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Uric Acid Levels in Obstructive Sleep Apnea Patients with Atrial Fibrillation

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Background and Aims. The objective of this observational study was to determine whether there is an association between atrial fibrillation (AF) and uric acid and to identify the risk markers for AF in obstructive sleep apnea (OSA).

Methods. Consecutive patients with newly diagnosed OSA were screened at baseline. The final study population consisted of 516 patients. One hundred and eight patients had AF. Demographic, clinical, laboratory, and echocardiographic characteristics were carefully recorded. Logistic regression was used for the multivariate analysis of independent risk factors.

Results. Uric acid, triglyceride, high-density lipoprotein, C-reactive protein (CRP), left atrial diameter, interventricular septum thickness, apnea hypopnea index, and Epworth sleepiness scale were significantly higher in OSA patients with AF than in those without AF ($p < 0.05$). Among these patients, multiple logistic analyses indicated the independent risk factors for AF occurrence in the OSA subjects included serum uric acid level, left atrial diameter, percentage of time with SaO_2 <90%, CRP. The diagnosis analysis showed that higher uric acid, CRP, left atrial diameter and percentage of time with SaO_2 <90% had a significant ability to reflect the presence of AF occurrence.

Conclusions. The novel finding of this study is that the occurrence of AF in OSA patients is strongly related to serum uric acid level, left atrial diameter, percentage of time with SaO_2 <90% and CRP level. These results may be helpful for monitoring AF occurrence in OSA patients.

Key Words: Obstructive sleep apnea, Atrial fibrillation, Uric acid, Risk factors.

Introduction

Atrial fibrillation (AF) is a rapidly emerging epidemic with different potential substrates and serious health consequences (1). The exact mechanisms underlying both the initiation and maintenance of AF are not well understood, but recent studies have implicated the involvement of both inflammation (2–4) and oxidative stress (5,6).

Obstructive sleep apnea (OSA) is a common chronic respiratory disorder and is associated with excessive daytime sleepiness, cognitive dysfunction, impaired quality of life, hypertension and an increased cardiovascular morbidity and mortality (7,8). Recent studies suggested that the prevalence and incidence of AF were significantly higher in patients with OSA and vice versa (9,10). OSA induces intermittent hypoxemia, hypercapnia, chemoreceptor excitation, autonomic nerve imbalance, inflammation, and abrupt surges in arterial pressure (11,12). Thus, the presence of OSA would predispose to the subsequent development of AF. Uric acid (UA) has emerged as a simple and independent marker of morbidity and mortality in a variety of cardiovascular disease states (13). Regardless of the debate whether it is a predictor or a causative factor, UA has been clearly associated with oxidative stress and inflammation in several pathological conditions (14).

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Although numerous clinical studies regarding AF in OSA patients have been published, there are few data addressing the association between uric acid levels and AF in OSA patients.

In this study we aimed to investigate the association between AF and serum uric acid (SUA) levels in patients with OSA as well as the other risk factors.

Patients and Methods

This study was performed in the Department of Respirology of the Affiliated Huai'an Hospital of Xuzhou Medical College in Huai'an, PR China. All participants gave informed consent. The study was approved by the Ethics Committee of the hospital in accordance with the Declaration of Helsinki. All patients with OSA were also diagnosed by polysomnography. Before enrollment, a spirometry was done on all patients, and all subjects were asked about their regular medications and medical history including cardiovascular diseases.

In this cross-sectional study we recruited consecutive OSA patients with or without a history of AF and who were seen in our hospital between January 2008 and December 2012. Exclusion criteria were thyroid dysfunction (including subclinical hyperthyroidism), history of coronary artery disease, valvular heart disease, congestive heart failure, previous cardiac surgery, myocardial infarction, hypertrophic and dilated cardiomyopathy, history of a disabling cerebral infarction or transient ischemic attack, recent infection, autoimmune or inflammatory diseases, malignancy (hematological malignancies and solid tumor), chronic respiratory disease (chronic obstructive disease, asthma and bronchiectasis, et al), chronic kidney disease, some drugs interfering with uric acid metabolism, and alcohol consumption.

Definition of AF

In the present study, AF was diagnosed using electrocardiography, including 12-lead surface electrocardiograms and 24-h Holter recordings at the initial visit.

Echocardiography

Two-dimensional echocardiography with M-mode recording was obtained according to American Society of Echocardiography guidelines (15) (iE33 xMATRIX Echocardiography System; Philips, The Netherlands). All studies were performed and interpreted by the same operator and recorded on videotape. Left ventricular end-diastolic dimension, left atrial diameter, left ventricular ejection fraction, interventricular septum thickness and left ventricular posterior wall were measured. The ejection fraction was calculated from area measurements using the area-length method applied to the average apical area. Echocardiographic data were recorded according to the guidelines of the American Society of Echocardiography.

Polysomnography

Polysomnography was started at 9 p.m. and ended at 6:30 a.m. All subjects underwent an attended overnight sleep study with the use of Jaeger Sleeplab 1000 (Jaeger, Würzburg, Germany) polysomnography system. The following signals were included: EEG, electroocculogram, submental electromyogram, and anterior tibialis electromyogram. Additionally, ECG and heart rate were recorded simultaneously. Snoring was recorded by a microphone placed at the jugular vein, and air flow was recorded by combined oronasal thermistors, while arterial oxyhemoglobin saturation was recorded by a finger pulse oximeter. Thoracic cage and abdominal motion were recorded by inductive plethysmography. EEG recordings were manually scored according to standard criteria (16).

Apnea was defined as the cessation of airflow at the nose and mouth lasting for $\geq$10 sec. Hypopnea was defined as a decrease of $\geq$30% in thoracoabdominal motion associated with a fall in the baseline oxygen saturation of $\geq$4%. All AHI values were calculated to express the number of episodes of apnea and hypopnea per hour of total sleep time.

Blood Collection and Biochemical Analysis

All blood samples were obtained between 8:00 and 9:00 a.m. Laboratory examinations including complete blood count and biochemical investigations were performed in the fasting state. Levels of total cholesterol, triglycerides, HDL-C, and LDL-C were measured by enzymatic colorimetric methods. White blood cell (WBC) count was determined using a Coulter counter. C-reactive protein (CRP) level was assayed with the immunonephelometric method (Dade Behring Marburg, Marburg, Germany). The reference concentration for CRP was $<$3 mg/L, and the intra-assay variability for the CRP was $<$4.3%. As a measure of renal function, baseline glomerular filtration was estimated (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) Study Equation (17): eGFR (mL/min/1.73 m^2 of body surface area) = 186 $\times$ (serum creatinine in mg/dL)$^{-1.154}$ $\times$ (age in years)$^{-0.203}$ $\times$ 0.742 in female subjects. Plasma uric acid levels were measured by standard uricase enzymatic test (normal range of uric acid levels: 150–440 μmol/L for men, 90–380 μmol/L for women).

Statistical Analysis

Continuous data are presented as mean $\pm$ standard deviation. Univariate analysis to assess the predictive value of clinical variables on AF occurrence was computed using the unpaired independent samples *t*-test for continuous variables and the χ^2 test and Fisher's exact test if necessary for categorical variables. A p value $<$0.05 was considered statistically significant. To test the independence of the risk factors for AF occurrence in OSA patients, the significant