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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.

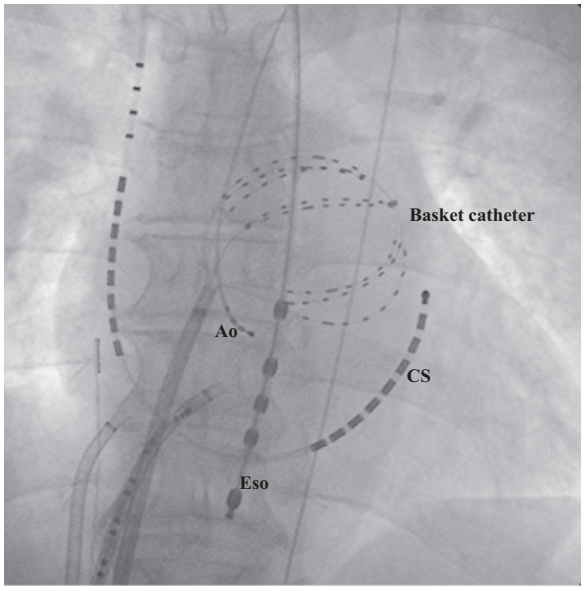

Fig. 1. Fluoroscopic view (anteroposterior projection) of the basket catheter position. The catheter is positioned at the anterior portion of the left atrium, ostium of the left atrial appendage, and antrum of the left superior pulmonary vein. Ao, catheter positioned at the noncoronary cusp; CS, catheter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

2.6. Evaluation of FI and DF after ATP injection

We injected ATP from the sheath placed in the right jugular vein and flushed with 20 mL of saline. Bipolar signals were recorded for 5 s after intravenous injection of 30 mg of ATP. All bipolar electrograms recorded from the basket catheter during the period of maximum ATP effect were analyzed offline on the NavX mapping system. The electrophysiologic effect induced by ATP was identified as an R–R interval of >3 s. The average FIs and DFs recorded using the basket catheter were compared between the PAF group and the PerAF group. The numbers and percentage areas of CFAE and high-DF sites were also compared between the two groups. To evaluate regional differences in CFAE and high-DF sites, we considered the basket catheter electrodes corresponding to the left PV antrum (the two distal bipolar pairs), the lateral LA (the next two bipolar pairs), and the middle LA (the two proximal bipolar pairs).

2.7. Statistical analysis

Continuous variables were expressed as means $\pm$ SD or medians with interquartile ranges. When values were normally distributed, between-group differences were analyzed by Student's unpaired *t* test. When values were not normally distributed, between-group differences were analyzed using the Mann–Whitney *U* test. Fisher's exact probability test was used to analyze differences in the distributions of dichotomous variables between the two groups. All statistical analyses were performed with JMP 8 software (SAS Institute, Cary, NC), and a *P*-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline clinical characteristics and echocardiographic variables

Table 1 shows baseline clinical characteristics and echocardiographic variables for all patients per group. There were no differences in baseline clinical characteristics between the two groups. LA dimensions (PerAF vs. PAF: 43.3 ± 6.8 vs. 36.9 ± 5.5 mm, respectively, $P=0.0036$), LA volumes (62.0 ± 23.1 vs. 39.7 ± 14.4 cm^3, $P=0.0015$), and end-systolic LV dimensions (34.7 ± 7.7 vs. 29.3 ± 4.7 mm, $P=0.0167$) were significantly greater in the PerAF group than in the PAF group.

3.2. FIs, DFs, and the distributions of CFAEs and high-DF sites

Of the 48 bipolar signals available to analyze FIs and CFAEs, 43.1 ± 3.8 signals ($89.5 \pm 7.8\%$) per patient were usable. The remaining 5.0 ± 3.8 bipolar signals ($10.5 \pm 7.8\%$) could not be used because of poor signal quality. For the DF recordings, 5.4 ± 4.2 of the 48 bipolar signals ($11.3 \pm 8.8\%$) per patient were of poor quality, leaving 42.6 ± 4.2 bipolar signals ($88.7 \pm 8.8\%$) available for analysis. The baseline FIs and DFs and the areas of CFAEs and high-DF sites are shown in Tables 2 and 3. The overall mean baseline FI was 110.4 ± 29.1 ms, and the overall mean baseline DF was 6.4 ± 0.6 Hz. Although there was no significant difference in the baseline FI between the PAF group and the PerAF group (108.2 ± 25.7 vs. 112.4 ± 32.6 ms, $P=0.6678$), the baseline DF was significantly higher in the PerAF group than in the PAF group (6.6 ± 0.7 Hz vs. 6.2 ± 0.5 Hz, $P=0.0429$). The overall baseline bipolar signals indicative of CFAE sites represented 32.1 ± 7.3 sites (percentage area of CFAE sites: $74.4 \pm 13.9\%$) of the available bipolar sites (43.1 ± 3.8). The baseline percentage area of high-DF sites, which was calculated as the number of high-DF sites (3.7 ± 3.9 sites) of all available bipolar sites (42.6 ± 4.2 sites), was $8.9 \pm 9.9\%$. There were no differences in the percentage areas of CFAE and high-DF sites between the PAF group and the PerAF group (CFAE, $73.5 \pm 14.4\%$ vs. $75.3 \pm 14.3\%$, $P=0.2054$; high DF, $6.5 \pm 6.8\%$ vs. $11.3 \pm 12.0\%$, $P=0.2598$).

3.3. Effects of ATP on the distributions of FIs and CFAEs in the two study groups

Examples of the changes in FIs and CFAE sites after ATP administration in the PAF and PerAF groups are shown in Figs. 2 and 3. In both groups, the mean FI calculated from all available bipolar electrograms recorded using a basket catheter decreased after ATP injection and the percentage area of CFAE sites increased, but the change in FI (red and white areas in Figs. 2 and 3) within the area of CFAE sites was greater in the PAF group than in the PerAF group. The changes in FI and the percentage area of CFAE sites after ATP administration in the two groups are shown in Table 2. Among all patients, the FI decreased from 110.4 ± 29.1 to

Table 1
Baseline clinical characteristics and echocardiographic variables of all patients per study group.

Characteristic/variable	All ($n=37$)	PAF ($n=18$)	PerAF ($n=19$)	*P*-value[a]
Age, years	56.9 ± 10.7	57.6 ± 12.1	56.3 ± 9.5	0.7184
Sex, male (%)	36 (97.3)	18 (100)	18 (94.7)	0.2628
AF duration, days (range)	690 (375–1800)	570 (450–1800)	675 (307–1627)	0.2729
Body mass index, kg/m^2	25.8 ± 4.0	25.4 ± 4.8	26.1 ± 3.1	0.5884
Casual factors				
Hypertension (%)	19 (52.8)	7 (43.8)	11 (55.0)	0.5153
Diabetes mellitus (%)	4 (11.1)	2 (12.5)	2 (10.03)	0.9061
Prior stroke (%)	4 (11.1)	1 (6.3)	3 (15.0)	0.3335
Heart failure (%)	5 (19.4)	3 (18.8)	4 (20.0)	0.7963
TTE measures				
LAD (mm)	40.3 ± 6.2	36.9 ± 5.5	43.3 ± 6.8	0.0036
LAV (cm^3)	51.7 ± 19.6	39.7 ± 14.4	62.0 ± 23.1	0.0015
LVDd (mm)	49.2 ± 5.9	47.1 ± 5.7	51.0 ± 6.0	0.0528
LVDs (mm)	32.2 ± 6.5	29.3 ± 4.7	34.7 ± 7.7	0.0167
LVEF (%)	64.1 ± 10.5	67.8 ± 6.6	61.0 ± 13.0	0.0601

LAD, left atrial dimension; LAV, left atrial volume; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; PerAF, persistent AF; TTE, transthoracic echocardiography.

[a] PAF group vs. PerAF group.

Table 2
Regional changes in FIs and percentage areas of CFAE sites after ATP injection in the 2 study groups.

	Section	Baseline	Post-ATP	Gradient	*P*-value[a]
FIs (ms)					
PAF group	Overall LA	108.2 ± 25.7	87.9 ± 22.6	−20.3 ± 20.5	0.0006
	Left PV antrum	99.7 ± 41.1	81.6 ± 28.4	−18.1 ± 25.8	0.0084
	Lateral LA	107.7 ± 27.5	90.0 ± 28.8	−17.8 ± 21.6	0.0030
	Middle LA	117.9 ± 22.4	92.6 ± 20.8	−25.3 ± 20.9	< 0.0001
PerAF group	Overall LA	112.4 ± 32.6	93.0 ± 26.9	−19.6 ± 14.5	< 0.0001
	Left PV antrum	103.8 ± 32.4	86.5 ± 28.9	−17.3 ± 18.5	0.0007
	Lateral LA	117.6 ± 40.3	95.9 ± 30.0	−21.7 ± 21.9	0.0004
	Middle LA	119.1 ± 54.8	98.1 ± 35.2	−21.5 ± 27.1	0.0035
% area of CFAEs (no. of sites)					
PAF group	Overall LA	73.5 ± 14.4 (33.7 ± 7.4)	83.1 ± 12.9 (38.1 ± 7.1)	+9.6 ± 13.3 (+4.4 ± 6.3)	< 0.0001
	Left PV antrum	26.6 ± 7.2	30.5 ± 5.6	+3.9 ± 6.0	0.0037
	Lateral LA	24.7 ± 5.9	28.0 ± 4.6	+3.3 ± 5.8	0.0267
	Middle LA	22.2 ± 5.7	24.6 ± 4.6	+2.4 ± 4.3	0.0675
PerAF group	Overall LA	75.3 ± 14.3 (30.6 ± 7.1)	81.1 ± 12.6 (33.0 ± 6.5)	+6.1 ± 6.1 (+2.4 ± 2.4)	< 0.0001
	Left PV antrum	28.5 ± 5.2	31.0 ± 6.0	+2.5 ± 3.4	0.0045
	Lateral LA	24.3 ± 6.0	25.4 ± 5.8	+1.0 ± 2.9	0.1515
	Middle LA	22.4 ± 7.6	25.0 ± 5.6	+2.6 ± 3.7	0.0119

ATP=adenosine triphosphate; CFAE=complex fractionated atrial electrogram; FI=fractionation interval; LA=left atrium; PAF=paroxysmal AF; PerAF=persistent AF, PV=pulmonary vein.

[a] Baseline vs. post-ATP injection.

Table 3
Regional changes in DFs and percentage areas of high-DF sites after ATP injection in the two study groups.

	Section	Baseline	Post-ATP	Gradient	*P*-value[a]
DF (Hz)					
PAF group	Overall LA	6.2 ± 0.5	7.2 ± 0.7	1.1 ± 0.8	< 0.0001
	Left PV antrum	6.1 ± 0.4	7.4 ± 0.7	1.2 ± 0.8	< 0.0001
	LA lateral body	6.2 ± 0.6	7.3 ± 0.8	0.9 ± 1.0	0.0003
	LA mid body	6.2 ± 0.6	7.1 ± 0.8	0.9 ± 0.9	0.0009
PerAF group	Overall LA	6.6 ± 0.7	7.0 ± 0.8	0.3 ± 0.6	0.0406
	Left PV antrum	6.7 ± 0.9	7.1 ± 0.8	0.4 ± 0.7	0.0372
	LA lateral body	6.5 ± 0.7	7.0 ± 0.8	0.5 ± 0.7	0.0129
	LA mid body	6.6 ± 0.7	6.8 ± 0.8	0.1 ± 0.8	0.3143
% area of high DF (no. of sites)					
PAF group	Overall LA	6.5 ± 6.8 (2.9 ± 3.0)	20.9 ± 28.6 (9.7 ± 13.6)	+14.4 ± 30.9 (+6.8 ± 14.5)	0.0644
	Left PV antrum	2.0 ± 2.7	8.4 ± 10.5	+6.3 ± 11.6	0.0325
	Lateral LA	1.9 ± 3.0	7.1 ± 9.6	+5.2 ± 10.5	0.0516
	Middle LA	2.6 ± 2.8	5.5 ± 9.4	+2.9 ± 10.2	0.2418
PerAF group	Overall LA	11.3 ± 12.0 (4.4 ± 4.6)	19.2 ± 15.2 (7.8 ± 6.4)	+7.9 ± 16.2 (+3.4 ± 6.7)	0.0400
	Left PV antrum	4.2 ± 6.1	8.5 ± 6.4	+4.3 ± 7.4	0.0193
	Lateral LA	2.9 ± 3.4	6.2 ± 6.0	+3.3 ± 5.8	0.0245
	LA mid body	4.2 ± 4.9	4.5 ± 4.3	+0.3 ± 7.0	0.8527

ATP, adenosine triphosphate; DF, dominant frequency; LA, left atrium; PAF, paroxysmal atrial fibrillation; PerAF, persistent AF; PV, pulmonary vein.

[a] Baseline vs. post-ATP injection.

90.5 ± 24.7 ms ($P < 0.0001$), and the percentage area of CFAE sites increased from 74.4 ± 14.1% (32.1 ± 7.3 sites) to 82.2 ± 12.6% (35.5 ± 7.2 sites) ($P < 0.0001$). The mean FI decreased from 108.2 ± 25.7 ms to 87.9 ± 22.6 ms ($P=0.0006$) in the PAF group and from 112.4 ± 32.6 ms to 93.0 ± 26.9 ms ($P=0.0007$) in the PerAF group. The decrease in FI with ATP administration did not differ significantly between the two groups (−20.3 ± 20.5 ms vs. −19.6 ± 14.5 ms, $P=0.6032$). The mean FI at baseline CFAE sites was 71.5 ± 7.5 ms, and decreased to 65.4 ± 10.3 ms after ATP administration ($P=0.0056$) in the PAF group, but not in the PerAF group (from 70.6 ± 7.2 ms to 69.6 ± 14.7 ms, $P=0.7385$). There was no difference in the increase of the percentage area of CFAEs between the PAF and PerAF groups (9.6 ± 13.3% vs. 6.1 ± 6.1%, $P=0.2014$). ATP administration did not result in between-group differences in either regional changes in FI or in the numbers of CFAE sites, i.e., no difference in changes in the left PV antrum, lateral LA, or middle LA (Table 2).

3.4. Effects of ATP on DFs and the distribution of high-DF areas in the two study groups

Examples of post-ATP injection change in the distribution of the high-DF sites in PAF and PerAF patients are shown in Figs. 4 and 5. In patients with PAF, both the DF and the percentage area of high-DF sites increased with ATP administration. In patients in the PerAF group, the pre-ATP DF was higher and the percentage area of DF sites was marginally greater, but the increases observed in DF and high-DFs area with ATP injection

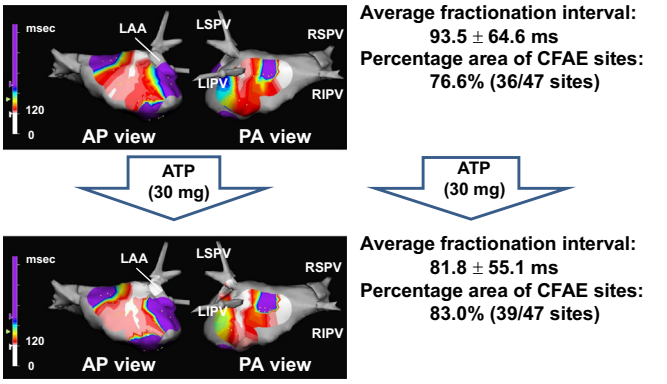

Fig. 2. Representative CFAE maps from a patient with PAF before and after ATP injection. The red areas show variable CFAE sites with a mean fractionation interval of 50–120 ms, and the white areas show continuous CFAE sites with a mean fractionation interval of <50 ms. The mean fractionation interval calculated from all available bipolar electrograms of the basket catheter was shortened by ATP injection from 93.5 ± 64.6 ms to 81.8 ± 55.1 ms ($P=0.0020$), and the percentage area of CFAE sites increased from 76.6% (36 sites) to 83.0% (39 sites). AP, anteroposterior; ATP, adenosine triphosphate; CFAE, complex fractionated electrogram; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PA, posteroanterior; PAF, paroxysmal atrial fibrillation; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

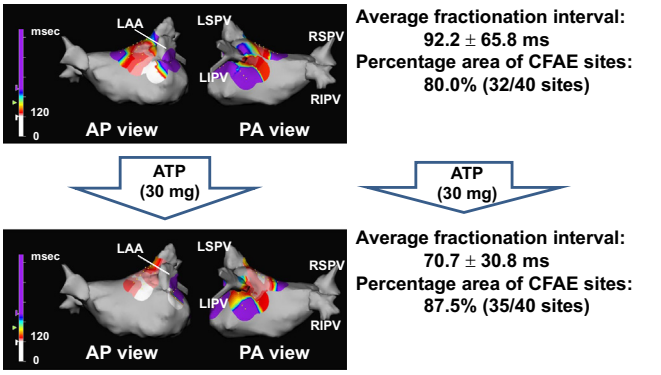

Fig. 3. Representative CFAE maps from a patient with PerAF before and after ATP injection. The fractionation interval calculated from all available bipolar electrograms of the basket catheter was shortened by ATP injection from 92.2 ± 65.8 ms to 70.7 ± 30.8 ms ($P=0.0010$), and the percentage area of CFAE sites increased from 80.0% (32 sites) to 87.5% (35 sites). Overall changes in CFAE by ATP seem to be similar between the PAF case shown in Fig. 2 and this case, but the fractionation intervals within the CFAE sites were shortened more in the PAF case than the PerAF case. AP, anteroposterior; ATP, adenosine triphosphate; CFAE, complex fractionated electrogram; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PA, posteroanterior; PAF, paroxysmal atrial fibrillation; PerAF, persistent atrial fibrillation; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

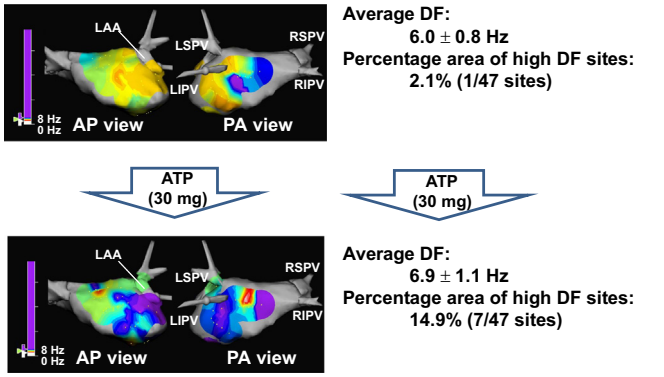

Fig. 4. Representative DF maps from a patient with PAF before and after ATP injection. The bright purple areas are high-DF sites (frequencies of >8 Hz). The overall DF increased from 6.0 ± 0.8 Hz to 6.9 ± 1.1 Hz ($P<0.0001$) after ATP injection, and the percentage area of high-DF sites increased from 2.1% (one site) to 14.9% (seven sites). AP, anteroposterior; ATP, adenosine triphosphate; CFAE, complex fractionated electrogram; DF, dominant frequency; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PA, posteroanterior; PAF, paroxysmal atrial fibrillation; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

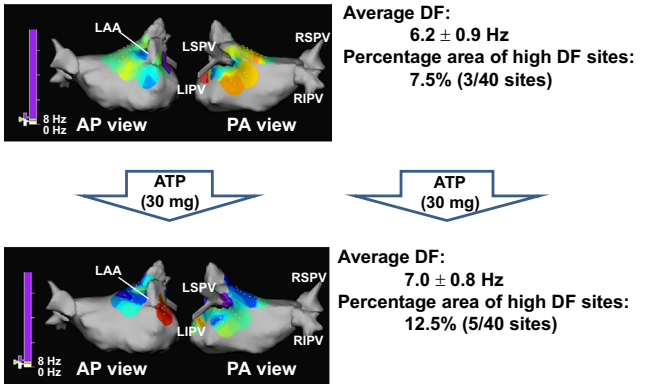

Fig. 5. Representative DF maps from a patient with PerAF before and after ATP injection. The overall DF value increased from 6.2 ± 0.9 Hz to 7.0 ± 0.8 Hz ($P<0.0001$) after ATP injection, and the percentage area of high-DF sites increased from 7.5% (three sites) to 12.5% (five sites). Note that in the PerAF case, baseline DF values were higher and the percentage area of DF sites was marginally greater, but the increases in the DF values and percentage areas of high DF by ATP injection were smaller than those in the PAF case shown in Fig. 4. AP, anteroposterior; ATP, adenosine triphosphate; CFAE, complex fractionated electrogram; DF, dominant frequency; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PA, posteroanterior; PAF, paroxysmal atrial fibrillation; PerAF, persistent atrial fibrillation; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

were smaller than those seen in patients with PAF. Changes in DF and percentage area of DF sites are shown in Table 3. In the total patient group, DF increased from 6.4 ± 0.6 Hz to 7.1 ± 0.8 Hz ($P<0.0001$) with ATP administration, and percentage area of high-DF sites increased from $8.9 \pm 10.0\%$ (3.7 ± 3.9 sites) to $20.0 \pm 22.4\%$ (8.8 ± 10.4 sites) ($P=0.0094$). The DF increased from 6.2 ± 0.5 Hz to 7.2 ± 0.7 Hz in the PAF group ($P<0.0001$) and from 6.6 ± 0.7 Hz to 7.0 ± 0.8 Hz in the PerAF group ($P=0.0406$). In the PAF group, the percentage area of high-DF sites increased, although not significantly, from $6.5 \pm 6.8\%$ (2.9 ± 3.0 sites) to $20.9 \pm 28.6\%$ (9.7 ± 13.6 sites) ($P=0.0644$) with ATP administration, and in the PerAF group, the percentage area of high-DF sites increased from $11.3 \pm 12.0\%$ (4.4 ± 4.6 sites) to $19.2 \pm 15.2\%$ (7.8 ± 6.4 sites) ($P=0.0400$). Only the increase in DF was significantly greater in the PAF group than in the PerAF group (1.1 ± 0.8 Hz vs. 0.3 ± 0.6 Hz, $P=0.0051$). The extent of change in the percentage area of high-DF sites after ATP administration did not differ significantly between the PAF group and the PerAF group ($14.4 \pm 30.9\%$ vs. $7.9 \pm 16.2\%$, $P=0.4228$). Regionally, in both groups, the increase in DF and the percentage area of DF sites occurred more toward the left PV antrum than in the middle and lateral portions of the LA (Table 3).

4. Discussion

4.1. Major findings

This study revealed differences in the FIs and DFs of the LA between patients with PAF and PerAF, and in the effects of ATP on these parameters. There was no difference in the baseline FIs between patients in the PAF and PerAF groups, but baseline DFs were significantly higher in the PerAF group. ATP shortened FIs, widened CFAE areas, increased DFs, and increased high-DF areas in

both groups. The ATP-induced decreases in FIs within the CFAE area and increases in DFs were more pronounced in the PAF group than in the PerAF group. The increases in DFs and percentage areas of high-DF sites in both groups occurred more frequently near the left PV antrum than at the lateral and mid portions of the LA, although the regional distributions of FIs and CFAEs did not differ between sites.

4.2. FIs, CFAE distributions, DFs, and distributions of high-DF sites in the PAF and PerAF groups

We found no significant difference in the FIs or percentage areas of CFAEs and high DFs between the PAF and PerAF groups. However, the DFs were significantly higher in PerAF patients than in PAF patients. Our findings are consistent with those of previous reports of shorter FIs, larger percentage areas of CFAEs, and higher DFs in patients with LA remodeling than in those without [7,13,16,17]. These findings may relate to the fact that the remodeled LA in patients with PerAF increases the electrical substrate for AF initiation and maintenance, such as that occurring as a result of focal-firing rotors or local reentry circuits.

4.3. Effects of ATP on CFAE and DF

The effects of adenosine or ATP on the atrial myocardium have been reported previously. Adenosine and acetylcholine (ACh) are known to activate the same Kir3.x subfamily of inward rectifier potassium channels through different signaling pathways [18]. ACh activates a specific population of K^+ channels called either *I*K, ACh or *I*K,Ado, leading to hyperpolarization of the cell membrane and shortening of the action potential duration and refractory period, and suppresses both spontaneous pacemaker discharge and early and delayed depolarizations through increased atrial K^+ conductance [8–10]. ATP facilitates reentry as a mechanism of AF maintenance, and can rule out an automatic or triggered mechanism. In the present study, ATP increased DFs and accelerated fractionated activity during AF. Similarly, Atienza et al. reported that ATP shortened FI and increased the DF of the PV-LA junction in PAF patients [3]. The results of Atienza et al.'s and the present study showing ATP can shorten mean FI and increase DF in patients with AF, suggesting that functional reentry plays an important role in maintaining AF. Because Atienza et al. evaluated limited sites in the posterior LA wall with a 20-pole spiral catheter [3], it is unclear whether the changes in the distributions of CFAEs or high-DF sites occurred throughout the LA. The use of a basket catheter, which enables recording from a wider area of the LA, demonstrated that ATP widened the overall areas of CFAEs through an increase in electrogram fractionation in the present study.

ATP shortened FIs, increased DFs, and increased CFAE and DF areas in both the PAF and the PerAF group, but only the extent of the increase in DF differed significantly between the groups. Similarly, *Atienza* et al. reported that ATP increases DFs, and that the increase in DF is significantly greater in the PAF patients than in PerAF patients [8]. We found that FIs within the CFAE area were more pronounced in the PAF group. Considering the mechanism of AF maintenance in PAF patients, this is a reasonable finding, i.e., the PV antrum in these patients has undergone less electrical and structural remodeling. Furthermore, after ATP injection, the DFs in the PAF patients were slightly higher at the PV antrum than at other areas in the LA, suggesting that the PV antrum might play an important role in the initiation and maintenance of AF in patients with PAF. The different responses of CFAE and DF sites to ATP in the PAF vs. PerAF groups could be due to the presence of more electrically and structurally remodeled atrial substrate in the patients in the PerAF group. Atrial myocytes adapt to chronically high atrial rates by down-regulation of the *I*K,ACh channel to counteract the shortening of the atrial effective refractory period resulting from electrical remodeling [19]. Furthermore, Jadidi et al. reported that slower and more organized electrical activity occurred at sites of atrial fibrosis in patients with PerAF [11]. Because functional reentrant circuits may be interrupted by fibrosis, the degree of FI shortening and DF increase induced by ATP might be less than that in patients with PAF.

4.4. Study limitations

This study contained a number of several limitations. The CFAE and DF sites were identified by means of a specific algorithm installed in the NavX mapping system. However, CFAE sites have been shown to differ very little in electrogram recordings over 5 s and validated extensively, and are therefore used clinically for AF ablation [12,13,20]. LA endocardial contact with the basket catheter also posed a technical limitation. Often, it is not possible for all of the electrodes to contact the endocardium. Furthermore, the basket catheter has been shown to cover only up to 50% of the LA surface [21]. No mapping of the right atrium or LA septal sites was performed, so it remains unclear whether our findings apply to these sites. We performed ATP injection only once because we did not conduct right ventricle pacing to determine the maximum effect on the atrioventricular node CFAE and DF were calculated. Performing large-dose ATP injection twice without back-up pacing increases patient discomfort. Therefore, we did not examine the reproducibility of the response to ATP injection.

5. Conclusions

In both the PAF group and the PerAF group, ATP shortened the CFAE mean cycle length associated with widening of the CFAE area. Similarly, the DFs and percentage areas of high DF in the LA increased after ATP injection. These data may indicate that reentrant AF drivers can be accelerated and manifested by ATP. The increase in DFs by ATP injection was enhanced predominantly in the PAF group rather than in the PerAF group, which might be due to the different AF substrates found in these different patients.

Conflict of interest

All authors declare no conflict of interest related to this study.

References

[1] Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: mapping of electrophysiologic substrate. J Am Coll Cardiol 2004;43:2044–53.
[2] Schmitt C, Estner H, Hecher B, et al. Radiofrequency ablation of complex fractionated atrial electrograms (CFAE): preferential sites of acute termination and regularization in paroxysmal and persistent atrial fibrillation. J Cardiovasc Electrophysiol 2007;18:1039–46.
[3] Atienza F, Calvo D, Almendral J, et al. Mechanisms of fractionated electrograms formation in the posterior left atrium during paroxysmal atrial fibrillation in humans. J Am Coll Cardiol 2011;57:1081–92.
[4] Moe GK, Mendez C. Basis of pharmacotherapy of cardiac arrhythmias. Mod Concepts Cardiovasc Dis 1962;31:739–44.
[5] Gerstenfeld EP, Lavi N, Bazan V, et al. Mechanism of complex fractionated electrograms recorded during atrial fibrillation in a canine model. Pacing Clin Electrophysiol 2011;34:844–57.
[6] Takahashi Y, Sanders P, Jaïs P, et al. Organization of frequency spectra of atrial fibrillation: relevance to radiofrequency catheter ablation. J Cardiovasc Electrophysiol 2006;17:382–8.
[7] Okumura Y, Watanabe I, Kofune M, et al. Characteristics and distribution of complex fractionated atrial electrograms and the dominant frequency during atrial fibrillation: relationship to the response and outcome of circumferential pulmonary vein isolation. J Interv Card Electrophysiol 2012;34:267–75.

[8] Atienza F, Almendral J, Moreno J, et al. Activation of inward rectifier potassium channels accelerates atrial fibrillation in humans. Circulation 2006;114:2434–42.
[9] Kabell G, Buchanan LV, Gibson JK, et al. Effects of adenosine on atrial refractoriness and arrhythmias. Cardiovasc Res 1994;28:1385–9.
[10] Belardinelli L, Shryock JC, Song Y, et al. Ionic basis of the electrophysiological actions of adenosine on cardiomyocytes. FASEB J 1995;9:359–65.
[11] Jadidi AS, Cochet H, Shah AJ, et al. Inverse relationship between fractionated electrograms and atrial fibrosis in persistent atrial fibrillation: combined magnetic resonance imaging and high-density mapping. J Am Coll Cardiol 2013;62:802–12.
[12] Nagashima K, Okumura Y, Watanabe I, et al. Does location of epicardial adipose tissue correspond to endocardial high dominant frequency or complex fractionated atrial electrogram sites during atrial fibrillation? Circ Arrhythm Electrophysiol 2012;5:676–83.
[13] Lin YJ, Tai CT, Kao T, et al. Spatiotemporal organization of the left atrial substrate after circumferential pulmonary vein isolation of atrial fibrillation. Circ Arrhythm Electrophysiol 2009;2:233–41.
[14] Verma A, Lakkireddy D, Wulffhart Z, et al. Relationship between complex fractionated electrograms (CFE) and dominant frequency (DF) sites and prospective assessment of adding DF-guided ablation to pulmonary vein isolation in persistent atrial fibrillation (AF). J Cardiovasc Electrophysiol 2011;22:1309–16.
[15] Kumagai K, Sakamoto T, Nakamura K, et al. Combined dominant frequency and complex fractionated atrial electrogram ablation after circumferential pulmonary vein isolation of atrial fibrillation. J Cardiovasc Electrophysiol 2013;24:975–83.
[16] Wu J, Estner H, Luik A, et al. Automatic 3D mapping of complex fractionated atrial electrograms (CFAE) in patients with paroxysmal and persistent atrial fibrillation. J Cardiovasc Electrophysiol 2008;19:897–903.
[17] Lin YJ, Tsao HM, Chang SL, et al. Role of high dominant frequency sites in nonparoxysmal atrial fibrillation patients: insights from high-density frequency and fractionation mapping. Heart Rhythm 2010;7:1255–62.
[18] Khositseth A, Clapham DE, Ackerman MJ. Intracellular signaling and regulation of cardiac ion channels. In: Zipes DP, Jalife J, editors. Cardiac electrophysiology: from cell to bedside. 4th ed.. Philadelphia, PA: WB Saunders Co; 2004. p. 33–41.
[19] Dobrev D, Graf E, Wettwer E, et al. Molecular basis of downregulation of G-protein-coupled inward rectifying K(+) current I(K,ACh) in chronic human atrial fibrillation: decrease in GIRK4 mRNA correlates with reduced I(K,ACh) and muscarinic receptor-mediated shortening of action potentials. Circulation 2001;104:2551–7.
[20] Jarman JW, Wong T, Kojodjojo P, et al. Spatiotemporal behavior of high dominant frequency during paroxysmal and persistent atrial fibrillation in the human left atrium. Circ Arrhythm Electrophysiol 2012;5:650–8.
[21] Buch EF, Nagel R, Benharash P, et al. Does the 64-pole basket catheter provide adequate spatial coverage and electrode contact for mapping atrial fibrillation in humans? Heart Rhythm 2014;5:S20.