Mechanism of Regular Atrial Tachyarrhythmias During Combined Pulmonary Vein Isolation and Complex Fractionated Electrogram Ablation in Patients With Atrial Fibrillation

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Background: Atrial tachyarrhythmias (ATA) frequently develop during catheter ablation of atrial fibrillation (AF), but the mechanism of ATA during combined pulmonary vein isolation (PVI) and complex fractionated electrogram-guided ablation (CFEA) has not been reported.

Methods and Results: This study involved 105 patients with symptomatic, drug-refractory AF. After PVI, CFEA was performed in the left/right atrium if AF remained inducible in paroxysmal AF (PAF) or persisted in persistent AF (PeAF). For the 70 PAF patients, PVI alone rendered AF non-inducible in 29 patients (41.4%), and converted inducible AF into inducible atrial flutter (AFI) in 10 patients (14.3%). For the remaining 31 PAF patients, additional CFEA rendered AF non-inducible in 11 patients (15.7%), whereas only AFI was inducible in 11 patients (15.7%). For 35 PeAF patients, PVI and CFEA converted AF into sinus rhythm in 2 (5.7%) and into AFI in 21 (60.0%) patients, while AF persisted in 12 patients (34.3%). The mechanism of ATA was focal (20/114, 17.5%), roof-dependent (20/114, 17.5%), peri-mitral (33/114, 28.9%), cavotricuspid isthmus-dependent (34/114, 29.8%) AFI or unknown (7/114, 6.1%). Successful ablation was achieved in 93/114 (81.6%) tachycardias.

Conclusions: The major mechanism of ATA during the combined approach of PVI and CFEA is macroreentry around large anatomic obstacles such as the pulmonary vein or the mitral or tricuspid annuli. (*Circ J* 2010; **74**: 434–441)

Key Words: Atrial fibrillation; Atrial flutter; Catheter ablation; Heart atria; Tachycardia

Recent advances in catheter ablation has lead to widespread application of atrial fibrillation (AF) ablation in clinical practice.^{1–6} Based on data from basic and clinical research,^{4,5} a tailored approach targeting complex fractionated electrograms (CFE) has been proposed.^{7–9} A combined approach of electrogram-guided CFE ablation (CFEA) and pulmonary vein isolation (PVI) could provide additional benefit in achieving the end-point of the procedure or long-term maintenance of sinus rhythm in catheter ablation of AF.

One of the clinical challenges during catheter ablation of AF is the occurrence of regular atrial tachyarrhythmias (ATA)

that are often difficult to deal with. The aim of the present study was to define the mechanism of atrial tachycardias occurring during combined PVI and CFEA.

Methods

Study Group

This prospective study comprised 105 consecutive patients with symptomatic, drug-refractory (≥ 1 class I, III antiarrhythmic drugs) paroxysmal AF (PAF) or persistent AF (PeAF). Patients' clinical and demographic features are summarized in **Table 1**. PAF and PeAF were defined as pre-

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Table 1. Clinical Characteristics of the Study Patients

	Paroxysmal AF (n=70)	Persistent AF (n=35)
Age (years)	54±11 (35–78)	52±11 (31–74)
Sex (M/F)	55/15	27/8
Past history of ischemic stroke	4	3
Hypertension	24	12
Hypertensive heart disease	11	5
Diabetes mellitus	8	5
Hyper/hypothyroidism	0/2	1/0
Coronary artery disease	4	3
Percutaneous coronary intervention or bypass graft	3	3
Congestive heart failure (NYHA ≥2)	2	6
Ejection fraction (%)	59.6±6.0 (range 46–70)	53.7±8.3 (range 29–68)
Left atrial dimension (mm)	40.5±5.3 (range 29–54)	44.2±5.2 (range 36–55)
Ejection fraction <50%	2	9
Follow-up	17.2±9.5	19.7±9.0

AF, atrial fibrillation; NYHA, New York Heart Association functional class.

viously described.¹⁰ Anticoagulation was maintained using an international normalized ratio >1.8 at least 4 weeks before the procedure. Transesophageal echocardiography was performed on the day of or the day prior to the procedure. The study protocol was reviewed and approved by the Institutional Committee on Human Research at Asan Medical Center and each patient provided written informed consent.

Electrophysiology Study

After discontinuation of all antiarrhythmic agents for at least 5 half-lives, an electrophysiological study was performed in the fasting state, typically under sedation with a continuous infusion of propofol (200–600 mg/h). Patients taking amiodarone were instructed to discontinue medication 1 month prior to the procedure. A 6F quadripolar catheter and a 7F decapolar catheter were introduced percutaneously through the femoral and jugular veins and placed in the His-bundle and coronary sinus (CS) regions, respectively. Two 8F sheaths (SL1, St Jude Medical, Inc) were introduced into the left atrium (LA) using a modified Brockenbrough technique. After transseptal puncture, intravenous heparin was injected as a bolus (80 IU/kg) and intermittently (1,000–2,000 IU/h) to maintain an activated clotting time >250 s. In addition, heparinized saline was continuously infused through the transseptal sheath (3 ml/min) to avoid formation of thrombi or air emboli. The infusion rate was increased to 17 ml/min (≤30 W) or 30 ml/min (>30 W) during radiofrequency (RF) application.

Multiple ECG leads (leads I, aV_F and V₁, filtered between 0.05 and 100 Hz) and intracardiac bipolar electrograms (filtered between 30 and 500 Hz) were simultaneously displayed and recorded on a digital electrophysiologic recording system (CardioLab®, Prucka Eng., Houston, TX, USA). The stimuli were delivered using a programmable digital stimulator (DTU-215, Bloom & Associates, Reading, PA, USA) at twice the diastolic threshold and with a 2-ms pulse width for conventional pacing, and at 10–20 mA for high output pacing. Conventional fluoroscopic mapping was used in 65 patients, and 3-dimensional (3D) mapping in 40 patients (NavX, ver 6.0 or 7.0, St Jude Medical, n=36 or Carto system, Biosense-Webster, n=4).

Circumferential PVI

PVI was performed 5–10 mm outside the PV ostia, with

isolation of 2 ipsilateral veins in 1 circumferential lesion. Ablation in the LA was performed using an irrigated catheter with a target temperature of 50°C, maximal power of 30 W, and an infusion rate of 17 ml/min. Power was temporarily increased to 40 W in an anterior circumference resistant to RF application. The endpoint of PVI was elimination or dissociation of the PV potentials (PVP). An ostial or carinal touch-up was additionally performed if PVP remained after PVI without an obvious gap along the line. Ablation at the PV ostia and within the CS was performed at 15–25 W and 50°C. Energy was applied for 40–60 s at each point until the loss of antral potential or the sharp component of the bipolar electrogram.

Study Protocol and CFEA

In patients with PAF, AF was induced before the procedure using a 5-s burst pacing from the distal and proximal CS and the right atrial electrodes. Pacing was begun at a cycle length (CL) of 250 ms and the CL was reduced in 10-ms intervals until atrial refractoriness or a CL of 200 ms was reached. Inducibility was defined as induction of AF lasting >2 min.

After completion of PVI, LA ablation targeting CFE was commenced by searching for the CFE from the posterior wall, the roof and the septum followed by the mitral annulus and base of the LA appendage (LAA). CFE was defined visually as a highly fractionated, nearly continuous electrogram. AF was re-induced if it terminated during the procedure, and abnormal electrograms were examined again if the re-induced AF lasted >2 min. If AF persisted or remained inducible after LA lesions, RF application was continued inside the CS and in the right atrium (RA), especially at the cavotricuspid isthmus, superior vena cava, crista terminalis, and the RA septum. The procedure endpoint was non-inducibility.

In patients with PeAF, CFEA was continued after PVI until AF termination, and the procedure endpoint was termination to sinus rhythm. In the last 3 patients with PeAF, a NavX-automated CFE detection algorithm was used. Automated CFE maps were created based on CFE CLs in an 8-s window, P-P sensitivity of 0.1 mV, width slider of 24 ms and refractory period of 49 ms.

Management of Regular Tachycardias

If a regular atrial tachycardia was induced or converted from AF during CFEA, activation mapping and multiple entrain-

Table 2. Distribution of Fractionated Atrial Electrograms Targeted for Ablation and Sites of AF Termination

	Paroxysmal AF (n=31)	Persistent AF (n=35)	Termination of AF into sinus rhythm or flutter (in PeAF)
Roof	13	25	2
Septum, left	13	25	3
Mitral annulus	17	24	2
LAA base	11	22	7
Posterior wall	1	9	3
Anterior wall	4	10	1
CS os	8	8	1
CS inside	7	18	3
Crista terminalis	7	7	0
Septum, right	4	7	1
RAA base	2	1	0
SVC isolation	7	3	0
Tricuspid annulus	2	0	0
Total	113	159	23
Mean ± SD	3.4 ± 2.2	4.5 ± 1.8	

AF, atrial fibrillation; PeAF, persistent AF; LAA, left atrial appendage; CS, coronary sinus; RAA, right atrial appendage; SVC, superior vena cava.

ment mapping were performed to identify its mechanism and location. Focal or isthmus ablation was performed accordingly to eliminate the tachycardia. Atrial tachycardias that could not be easily mapped and localized or were resistant to RF applications were cardioverted. Also, AF persistent after PVI and CFEA was electrically cardioverted at the end of the procedure.

Reentrant peri-mitral atrial flutter (AFL) was defined as regular atrial tachycardia with matching PPI (PPI-TCL <20 ms) in at least 2 peri-mitral regions. Roof-dependent AFL was diagnosed when PPI matched TCL in the posterior wall and

in the roof or anterior wall. When the entrainment mapping results were not compatible with the above reentrant AFL, and the activation sequence showed a centrifugal propagation from a limited area of atrium, focal ablation targeting the earliest activation was performed. A focal mechanism in our study was confirmed using the following criteria: (1) failure to meet the entrainment result in >2 atrial regions, (2) centrifugal propagation of activation, and (3) termination by focal ablation. However, the term “focal” does not differentiate between true focal automatic tachycardia and focal micro-reentry.

Figure 2. Effect of CFEA in patients with PeAF. Surface ECGs from leads II, III, aVF, and V₁ and intracardiac electrograms from the coronary sinus, Lasso and ABL catheters are shown. (A) A 31-year-old male patient with PeAF. Post-PVI CFE remain in the roof, mitral annulus, septum, LAA base, and inside the coronary sinus. During RF application in the septum, AF terminated directly into sinus rhythm after prolongation of the AF CL in the ABL catheter electrograms. (B) A 38 year-old male patient with PeAF. Post-PVI CFE remained in the septum, roof and inside the coronary sinus. AF was converted into AFI during RF application inside the coronary sinus region. ABL, ablation; AF, atrial fibrillation; AFI, atrial flutter; CFE, complex fractionated electrograms; CFEA, continuous fractionated electrogram-guided ablation; CL, cycle length; LAA, left atrial appendage base; PeAF, persistent AF; PVI, pulmonary vein isolation; RF, radiofrequency.

Post-Ablation Care and Follow-up

Subcutaneous low-molecular-weight heparin and warfarin were administered for 3 days commencing on the evening of the procedure day. Warfarin was continued for >3 months and ceased if the patient did not have risk factors for thromboembolism. Anti-arrhythmic drugs were continued for 1–3 months in patients with a history of PeAF and were re-initiated if symptomatic AF recurred in patients with PAF.

Patients were seen in the outpatient clinic at 1-month intervals for the first 3 months, and then every 2–3 months thereafter. ECGs were checked on each visit and, if indicated, a

Holter or event recording was used for detection of recurrent AF.

All patients were advised to visit outpatient clinics or emergency rooms for symptomatic episodes of palpitations, and in cases of persistent arrhythmia episodes, to obtain ECG documentation of the underlying rhythm. The absence of AF and AFI was confirmed in all asymptomatic patients with serial ECGs and/or 24-h Holter recordings. A successful outcome over the follow-up period was defined as the lack of electrocardiographically recorded AF, and no PAF on Holter or event recording, and subjective symptomatic improvement

Figure 3. Localization of CFE using 3D automated CFE detection program. In the last 3 patients with PeAF, an automated 3D CFE detection program was used for localization of CFE. (A) CFE map obtained from a 52-year-old female patient with PeAF. Post-PVI CFE was localized in the low septal region and near the LAA base (white color). (B,C) During RF application in the LAA base followed by RF in the low septum, AF was converted into AFL. AFL was again eliminated by linear lesion in the roof and in the LA isthmus. AF, atrial fibrillation; AFL, atrial flutter; CFE, complex fractionated electrogram; 3D, 3-dimensional; LAA, left atrial appendage; PeAF, persistent AF; PVI, pulmonary vein isolation; RF, radiofrequency.

after an 3-month blanking period.^{11,12}

Data Analysis

Data are expressed as mean±SD. Student's t-test was used for statistical comparison. A P-value <0.05 was considered to indicate significant difference.

Results

Results of RF Ablation

For the 70 PAF patients, PVI alone rendered AF non-inducible in 29 (41.4%), and only AFL were inducible in 10 (14.3%) patients. For the remaining 31 (44.3%) PAF patients, additional CFEA rendered inducible AF non-inducible in 11 (15.7%) patients, and converted it into AFL in 11 (15.7%) patients. AF persisted in 9 (12.9%) patients after the combined ablation procedure.

For the 35 PeAF patients, PVI alone failed to terminate AF into sinus rhythm in any patient. Additional CFEA resulted in AF being terminated into sinus rhythm in 2 of 35 (5.7%) patients, and into AFL in 21 of 35 (60.0%) patients. The additional CFEA had no effect in 12 (34.3%) PeAF patients (Figure 1).

The duration of RF application for PVI were 3,855±1,515 s

for PAF and 3,978±1,807 for PeAF. Although the mean duration of RF application during CFEA appeared to be longer in patients with PeAF (1,032±590 vs 1,549±753 s), this difference did not quite reach statistical significance (P=0.06).

Distribution of Fractionated Electrograms and Results of CFEA

Fractionated electrograms were more commonly associated with specific LA regions such as the roof, septum, lateral mitral annulus, and base of the LAA. Table 2 summarizes the distribution of the CFE areas targeted for CFEA. The mean number of atrial regions targeted for CFEA was higher in patients with PeAF than in patients with PAF (3±2 vs 5±2 regions, P<0.05). Most of the RF lesions targeting CFE were delivered in a circumscribed area, creating a coin lesion. If CFE electrograms were distributed in a large area, especially in the posterior wall, roof or septum, a linear lesion was made across the CFE area.

Post-PVI CFEA rendered inducible AF either into inducible AFL or non-inducible in patients with PAF. PeAF terminated directly to sinus rhythm in 2 patients and converted into AFL in 21 patients (Figures 2,3). Conversion occurred during CFEA at the LAA, CS inside, roof, septum or mitral annulus etc (Table 2).

Table 3. Mechanisms of Atrial Tachycardia During or After PVI and CFEA

Mechanism	Paroxysmal AF (total number/successful ablation)	Persistent AF (total number/successful ablation)	Success rate (total number/successful ablation, %)
Focal	11 (11)	9 (8)	20 (19, 95.0%)
Peri-mitral	16 (11)	17 (14)	33 (25, 75.8%)
Roof-dependent	11 (10)	9 (7)	20 (17, 85.0%)
Right isthmus	20 (20)	14 (12)	34 (32, 94.1%)
Unknown	2 (0)	5 (0)	7 (0, 0%)
Total	60 (52)	54 (41)	114 (93, 81.6%)

PVI, circumferential pulmonary vein isolation; CFEA, continuous fractionated electrogram-guided ablation; AF, atrial fibrillation.

Mechanisms of Atrial Tachycardias and Results of Catheter Ablation

A total of 114 atrial tachycardias or flutters were observed during combined PVI and CFEA procedures (60 in PAF, 54 in PeAF patients). The tachycardia mechanisms were focal (20/114, 17.5%), roof-dependent (20/114, 17.5%), peri-mitral (33/114, 28.9%), cavotricuspid isthmus-dependent (34/114, 29.8%), or unknown (7/114, 6.1%). The major mechanism of tachycardia was macroreentry around large anatomic obstacles such as the PV and mitral or tricuspid annuli (87/114, 76.3%). Focal mechanism was responsible in 18.3% (11/60) of tachycardias in PAF patients and in 16.7% (9/54) of tachycardias in PeAF patients. The mechanism of some tachycardias was difficult to identify because of the coexistence of multiple tachycardias, inconsistent entrainment results, and frequent termination or transition to other tachycardia during entrainment pacing. **Table 3** summarizes the tachycardia mechanisms and results of catheter ablation. Successful

ablation was achieved in 93/114 cases (81.6%) (**Table 3**).

Clinical Results and Complications

Complications comprised transient ischemic attack in 1, pericardial effusion requiring drainage in 2, and groin hematoma in 2 patients.

The 70 PAF patients had a mean follow-up of 17 ± 10 months. Recurrent tachyarrhythmias occurred in 11 patients, comprising persistent AFI (3 patients), PAF (7 patients), and AV nodal reentry tachycardia (AVNRT: 1 patient). Repeat procedures were performed in 1 AVNRT, 3 AFI and in 4 PAF patients. Atrial arrhythmias did not recur after this second procedure in 6/7 patients. One patient experienced recurrent episodes of PAF after the second procedure and 3 patients refused to undergo a redo ablation: 3 of these 4 patients were managed with intermittent (1 patient) or regular (2 patients) medication with class IC antiarrhythmic agents. In 1 patient, AF became persistent, and a rate control strategy was used.

The 35 PeAF patients had a mean follow-up of 20±9 months: 18 patients developed persistent AFL (5 patients) or PeAF (13 patients) and of those, 5 AFL patients and 7 AF patients underwent repeat procedures. The remaining 6 AF patients refused to undergo a second procedure. All the 5 AFL patients and 2 of the 7 PeAF patients regained sinus rhythm after the second procedure. In 2/7 patients who underwent redo procedures, and in 1/6 patients who did not receive redo procedure, previously ineffective class IC antiarrhythmic agents were effective for maintaining sinus rhythm. For 3 patients in whom AF recurred after the second procedure and 5 of the 6 patients who refused a repeat procedure, a rate control strategy was used. Overall, sinus rhythm was maintained without antiarrhythmic agents in 24 (69%) patients, and with previously ineffective antiarrhythmic drugs in 3 (9%) patients. AF persisted in the remaining 8 (23%) patients.

Discussion

The present study investigated the incidence and mechanism of regular ATA occurring during the combined approach of PVI and CFEA in catheter ablation of AF. We found that CFEA after PVI was able to render AF non-inducible in PAF patients or to convert AF to AFL in PeAF patients. The major mechanism underlying induced or converted AFLs during this combined procedure was macroreentry around large anatomic obstacles such as the tricuspid/mitral annulus or PVs. This result suggests that it is possible to take a step-wise, patient-specific approach based on individual differences in the electrophysiological substrate of AF.

Efficacy of Post-PVI CFEA and Its Implication on the Mechanism of AF

The inducibility of AF by pacing is a major determinant of recurrence after PV isolation.^{11–14} The recurrence rate ranges from 30% to 50% when AF remains inducible, as compared to 10–20% when non-inducibility is achieved. In the present study, AF became non-inducible with PVI alone in 55.7% of PAF patients, and became non-inducible in a further 31.4% of patients after additional CFEA. In PeAF patients, PVI alone was not successful in terminating AF in any patient, whereas additional CFEA resulted in AF termination into sinus rhythm in 5.7% of patients or into AFL in 60.0% of patients. Therefore, while the long-term success of these CFEA outcomes remains unknown, CFEA resulted in greater achievement of the procedural endpoint.

The results of the CFEA provide 2 important mechanistic implications for the maintenance of AF. First, the fact that CFEA renders inducible AF non-inducible or into inducible AFL implies that the region targeted for CFEA could have played an active role in the perpetuation of AF. Second, the transition or termination of PeAF into AFL and subsequent revelation of macro-reentrant or focal tachycardia suggests that AF comprises different subsets of arrhythmia mechanisms. The focal or micro-reentrant mechanisms around or within the PV antrum are eliminated by a debulking PVI procedure. Further reduction of the arrhythmia burden is achieved by CFEA, leaving a few macroreentrant or focal tachycardias at the final stage of the ablation procedure. The stepwise transition of atrial arrhythmias during this combined procedure suggests a stepwise reduction of the arrhythmia burden that maintains AFL.

Anatomical Distribution of Fractionated Electrograms in AF

Fractionated electrograms targeted for ablation were dis-

tributed most frequently in the LA roof, septum, mitral annulus and appendage. Anatomical landmarks harboring these abnormal electrograms were similar to those proposed by Nademanee et al⁷ and Haissaguerre et al.¹⁵ The distribution of these abnormal electrograms were similar in patients with paroxysmal or PeAF. These anatomical structures have been shown to consist of heavily intermingled atrial fibers of septopulmonary and septoatrial bundles with abrupt changes and overlap in the fibers orientation.¹⁶ This structural distinction provides the anatomical basis for formation of reentrant arrhythmia. However, the possibility of bystander complex electrograms that do not play an active role but are generated passively by the inherently abnormal fiber connections, and thus generating a pseudo-CFE, should also be considered.

Mechanism of Regular Tachycardia Induced or Converted From AF During the Combined Ablation Procedure

Inducible AF was converted into inducible AFL in 21 of the 70 PAF patients who underwent PVI and/or CFEA, while AF terminated into AFL in 21 of the 35 PeAF patients. The majority (87/114, 76.3%) of the tachycardias were peri-mitral, roof-dependent peri-PV or cavotricuspid isthmus-dependent tachycardias, which emphasizes the importance of large anatomical barriers. Focal tachycardia frequently originated from the posterior wall or the septum. Successful ablation was possible in 95% of the focal tachycardias.

Differential diagnosis of these regular tachycardias was sometimes difficult because of the coexistence of multiple tachycardias, frequent and subtle changes in the activation sequence or tachycardia CLs during entrainment pacing.¹⁷ Focal tachycardias, because of previous ablation lines (roof line, mitral or cavotricuspid isthmus line), frequently showed CL coverage greater than 50% and mimicked reentrant tachycardia. An integrative analysis of activation and entrainment mapping results was necessary for differential diagnosis of these tachycardias.

Study Limitations

We did not systematically map all areas of fractionated electrograms before ablation, which might have precluded description of the global distribution of fractionated electrograms or their changes after ablation. A 3D mapping system-guided identification of CFE is currently underway in our laboratory to display the location and distribution of CFE areas.

The data describe the immediate results of CFEA. To verify the true nature of this incremental change, a randomized study comparing the various strategies is required (ie, PVI alone vs CFEA alone vs PVI+CFEA).

Although the additive effect of CFEA is described, it remains unclear whether this resulted from abolition of AF drivers or from non-specific atrial damage and atrial mass reduction. In addition, not all of the areas with fractionated electrograms may represent true AF drivers. Future studies should obtain more data regarding the nature of electrograms at or near the AF drivers in order to reduce unnecessary RF application.

Finally, the clinical outcome was judged by documented ECGs or Holter recordings obtained intermittently during outpatient clinic follow-up or emergency room visits. A more comprehensive follow-up program, such as trans-telephonic transmission or event recording, could have detected more cases of asymptomatic occurrence of AF in our study subjects and resulted in a lower success rate.

Conclusion

CFEA after PVI resulted in non-inducibility of AF or conversion of inducible AF into inducible AFL in patients with PAF. CFEA terminated AF into sinus rhythm or into AFL in patients with PeAF. The major mechanism of the induced or converted AFLs during this combined procedure was macroreentry around large anatomical obstacles such as the tricuspid/mitral annulus or PVs.

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