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Original article

Increased ventricular pacing threshold levels in patients with high serum uric acid levels

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ABSTRACT

Background: Permanent cardiac pacemakers (PCM) are accepted as the most effective treatment for symptomatic bradyarrhythmias. Serum uric acid (UA) levels are associated with various inflammatory markers, oxidative stress, and endothelial dysfunction. This study aimed to investigate the association between serum UA and ventricular pacing threshold (VPT) levels in patients who underwent permanent pacemaker implantation.

Materials and methods: We retrospectively analyzed a total of 198 patients who underwent PCM implantation for indications such as symptomatic bradycardia without a reversible etiology and high-degree and complete atrioventricular block.

Results: VPT values were found to correlate with serum UA levels ($r = 0.591$, $p < 0.001$), high sensitivity C-reactive protein (hs-CRP) levels ($r = 0.505$, $p < 0.001$), and ventricular impedance ($r = 0.220$, $p = 0.016$). The serum UA levels and hs-CRP levels were also correlated ($r = 0.691$, $p < 0.001$). To identify independent risk factors for VPT values, a multivariate linear regression model was conducted, and serum UA levels ($\beta = 0.361$, $p = 0.001$), hs-CRP levels ($\beta = 0.277$, $p = 0.012$), and impedance values ($\beta = 0.207$, $p = 0.011$) were found to be independent risk factors for VPT.

Conclusion: In the present study, VPT values at the time of implantation and at the 30th day were increased in patients with high serum UA levels. To further extend the life of pacemakers, as well as other factors that affect threshold values, serum UA levels should be noted.

Introduction

Permanent cardiac pacemakers (PCM) are accepted as the most effective treatment for symptomatic bradyarrhythmias and play an important role in interventional cardiology practices worldwide. During PCM implantation, three essential pacing parameters should be tested: sensing, lead impedance, and pacing threshold. Pacing threshold [measured in volts (V)] and pulse width [in milliseconds (ms)] is defined as the minimum amount of energy needed to capture the myocardial tissue electrically. Unnecessary high pacing output adversely shortens the battery life of the PCM and is influenced by physiologic and pharmacologic factors. Several factors such as myocardial infarction, hyperkalemia, severe acidosis or alkalosis, or drugs such as bretylium, flecainide, propafenone, sotalol, and others [1–3] may increase pacing thresholds.

Uric acid (UA) is the end product of purine metabolism catalyzed by xanthine oxidase from hypoxanthine or xanthine. The serum UA level has been shown to be an important and independent risk factor in the development of cardiovascular disease [4–6]. Additionally, serum UA levels are associated with various inflammatory markers, oxidative stress, and endothelial dysfunction [7–10]. However, to our knowledge, no study has investigated the effects of serum UA levels on pacing thresholds. This study aimed to investigate the association between serum UA and ventricular pacing threshold levels in patients who underwent PCM implantation.

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Methods

Study design and population

We retrospectively analyzed a total of 198 patients who underwent PCM implantation at our institution between 2010 and 2013 with the indications including symptomatic bradycardia without a reversible etiology and high-degree and complete atrioventricular block. In the first stage, without knowledge of the patients' pacing parameters, two different cardiologists collected demographic/clinical data, echocardiographic data, and biochemical/hematological laboratory results from digital/non-digital records. Patients were excluded according to the following criteria: left ventricular systolic dysfunction (left ventricular ejection fraction < 45%), acute coronary syndrome, history of myocardial infarction, serum creatinine > 1.5 mg/dL, hypo- or hyperthyroidism, right ventricular leads located in an area other than apex, active fixation mechanism, epicardial leads, and patients taking antiarrhythmic and UA lowering drugs. Such patients were excluded because they may have other reasons than UA to have higher ventricular pacing thresholds (*e.g.* fibrosis, scar). In the last stage, a different experienced interventional cardiologist evaluated the remaining 121 patients. The patients were divided into two groups: normal serum UA level (<7 mg/dL as Group 1) or higher serum UA level (≥7 mg/dL as Group 2) according to the upper-normal limit of 7 mg/dL.

Patient charts were reviewed for demographic data such as diabetes, hypertension, hyperlipidemia, smoking, coronary artery disease, and drug usage for the last three-month period. Left ventricular ejection fraction was measured using echocardiography (General Electric, Vivid S5, Wauwatosa, WI, USA) after admission.

Blood samples were obtained by venipuncture on the same day of the procedure after 12 h fasting and drawn into standardized tubes that were delivered to the laboratory within a few minutes. Serum UA levels were measured in a clinical chemistry autoanalyzer (Modular P, Roche Diagnostics, Basel, Switzerland) using an enzymatic colorimetric method, high-sensitivity C-reactive protein (hs-CRP) concentration was determined by an immunoturbidimetric test (Roche Diagnostics), and other blood parameters were measured using standard methods.

Pacemaker implantation and measurements

We implanted isoFlex S model (St. Jude Medical, St. Paul, MN, USA) or CapSure SP novus (Medtronic, Minneapolis, MN, USA) bipolar ventricular leads in all patients. All ventricular leads were steroid-eluting with a passive fixation mechanism and were implanted into the right ventricular apex *via* a percutaneous subclavian vein puncture. The lead impedance and R-wave amplitude were assessed at the time of implantation. Pacing threshold was defined as the minimum voltage that could produce five consecutive stimuli and was measured at a pulse duration of 0.5 ms. The pacing threshold of all implanted ventricular leads was under 1.0 V. After reaching a satisfactory measurement, the leads were implanted in the optimal position, and then the pacemaker generators were placed in the subpectoral area. All patients were reevaluated 30 days later after implantation.

Ethical considerations

The study was approved by the local Ethics Committee on the basis of strict maintenance of participant anonymity. Individual informed consent was obtained from all subjects.

Statistical analysis

Continuous data are presented as means ± SD. Differences in continuous variables between groups were determined by *t*-test. The Kolmogorov–Smirnov test was used to evaluate the distribution of continuous variables. Categorical variables were summarized as percentages and compared with the Chi-square test. Correlation analysis was performed using Pearson's test. The variables including age, sex, diabetes mellitus, history of cardiovascular disease, serum UA, ventricular impedance, and ejection fraction were identified as potential risk markers and included in the full multivariate regression model as covariates. Results were considered significant when the *p*-value was <0.05. All statistical analyses were performed with the SPSS version 20 (Cary, NC, USA).

Results

Demographic and clinical characteristics of the study groups are shown in Table 1. The study population consisted of 121 patients [mean age, 69.07 ± 13.06 years; 57 females (47.1%)], of whom 83 were in Group 1, with normal UA levels [(mean age, 68.71 ± 11.96 years; 41 females (49.4%)] and 38 were in Group 2, with high UA levels [mean age, 69.86 ± 15.35 years; 16 females (42.1%)]. The baseline demographic and clinical characteristics of the two groups were similar. Laboratory measurements, left ventricular ejection fraction, and medications were also similar in both groups, except that the mean serum UA and hs-CRP levels were higher in Group 2 (5.06 ± 1.05 mg/dL *vs.* 8.44 ± 1.19 mg/dL, 2.52 ± 0.25 mg/dL *vs.* 3.69 ± 0.75 mg/dL, $p < 0.001$, respectively) at the time of implantation, as expected. Serum UA and hs-CRP levels of the groups 30 days later were also higher in Group 2 (4.86 ± 1.00 mg/dL *vs.* 8.20 ± 1.29 mg/dL, 2.40 ± 0.28 mg/dL *vs.* 3.53 ± 0.72 mg/dL, $p < 0.001$, respectively). But there are no differences with regard to median decreases in the serum UA (0.19 ± 0.33 mg/dL *vs.* 0.23 ± 0.20 mg/dL, $p = 0.382$) and hs-CRP levels between the groups 0.12 ± 0.15 mg/dL *vs.* 0.17 ± 0.32 mg/dL,

Table 1
Baseline clinical and laboratory characteristics of the study population.

Parameters	Group 1 *N* = 83	Group 2 *N* = 38	*p*-Value
Age (years)	68.71 ± 11.96	69.87 ± 15.35	0.682
Female (*n*, %)	41 (49.4)	16 (42.1)	0.456
DM (*n*, %)	20 (24.1)	8 (21.1)	0.713
HT (*n*, %)	41 (49.4)	22 (57.9)	0.385
Smoking (*n*, %)	11 (13.3)	8 (21.1)	0.274
Hyperlipidemia (*n*, %)	17 (20.5)	10 (26.3)	0.474
History of CAD (*n*, %)	33 (39.8)	16 (42.1)	0.807
Ejection fraction (%)	55.96 ± 4.61	55.67 ± 4.44	0.769
Glucose (mg/dL)	103.18 ± 37.03	106.15 ± 41.68	0.713
Creatinine (mg/dL)	.91 ± .21	.95 ± .27	0.391
Na (mEq/L)	137.04 ± 3.60	137.56 ± 3.57	0.460
Ca (mEq/L)	8.67 ± .63	8.57 ± .59	0.388
K (mEq/L)	4.18 ± .54	4.19 ± .55	0.934
AST (mg/dL)	19.88 ± 12.80	18.76 ± 13.51	0.666
ALT (mg/dL)	18.17 ± 14.93	17.45 ± 15.76	0.809
hs-CRP (mg/dL)	2.52 ± 0.25	3.69 ± 0.75	**<0.001**
Uric acid (mg/dL)	5.06 ± 1.05	8.44 ± 1.19	**<0.001**
Medications			
Acetylsalicylic acid (*n*, %)	31 (37.3)	16 (42.1)	0.618
Statin (*n*, %)	10 (12.0)	5 (13.2)	0.863
ACE inhibitor (*n*, %)	14 (16.9)	11 (28.9)	0.128
ARB (*n*, %)	24 (28.9)	15 (39.5)	0.249
NSAID use (*n*, %)	28 (33.7)	13 (34.2)	0.959

DM, diabetes mellitus; HT, hypertension; CAD, coronary artery disease; Na, sodium; Ca, calcium; K, potassium; AST, aspartate transaminase; ALT, alanine transaminase; hs-CRP, high-sensitivity C-reactive protein; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAID, non-steroidal anti-inflammatory drug. *p*-Value of <0.05 was considered significant.