High-Sensitivity C-Reactive Protein: A Novel Predictor of Recurrence of Atrial Fibrillation After Initial Catheter Ablation of Paroxysmal Atrial Fibrillation

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Background: High-sensitivity C-reactive protein (hs-CRP) elevation is a known contributor to the inflammatory response. This study was designed to assess whether the inflammatory state influences the recurrence of atrial fibrillation (AF) after treatment of paroxysmal AF by pulmonary vein isolation (PVI).

Methods and Results: Twenty-three patients who were referred to undergo PVI for drug refractory paroxysmal AF (mean duration: 70.1 ± 69.2 months) were included in the study. Body weight (BW), serum hs-CRP, brain natriuretic peptide (BNP), interleukin-6 (IL-6), carboxyl-terminal telopeptide of collagen I (ICTP), left atrial diameter (LAD), and left ventricular ejection fraction (LVEF) were measured before cardioversion. PVI was successful in all patients, but the AF recurred in 7 patients (30%) during the 2–24 month follow-up period. There were no significant differences in age, AF duration, LVEF, or baseline BNP, IL-6, ICTP levels between patients with recurrent AF and those without. However, baseline hs-CRP was significantly higher in the patients with recurrent AF than in those without (1,256 ± 940 vs. 745 ± 841 ng/ml, respectively, P = 0.02). BW and LAD tended to be greater in patients with recurrent AF than in those without (BW: 73.1 ± 13.8 vs. 62.3 ± 12.1 kg, P = 0.06; LAD: 41.0 ± 8.2 mm vs. 34.9 ± 5.9 mm, P = 0.08).

Conclusion: The inflammatory state may contribute to the pathogenesis of paroxysmal AF and may be useful for predicting the recurrence of AF after PVI.

Key words: paroxysmal atrial fibrillation, pulmonary vein isolation, high-sensitivity CRP, recurrence, LAD

Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and affects about 5% of persons above 65 years. The prevalence increases in higher age groups and age-standardized prevalence has been shown to be increasing in the male population. Importantly, AF could lead to increased rates of death, stroke, and other thromboembolic events. Inflammation is known to play a role in the pathophysiology of AF, and low levels of inflammatory markers have been to be predictive of successful cardioversion and maintenance of sinus rhythm in patients with AF. However, recurrence of atrial arrhythmia is frequently observed after the blanking period, and multiple procedures are often required in some patients. Increasing evidence has demonstrated that inflammation plays an important role in the genesis and perpetuation of AF. The aim of this study was to test the hypothesis that hs-CRP has a prognostic impact on patients with paroxysmal AF treated with radiofrequency catheter ablation.

Methods

Patients

The study group comprised 23 patients with drug refractory non-valvular paroxysmal AF (PAF; < 7 days) who were scheduled for PVI at Nihon University Itabashi Hospital between 2011 and 2012 (Table 1). All provided written informed consent for participation in the study before the PVI procedure. All underwent ECG and transthoracic and transesophageal echocardiography before PVI. No patient who had undergone a previous ablation procedure, had undergone surgery within the prior 60 days, had presented with acute coronary syndrome within the prior 60 days, had a recent infection, or had a history of collagen vascular disease was included. The study protocol was approved by the Human Research Ethics Committees of Nihon University Itabashi Hospital.
PVI procedure

Before PVI, warfarin was administered to all patients for ≥ 1 month, and anticoagulation (international normalized ratio, 2–3) was achieved. In addition, left atrial thrombus was ruled out on the recently obtained transesophageal echocardiogram. Antiarrhythmic drugs were discontinued before the procedure, for a washout period of at least 5 half-lives (no patient was taking amiodarone). Ablation was performed under sedation achieved with intravenous infusion of dexmedetomidine, propofol, and fentanyl, as previously described. In brief, after vascular access was obtained, single transseptal puncture was performed, and heparin was then administered intravenously to maintain an activated clotting time of > 300 seconds. After 3 long sheaths (2 SR0 sheaths and 1 SL1 sheath; St. Jude Medical, St. Paul, MN, USA) were inserted into the left atrium (LA) via the transseptal puncture, 2 decapolar circular mapping catheters (Lasso; Biosense Webster, Diamond Bar, CA, USA) and an irrigated 3.5-mm-tip mapping and ablation catheter (Thermocool; Biosense Webster) were advanced into the LA. Extended encircling ipsilateral PVI was performed, guided by the 2 Lasso catheters and a 3-dimensional electroanatomical mapping system (CARTO 3; Biosense Webster). Targeting ipsilateral PVs in pairs, we placed radiofrequency (RF) lesions at least 1 cm outside the PV ostia. Ablation was allowable within 1 cm of the ostium of the left superior PV (LSPV) because of the narrow ridge of tissue between the anterior aspect of the LSPV and the LA appendage. RF energy was delivered for 30 sec at a power of 20 to 35 W with an irrigation flow rate of 17 to 30 mL/min. The upper temperature limit was set to 41°C. On the posterior wall, the RF power was reduced to 25 W with a flow rate of 17 mL/min. Patients remaining in AF at the end of the procedure were electrically cardioverted back to sinus rhythm. After cardioversion, remapping of all PVs was performed to confirm PVI. The procedure was considered complete when spontaneous associated PV potentials were no longer recorded by the circular mapping catheter (entrance block) and PV to LA dissociation was noted either spontaneously or with PV pacing (exit block). A waiting time of ≥ 20 minutes after the index isolation was used to monitor for early PV reconnection, and if spontaneous reconnection occurred, reconnected PVs were reisolated. No induction testing (via burst pacing or isoproterenol infusion), prophylactic linear ablation, or complex fractionated atrial electrogram ablation was performed.

Hematologic measurements

Blood samples were collected from the femoral vein before ablation for baseline hematologic measurements. Serum high-sensitivity CRP (hs-CRP) was measured by immunonephelometry with a Dade Behring BNII analyzer (Dade Behring, Deerfield, IL, USA) according to the manufacturer’s recommended protocol. The hs-CRP detection limit was 0.175 mg/L. Brain natriuretic peptide (BNP) was measured with a chemiluminescent enzyme immunoassay kit (Shionogi Co., Ltd., Tokyo, Japan). Interleukin-6 (IL-6) was measured with a commercially available ELISA kit (Fujirebio Inc., Tokyo, Japan). Carboxyl-terminal telopeptide of collagen I (ICTP) was measured by radioimmunoassay (Orion Diagnostica, Espoo, Finland).

Echocardiographic evaluation

Comprehensive transthoracic echocardiography was performed 1 day before the ablation procedure with an ACUSON Sequoia C256 echocardiography system (Siemens Medical Solutions USA, Inc., Malvern, PA, USA). Left atrial dimension (LAD) was measured in the parasternal long axis view at end systole, and left ventricular ejection fraction (LVEF) was assessed by means of M-mode echocardiography (Teichholtz method). Measurements from 3 consecutive beats were averaged.

Post-ablation follow-up

Patients’ previously prescribed antiarrhythmic drugs were resumed after the ablation procedure but stopped 2 months later. Other prescribed drugs were not changed during the follow-up period. All patients underwent routine follow-up at our outpatient clinic where clinical evaluation and 12-lead ECG were performed at 2 weeks, 1 month, and then every 1–3 months after ablation. Twenty-four-hour Holter ECG recordings were obtained 3–6 months after ablation. When patients developed symptoms suggestive of tachycardia after ablation, 24-hour Holter monitoring and/or cardiac event recording with a recording duration of 1 week were performed to identify the cause of the clinical symptoms. Recurrence of an atrial arrhythmia was defined as an episode lasting > 30 seconds and confirmed by electrocardiography 2 months after ablation (blanking period). The study endpoint was a clinically documented recurrence of the atrial arrhythmia or a repeat ablation procedure.

Statistical analysis

Data are presented as mean ± SD for normally distributed variables. Follow-up time, duration of AF, hs-CRP, ANP, BNP, IL-6, and ICTP levels were not normally distributed, so each of these variables is presented as the median value with the interquartile range. Patients were divided between those in whom

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AF did not recur and those in whom AF did recur, and differences in study variables between these 2 groups were analyzed by unpaired Student’s $t$-test, Mann-Whitney $U$ test, or Fisher’s exact probability test, as appropriate. All statistical analyses were performed with JMP 8 software (SAS Institute, Cary, NC, USA), and $P < 0.05$ was considered statistically significant.

**Results**

Baseline clinical characteristics of the 23 study patients are shown in Table 1. Six patients had hypertension, 2 patients had diabetes mellitus, 1 patient had old cerebral infarction, 2 patients had dyslipidemia, and 1 patients had healed hyperthyroidism. Recurrence of AF was observed in 7 of the 23 patients during a mean follow-up period of 200 ± 275 days.
The major underlying cause of AF in some patients.

findings suggest that myocardial inflammation is the primary cause of AF. In patients with paroxysmal AF treated by PVI, pre-PVI hs-CRP elevation appears to predict AF recurrence.
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