Lengthening of Intraatrial Conduction Time in Atrial Fibrillation and Its Relation with Early Recurrence of Atrial Fibrillation

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SUMMARY

Intraatrial conduction delay in atrial fibrillation (AF) that is considered a component of atrial electrical remodeling has been demonstrated previously in experimental models and it is considered an important factor for the induction or stabilization of AF. However, it is not known if this phenomenon exists in human AF. The present study aimed to compare intraatrial conduction time (IACT) in patients with chronic atrial fibrillation who were converted to sinus rhythm and a matched control group, and to investigate its relation with early AF recurrence.

Seventeen patients with chronic AF (mean duration of 20.71±16.35 months) were enrolled in the study (7 males, 10 females, 63±8 years). An age and sex matched control group (n=12) consisted of patients with sinus rhythm who underwent electrophysiological study (EPS). None of the patients were on any antiarrhythmic treatment during the procedures. Cardioversion was performed via external DC cardioversion. Eight patients in the control group were delivered a DC shock because of induced ventricular tachycardia during EPS. IACT was defined as the interval between the onset of P wave surface ECG and the beginning of A wave at high right atrium (IACT 1) and low right atrium (IACT 2). Additionally, the interval between A wave at high right atrium and low right atrium was measured (IACT 3).

Patient characteristics such as age, sex and echocardiographic variables were not different between the AF group and the control group. Heart rate after cardioversion was found to be similar between the two groups. Total delivered energy was significantly higher in the AF group than in the control group (464.47±165.82 joules vs. 315.00±27.77 joules, p<0.001). IACT 1 (15.30±7.61 msec vs 8.50±5.29 msec, p<0.02), IACT 2 (45.25±8.36 msec vs 26.44±10.45 msec, p<0.001) and IACT 3 (26.9±8.26 msec vs. 18.67±10.05, p<0.05) significantly lengthened in the AF group after maintenance of sinus rhythm compared to the control group. There were 6 early AF recurrences during the 1 week follow-up period. Multivariate analysis, revealed IACT 2 and IACT 3 were significantly different between the control group, the patient with recurred AF and the patients with maintained sinus rhythm. Post-hoc analysis revealed that IACT 2 and IACT 3 significantly lengthened in the patients with recurred AF compared to both the control group

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and patients with maintained sinus rhythm. On the other hand, only IACT 2 patients with maintained sinus rhythm were found to be higher than those of the control group.

The present study indicated that intraatrial conduction was disturbed in patients with AF, a finding which is consistent with those of previous experimental studies. Additionally, such a phenomenon may be a risk factor for the early recurrence of AF after cardioversion to sinus rhythm. (Jpn Heart J 2001; 42: 575-584)

Key words: Atrial fibrillation, Intraatrial conduction, Electrical remodeling

ATRIAL fibrillation (AF) is the most prevalent arrhythmia and its prevalence is reported to be 0.4% to 0.9%. Its incidence increases with aging and reaches 2% to 4% over age 60.[1,2] An important point regarding AF is the self perpetuation of the arrhythmia once it initiates. The reason for this phenomenon is thought to be the remodeling of atria due to the arrhythmia. This remodeling is believed to occur anatomically (atrial dilatation), at the cellular level (cellular necrosis, fibrosis, mitochondrial swelling, ATP depletion) and electrophysiologically.[3,4] Electrical remodeling in atrial fibrillation is defined as: 1-Shortening of the atrial effective refractory period (AERP), 2-Maladaptation of AERP to heart rate changes, and 3-Lengthening of intraatrial conduction time (IACT).[5] The wavelength of an impulse is the product of the effective refractory period and conduction velocity.[6] Shortening of the effective refractory period or lengthening of intraatrial conduction time result in wavelength shortening which would cause AF to perpetuate, since at least 4-6 wavelets, at the same time, are thought to be essential for AF to be persistent.[7-10]

In both AF and rapid atrial arrhythmias, changes in AERP have been demonstrated both in humans and experimental models.[5,11-13] However, in what way does AF affect intraatrial conduction is controversial. Elvan, *et al*[14], in an experimental model, have documented lengthening of IACT. Contrary to their findings Wijffels, *et al*[5] have reported no change in the conduction velocity of Bachman bundle. Kumagai, *et al* showed that both intraatrial and interatrial conduction lengthened in humans with lone AF after electrocardioversion.[15] In the present study, we aimed to measure IACT in patients with chronic AF who were converted to sinus rhythm by direct current cardioversion (CV), compare it with a control group and search for a potential relationship between the early recurrence of AF and conduction properties of atrium.

METHODS

The study group consisted of 17 patients with AF (7 males, 10 females aged 63±8) who were converted to sinus rhythm by external DC CV. The probable eti-

ologies of AF were hypertension in 15 patients and idiopathic dilated cardiomyopathy in 2 patients. To be included in this study, patients had to undergo their first cardioversion. The mean duration of AF was 20.7±16.3 months. None of the patients in the study group received antiarrhythmic medications at the time of a procedure. The medications used in the study group were as follows; digoxin (10 patients), angiotensin converting enzyme inhibitors (10 patients), beta blockers (8 patients) and diuretics (2 patients). Patients were anticoagulated for at least 3 weeks so as to keep an INR level of 2.5-3.5. After cessation of AF, no patients were given any antiarrhythmic drugs.

The control group constituted of patients who were in sinus rhythm and without any history of AF. There were 12 patients in the control group (5 male, 7 female, aged 60±7 years) and none of the patients were on antiarrhythmic treatment at the time of IACT measurement. Eight patients in the control group were given DC shock because of induced ventricular tachycardia. In these patients IACT was measured after DC CV. The rest of the control group (4 patients) underwent electrophysiological study due to documented supraventricular tachycardia and IACT was measured before induction of any arrhythmia.The study was approved by our Institutional Review Board and written informed consent was given by all patients.

All the patients with AF underwent a transthoracic echocardiography study in the last 24 hours prior to DC CV and transoesophageal echocardiography study in the last 12 hours prior to DC CV according to the criteria of the American Society of Echocardiography.[16] We searched for the presence of left atrial or left atrial appendage thrombus and those who had thrombus were not converted.

Cardioversion protocol: Electrical cardioversion was performed in the postabsorbtive state during light anesthesia by using midazolam intravenously (0.04 mg/kg). One defibrillator pad with a diameter of 10 cm (S&W, Model 730) was placed in the second intercostal space on the right side parasternally; the other was placed in a left-sided lateral position along the midaxillary line. Cardioversion procedure started with 200 J of stored energy followed by 300 J and then twice with 360 J until the restoration of sinus rhythm or until failing to convert.

Measurement of IACT (Intraatrial conduction time): Because IACT would be measured invasively by means of femoral vein cannulation, we discontinued warfarin 3 days before the procedure to prevent complication by bleeding. After CV and establishing hemostasis, intravenous heparin and oral warfarin were initiated together and heparin continued until INR reached a level of 2.5.

After maintenance of a stable sinus rhythm, two quadripolar electrodes were placed at the lateral wall of the right atrium. One electrode was located immediately below the superior vena cava (high right atrium) and the other was positioned immediately superior to the inferior vena cava (low right atrium).

Intracardiac ECG was gained from the distal 2 pairs of these electrodes and filtered between 40-400 Hz. Four surface ECG channels, in which the onset of P waves were best defined, and electrical activity from the two atrial electrodes were recorded simultaneously with a paper speed of 100 and 200 mm/second. IACT was defined as the interval between the beginning of P wave on the surface ECG and the onset of A wave obtained from the high right atrium (IACT 1) and the low right atrium (IACT 2) as described by Elvan, *et al*.[14] Additionally, we also measured the time interval for the A waves in the upper and lower right atrial electrodes (IACT 3). All measurements were performed independently by two authors (ÖA and TS) using the electronic caliper of EPS equipment. IACT variables were measured on at least 10 cardiac cycles and an averaged value was calculated for each.

Statistics: Continuous variables are presented as mean±SD. The normal distribution of the data was tested with the Kolmogorov-Smirnov test. If the data had a normal distribution, comparison between the AF group and control group was performed by means of unpaired Student *t* test, otherwise an appropriate nonparametric test was used. ANOVA and Tukey's B post-hoc analysis were performed to detect differences between patients with early AF recurrence, those with maintained sinus rhythm and the control subjects. Categorical variables were compared with Fischer's exact *t* test. A P value <0.05 was considered significant.

RESULTS

Patient characteristics are given in Table I. The control group was similar to the AF group in terms of age and sex. The AF group had slightly higher left ventricular fractional shortening that did not reach statistical significance. Left atrial

Table I. Patient Characteristics

	AF group (*n*=17)	Control Group (*n*=12)	*p*
Age (years)	62.5±8.0	58.6±6.4	0.2
Sex (M:F)	7:10	5:7	0.5
IVS (mm)	12.4±1.9	11.3±1.5	0.1
PW (mm)	11.7±2.1	10.7±1.2	0.2
FS (%)	38.7±6.2	33.8±6.1	0.1
LAd (mm)	48.6±6.0	41.0±4.6	<0.001

AF=atrial fibrillation; M:F=male: female; IVS=thickness of interventricular septum; LAd=left atrial diameter; PW=left ventricular posterior wall thickness.

diameter was significantly higher in the AF group ($p<0.001$). Interventricular septum and left ventricular posterior wall was thicker in AF patients (p=NS).

The mean cumulative energy used in the AF group was higher than in the control group that was used for treating induced ventricular tachycardia episode (436.5±16.8 j vs. 315±27.8 J, p=0.007). Heart rate after CV was similar in both groups. In the AF patients, IACT 1, IACT 2 and IACT 3 significantly lengthened as compared to the control group (Table II).

In the one week follow-up of the patients converted to sinus rhythm, 6 patients experienced early recurrence of AF. According to multiple variance analysis, IACT 2 and IACT 3 was different between the stable sinus rhythm group, early relapsed AF group, and the control group (Table III). Post-hoc analysis revealed that IACT 2 and IACT 3 were significantly high in subjects with early relapsed AF as compared to patients with maintained sinus rhythm and controls (Figure 1). IACT 1 was similar among the three groups. In the non-relapsed

Table II. Comparison of Studied Parameters between AF Group and Control Group after Cessation of Atrial Fibrillation

	AF group (n=17)	Control Group (n=12)	p
Heart rate*	81.0±12.5	77.1±14.7	0.5
Cumulative energy (joule)	464.47±165.82	315.00±27.77	<0.001
IACT1 (ms)	15.30±7.61	8.50±5.29	0.01
IACT2 (ms)	45.25±8.36	26.44±10.45	<0.001
IACT3 (ms)	26.9±8.26	18.67±10.05	0.04

*:Average heart rate after maintenance of sinus rhythm; AF=atrial fibrillation; IACT: see text.

Table III. ANOVA Results of Studied intraatrial Conduction Parameters and Clinical Variables in Patients with Relapsed AF, Those with Maintained Sinus Rhythm and Controls

	Ralapsed AF (n=6)	Maintained sinus rhythm (n=11)	Control (n=12)	p
Age (years)	60.9±8.1	63.3±8.2	58.6±6.4	0.2
AF duration (months)	17.1±14.7	24.2±18.1	–	0.4
LAd	49.8±7.9	47.9±5.2	41.0±4.6	0.02
IACT1 (ms)	14.9±5.3	15.5±8.8	8.5±5.3	0.06
IACT2 (ms)	54.2±6.3*	39.9±7.1†	26.4±10.5	<0.001
IACT3 (ms)	33.8±4.3‡	24.4±8.0	18.7±10.1	0.02

*: versus maintained sinus rhythm, p=0.001; †: versus control group, p=0.003; ‡: versus maintained sinus rhythm, p=0.03. AF=atrial fibrillation; LAd=left atrial diameter.

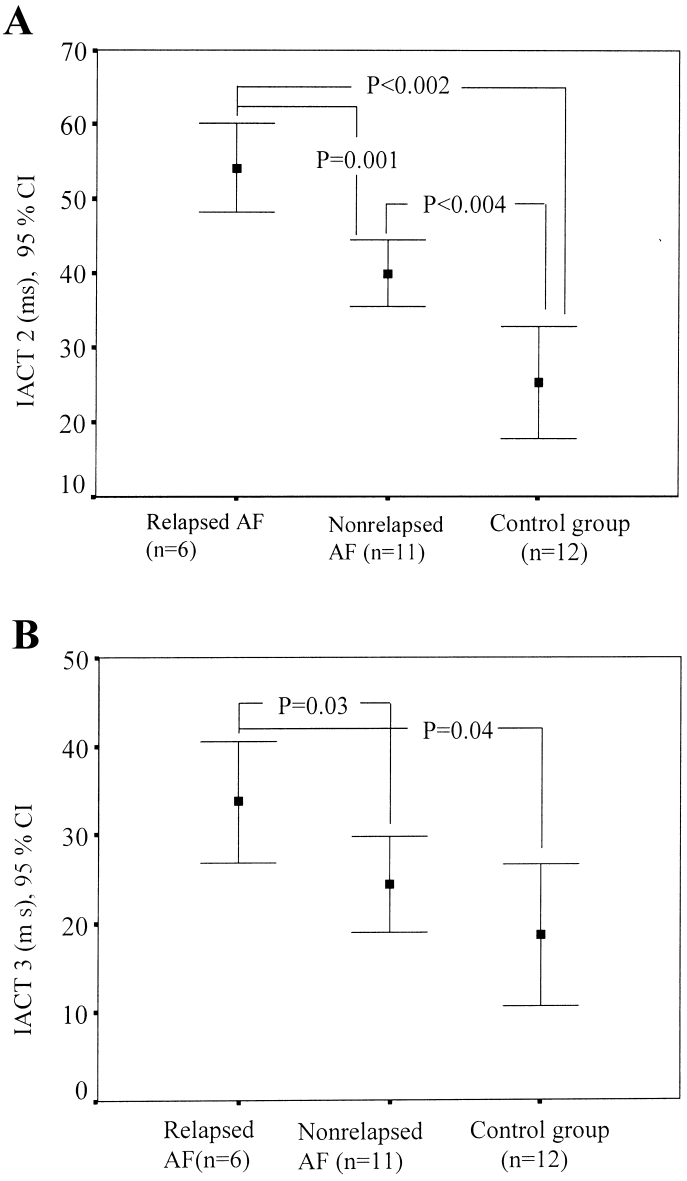


Figure 1A and B: Comparison of IACT 2 and IACT 3 between relapsed AF group, those with maintained sinus rhythm and control subjects. Note that both parameters significantly lengthened in relapsed patients.

AF group, IACT 2 was significantly longer with respect to the control group ($p<0.004$). IACT 1 and IACT 3 were similar in patients with non-relapsed AF and the controls. Potential risk factors of early recurrence of AF, i.e. age, left atrial diameter, and duration of AF were similar between the patients who experienced early AF relapse and those with maintained sinus rhythm.

DISCUSSION

There are 2 main findings in our study. First, we showed that in patients with chronic AF, after conversion to sinus rhythm, IACT was found to be prolonged with respect to an age and sex matched control group. Second, lengthening in IACT may be related with early recurrence of AF. We noted that IACT was prolonged in patients with maintained sinus rhythm with respect to the control group as well but patients who experienced early recurrence of AF had significantly longer IACT compared to patients with maintained sinus rhythm and the control group.

The hypothesis of Moe, *et al* regarding the mechanism of AF is the most widely accepted model. According to this model, the stability of AF depends on a certain amount of reentry cycles at a given point of time (multiple reentry theory).[7,8] The hypothesis of Moe could be confirmed in the 1980s both in experimental models and humans by mapping of the atrial activation pattern of AF.[9,10]

Multiple wandering wavelets in the atria are the basis of AF. The wavelength of these wavelet is the distance traveled by the depolarization wave during the duration of its refractory period (wavelength=effective refractory period x conduction velocity). Then, as the effective refractory period shortens or conduction velocity decreases (in other words IACT increases), the wavelength decreases. According to the calculations of Moe, *et al*[7,8] for the induction and stabilization of AF there needs to be 4-6 surrounding reentry wavelets in both atria at a given point of time.[7,8] The number of wavelets that can coexist in the atria is determined both by the atrial tissue mass (or surface area), and the wavelength of the atrial impulse.[17,18] If the wavelength of the depolarization wavelets are short enough, a given amount of reentry wavelets can fit into a certain amount of atrial mass.

Atrial electrical remodeling has three components ; 1-shorthening of AERP, 2-maladaptation of AERP to rate changes, and 3-changes in intraatrial conduction velocity. Olsson, *et al* [19] were the first to demonstrate shortening of atrial monophasic action potentials after cessation of AF. Cotoi, *et al,*[20] in a similar study, reported a strong correlation between monophasic action potential duration and stabilization of sinus rhythm. Attuel, *et al*[11,12] demonstrated that patients with AF had abnormally short AERP, that could not adapt to heart rate changes (i.e.

lengthening of AERP with acceleration of atrial rate). Wijffels, *et al,*[5] in their experimental model, demonstrated the strong correlation between shortening of AERP and stabilization of AF. Goette, *et al*[21] reported that shortening in AERP began in such a short period as 30 minutes. After conversion to sinus rhythm, changes in AERP may continue up to one week and shows close correlation with AF recurrence.[5] Many studies have demonstrated that changes in AERP are an important component of atrial electrical remodeling which is an integral part of the concept "AF begets AF". [5,13,14,21,22]

Although alterations in AERP have been well documented, the influence of AF on intraatrial conduction is controversial. Wijffels, *et al,*[5] in the same experiment have demonstrated shortening of AERP but noted that intraatrial conduction velocity in the Bachman bundle was not influenced from AF. However, Elvan, *et al,*[14] in a similar model, reported lengthening of P the wave duration and P-A interval. Kumagai, *et al* showed that both intraatrial and interatrial conduction lengthened in humans with lone AF after electrocardioversion.[15] Our results confirmed the findings of Kumagai, *et al*. Moreover, the present study also showed that disturbed intraatrial conduction might have some clinical implications. The early recurrence group had lengthened IACT as compared to those with stable sinus rhythm and the control group. Because the early relapsed group and nonrelapsed group had similar potential predictors of recurrence (age, duration of AF), the difference could be explained by IACT lengthening. Antiarrhytmic drugs, when used to prevent AF recurrences and help for conversion to sinus rhythm, seem to act through AERP and conduction velocity. Wijffels, *et al*[23], in an experimental study investigating the effects of class I and class III antiarrhythmic drugs in AF, found that these drugs increased the excitable gap which is a paradoxical finding facilitating the stabilization and induction of AF. In their study, the observed findings were probably due to a marked decrease in the conduction velocity (although AERP was prolonged). Shinagawa, *et al*[24] had supported this hypothesis. They administered pilsicainide during AF (a sodium channel blocker) and showed that AERP was prolonged but conduction velocity was decreased. The net effect was a decrease in the excitable gap. In the present study, we point out that prolonged IACT is a parameter that can influence AF recurrences. Probably, that was due to a shortening in wavelength. Regarding the previous studies and our data the antiarrhythmic drug that would be used in AF should not affect conduction velocity or even if it has an effect on that parameter it should be opposed with an increase in AERP.

The exact reason for atrial electrical remodeling is unknown. It is thought to be related with intracellular calcium kinetics.[25–27] In experimental models of ventricular fibrillation, in which coronary perfusion was maintained and intracellular pH was kept constant, it was demonstrated that the amount of intracellular cal-

cium increases to 4-5 fold.[28] This observation was projected to AF. Goette, *et al,*[21] in experimental models of AF, demonstrated that calcium infusion caused electrical atrial remodeling to occur earlier while verapamil infusion reversed atrial electrical remodeling. Tieleman, *et al* [23] in a similar experimental model found that verapamil decreased the shortening of AERP and corrected its maladaptation to heart rate changes. On the other hand, IACT in the control group and in the verapamil group was not different in that study. Research at the molecular level has demonstrated that during AF, both sarcoplasmic calcium kinetics and membranous calcium channels are spoiled.[29,30] During AF oxygen consumption of the atria increases and this causes intracellular ATP depletion.[31] Due to the decreased ATP levels calcium can not be removed from the intracellular milieu, accumulate intracellularly and secondary to that, ATP dependent potassium channels are opened[32,33] that will result in action potential shortening. In addition, the number of pumps removing calcium from the sarcoplasmic reticulum decreases as time passes.[29] Although the relation between the intracellular calcium overload and AERP has been documented in AF, the relation between the calcium overload and conduction velocity is not clear. Together with electrophysiological changes, structural changes in the atria, secondary to AF, such as degenerative process, fibrosis, and cell loss due to apoptosis might cause intraatrial conduction blocks.[4,34]

In conclusion, in the present study we demonstrated that AF causes a marked prolongation in IACT which may be a risk factor for the early recurrence of the arrhythmia.

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