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The relationship between hyperuricemia and atrial fibrillation in patients with heart failure

Oguzhan Birdal[a,*], Emrah Aksakal[b], Sidar Siyar Aydin[b], Ibrahim Sarac[b], Ahmet Cagdas Yumurtas[c], Muhammed Cuneyt Seker[a]

[a] *Atatürk University, Faculty of Medicine, Department of Cardiology, Erzurum, Türkiye*
[b] *Erzurum City Hospital, Department of Cardiology, Erzurum, Türkiye*
[c] *Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training Hospital, Department of Cardiology, Istanbul, Türkiye*

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Abstract

Aim: Uric acid is the end product of purine metabolism. Overproduction and insufficient excretion cause an increase in serum uric acid (SUA) levels. In some studies, it has been shown that hyperuricemia is an independent predictor of cardiovascular mortality and poor prognosis of heart failure (HF). It has been found that the level of SUA may also be a biomarker to be used in demonstrating inflammation and oxidative stress. Recent studies have shown that inflammation and oxidative stress play a role in the pathogenesis of both HF and atrial fibrillation (AF). In this study, we aimed to investigate whether the level of SUA is associated with the development of AF in patients with HF.

Materials and Methods: A total of 1,342 patients with HF who applied to outpatient clinic between 2018 and 2022 were scanned. Patients with one of the exclusion criteria were not included in the study. As a result, 538 HF patients were included. These patients were divided into 2 groups as new-diagnosed AF patients and patients without AF.

Results: SUA level was 9.29±2.93 mg/dL in patients with AF and 7.67±2.5 mg/dL in patients who did not develop AF, which was statistically significant ($p<0.001$) Also furosemide use was 92.5% and 72.6% in patients with and without AF, respectively ($p<0.001$). Other results of the study are described in the main text. In our multivariate analysis, SUA level and furosemide use were found to be associated with the development of AF [1.21 (1.09-1.35) $p<0.001$ for SUA; 5.33 (1.87-15.18) ($p=0.002$) for furosemide].

Conclusion: Hyperuricemia may increase the development of AF in patients with HF. According to this, correction of hyperuricemia can contribute positively to mortality and morbidity in HF patients.

Introduction

Uric acid is the final product of purine metabolism in people, and this process is mediated by xanthine oxidase. It is produced in the muscles and liver and is primarily excreted by the kidneys. Its overproduction may lead to a rise in serum uric acid (SUA) levels [1, 2]. Regardless of gender or age, serum urate levels exceeding 7.0 mg/dL are regarded as a sign of hyperuricemia [3]. According to certain studies, hyperuricemia can predict mortality and cardiovascular disease on its own [4, 5]. Some studies claim that hyperuricemia in HF patients is a stand-alone indicator of a bad prognosis [6].

Arrhythmias of the atrial fibrillation (AF) variety are frequent. According to reports, AF makes HF patients more likely to die from any cause or from pump failure [7]. Recent research has demonstrated that oxidative stress and inflammation are factors in the pathophysiology of HF and AF. It has been discovered that SUA level can be utilized as a marker to demonstrate oxidative stress and inflammation in this population. Recent research has shown that the pathogenesis of HF and AF is influenced by oxidative stress and inflammation. Additionally, it has been suggested that SUA levels might be used as indicators of inflammation and oxidative stress in HF and AF patients [8–10].

In this regard, this study was conducted to ascertain whether SUA level is connected to the onset of AF in HF patients.

*Corresponding author:
Email address: droguzhanbirdal@gmail.com (Oguzhan Birdal)

Materials and Methods

Population&Sample

The 1342 patients with HF who applied to the Atatürk University cardiology outpatient clinic between 2018 and 2022 made up the population of this single-center, retrospective study. The study excluded patients with acute coronary syndrome, acute and chronic renal failure, hematological disease, active malignancy, gout, myocardial infarction within the previous 4 weeks, and acute HF-related hospitalization. In all, 538 HF patients made up the study sample. These patients were split into two groups according on their AF status: those with new-onset AF (n=133) and those without AF (n=405) (Figure 1).

Definitions

According to the European Society of Cardiology (ESC) 2021 Guidelines, HF was classified for the purposes of this study as having reduced ejection fraction (EF-HFrEF), mildly reduced EF (HFmrEF), and preserved EF (HFpEF) [11].

The AF group consisted of patients whose new-onset AF was identified during the clinical follow-up. Antihypertensive drugs were administered to patients who had known hypertension (HT) and whose blood pressure was greater than 140/90 mmHg twice or more. Patients with known diabetes mellitus (DM) who were on a diet, receiving antidiabetic medication, or who had a fasting blood glucose of greater than 126 mg/dL were, on the other hand, deemed to have DM. Additionally, coronary artery disease (CAD) was assumed to exist in patients with invasive or non-invasive imaging results. Based on the Modification Diet in Renal Disease (MDRD) formula, the estimated glomerular filtration rates (eGFR) of the patients were determined [12].

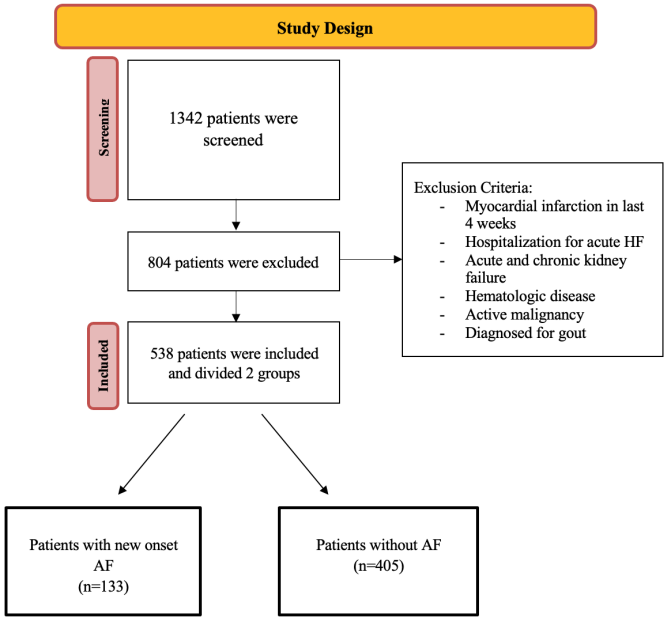

Figure 1. Consort flow patient inclusion/exclusion diagram.

Analysis of blood samples

Immediately following the diagnosis of AF, blood samples from the patients were drawn and placed in tubes containing potassium ethylenediaminetetraacetic acid (EDTA) solution for total blood count analysis. Standard laboratory procedures were used to measure the patients' hemoglobin and hematocrit levels, platelet and white blood cell (WBC) counts, and electrical impedance assay results (Beckman Coulter LH 780, Miami, FL, USA). The Beckman Coulter AU5800 analytical platform was used to measure the levels of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). Based on the Friedewald formula, low-density lipoprotein cholesterol (LDL-C) levels were computed.

Statistical analysis

The software program SPSS 22.0 (Statistical Product and Service Solutions for Windows, Version 22.0, IBM Corp., Armonk, NY, U.S., 2013) was used to conduct the statistical analyses. Power analysis was made with G Power Package program and the number of patients was calculated. When continuous variables were found to either conform or not to conform to the normal distribution, the descriptive statistics derived from the collected data were expressed as mean±standard deviation or median (interquartile range-IQR) values, and when categorical variables were involved, they were expressed as percentage values. Based on predetermined sub-groups, baseline characteristics were categorized and assessed using suitable statistical tests, such as the independent samples t-test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and the appropriate chi-square test for categorical variables. Parameters that were statistically significant in the univariate analysis were included in the correlation analysis. Parameters with high correlation were not included in the regression analysis. The associations between AF and the study's parameters were examined using logistic regression analysis with enter method. Statistical significance was considered to be indicated by the probability (p) statistics of 0.05 or lower.

Results

HF patients with and without AF had median ages of 68 (range: 62–72.5) and 66 (range: 58–74) years, respectively. Males made up 61.7% and 62.5% of the HF patients with and without AF, respectively, in terms of gender. Age and gender did not significantly differ between HF patients with and without AF (p=0.353 and p=0.483, respectively). Additionally, there was no discernible difference in creatinine levels between HF patients with and without AF (1.30±0.59 mg/dL vs. 1.31±0.81 mg/dL, p=0.194). However, HF patients with AF had significantly higher SUA levels than HF patients without AF (9.29±2.93 mg/dL vs. 7.67±2.5 mg/dL, p: 0.001). HF patients with AF were considerably more likely to use beta-blockers (BB) than HF patients without AF (78.9% vs. 70.4%, p=0.027). Similar to this, HF patients with AF used furosemide substantially more frequently than HF patients without AF (92.5% vs. 72.6%, p<0.001). Additionally, HF patients with AF used mineralocorticoids (MRA)

Table 1. Baseline demographic and clinical characteristics of the whole cohort.

Parameters	AF absence (n=405)	AF presence (n=133)	p-value
Age years (median)	66 (58-74)	68 (62-72.5)	0.353
Gender, n (%)	253 (62.5)	82 (61.7)	0.483
HT, n (%)	105 (25.9)	33 (24.8)	0.799
DM, n (%)	38 (9.4)	11 (8.2)	0.112
CAD, n (%)	239 (59)	84 (63.2)	0.398
Wbc, 10^9/L	9.07±3.39	9.19±3.81	0.844
Hgb, g/dL	13.5±2.1	13.8±1.8	0.118
Creatinine, mg/dL	1.31±0.81	1.30±0.59	0.194
ALT, U/L	19 (14-29)	20 (15-31)	0.256
Uric acid, mg/dL	7.67±2.5	9.29±2.93	**<0.001**
Glucose, mg/dL	144.3±70.3	140.2±76.3	0.429
Na, mmol/L	136.7±4.4	136.3±4,5	0.590
K, mmol/L	4.54±0.66	4.48±0.67	0.621
HDL, mg/dL 3	4 (27-42)	32 (27-38)	0.052
LDL, mg/dL	106.2±38.4 1	06.8±35.2	0.657
TG, mg/dL	113 (84-163)	106 (78.5-149.2)	0.290
TC, mg/dL	162.8±49.4	161.1±45.1	0.906
ASA, n (%)	288 (71.1)	50 (37.6)	**<0.001**
Clopidogrel, n (%)	81 (20)	20 (15)	0.229
ACEI, n (%)	184 (45.4)	66 (49.6)	0.333
ARB, n (%)	78 (19.3)	25 (18.8)	0.966
BB, n (%)	285 (70.4)	105 (78.9)	**0.027**
CCB, n (%)	42 (10.4)	68 (51.1)	0.287
Thiazide, n (%)	135 (33.3)	53 (39.8)	0.137
Furosemid, n (%)	294 (72.6)	123 (92.5)	**<0.001**
MRA, n (%)	151 (37.3)	68 (51.1)	**0.003**
ARNI, n (%)	1 (0.2)	1 (1.8)	0.400
Statin, n (%)	195 (48.1)	44 (33.1)	**0.004**
LVEF, n%±SD	38.6±13.9	39.4±11.9	0.847

Abbreviations: HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, Wbc: White blood cell, Hgb: hemoglobin, ALT: alanine aminotransferase, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglyceride, TC: total cholesterol, ACEİ: angiotensin-converting enzyme inhibitör, ARB: angiotensin receptor blocker, BB: beta-blocker, CCB: calcium channel blocker, MRA: mineralocorticoid receptor antagonist. LVEF: left ventricular ejection fraction, SD: standard deviation.

substantially more frequently than HF patients without AF (51.1% vs. 37.3%, p=0.003). Statin use, however, was considerably higher in HF patients without AF compared to HF patients with AF (48.1% vs. 33.1%, p=0.004). Table 1 displays the baseline demographic features of HF patients according to the existence of AF.

In the correlation analysis; betweeen SUA and furosemid use r^2 value was: 0.241, between SUA and MRA r^2: 0.101, between furosemid and MRA r^2: 0.377.

The results of multivariate analysis showed that the development of AF was favorably connected with SUA level and furosemide use, while negatively correlated with statin use [0.35 (0.9-0.64), p=0.001]. Table 2 presents the findings of the regression analysis.

Discussion

The results of this study suggested that high SUA levels may increase the likelihood that HF patients will get AF.

According to reports, the presence of both AF and HF is a sign of poor prognosis and is linked to higher mortality

Table 2. The regression model investigating Atrial Fibrillation (AF) development predictors.

Variables	Univariate	p	Multivariate	p
	OR, 95 CI%		OR, 95 CI%	
Age	1.01 (0.99-1.03)	0.353	0.99 (0.97-1.02)	0.897
HT	0.94 (0.60-1.48)	0.799	0.66 (0.34-1.25)	0.204
DM	0.82 (0.68-1.12)	0.112	0.78 (0.54-1.20)	0.186
CAD	1.19 (0.79-1.78)	0.398	0.85 (0.45-1.59)	0.621
Uric acid	1.24 (1.13-1.36)	**<0.001**	1.21 (1.09-1.35)	**<0.001**
BB	1.72 (1.06-2.80)	**0.027**	1.28 (0.62-2.63)	0.503
Furosemide	5.64 (2.67-11.93)	**<0.001**	5.33 (1.87-15.18)	**0.002**
MRA	1.82 (1.22-2.71)	**0.003**	0.80 (0.43-1.48)	0.483
Statin	0.54 (0.36-0.82)	**0.004**	0.35 (0.09-0.64)	**0.001**

Abbreviations: HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, BB: beta-blocker, MRA: mineralocorticoid receptor antagonist.

and morbidity [13]. In affluent nations, HF affects 2-3% of the population [14]. In fact, HF has a 5-year death rate that is 50%, which is higher than the majority of cancers [15]. According to a meta-analysis, having AF raised the risk of mortality in HF patients by 33% [16]. Similar to the previous study, another one found that patients with HF and AF had a higher risk of hospitalization and mortality [17]. It is obvious that there will be a huge load on healthcare systems in many nations given that both AF and HF are anticipated to increase dramatically during the next 20 years worldwide.

In order to better understand the epidemiology, pathophysiology, detection, and treatment of AF and HF, further study is required [18]. The cause-and-effect link between HF and AF is still not completely understood. The heart is predisposed to HF and AF by co-existing risk factors like HT, obesity, DM, ischemia, and non-ischemic structural heart disease; however, these risk factors have also been linked to myocardial extracellular changes, electrophysiological changes, and neurohormonal changes [19]. It has been demonstrated that inflammation and oxidative stress play crucial roles in the development of AF [20, 21] despite the fact that the pathophysiology of AF is unclear. Insulin resistance, oxidative stress, abnormally high levels of inflammatory markers, and elevated SUA were all linked together [22–24]. High SUA levels in this situation are thought to enhance the development of AF by causing inflammation [25]. The electrical re-modeling of the left atrial is caused by free radical superoxide anion production, oxidative stress, and other factors, and SUA is crucial in this process [9, 26]. In parallel, a different study discovered a substantial correlation between SUA level and left ventricular mass and left atrial diameter. All of these findings point to the possibility that hyperuricemia may contribute to the remodeling of the left atrium and left ventricle and, consequently, to the onset of AF [27]. There is proof that elevated SUA levels can be cardiotoxic. Both structural remodeling of the heart and proarrhythmic imbalance (electrical remodeling) between ion channels may result from hyperuricemia. The toxicity of hyperuricemia to endothelial cells may be explained by uric acid's antagonistic impact on nitric oxide and nitric oxide synthase [1,

28, 29]. In fact, it was noted that patients with hyperuricemia had a greater rate of AF formation [30].

For males, the normal SUA level range is between 6.5 and 7 mg/dL and for females, between 6 and 6.5 mg/dL [31]. When a patient has a higher cardiovascular risk, it is advised to keep their SUA level below 5 mg/dL [32, 33]. SUA levels are also related to proinflammatory cytokine release and regional renin-angiotensin system activation [34, 35]. Due to increased cell death, inflammation also raises SUA levels [36]. In patients with mild to severe chronic HF, elevated SUA levels are a reliable indicator of a poor prognosis [6]. It is currently unknown how therapy intended to lower the SUA level will affect the prognosis for AF and HF. According to a study on the effectiveness of low-dose allopurinol therapy, the patients' prognosis did not improve [37].

In a study conducted in India that included 2976 people, the relationship between SUA levels and cardiovascular risk factors was investigated and a positive correlation was shown [38]. In another study conducted in China, 25284 people without risk factors were examined and the relationship between SUA level and cardiovascular diseases in these individuals and what the most appropriate SUA level should be to prevent cardiovascular diseases were investigated. While it was observed that cardiovascular events increased with the increase in SUA level and it was shown that the optimal SUA level could be 5 mg/dL [39].

In a prospective study among patients with diabetes, including 7101 patients, a relationship was sought between SUA level and all-cause and cardiovascular mortality. In this study, it was observed that high SUA level was associated with high all-cause and cardiovascular mortality [40].

In another study examining patients with hypertension, the relationship between uric acid/HDL-cholesterol ratio (UHR) and controlling arterial blood pressure in these patients was examined and it was observed that it is difficult to control high hypertension in patients with high UHR [41].

We came to the conclusion that using loop diuretics might hasten the onset of AF. Diuretic usage has been demonstrated to cause hyperuricemia by boosting uric acid (UA) reabsorption and reducing UA secretion [42]. It was suggested that the use of diuretics may be preventive against the development of AF in a trial including individuals with HT [43]. The use of diuretics, on the other hand, increased cardiac death and all-cause mortality, according to an observational research involving patients with intact ejection fraction (EF) [44]. The use of high-dose diuretics raised the risk for arrhythmias including AF, renal failure, and hospitalization, according to another study done with HF patients [45]. The results of our investigation also point to a possible link between diuretic use-induced hyperuricemia and the emergence of new-onset AF.

Limitations

Our study's single-center, retrospective methodology and relatively small sample size were its main drawbacks.

Conclusion

The results of this study imply that HF patients with hyperuricemia may be predisposed to AF. In light of this, lowering mortality and morbidity rates in HF patients with hyperuricemia may be beneficial.

Ethical approval

Ethical approval was obtained for this study from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Decision no: 2022-10/66).

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