Heart, Lung and Circulation (2014) **23,** 636–643
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2014.02.003

ORIGINAL ARTICLE

Serum Inflammation Markers Predicting Successful Initial Catheter Ablation for Atrial Fibrillation

Takehiro Kimura, MD, PhD*, Seiji Takatsuki, MD, PhD, Kohei Inagawa, MD, PhD, Yoshinori Katsumata, MD, PhD, Takahiko Nishiyama, MD, PhD, Nobuhiro Nishiyama, MD, PhD, Kotaro Fukumoto, MD, PhD, Yoshiyasu Aizawa, MD, PhD, Yoko Tanimoto, MD, PhD, Kojiro Tanimoto, MD, PhD, Keiichi Fukuda, MD, PhD

Department of Cardiology, Keio University School of Medicine, Tokyo, JAPAN

Received 8 August 2013; received in revised form 26 October 2013; accepted 6 February 2014; online published-ahead-of-print 18 February 2014

Background We investigated various serum inflammatory markers to predict ablation responders who have no atrial fibrillation (AF) relapse after the initial ablation.

Methods Forty-four consecutive AF patients (age: 59 ± 8 years, paroxysmal: 31, $CHADS_2$: 1.1 ± 1.1) who underwent an initial pulmonary vein isolation were investigated. Various serum inflammatory markers, such as adiponectin, ANP, BNP, 1CTP, F1+2, hs-CRP, IL-6, intact P1NP, MDA-LDL, MMP-2, TGF-β, TIMP-2, and TNF-α, were evaluated prior to ablation. AF relapse was defined as AF documented in telemonitoring electrocardiograms twice a day during 9.7 ± 2.4 months of follow-up with three months of a blanking-period.

Results A total of 29 patients (paroxysmal: 21) maintained sinus rhythm after the initial catheter ablation. These ablation responders had significantly lower MMP-2 (Sinus vs. Relapsed: 748 ± 132.7 vs. 841.2 ± 152.4 ng/mL, P=0.042) and TNF-α (1.1 ± 0.4 vs. 1.8 ± 1.7 pg/mL, P=0.046) levels prior to ablation. A BNP-adjusted Cox multivariate regression analysis revealed that the independent predictive factor for AF recurrence was high MMP-2 levels (>766 ng/mL) accompanied by high TNF-α levels (>1.2 pg/mL).

Conclusions The levels of MMP-2 and TNF-α might be useful for predicting initial AF catheter ablation responders.

Keywords Atrial fibrillation • Catheter ablation • Follow-up, inflammation • Matrix metalloproteinase-2 • Tumour necrosis factor-α

Introduction

Inflammation is known to be associated with the existence and persistence of AF [1,2]. Serum inflammatory markers are reported to reflect the duration of AF [3] which exacerbates atrial electrical and structural remodelling. These inflammatory markers are also known to be normalised in patients who were free of AF at follow up [4]. However, a treatment of patients with paroxysmal AF and hypertension with candesartan known as ''up-stream therapy'' failed to have an advantage over amlodipine in the reduction of AF attacks [5]. High-dose atorvastatin did not reduce the recurrence of AF after cardioversion, known as the SToP AF trial [6]. The direct explanation of whether inflammation is the cause of its

Abbreviations: AF, atrial fibrillation; BMI, body mass index; LA, left atrium; LAA, left atrial appendage

*Corresponding author at: 35 Shinanomachi Shinjuku-ku Tokyo, JAPAN 160-8582, Department of Cardiology, Keio University School of Medicine.
Tel.: +81-3-3353-1211; fax: +81-3-5363-3875, Email: kimura@z7.keio.jp

initiation or the result of its duration has not been clarified yet. That is quite reasonable given that these inflammatory changes are not affected only by AF, but by various atherosclerotic risks.

Catheter ablation is widely approved as a cure for atrial fibrillation (AF) represented by pulmonary vein (PV) isolation [7,8], and its indication has been broadened along with its technical development [9,10]. It is important to predict curable AF patients under various conditions regardless of prevailing risk factors for AF recurrence. Systemic inflammatory markers can be an integrated risk factor that reflects various systemic factors. Therefore, we aimed to evaluate the usefulness of serum inflammatory markers to predict responders of an initial AF catheter ablation.

Material and Methods

Study population

This study was approved by our institutional review board based on the ethical guidelines of the Declaration of Helsinki, and all patients provided written informed consent to participate. A total of 44 consecutive AF patients (paroxysmal AF: 31, persistent AF: 13, $CHADS_2$ score: 1.1 ± 1.1, age: 59 ± 8 years) who received an initial catheter ablation between February 2011 and November 2011 were included in this study. All patients had symptomatic and drug-resistant AF and ranged in age from 20 to 75 years. Multi-detector computed tomography (MDCT) was performed to reveal the anatomy of the PVs and the LA before catheter ablation. The patients were maintained on oral anticoagulation therapy for more than one month. Warfarin was administered to 40 patients and then switched to intravenous heparin administration that was terminated four hours prior to ablation. Dabigatran was administered to four patients and discontinued 24 hours prior to ablation. Transoesophageal echocardiography was performed to rule out thrombi in the LA within the two days prior to ablation.

Ablation procedure

The patients were sedated with a continuous intravenous infusion of propofol (20-40 mL/h) and monitored with a BIS monitor (Aspect Medical Systems, Newton, MA, USA). An 8 polar electrode catheter was introduced to the right ventricle from the left femoral vein (Inquiry™ L1/XL1, St. Jude Medical, St. Paul, MN, USA). A 14 polar electrode catheter was introduced to the coronary sinus from the right jugular vein (Inquiry™ SC1, St. Jude Medical). Two long sheaths were introduced from the right femoral vein for the catheter manipulation in the LA. After the delayed phase of the right atriography revealed the LA anatomy, a double transseptal puncture was performed, and two long sheaths were placed in the LA after the administration of 100 U/kg of intravenous heparin. The activated clotting time was maintained at 300 to 350 msec, measured every 30 minutes throughout the ablation procedure. A circular mapping catheter (Inquiry™ Afocus™, St. Jude Medical) and a 3.5 mm saline-irrigated mapping catheter (Navi-Star™ Thermocool™, Biosense Webster, Diamond Bar, CA, USA) were introduced. The ipsilateral superior and inferior pulmonary venography was obtained simultaneously from both sides of the PVs. Radiofrequency (RF) energy was delivered continuously, encircling the ipsilateral superior and inferior PVs under the guidance of the CARTO™ system (Biosense Webster) with the three-dimensionally reconstructed LA geometry obtained from the MDCT images. The RF power was cut off at 43 degrees and delivered with 30-35 W at the anterior wall with a saline irrigation rate of 17 or 30 mL/min and with 20-25 W at the posterior wall with 17 mL/min saline. The PV isolation was confirmed by the elimination of PV potentials recorded by the circular mapping catheters even under a rapid infusion of 20 mg of adenosine triphosphate (ATP). A conduction block from the PVs to the LA was also confirmed by applying 25 mA output pacing from the PVs.

All patients received circumferential PV isolation and focal and linear ablation for extra PV origin, and ablation for the complex fractionated atrial electrogram (CFAE) were added if necessary.

Follow-up

The patients were followed-up by telemonitored electrocardiogram (ECG) after the procedures. The patients recorded a 30-second ECG twice a day regularly and upon symptoms. Holter monitoring was also performed every three months. AF recurrence was defined as a documented AF for more than 30 seconds after three months of a blanking-period.

Serum inflammatory markers

A total of 13 serum inflammatory markers were measured: adiponectin, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), carboxyterminal telopeptide of type 1 collagen (1CTP), prothrombin fragment 1+2 (F1+2), high-sensitivity c-reactive protein (hs-CRP), interleukin-6 (IL-6), intact aminoterminal propeptide of type 1 procollagen (intact P1NP), malondialdehyde-modified low-density lipoprotein (MDA-LDL), matrix metalloproteinase-2 (MMP-2), transforming growth factor-β (TGF-β), tissue inhibitor of metalloproteinase-2 (TIMP-2), and tumour necrosis factor-α (TNF-α). Blood sampling was performed prior to catheter ablation from the sheath introduced to the right jugular vein.

The data for the serum inflammatory markers were evaluated and compared between the sinus rhythm patients and relapsed patients (Fig. 1). The data for the transthoracic and transoesophageal echocardiography, medications, and other biochemical blood sampling tests were also compared among the patients.

Statistical methods

Parametric data were expressed as the means ± standard deviation. Student's unpaired test and the chi-square test were used to compare differences across the groups. The relationship among the parameters was investigated by Pearson's correlation coefficient test. The odds ratio (OR) and 95%