictors of AF. The sensitivity and specificity values of AF predictors were determined by receiver operating characteristic (ROC) analysis. *P*-value < 0.05 was considered significant.

Results

Forty AF patients without structural heart disease and 40 healthy control cases were included in the study, and the patient's demographic data are shown in Table 1.

Table 1. Demographic and Laboratory Values of the Groups

Variables	Control Group	AF Group	*P*
Age (mean ± SD)	40.20 ± 11.03	44.95 ± 10.76	0.04
Gender			1
Female	20 (50%)	20 (50%)	
Male	20 (50%)	20 (50%)	
BMI (kg/m^2) (mean ± SD)	24.05 ± 2.24	27.26 ± 2.97	<0.001
EF (%) (mean ± SD)	59.80 ± 2.46	59.60 ± 2.67	0.97
Mean heart rate (Holter) (median ± SD)	78.9 ± 24.7	84.4 ± 31.2	0.074
Hemoglobin (g/dL) (mean ± SD)	13.56 ± 2.02	13.66 ± 2.80	0.93
WBC (µL) (mean ± SD)	6716.50 ± 1532.34	7931.50 ± 1176.41	<0.001
Platelet (µL) (mean ± SD)	277.87 ± 79.33	287.27 ± 92.83	0.62
Na (mmol/L) (mean ± SD)	139.35 ± 3.19	139.45 ± 3.23	0.91
K (mEq/L) (mean ± SD)	4.20 ± 0.50	4.14 ± 0.50	0.64
Creatinine (mg/dL) (mean ± SD)	0.62 ± 0.09	0.64 ± 0.10	0.31
GFR (mL/min) (median ± SD)	142.45 ± 45.36	136.65 ± 46.62	0.46
Metanephrine (µg/day) (mean ± SD)	74.27 ± 15.55	97.50 ± 17.19	<0.001

AF, atrial fibrillation; BMI, body mass index; EF, ejection fraction; GFR, glomerular filtration rate; SD, standard deviation; WBC, white blood cell.

The number of men (n=20) and women (n=20) in the AF and control groups was the same. The mean age of the control group was lower than the patients in the AF group (respectively, 40.20 ± 11.03, 44.95 ± 10.76, *P*=0.04). The hematologic and biochemical parameters of AF patients and the control group were similar. There was no difference between the groups in terms of EF evaluated in TTE (control group: 59.80 ± 2.46, AF group: 59.60 ± 2.67, *P*=0.97), median heart rate in Holter recordings (control group: 78.9 ± 24.7, AF group: 84.4 ± 31.2, *P*=0.074), and calculated glomerular filtration rate (GFR) values (control group: 142.45 ± 45.36, AF group: 136.65 ± 46.62, *P*=.46). Metanephrine level in urine was significantly higher in the AF group compared to the control group (97.50 ± 17.19 vs. 74.27 ± 15.55, *P* < 0.001). Body mass index and WBC values were significantly higher in the AF group compared to the control group (for BMI: control group: 24.05 ± 2.24, AF group: 27.26 ± 2.97, *P* < 0.001; for WBC: control group: 6716.50 ± 1532.34, AF group: 7931.50 ± 1176.41, *P* < 0.001). Since there were only 10 patients with persistent AF in the AF group, no subgroup analysis was performed for patients with persistent AF. In subgroup analyses comparing paroxysmal AF and control groups, BMI, metanephrine, and WBC were significantly different between the 2 groups (respectively, *P*=0.0049, *P*=0.027, and *P*=0.03). Statistical analyses for sex, hemoglobin, platelet count, sodium, potassium, creatine, and GFR showed no significant difference between the 2 groups.

Parameters found to be significantly different between the 2 groups were evaluated with multivariate linear regression analysis to show the presence of AF. As a result of this evaluation, it was determined that BMI and urinary metanephrine levels were independent parameters in terms of delivering the presence of AF in patients without risk factors (unstandardized coefficient beta [UCB]=0.044, *P*=0.02 for BMI and UCB=0.013, *P*=0.002 for urinary metanephrine). Although age and WBC levels were significantly different between the 2 groups, they were not found to be independent parameters to indicate the presence of AF in multivariate linear regression analysis (UCB < 0.001, *P*=.32) (Table 2).

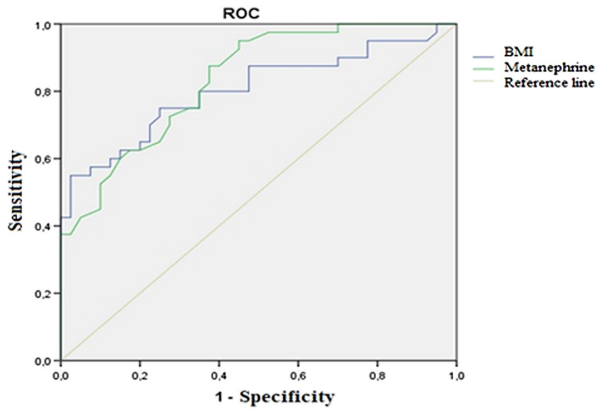
Spearman correlation analysis was used to show the relationship between BMI and urinary metanephrine level. There was a significant increase in urinary metanephrine excretion in obese patients (BMI >30 kg/m^2) compared to non-obese patients (BMI ≤ 30 kg/m^2) (correlation coefficient=0.84, *P*=0.003).

According to the ROC analysis performed to predict AF, the metanephrine value was 0.86 µg/day, with 73% sensitivity and 73% specificity (area under the curve (AUC)=0.834, *P* < 0.001), BMI value was 26 kg/m^2, with 70% sensitivity and 77% specificity (AUC=0.803, *P* < 0.001) predicted the probability of AF (Figure 2).

Table 2. Intergroup Multivariate Linear Regression Analysis

Variables	Unstandardized Coefficient Beta	Standardized Coefficient Beta	*T* Value	*P*
Age	0.003	0.074	0.804	0.42
BMI (kg/m^2)	0.044	0.266	2.334	0.02
WBC (µL)	0.00005	−0.148	−0.983	0.32
Metanephrine (µg/day)	0.013	0.522	3.152	0.002

BMI, body mass index; WBC, white blood cell.



Variables	AUC	95% CI	P Value
Metanephrine	0.834	0.749 – 0.919	< 0.001
BMI	0.803	0.705 – 0.902	< 0.001

BMI: Body mass index

Figure 2. ROC analysis for metanephrine in urine and BMI. ROC, receiver operating characteristic; BMI, body mass index.

Discussion

Our study observed that urinary metanephrine values in AF patients were higher than in the normal population, and urinary metanephrine values and BMI were independent parameters in terms of showing the possibility of AF.

The incidence of AF is associated with age and underlying structural heart disease. No underlying structural heart disease or associated risk factor was found in 2%-30% of AF patients.[15,16] Although this group, which generally represents younger patients, has a lower risk of developing permanent AF, they still face an increased risk of thromboembolic events and heart failure compared to the normal population.

A limited number of studies revealing the mechanisms of AF by examining the relationship between the autonomic nervous system and AF have shown that increased vagal or sympathetic stimulation can lead to AF triggering.[17,18] The lack of a gold standard method for assessing autonomic nervous system activity and measurement difficulties has prompted researchers to seek a simple and more effective way of measuring the effects of the autonomic nervous system on the heart. Heart rate variability is an ideal method to measure autonomic nerve activity, and some studies have examined the relationship between autonomic nervous system activity and AF over heart rate variability.[19,20] Decreased heart rate variability was associated with increased sympathetic activity. In these studies, it has been shown that the morning hours, when the activation of the sympathetic nervous system is at the highest level, is associated with AF and other arrhythmias and decreased heart rate variability in these patients. These studies are essential in showing that even fluctuations in autonomic tone during the day can trigger the development of AF.

A significant increase in catecholamine levels is expected in cases where sympathetic activity is at the forefront, such as pheochromocytoma. Atrial fibrillation is not known as a disease in which sympathetic activity is at the forefront. In our study, urinary metanephrine levels were significantly higher in AF patients without structural heart disease than in the control group. However, none of the collected urine samples had metanephrine levels above 312 µg/day, considered the normal population's upper pathological limit. Within normal limits, metanephrine was 31.3% higher in the AF group than in the control group. Although catecholamine levels were not at pathological levels, an independent relationship was found between increased catecholamine levels and the development of AF.

The relationship between BMI and AF has been demonstrated by various studies.[21-24] In particular, increased BMI with abdominal obesity is closely associated with AF, diabetes, hypertension, and coronary artery disease.[25] While increasing sympathetic tone in parallel with weight gain increases the risk of AF, weight loss in obese AF patients is associated with a better prognosis and less recurrence.[26,27] In a study in which most patients had AF without structural heart disease, the incidence of AF was higher in obese individuals than in the general population.[28] Similarly, in our study, BMI was significantly higher in the AF group than in the control group, and there was an independent relationship between BMI and the development of AF. Since our study was cross-sectional and the sample size was not large enough, the threshold values for urinary metanephrine level and BMI resulting from ROC analysis are not indicative. Prospective studies with larger populations are needed.

Inflammatory processes play an essential role in the development of AF. Inflammatory indicators and leukocyte count increased due to cardiac surgery, acute infection, coronary artery disease, hypertension, heart failure, and AF.[29,30] However, there is insufficient data on the increased leukocyte count in AF patients without structural heart disease. In our study, although the leukocyte count in the AF group was numerically more, none of the patients had a pathologically high leukocyte count, and no independent relationship was found between leukocytes and AF. In addition, our study found that leukocyte counts were lower in AF patients due to the absence of structural heart disease.

Atrial fibrillation is an arrhythmia that increases in frequency with age, and its incidence reaches 10% over 80. Age increases risk factors such as heart failure, coronary artery disease, hypertension, and heart valve diseases.[31] In our study, although the age was significantly higher in the AF group, no significant correlation was observed between age and AF.

The first limitation of our study is that paroxysmal and persistent AF patients could not be represented equally. Persistent AF patients constitute one-fourth of the treatment group. The second limitation of the study is that, due to the dynamic nature of AF and its spontaneous start and end, metanephrine levels in urine cannot be compared to AF attack and sinus rhythm. The third limitation of the study is the relatively small size of the study population. The significant difference in age and BMI between AF and control groups is another important limitation of this study. Due to the small number of people included in the study, a propensity analysis could not be performed. To put the study results into daily practice, there is a need for studies that are matched in terms of baseline characteristics and will be designed with a more significant number of patients.

Conclusions

The autonomic nervous system is essential in patients who develop AF without structural heart disease. The study's findings suggest that in addition to the role of the atrial substrate, sympathetic nervous system activity may play an essential role in AF without structural heart disease. The urinary metanephrine level was not at pathological levels in any patient. Since high BMI is more common in AF patients, there is a need to determine the effect of sympathetic nervous system in AF patients using matched samples.

Ethics Committee Approval: Ethics committee approval of the study was obtained with Bursa Yüksek İhtisas Training and Research Hospital clinical research ethics committee (Approval number: 2011-KAEK-25 2020/05-01, Date: May 27, 2020.

Informed Consent: Written informed consent was obtained from all atrial fibrillation and control group patients participating in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.P., Ç.K.; Writing – F.P., Ç.K.; Critical Review – F.P., Ç.K.

Declaration of Interests: None.

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Comparison of Patients With Atrial Fibrillation Without Structural Heart Disease and Normal Population in Terms of Urine Catecholamines

	Atrial Fibrilation Group (n=40)		Healty Control Group (n=40)	
Metanephrine Value in Urine	97.50 ± 17.19 µg/day	vs	74.27 ± 15.55 µg/day	P < 0.001
The Body Mass Index	27.26 ± 2.97 kg/m2	vs	24.05 ± 2.24 kg/m2	P < 0.001

Urinary metanephrine levels were higher in patients with atrial fibrillation without structural heart disease, and metanephrine values predicted the development of atrial fibrillation.

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