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Reversal of atrial electrical remodeling following cardioversion of long-standing atrial fibrillation in man

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Abstract

Background: In animal studies, atrial fibrillation has been shown to shorten the atrial refractory period and impair its rate adaptation. However, little is known about the effects of chronic atrial fibrillation on atrial electrophysiology and its recovery course in humans. **Methods and results:** Nineteen patients, mean age 64±14 years, with chronic atrial fibrillation of more than six months duration were included in this study. All of them were successfully converted to sinus rhythm with an external defibrillator. Atrial effective refractory periods at right atrial appendage and distal coronary sinus were determined with five pacing cycle lengths (300, 400, 500, 600 and 700 ms) at 30 min after cardioversion and once a day for four days. The atrial conduction properties, including P wave duration of surface ECG, and right and left atrial conduction times, were also measured at the same time interval. Twenty age-matched patients without a history of atrial tachyarrhythmia were evaluated as controls. In comparison with controls, chronic atrial fibrillation significantly shortened the atrial effective refractory period, impaired its rate adaptation response, especially at distal coronary sinus, and depressed the conduction properties of atria. The atrial conduction properties did not change during the four-day follow-up period; however, the atrial effective refractory period was gradually prolonged and its rate adaptation response improved after restoration of sinus rhythm. **Conclusions:** In humans, chronic atrial fibrillation significantly shortened the atrial effective refractory period, and impaired its rate adaptation response. Restoration and maintenance of sinus rhythm could reverse these electrophysiological changes.

Keywords: Atrium; Cardioversion; Fibrillation; Electrophysiology

1. Introduction

Clinical observations have shown that paroxysmal atrial fibrillation could progress to sustained atrial fibrillation, even in patients without underlying heart disease [1]. In addition, the possibility of conversion and maintenance of sinus rhythm was decreased as the duration of atrial fibrillation increased [2,3]. These findings suggest that atrial fibrillation is a self-perpetuating arrhythmia. Wijffels et al. [4] demonstrated that maintenance of atrial fibrillation by pacing for two to three weeks led to a sustained atrial fibrillation in healthy goats. The major electrophysiological changes were shortening of the atrial effective refractory period and loss of its normal rate-dependent change; these electrophysiological changes recovered after termination of atrial fibrillation. They coined the term ''electrical remodeling'' for these electrophysiological changes. In humans, a short duration of atrial fibrillation has also been demonstrated to cause a significant shortening of the atrial effective refractory period, which recovered in minutes after termination of atrial fibrillation [5–7]. However, little is known about the effects of chronic atrial fibrillation on atrial electrophysiology in humans. We hypothesized that chronic atrial fibrillation

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could lead to an electrical remodeling of atrium in humans. Thus, conversion of atrial fibrillation and maintenance of sinus rhythm would reverse the adverse electrophysiological effects of chronic fibrillation. This study was conducted to verify this hypothesis.

2. Methods

2.2. Patients

Nineteen patients, 15 men and four women (mean age, 64±14 years), with chronic atrial fibrillation of more than six months duration (mean, 62±36 months; range, 16 to 132 months) were included in this study. All patients were evaluated by taking a detailed clinical history, by performing a physical examination, and using routine laboratory thyroid function test, transthoracic and transesophageal echocardiography, coronary angiography and left ventriculography. Sixteen patients had other cardiovascular diseases (13 had hypertensive cardiovascular disease, two had mitral valve prolapse with mild mitral regurgitation and one had coronary artery disease with stable angina). The clinical characteristics of these patients are shown in Table 1. They were anticoagulated with warfarin with a prothrombin time at INR 2.0 to 3.0 for at least three weeks. Patients with any of the following conditions were excluded from the study: (1) atrial fibrillation (AF) due to reversible causes; (2) myocardial infarction within six months or unstable angina; (3) a history of thromboembolism within six months; (4) a left atrial thrombus or moderate-to-severe spontaneous echo contrast by a transesophageal echocardiography obtained within two days before cardioversion; (5) digitalis intoxication; (6) significant electrolyte imbalance or (7) an implanted pacemaker or defibrillator.

All patients gave informed consent, and the study protocol was approved by the Review Board of Human Research of this hospital. The investigation conforms with the principles outlined in the Declaration of Helsinki.

2.2. Electrical cardioversion

Digitalis and all antiarrhythmic drugs were discontinued for at least five half-lives and warfarin was replaced with heparin three days before cardioversion. A transesophageal echocardiography was performed 24 to 48 h before cardioversion, to evaluate whether there was an intracardiac thrombus or spontaneous echo contrast. Four hours before the patient was brought to the electrophysiological laboratory, heparin was discontinued. Two ten-polar electrode catheters with 2 mm intra-pair and 5 mm inter-pair distances (Daig Inc.) were inserted from the right internal jugular vein, and positioned at the right atrial appendage and the distal coronary sinus. After the patients were adequately anesthetized with methohexital sodium (30 to 50 mg, Eli Lilly), a direct current shock synchronized to the R wave was delivered from an external defibrillator (CodeMaster XL$^+$, Hewlett-Packard). The location of the paddle was oriented in the apex–sternum direction and the energy of the shock was started at 50 Joules and increased in 50-Joule increments until any of the following conditions were achieved: sinus rhythm, maximal energy of 360 Joules and two episodes of immediate recurrence of AF (defined as recurrence of atrial fibrillation within 60 s). Those who failed to achieve sinus rhythm or needed antiarrhythmic drugs to facilitate cardioversion were excluded from further study. There was a total of 80 patients surveyed and only 19 patients entered this study. Twelve patients could not be converted to sinus rhythm, 21 patients needed antiarrhythmic drugs to facilitate cardioversion and 27 patients experienced spontaneous recurrence, therefore, only 19 patients were included in the study. Three recurrences were related to measurement of the atrial effective refractory period.

Table 1
Clinical characteristics of patients and controls

	AF	Control
Age (years)	64±14	63±14
Gender (F/M)	4/15	5/15
LAD (mm)	45±6[a]	35±4
LVEF (%)	46±8[a]	54±5
Heart disease	13 HCVD, 1 CAD, 2 MVP[b]	4 MVP[b]

[a] $P<0.05$ for comparison between those with atrial fibrillation (AF) and controls.

[b] CAD, coronary artery disease; LAD, left atrial dimension; LVEF, left ventricle ejection fraction; HCVD, hypertensive cardiovascular disease, MVP: mitral valve prolapse.

2.3. Electrophysiological study

2.3.1. Determination of the atrial effective refractory period

Thirty minutes after restoration of sinus rhythm, effective refractory periods of the right atrial appendage and distal coronary sinus were determined. The distal pair of both electrode catheters were used for pacing and the proximal four pairs were used for recording. Pacing was performed at twice the diastolic threshold. The atrial effective refractory period was determined using an incremental method; atrial extrastimuli were applied with 2-ms increments after every eight beats of atrial pacing. Surface ECG and ten endocardial electrograms from both catheters were continuously monitored and stored in a computer-based digital amplifier/recorder system with an optical disk storage for off-line analysis (Cardiolab, Prucka Engineering). Intracardiac electrograms were filtered from 30 to 500 Hz, and measured with a computer-assisted calipers. The atrial effective refractory period was defined as the longest S1–S2 coupling interval that failed to result in atrial capture. For evaluation of the rate adaptation of

the atrial refractory period, five atrial pacing cycle lengths (700, 600, 500, 400 and 300 ms) were used in random sequence; and gaps of 2 min were interspersed between each change of atrial pacing cycle length. In each patient, the rate adaptation was calculated as the slope of the atrial effective refractory period against the pacing cycle length. After the effective refractory period study was completed, the position of the electrode catheters was recorded on biplane x-ray film and the catheters and sheaths were retained for a follow-up study (eight patients had retained sheaths, and 11 patients had retained sheaths and catheters). The temporal change of the atrial effective refractory periods and their rate adaptation properties were followed for four days with the same catheters. At each following study, the position and threshold of the catheters were checked and adjusted to the previous level.

2.3.2. Determination of the atrial conduction time

Global atrial conduction after cardioversion was evaluated by P-wave duration of ECG lead II, and the local right atrial and left atrial conduction properties were measured by conduction time from the second to the fifth pairs of electrodes, while the first pair was used for pacing. The atrial conduction times were measured at both basic cycle length and the earliest capture stimulus. The duration of the P-wave was measured with a sweep speed of 100 mm/s and a gain setting of 2 cm/mV. The endocardial electrograms were filtered with 30–500 Hz, and measured with a computer-assisted calipers at a sweep speed of 200 mm/s. The onset of electrograms was defined as the first deflection from baseline. All of the measurements were done by two investigators and the differences were less than 10 ms.

2.3.3. Control study

Twenty age-matched patients with supraventricular tachycardia (12 atrioventricular nodal reentrant tachycardia and eight atrioventricular reciprocating tachycardia) were included for control. They were free from structural heart disease, and without clinical atrial flutter, fibrillation or other atrial tachyarrhythmias. Their clinical characteristics are shown in Table 1. Atrial effective refractory periods, their rate adaptation properties and conduction time were measured as the study group.

2.4. Statistical analysis

All data are presented as mean±SD. The series changes of atrial effective refractory periods were analyzed by ANOVA with multiple comparisons. Paired and unpaired Student's *t*-test was used to compare the data when appropriate. A value of $P<0.05$ was considered to be statistically significant.

3. Results

3.1. Change of the atrial effective refractory period in chronic AF

Chronic atrial fibrillations were successfully converted to sinus rhythm with a mean energy of 185±72 Joules. The diastolic capturing thresholds were 0.9±0.4 and 1.0±0.6 mA for the right atrial appendage and distal coronary sinus, respectively. There were no significant changes in the thresholds throughout the study. Thirty minutes after restoration of sinus rhythm, the mean sinus cycle length was 791±93 ms. The effective refractory period of the right atrial appendage and distal coronary sinus were 210±18 and 217±14 ms, respectively, at a pacing cycle length of 700 ms. When the pacing cycle length was reduced, the effective refractory periods of the right atrial appendage and distal coronary sinus were both shortened, as shown in Fig. 1. At a pacing cycle length of 300 ms, the effective refractory period of the right atrial appendage and distal coronary sinus were 191±11 and 183±12 ms, respectively. The mean slopes of rate-adaptation were 0.049±0.024 for the right atrial appendage, and 0.098±0.042 for the distal coronary sinus ($P=0.01$ vs. the right atrial appendage).

In the control group, the effective refractory periods of the right atrial appendage and distal coronary sinus were 233±18 and 264±27 ms, respectively, at a pacing cycle length of 700 ms; they were 199±14 and 200±17msec, respectively, at pacing cycle length of 300 ms. The mean slopes of rate-adaptation were 0.074± 0.016 for the right atrial appendage, and 0.162±0.040 for the distal coronary sinus ($P<0.01$ vs. the right atrial appendage), respectively. The change in atrial effective refractory periods and its rate-adaptation in chronic AF are summarized in Table 2. The atrial effective refractory period of chronic AF were significantly shorter than those of the control group and its rate adaptation response was impaired in comparison to the control group. In addition, the impairment of rate adaptation was more profound at the distal coronary sinus than the right atrial appendage (right atrial appendage, 0.049±0.024 vs. 0.074±0.016, −27%; $P=0.02$; distal coronary sinus, 0.098±0.042 vs. 0.162±0.040, −60%; $P=0.005$).

The temporal change in the atrial effective refractory period is shown in Fig. 2. After restoration of sinus rhythm, the atrial effective refractory period was gradually prolonged during the follow-up study. At a pacing cycle length of 700 ms, the effective refractory period of the right atrial appendage and distal coronary sinus increased from 210±18 and 217±14 ms at 30 min after cardioversion to 261±17 and 280±33 ms on the fourth day after cardioversion. At a pacing cycle length of 300 ms, the effective refractory period of the right atrial appendage and distal coronary sinus increased from 191±14 and 181±20 ms at 30 min after cardioversion to 236±17 and 208±16

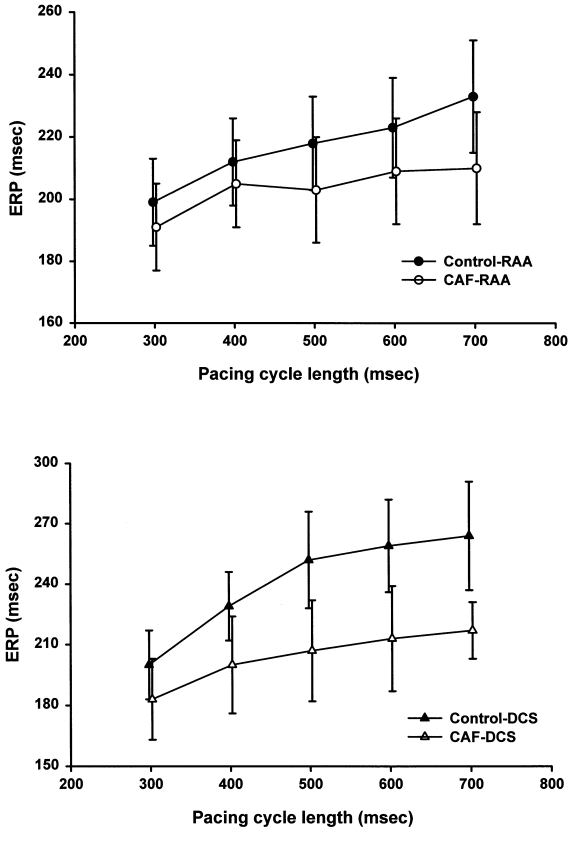

Fig. 1. Effective refractory periods of the right atrial appendage and distal coronary sinus, determined at five pacing cycle lengths (700, 600, 500, 400 and 300 ms). The data are presented as mean±SD. In the control group, the effective refractory period of the right atrial appendage (●) and distal coronary sinus (○) increase as the pacing cycle length is increased. The mean slope of the distal coronary sinus is steeper than that of the right atrial appendage (0.162±0.040 vs. 0.074±0.016, $P<0.01$). In patients converted from chronic atrial fibrillation, the effective refractory periods of the right atrial appendage (▲) and distal coronary sinus (△) are shorter than those of controls at corresponding pacing cycle lengths. In addition, the mean slopes of both the right atrial appendage (0.049±0.024 vs. 0.074±0.016, $P<0.01$) and the distal coronary sinus (0.098±0.042 vs. 0.162±0.040, $P<0.01$) were less steep than those of controls.

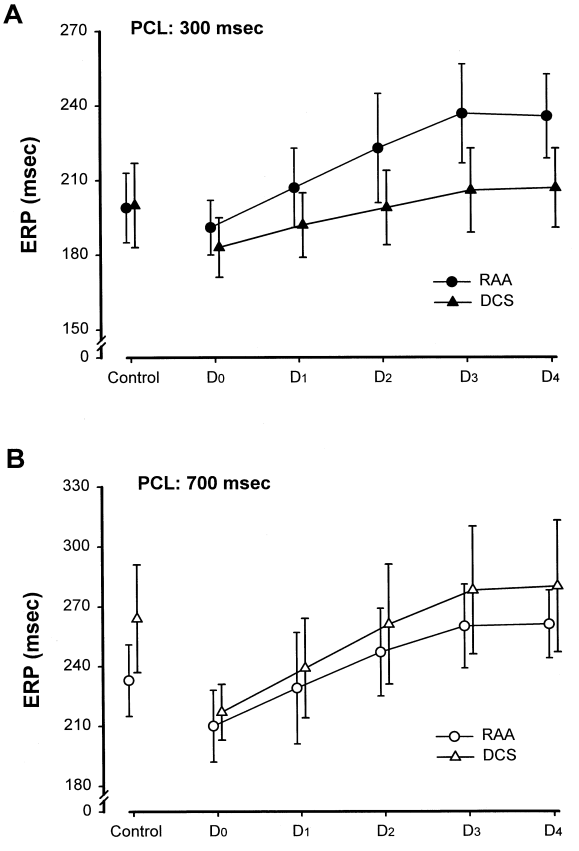

Fig. 2. Temporal changes in effective refractory periods of the right atrial appendage (●) and distal coronary sinus (▲) at a pacing cycle length of 300 ms are shown in panel A. Similarly, the temporal changes in the effective refractory period of the right atrial appendage (○) and distal coronary sinus (△) at a pacing length of 700 ms are shown in panel B. The effective refractory periods of both the right atrial appendage and the distal coronary sinus gradually increase and reach a stable level on the third day after cardioversion.

ms on the fourth day after cardioversion. Prolongation of the effective refractory period reached a stable level on the third day after cardioversion.

The rate adaptation of the effective refractory period also improved during the follow-up study, because prolongation of the effective refractory period was more prominent at long pacing cycle lengths. On the fourth day after cardioversion, the rate-adaptation slope at the right atrial appendage was similar to that of the control group (0.066±0.027 vs. 0.074±0.016, $P>0.05$), and the rate-adaptation slope at the distal coronary sinus also was not different from that of the control group (0.186±0.101 vs. 0.162±0.040, $P>0.05$).

Table 2
Comparison of atrial refractoriness and its adaptation between AF and control groups

	RA-300[b]	RA-700[b]	Slope	CS-300[b]	CS-700[b]	Slope
AF	191±11[a]	210±18[a]	0.049±0.024[a]	183±12[a]	217±14[a]	0.098±0.042[a]
Control	199±14	233±18	0.074±0.016	200±17	264±27	0.162±0.040

[a] $P<0.01$ between AF and control.

[b] RA-300, effective refractory period (ERP) of the right atrial appendage at a pacing cycle of 300 ms; RA-700, ERP of the right atrial appendage at a pacing cycle of 700 ms; CS-300, ERP of the distal coronary sinus at a pacing cycle of 300 ms and CS-700, ERP of the distal coronary sinus at a pacing cycle of 700 ms.

3.2. Changes in atrial conduction properties in chronic atrial fibrillation

Comparison of atrial conduction properties between those with atrial fibrillation and the control group are shown in Fig. 3. The duration of the P-wave was longer in the AF group than the control group; the conduction times measured at both a basic cycle length and the earliest capture beat were also significantly longer in the AF group. These conduction properties did not show any significant change during the follow-up studies. On the fourth day after cardioversion, the P-wave duration was 138±10 ms ($P>0.05$) vs.144±13 ms, 30 min after cardioversion, the right atrial conduction time at a basic pacing cycle was 23±2 ms ($P>0.05$) vs. 23±2 ms, 30 min after cardioversion, and the left atrial conduction at a basic pacing cycle length was 19±4 ms ($P>0.05$) vs. 19±4 ms, 30 min after cardioversion. Similarly, the atrial conduction times measured at the earliest capture beat did not change during the four-day follow-up study.

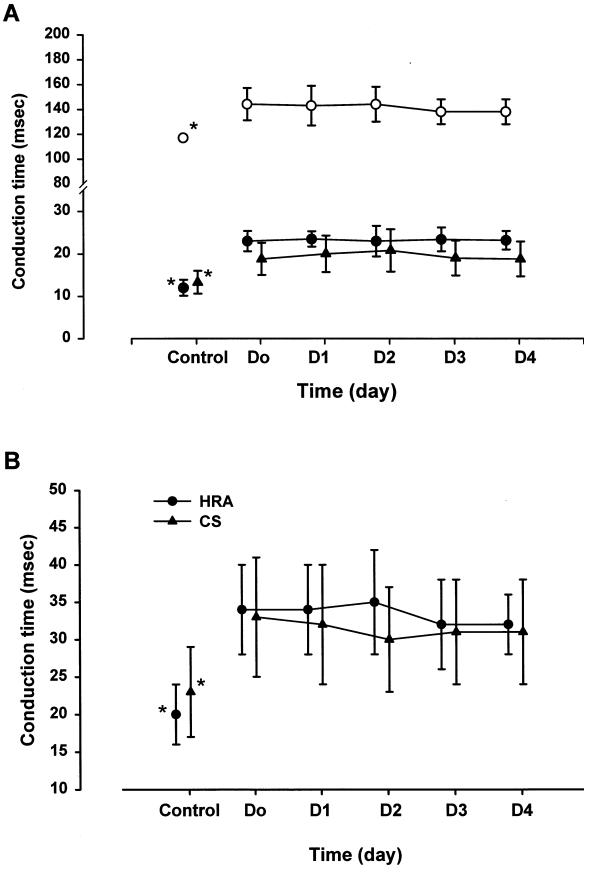

Fig. 3. Right atrial conduction time (●), left conduction time (▲) and ECG P-wave duration (○) in patients converted from chronic atrial fibrillation. These times are longer in patients converted from chronic AF compared to controls. Please note that the data for the control group are on the left side. In addition, there are no significant changes in the conduction properties during the post-cardioversion four-day follow-up study. In panel A, the atrial conduction times were measured at a basic pacing cycle length; in panel B, the atrial conduction times were measured at the earliest capture beat. *$P<0.01$ for comparison between AF and controls.

4. Discussion

4.1. Main findings

In patients with chronic atrial fibrillation, the atrial effective refractory period was shorter than in controls, and its rate adaptation response was also impaired, especially at the distal coronary sinus. Maintenance of sinus rhythm after cardioversion prolonged the atrial effective refractory period; prolongation of the effective refractory period reached a stable level on the third day after cardioversion. Furthermore, maladaptation of the effective refractory period was also improved because prolongation of the effective refractory period at long pacing cycle lengths was more prominent than that at short pacing cycle lengths. Impairment of atrial conduction properties was also noted, however, it did not change during the four-day follow-up study.

4.2. Atrial electrophysiological change in chronic atrial fibrillation

Atrial fibrillation is supposed to be a multiple wavelets reentrant tachycardia [8-10]. The wavelength of the wavelets, which is defined as the product of the effective refractory period and conduction velocity, plays a critical role in the initiation and maintenance of atrial fibrillation [11,12]. Previous animal studies have shown that rapid atrial pacing or atrial fibrillation for three to six weeks led to shortening of the atrial effective refractory period [4,13]. Monophasic action potential recording in humans also showed shortening of the atrial effective refractory period [14-16]. In the present study, we directly measured the atrial effective refractory period at the right atrial appendage and the distal coronary sinus, and showed that the effective refractory period at both sites was shorter in patients converted from chronic atrial fibrillation than in age-matched controls. In addition to the shortening of refractoriness, the conduction properties of both atria were also depressed in patients with chronic atrial fibrillation. Therefore, this shortening of the effective refractory period and depressed atrial conduction properties could lead to a shorter wavelength and an increase in atrial vulnerability to fibrillation. Duytshaever et al. [17] reported that the development of chronic atrial fibrillation in the goat was dependent on the intra-atrial conduction velocity. However, studies of atrial conduction properties were not consistent; Wijffels et al. [4] observed no change in the atrial conduction velocity in the goat model, and Gaspo et al. [19] and Elvan et al. [19] observed decreases in the conduction velocity in a chronic dog model. These divergent results might be due to the different durations of

rapid pacing or fibrillation; the duration of pacing in the studies of Elvan et al. [19] and Gaspo et al. [18] was longer than that used by Wijffels et al. [4]. Furthermore, Gaspo et al. [20] showed that the decrease in conduction velocity developed more slowly than the shortening of the refractory period. In the present study, the duration of atrial fibrillation was much longer than that of the animal model; the impairment of atrial conduction was also profound. However, we could not exclude the possibility that the change in conduction was due to the nature of atrial degeneration.

Another major electrophysiological change in chronic atrial fibrillation was the loss of physiological rate adaptation [4]. Interestingly, we found that the rate adaptation response was different between the right atrial appendage and the distal coronary sinus in both the control and atrial fibrillation groups. In the controls, rate adaptation at the distal coronary sinus was more pronounced than at the right atrial appendage, whereas, after cardioversion of atrial fibrillation, this difference was decreased. Therefore, AF seemed to cause more profound impairment of rate adaptation in the distal coronary sinus. Attuel et al. [21] reported that the loss of physiological rate adaptation of the atrial effective refractory period was associated with a higher incidence of atrial tachyarrhythmia. In atrial tissue with normal rate adaptation, the refractory period is prolonged as the cycle length increases; therefore, there is a relatively fixed vulnerable zone for an atrial premature depolarization. If the refractory period of atrial tissue was not prolonged as the cycle length was increased, the vulnerable zone of atrial premature depolarization would increase. Thus, maladaptation of the effective refractory period might also increase the vulnerability of the atrium to fibrillation. Furthermore, the shortening of the effective refractory period and its maladaptation to rate were more profound in the distal coronary sinus. These findings suggested that there might be a site-dependent difference in atrial remodeling. In our laboratory, we also demonstrated the site-dependent difference of maladaptation and its correlation with reinitiation of atrial fibrillation in an animal study [22].

4.3. Temporal recovery of electrical remodeling after conversion of atrial fibrillation

In the present study, we showed that shortening of the effective refractory period and loss of its rate adaptation were reversible, even in patients with long-standing atrial fibrillation (mean duration, 62 ± 36 months). The effective refractory period was gradually prolonged and the rate adaptation response progressively improved after conversion of atrial fibrillation to sinus rhythm. On the third day after cardioversion, they reached steady levels, which were not different from those of the control group. These data support the theory that these electrophysiological changes are secondary to atrial fibrillation. Wijffels et al. [4] showed similar findings in pacing-induced atrial fibrillation [4]. On the other hand, the depressed conduction properties in chronic atrial fibrillation did not show evidence of recovery during the four-day follow-up period. It might be an irreversible change, but we could not rule out a late recovery. However, clinical observations have demonstrated that the recurrence of atrial fibrillation was frequently clustered in the first month after cardioversion [23–26]. Furthermore, several studies have demonstrated that the electrophysiological changes are related to calcium current [6,7,27,28]. Recently, Tieleman et al. [29] showed that most recurrences occurred during the first five days after cardioversion and that the use of calcium-lowering drugs reduced the incidence of recurrence. All of these data support the view that atrial fibrillation causes electrical remodeling, which facilitates the perpetuation of atrial fibrillation itself. From the clinical viewpoint, the early recurrence of atrial fibrillation after a successful cardioversion may be due to the adverse effects of electrical remodeling, and calcium-blocker might provide a beneficial effect in this situation.

4.4. Study limitations

First, we included only patients who could maintain sinus rhythm without antiarrhythmic drugs for at least four days. These might represent a group with less severe atrial disease, so they had a high probability to recovering from electrical remodeling. Second, in contrast to patients with chronic fibrillation, the patients in the control group were free of structural heart disease. This mismatch might account for the differences between the control group and 30 min after restoration of sinus rhythm. Third, the autonomic tone and hemodynamic state were changed after conversion of atrial fibrillation to sinus rhythm; they might have some influence on the electrophysiological properties after cardioversion. Recently, Jayachandran et al. [30] reported that rapid atrial pacing might produce heterogeneous changes in atrial sympathetic innervation. However, previous study has shown that autonomic tone or atrial pressure changes did not play an active role in electrical remodeling of atrial fibrillation [31]. The interaction between autonomic innervation and electrical remodeling in atrial fibrillation should be investigated further.

5. Conclusions

Chronic atrial fibrillation led to shortening of the atrial effective refractory period and to loss of its physiological rate adaptation, which could make atria more vulnerable to fibrillation. Conversion of atrial fibrillation and maintenance of sinus rhythm could abolish the adverse effects of ‘‘electrical remodeling’’.

Acknowledgements

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