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Original Article

Effect of adenosine triphosphate on left atrial electrogram interval and dominant frequency in human atrial fibrillation ☆

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ABSTRACT

Background: Complex fractionated atrial electrograms (CFAEs) and high dominant frequency (DF) are targets for atrial fibrillation (AF) ablation. Although adenosine triphosphate (ATP) is known to promote AF by shortening the atrial refractory period, its role in the pathogenesis of CFAEs and DF during AF is not fully understood.

Methods: We recorded electrical activity from a 64-electrode basket catheter placed in the left atrium (LA) of patients with paroxysmal AF (PAF, $n=18$) or persistent AF (PerAF, $n=19$) before ablation. Atrial electrogram fractionation intervals (FIs) and DFs were measured from bipolar electrograms of each adjacent electrode pair. Offline mean atrial FIs and DFs were obtained before bolus injection of 30 mg ATP. Peak effect was defined as an R–R interval >3 s.

Results: With ATP, the mean FI decreased (from 110.4 ± 29.1 ms to 90.5 ± 24.7 ms, $P<0.0001$) and DF increased (from 6.4 ± 0.6 Hz to 7.1 ± 0.8 Hz, $P<0.0001$) in all patients. There was no difference in the FI decrease between the two groups (-20.3 ± 20.5 ms vs. -19.6 ± 14.5 ms, $P=0.6032$), but the increase in DF was significantly greater in PAF patients (1.1 ± 0.8 Hz vs. 0.3 ± 0.6 Hz, $P=0.0051$).

Conclusions: ATP shortens atrial FIs and increases DFs in both PAF and PerAF patients. The significant increase in DF in PAF patients suggests that pathophysiologic characteristics related to the frequency of atrial fractionation change as atrial remodeling progresses.

1. Introduction

Complex fractionated atrial electrograms (CFAEs) derived from time domain analysis and dominant frequency (DF) identified by fast Fourier transform (FFT) spectral analysis are widely used electrical parameters for understanding the initiation and perpetuation of atrial fibrillation (AF) [1–7]. CFAEs are now considered to reflect simply (1) dyssynchronous activation of separate cell groups at pivot points, (2) wave collision, far-field potentials, (3) critical zones of repetitive activations of AF driver(s), or (4) local reentry circuits [1–5], whereas high DF is reported to be related to the center of a focal-firing rotor or local reentry circuit [6,7]. Clinically, CFAE and/or high-DF sites have been demonstrated as effective targets for AF termination, suggesting their importance in the maintenance of AF [1–7]. Nonetheless, the pathogenesis of CFAE and DF are not fully understood. Adenosine triphosphate (ATP) is known to promote AF by shortening the atrial action potential duration and refractory period [8–10]. In patients with paroxysmal AF (PAF), ATP infusion increases DF, particularly at the pulmonary vein (PV)–left atrial (LA) junction. DF is higher in patients with persistent AF (PerAF) than in patients with PAF at all the LA regions surveyed, but the extent of the DF increase with ATP is less in PerAF patients than that in PAF patients. Our preliminary results suggest that the ability of ATP to highlight sites driving PAF that could be targeted for ablation, whereas non-PV locations are more likely. Jadidi et al. reported [11] that atrial fibrosis as defined by delayed enhanced magnetic resonance imaging is associated with slower and organized electrical activity

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but lower voltage than healthy atrial sites in patients with long-lasting PerAF. Therefore, PerAF patients in the present study may represent electrical remodeling as demonstrated by higher DF and structural remodeling as shown by lower responses to ATP infusion, possibly due to patchy fibrosis around higher DF sites. In such cases, PV isolation plus LA ablation targeted at rotors in the LA body might be necessary. We therefore hypothesized that ATP may spatially affect the atrial electrogram interval determined by time domain and frequency domain analyses during AF. We investigated the effects of ATP on the atrial electrogram interval and DF characteristics in human AF, and evaluated whether these effects are influenced by the progression of atrial remodeling.

2. Material and methods

2.1. Study patients

This study included 37 consecutive patients (36 men and one woman; mean age 56.9 ± 10.7 years) scheduled to undergo first catheter ablation for AF. Eighteen had PAF (AF lasting < 7 days), and 19 had PerAF (AF lasting ≥ 7 days). Patients with cardiomyopathy, valvular heart disease, or congenital heart disease were excluded. Adequate oral anticoagulation therapy was administered for at least 1 month before the ablation procedure, and all antiarrhythmia drugs were discontinued for at least 5 half-lives before the procedure. Upon admission, transesophageal and transthoracic echocardiography were performed, and baseline characteristics including maximum LA volume (determined by the prolate-ellipsoid method) and left ventricular (LV) ejection fraction (determined by the Teichholz method) were obtained. The study protocol was approved by the Institutional Review Board of Nihon University Itabashi Hospital (December 7, 2012, RK-121109-5), and all patients provided written informed consent for their participation in the study.

2.2. Electrophysiologic studies

Electrophysiologic studies were performed under conscious sedation using dexmedetomidine, propofol, and fentanyl as described previously [7,12]. After vascular access was obtained, single transseptal puncture was performed and intravenous heparin was administered to maintain an activated clotting time of > 300 s. After two long sheaths (one SL0 sheath and one Agilis sheath; St. Jude Medical, Inc., St. Paul, MN) were inserted into the LA via the transseptal puncture, the three-dimensional geometry of the LA and four PVs was reconstructed using an EnSite NavX mapping system (version 8.0; St. Jude Medical, Inc) and a 20-pole circular mapping catheter with 1.5-mm interelectrode spacing (Livewire Spiral HP catheter, St. Jude Medical, Inc.). To record multiple bipolar signals (filter setting, 30–400 Hz) simultaneously, we used a multi-electrode basket catheter (Constellation; EP Technologies/Boston Scientific Corporation, San Jose, CA), which consisted of eight splines (A–H), each with eight electrodes 4 mm in length. The basket catheter was deployed in the LA, and the distal end was placed at the left PV antrum (Fig. 1). A basket catheter of adequate size (38 mm with inter-electrode spacing of 3 mm, 48 mm with inter-electrode spacing of 4 mm, or 60 mm with interelectrode spacing of 5 mm) was chosen to allow consistent contact with the LA endocardium. If the patient was in sinus rhythm, AF was induced by rapid atrial pacing from the coronary sinus ostium to record the CFAEs and DFs 5 min after AF induction.

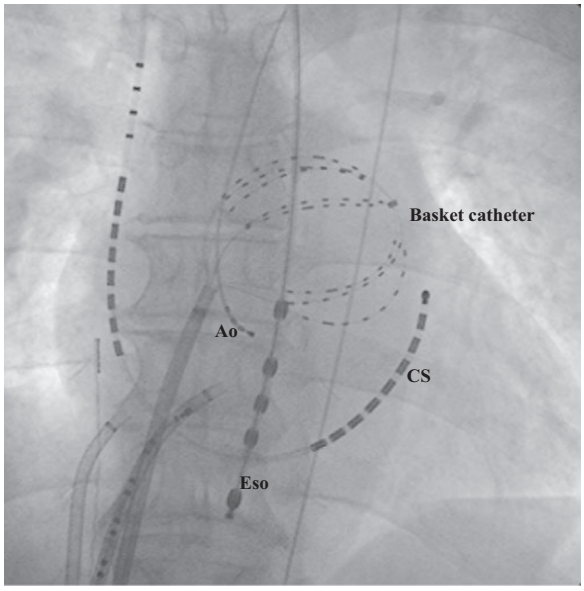

Fig. 1. Fluoroscopic view (anteroposterior projection) of the basket catheter position. The catheter is positioned at the anterior portion of the left atrium, ostium of the left atrial appendage, and antrum of the left superior pulmonary vein. Ao, catheter positioned at the noncoronary cusp; CS, catheter positioned in the coronary sinus; Eso, esophageal temperature monitoring catheter.

2.3. Bipolar signal recordings

Because of the limited number of electrodes that can be applied during the use of the EnSite Classic mapping system, signals from one proximal electrode from each spline of the basket catheter could not be recorded. Thus, six of seven bipolar electrode pairs at each spline totaling 48 bipolar electrograms (six pairs $\times$ eight splines) were entered into the analysis. With the basket catheter sitting in a stable position, baseline bipolar signals from each electrode pair representing the 48 bipolar atrial electrograms were recorded for 5 s during AF and stored in the NavX mapping system.

2.4. Time domain atrial electrogram interval analysis

For atrial electrogram interval analysis, the NavX mapping parameters were set to the CFAE-mean, an algorithm was used to determine the average time of the atrial electrogram interval (fractionation intervals [FIs]) at each site, and a color map of the FIs was constructed [7,12,13]. The mean FI was taken as the average time between consecutive deflections during 5-s recording periods. The settings included a refractory period of 40 ms, peak-to-peak sensitivity between 0.05 mV and 0.1 mV, and electrogram duration of < 10 ms. In addition, continuous CFAEs were defined as those with a mean FI of < 50 ms and variable CFAEs as having an FI of 50–120 ms.

2.5. FFT analysis

For FFT analysis, the DF (the highest power frequency) was analyzed using the DF software installed in on the NavX mapping system (sampling rate, 1200 Hz; resolution, 0.14 Hz; low-pass filter, 20 Hz; high-pass filter, 1 Hz with a Hamming window function) as previously reported [7,12,13]. Five-s bipolar signals recorded during AF were used for DF analysis. A high-DF site was defined as a site with a frequency of $>$ 8 Hz [14,15]. The regularity index was taken as the area within the 0.75-Hz band around the DF divided by the area of the frequencies sampled from 3 Hz to 14 Hz [8,16]. A regularity index of < 0.2 meant exclusion from the study.