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Serum uric acid to HDL-cholesterol ratio could be promising predictor of atrioventricular nodal reentrant tachycardia

Ibrahim Donmez[a,*], Mehmet Cosgun[a], Muhammed Fatih Bayraktar[a], Ufuk Turan Kursat Korkmaz[b], Mustafa Enes Demirel[c], Emrah Acar[a], Yilmaz Gunes[a]

[a] *Bolu Abant Izzet Baysal University, Faculty of Medicine, Department of Cardiology, Bolu, Türkiye*
[b] *Bolu Abant Izzet Baysal University, Faculty of Medicine, Department of Cardiovasculer Surgery, Bolu, Türkiye*
[c] *Bolu Abant Izzet Baysal University, Faculty of Medicine, Department of Emergency Medicine, Bolu, Türkiye*

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Abstract

Aim: Paroxysmal supraventricular tachycardia (PSVT), particularly atrioventricular nodal reentrant tachycardia (AVNRT), is a common arrhythmia with no associated structural heart disease. Inflammation has been implicated in the pathogenesis of arrhythmias. Uric acid to high density lipoprotein (HDL)-cholesterol ratio (UHR) is a novel inflammation marker that has been investigated in various conditions. This study aimed to explore the potential association between UHR and AVNRT.

Materials and Methods: A total of 136 patients were included in the study, including 86 patients with AVNRT and 50 controls with normal electrophysiological study. All patients' medical records were reviewed, and data were obtained retrospectively. We recorded baseline features, hematologic and biochemical markers, and determined the UHR value.

Results: UHR (p=0.031) and uric acid (p<0.001) levels were significantly higher, while HDL cholesterol (p=0.031) levels were significantly lower in the AVNRT group. Neutrophil leukocyte ratio (NLR) was also higher in the AVNRT group (p=0.034). However, in multivariate analysis, only UHR emerged as an independent predictor for AVNRT (OR: 1.088; 95%CI: 1.022 – 1.159; p=0.008). ROC curve analysis suggested a UHR cut-off > 14.05 for predicting AVNRT with 56% sensitivity and 76% specificity.

Conclusion: This study identifies UHR as a promising predictor for AVNRT, shedding light on the potential role of inflammation in the arrhythmia's development. Utilizing UHR as a readily accessible marker in the evaluation of AVNRT patients may have clinical implications.

Introduction

The arrhythmia known as paroxysmal supraventricular tachycardia (PSVT) is characterized by a rapid heart rate and the abrupt beginning and ending of heart palpitations [1]. The majority of patients with PSVT do not have any underlying structural heart disease. PSVT is frequently caused by the re-entry mechanism [2]. The onset of tachycardia may be triggered by pacing maneuvers or pharmacologic agents [3]. Atrioventricular nodal re-entrant tachycardia (AVNRT) is the most prevalent form of PSVT [2]. Except for tachycardia attacks, AVNRT is extremely difficult to recognize in routine cardiac examinations in individuals with palpitations, as in other PSVTs.

In recent studies, inflammation has been proposed as a potential mechanism in the development of arrhythmias [4,5]. The uric acid/ high density lipoprotein (HDL)-cholesterol ratio (UHR) is a recently found measure in the diagnosing diabetes mellitus and various heart diseases [6]. HDL levels are inversely correlated with inflammation and oxidative stress in chronic diseases [7]. In addition, several studies have shown that high uric acid levels increase the risk of cardiovascular problems [8]. It is well-established that uric acid and inflammation are positively and significantly associated. The pro-inflammatory mechanism of uric acid may contribute to increased mortality and unfavorable prognosis [9]. An elevation in UHR can be attributed to either increased uric acid levels or decreased HDL levels.

As far as we know, no prior studies have investigated the association between UHR and AVNRT. In the present

*Corresponding author:
Email address: dr_ibrahimdonmez@hotmail.com (Ibrahim Donmez)

study, we hypothesized that high levels of UHR could predict AVNRT. Therefore, we aimed to investigate the possible association between UHR, measured before the electrophysiological study (EPS) procedure, and the risk of AVNRT.

Materials and Methods

Study design and population

This was a single-centered retrospective cross-sectional study, and performed at the department of cardiology of a tertiary referral hospital in Turkey. We screened a total of 162 SVT ablation of patients older than 18 years who had an electrophysiology study owing to palpitations or verified supraventricular tachycardia on an electrocardiogram (ECG) between December 2017 and September 2019. When repeated procedures for the same patient were extracted, 148 SVT ablation patients were obtained. The study excluded 36 patients due to the absence of complete blood count (CBC) recording concurrent with the diagnosis of SVT in the system, and 16 patients were not included because of having exclusion criteria. 28 patients were excluded from the study due to non-AVNRT ablation of SVT. As a result, 136 patients with AVNRT ablation and 50 patients with normal EPS findings were analyzed in two groups. The flowchart of the study is presented in Figure 1.

The study had specific exclusion criteria, which encompassed patients with recent infections or surgeries, morbid obesity (defined as a body mass index $\geq$35 kg/m^2), coronary artery disease, severe renal or liver dysfunction, moderate to severe valvular diseases, peripheral or cerebral vascular disease, heart failure, malignancies, hematological disorders, inflammatory diseases, and individuals who were using medications, including antiarrhythmic agents. Patients meeting any of these exclusion criteria were not included in the study to ensure a more homogeneous and well-defined study population.

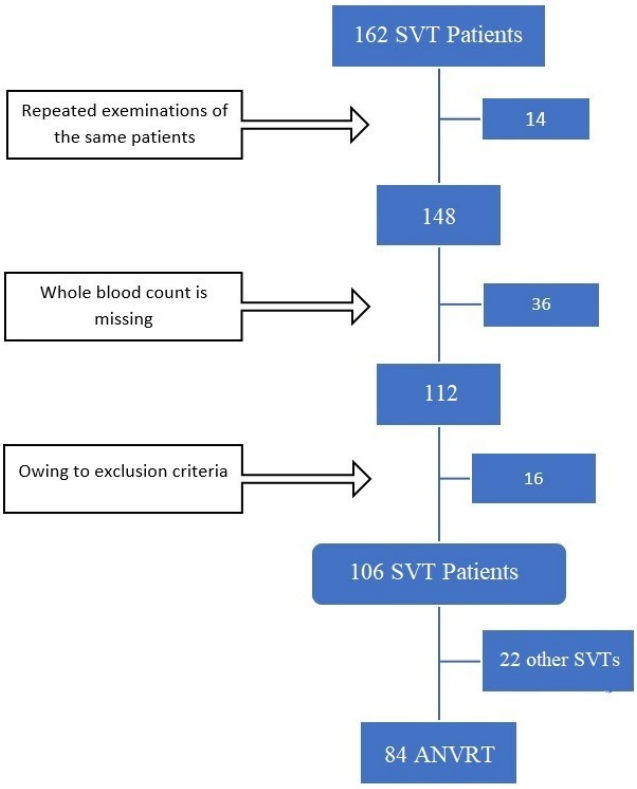

Figure 1. Selection of the study population.

The patients' basic demographic and clinical characteristics as well as laboratory data were obtained via the medical electronic database of the hospital, recorded for the analyses, and then compared between the groups.

Our cross-sectional study was approved by Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (Decision No: 2022/113, Date: 26/04/2022). Before the operation, all patients were informed about the operation and the perioperative process, and verbal and written consent was obtained. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Laboratory analysis

At the initial presentation before the EPS procedure, peripheral venous blood samples were collected from the antecubital vein. The collected blood samples were used to measure various biochemical parameters using an automatic biochemical analyzer called Architect C8000 (USA). The measured parameters included fasting plasma glucose, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), HDL-cholesterol, and uric acid. Additionally, a CBC were studied in an automatic CBC analysis device (Beckman Coulter Inc., CA, USA). For the post hoc analysis, inflammatory indexes were calculated based on the values of neutrophils (N), lymphocytes (L), platelets (P), and monocytes (M): neutrophils-lymphocyte ratio (NLR) was defined as N/L, platelet-lymphocyte ratio (PLR) was defined as P/L, and monocytes-lymphocyte ratio (MLR) was defined M/L.

To calculate the Uric acid to HDL-cholesterol ratio, the serum uric acid level was divided by the HDL-cholesterol level obtained from the blood samples. This ratio was then used as a marker to assess the potential association between uric acid and HDL-cholesterol levels in relation to AVNRT in the study participants.

Statistical analysis

The statistical software SPSS 25.0 for Windows, manufactured by SPSS Inc, Chicago, Illinois, USA was employed to analyze all data. Shapiro-Wilk test was used in order to assess the normality of variables. For continuous variables, the mean and standard deviation were employed to express normal distribution, while the median with minimum and maximum values were utilized for abnormal distribution. Categorical variables were expressed as frequency and percentage. Independent Student's t-test and Mann-Whitney U test were employed to assess differences between the two groups, and the chi-square test was employed for categorical variables. Risk factors with a p-value below 0.05 were integrated into the univariate logistic regression analysis. The original model encompassing

all significant independent variables was adjusted for logistic regression analysis with multiple explanatory variables. Next, a backward-elimination approach was utilized in a multiple explanatory variable logistic regression model to assess potential confounding effects. Receiver operating characteristic (ROC) curves were generated to offer data on the predictive potential of systemic inflammatory indices in forecasting AVNRT, and the area under the curve (AUC) was utilized to quantify the ROC curve. The best cut-off value was calculated using the Youden index. All comparisons were deemed statistically significant at a significance level of $p<0.05$.

Results

Demographic and clinical data of patients are summarized in Table 1. Baseline demographic factors such as gender, age, frequency of coronary artery disease, hypertension, diabetes, and smoking did not differ substantially across groups.

Table 2 summarizes the laboratory data of the research groups. Uric acid (6.64±2.18 vs. 5.56±1.66, p=0.031) and UHR were considerably higher (16.11±6.36 vs. 11.88±4.57, p0.001) in the AVNRT group, although HDL was significantly lower (46.18±12.13 vs. 50.74±16.02, p=0.035). In addition, the NLR value in the AVNRT group was substantially higher (2.79±1.20 vs. 2.34±0.79, p=0.034). The fasting glucose, creatinine, AST, ALT, CRP, and hemogram parameters except N/R ratio did not change substantially between the groups (Table 2).

Table 1. Baseline characteristics of the study groups.

Variables	AVNRT (n=84)	Control (n=50)	P value
Demographic			
Age (years)	54.83 ± 14.93	60.70 ± 13.57	0.937
Gender, Female/Male	28/56	17/33	0.664
Medical History			
Hypertension	39 (46.4%)	24 (48.0%)	0.860
Diabetes Mellitus	25 (29.7%)	15 (30.0%)	0.977
Coronary Artery Disease	9 (10.7%)	11 (22.0%)	0.441
Smoking	31 (36.9%)	19 (38.0%)	0.889

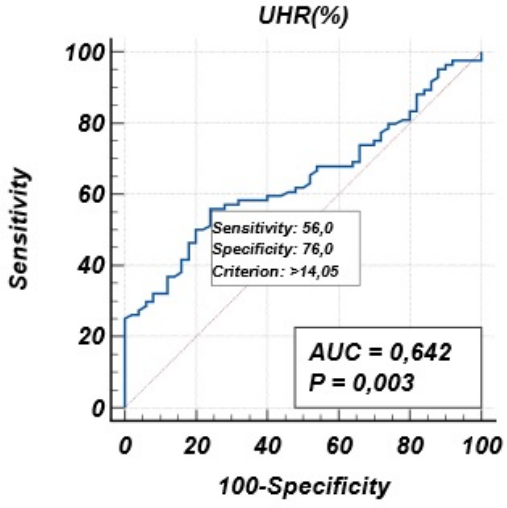

Figure 2. The results of ROC curve analysis for UHR.

Table 2. Laboratory findings of the study groups.

Variables	AVNRT (n=84)	Control (n=50)	P value
Fasting plasma glucose (mg/dl)	89 (71 – 236)	93 (74 – 256)	0.326
Creatinine (mg/dl)	1.31 ± 0.28	1.38 ± 0.35	0.157
AST (U/L)	30 (15 – 116)	27 (18-85)	0.445
ALT (U/L)	35 (12 – 71)	21 (12 – 50)	0.267
Uric acid (mg/dl)	**6.64 ± 2.18**	**5.56 ± 1.66**	**0.031**
HDL-cholesterol (mg/dl)	**46.18 ± 12.13**	**50.74 ± 16.02**	**0.035**
UHR (%)	**16.11 ± 6.36**	**11.88 ± 4.57**	**<0.001**
CRP (mg/L)	7.2 (0.3 – 76.6)	6.6 (0.1 – 51.4)	0.437
Hemoglobin (g/dl)	13.24 ± 1.51	13.14 ± 1.49	0.668
WBC (u/mm$^{3)}$	7.67 ± 2.42	7.51 ± 2.34	0.630
Platelet (10^3/mm^3)	278.00 ± 78.57	243.90 ±85.25	0.387
Neutrophil (u/mm^3)	4.89 ± 1.71	4.69 ± 1.68	0.941
Lymphocyte (u/mm^3)	1.88 ± 0.63	2.07 ± 0.64	0.729
Monocyte (u/mm^3)	0.63 ± 0.35	0.59 ± 0.23	0.743
RDW (%)	13.93 ± 1.97	14.21 ± 1.93	0.954
MPV (fL)	10.41 ± 1.26	10.77 ± 1.37	0.552
PCT (%)	0.29 ± 0.07	0.27 ± 0.06	0.773
PDW (%)	13.93 ± 1.97	14.21 ± 1.93	0.954
NLR	**2.79 ± 1.20**	**2.34 ± 0.79**	**0.034**
PLR	148.95 (31.19 – 465.82)	124.34 (4.13 – 318.34)	0.127
MLR	0.30 (0.10 – 0.67)	0.27 (0.12 – 0.68)	0.273

Abbreviations: AST: aspartate aminotransferase; ALT: Alanine aminotransferase; HDL, High-density lipoprotein; UHR: Uric acid to HDL ratio; CRP: C- reaktive protein; ; WBC: White blood cell; RDW: Red blood cell distribution width; MPV, Mean platelet volume; PCT, Plateletcrit; PDW: platelet distribution width; NLR: Neutrophil/lymphocyte ratio; PLR, Platelet/lymphocyte ratio; MLR, Monocyte/lymphocyte ratio.

Table 3. The results of multıvariate logistic regression analysis for the prediction of SVT.

Variables	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value
Uric acid	**1.330 (1.093 – 1.618)**	**0.004**	1.039 (0.727 – 1.487)	0.832
HDL- cholesterol (mg/dl)	0.976 (0.952 – 1.002)	0.070		
UHR (%)	**1.098 (1.034 – 1.166)**	**0.002**	**1.088 (1.022 – 1.159)**	**0.008**
NLR	**1.577 (1.061 – 2.344)**	**0.024**	1.388 (0.920 – 2.095)	0.118

Abbreviations: CI: Confidence interval; HDL, High-density lipoprotein; UHR: Uric acid to HDL ratio; NLR: Neutrophil/lymphocyte ratio.

Multiple logistic regression analysis was performed to determine the predictive value of factors related to the presence of AVNRT. This model included uric acid, HDL, UHR, and NLR. In univariate analysis, uric acid, UHR, and NLR were significant, but only UHR (OR: 1.088; 95%CI: 1.022 – 1.159; p=0.008) was independently associated with AVNRT in multivariate analysis (Table 3).

ROC curve analysis revealed that a cut-off > 14.05 UHR

values for predicting the AVNRT with 56% sensitivity and 76% specificity (AUC=0.642, p=0.003) (Figure 2).

Discussion

The primary purpose of this study was to determine whether there was a possible prognostic relationship between UHR, a novel inflammation marker, and AVNRT. The present study found that increased UHR levels could be associated with AVNRT. Although NLR, uric acid, and UHR levels were significantly higher and HDL-cholesterol was significantly lower in the AVNRT group, according to multivariate regression analysis, only UHR arrived at statistical significance and was considered an independent predictor for the AVNRT.

There is evidence to suggest that systemic inflammation can be linked to arrhythmogenesis through various mechanisms. In particular, inflammatory cytokines may have a significant role in this process by potentially lowering the arrhythmogenic threshold in individuals prone to arrhythmias [4,10,11]. For example, TNF-α, a pro-inflammatory cytokine, has been implicated in exerting arrhythmogenic effects at the cellular level. These effects may manifest through electrophysiological abnormalities, leading to phenomena like enhanced automaticity and the formation of reentrant loops. This can arise as a result of sodium channel hyperactivation, aberrant calcium handling, or prolonged action potential duration [12]. These inflammatory processes may contribute to the development of arrhythmias, including AVNRT, by disrupting the normal electrical activity of the heart and facilitating the initiation and maintenance of abnormal rhythms.

The NLR, a marker of inflammation, has been found to be associated with various cardiovascular diseases [13-15]. Aydn et al. studied 150 patients who had catheter ablation for SVT and 98 healthy people. Higher NLR levels were shown to be associated with SVT in their retrospective cross-sectional investigation. Additionally, in patients undergoing electrophysiological study, those with induced tachycardia had higher NLR values compared to those without tachycardia induction. We also discovered comparable NLR levels between the control group and the AVNRT patients, supporting Aydn et al.16 findings; however, NLR was not an independent predictor according to the multivariate analysis results in our study. There are similar conflict results in the literature [16,17].

Both HDL and uric acid are easily measurable parameters in peripheral blood sample. The enzyme xanthine oxidase synthesizes uric acid, the final result of purine metabolism. Several studies have linked hyperuricemia (elevated uric acid levels) to various cardiovascular diseases, vascular dementia, hypertension, metabolic syndrome, preeclampsia, and kidney disease [9,18,19]. It is evident that uric acid is not merely a catabolic marker, as it seems to play a role in the common pathway of systemic inflammation, which contributes to conditions like hypertension, vascular diseases, and renal insufficiency [20].

In our study, we observed that HDL cholesterol levels were lower in patients with AVNRT. HDL cholesterol is known to possess antioxidant and anti-inflammatory properties [19]. However, during inflammation, there are considerable alterations in HDL-associated proteins, leading to changes in HDL levels [21]. Despite finding significant differences in uric acid and HDL cholesterol values between the AVNRT patients and the control group, they were not identified as independent predictors for AVNRT in our study.

UHR is a novel measure that combines uric acid with HDL cholesterol. Recent studies have indicated its potential as a predictor for various conditions. The research findings revealed that UHR is significantly linked to metabolic syndrome in patients diagnosed with type 2 diabetes mellitus. Moreover, due to its remarkable sensitivity and specificity, UHR was proposed as a potential marker for assessing diabetes control6. Another study demonstrated that UHR could predict the presence of coronary artery fistulas [22].

Given that inflammation has been linked to the pathogenesis of arrhythmias, UHR may also play a role in the mechanism of AVNRT. In our study, it was determined that UHR predicted AVNRT more effectively than NLR. Probably UHR may predict inflammation more effectively than NLR [23,24]. This hypothesis can be tested in future studies. In patients with AVNRT, the UHR may reflect a lower level of HDL cholesterol or a higher level of uric acid, or both, indicating potential inflammation involvement. Therefore, UHR could be a valuable parameter to investigate in AVNRT patients, as it offers advantages such as cost-effectiveness, simplicity, and widespread availability.

However, it is essential to acknowledge some limitations of the study, such as its single-center and retrospective design. Further research, particularly cellular studies, is needed to understand the mechanisms linking high UHR levels to AVNRT. Nevertheless, this study is the first to highlight a significant association between high UHR and AVNRT, providing a foundation for future investigations.

Conclusion

In conclusion, our study demonstrated that UHR, a cheap, universal, and easily evaluable marker, was a novel and independent predictor of AVNRT. Nevertheless, prospective, large-scale, well-designed studies are required to support of our findings and obtain stronger scientific evidence. Our findings may encourage further studies.

Ethical approval

Our study was approved by Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (Decision No: 2022/113, Date: 26/04/2022).

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