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Electrophysiology

Action Potential Duration Restitution Kinetics in Human Atrial Fibrillation

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OBJECTIVES We undertook this study to determine whether human atrial fibrillation (AF) relates to steeply sloped action potential duration restitution (APDR) kinetics and whether the spatial nonuniformity of APDR promotes persistence of AF.

BACKGROUND A steeply sloped APDR curve is known to be an important determinant of the induction of more complex action potential duration (APD) dynamics and fibrillation.

METHODS Patients with chronic atrial fibrillation (CAF) (n = 18), paroxysmal atrial fibrillation (PAF) (n = 14) and normal control subjects (n = 9) were studied. The monophasic action potential duration at 90% repolarization (APD_{90}) and the effective refractory period (ERP) were measured at six sites in the right atrium. After AF was electrically converted, APDR was assessed by delivering a single extrastimulus after a train of stimuli at a cycle length of 600 ms (S_1S_2) at six different sites of the right atrium, as well as rapid pacing at cycle lengths that induced APD alternans.

RESULTS The APD_{90} and ERP in patients with CAF were shorter than those in patients with PAF and control subjects ($p < 0.05$); however, the dispersions of APD_{90} and ERP in each group were similar. The maximal slopes of APDR by S_1S_2 and rapid pacing in patients with CAF (1.2 ± 0.4 and 1.7 ± 0.2) and PAF (1.1 ± 0.4 and 1.3 ± 0.4) were higher than those in control subjects (0.5 ± 0.3 and 0.8 ± 0.2, respectively; $p < 0.01$). The maximal slope obtained by S_1S_2 did not differ from that obtained by rapid pacing in any group. The inter-regional difference of the maximal slope in patients with CAF (1.6 ± 0.4, $p < 0.05$) was greater than that in patients with PAF (1.2 ± 0.3, p = NS vs. control) and control subjects (0.4 ± 0.2).

CONCLUSIONS Atrial fibrillation was related to steeply sloped (>1) APDR kinetics. The spatial dispersion of APDR in patients with chronic AF was greater than that of patients with paroxysmal AF and control subjects, indicating that the heterogeneity of APDR of the atrium plays an important role in the persistence of AF. (J Am Coll Cardiol 2002;39:1329–36) © 2002 by the American College of Cardiology Foundation

It is known that the dispersion of refractoriness is important in the induction of re-entrant arrhythmias and causes instability of re-entrant circuits (1–3). Recently, dynamic heterogeneity arising from cardiac restitution properties has been demonstrated to be a more important determinant (4–8). When the slope of the action potential duration restitution (APDR) curve, in which the action potential duration (APD) is plotted against the preceding diastolic interval (DI), is >1, the APD along the re-entrant wave fronts will undergo beat-to-beat oscillations. If this oscillation in the APD grows large enough, localized conduction block occurs, causing the wave break that is necessary for fibrillation.

However, the relationship between the APDR properties in the human atrium and its role in the mechanisms that determine the stability of atrial fibrillation (AF) have not been examined. Electrically induced and chronic atrial fibrillation (CAF) both lead to electrical remodeling and associated structural changes, which explain the progressive nature of AF (9,10). In addition, nonuniform electrical remodeling promotes increased atrial vulnerability to AF and increased AF duration (11).

The present study was designed to test the hypothesis that human AF relates to steeply sloped APDR kinetics, and that these differ from those observed in patients with CAF and paroxysmal atrial fibrillation (PAF). Furthermore, the APDR characteristics are not uniform throughout the atrium, which may be one of the important mechanisms responsible for the persistence of AF.

METHODS

Study group. The study group consisted of 18 patients with CAF (AF lasting >1 week) and 14 patients with PAF (AF lasting <2 days), who were referred for cardioversion. The mean duration of the AF episodes in patients with CAF was 28 ± 21 months (range 6 to 45 months). The mean duration of symptoms in those with PAF was 10 ± 9 months (range 1 to 22 months), and these patients experienced, on average, two episodes (range 1 to 6 episodes) of AF per month, lasting from 1 to over 48 h. Atrial fibrillation was documented by 12-lead electrocardiography and/or Holter monitoring. Patients with the following criteria were

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Abbreviations and Acronyms

AF = atrial fibrillation
APD = action potential duration
APD_{90} = action potential duration at 90% repolarization
APDR = action potential duration restitution
BCL = basic cycle length
CAF = chronic atrial fibrillation
DI = diastolic interval
ERP = effective refractory period
HL = high lateral
HS = high septal
LVEF = left ventricular ejection fraction
ML = mid lateral
MP = mid posterior
PAF = paroxysmal atrial fibrillation
MAP = monophasic action potential

excluded: unstable angina or myocardial infarction, class III or IV heart failure, the presence of left atrial thrombi, significant valvular heart disease, reversible causes of AF (e.g., electrolyte imbalance) and a contraindication to long-term anticoagulant therapy.

The control group consisted of nine patients without underlying structural heart disease, who underwent electrophysiologic study for supraventricular or ventricular tachycardia. None had experienced any spontaneous episodes of AF.

Written, informed consent was obtained from all patients. The study protocol was approved by the institutional Review Committee of the Korea University Hospital.

Electrical cardioversion and recording of monophasic action potentials (MAPs). All patients were studied in the postabsorptive, nonsedated state, and all antiarrhythmic drugs were discontinued for at least five half-lives before the beginning of the study. No patient was receiving amiodarone therapy. All patients with CAF received at least four weeks of anticoagulation with warfarin, and the absence of left atrial thrombi was confirmed by transesophageal echocardiography before undergoing transthoracic direct-current cardioversion. A 7F MAP recording catheter (Boston Scientific EP Technologies, San Jose, California) was inserted through the right femoral vein under fluoroscopic control and positioned at six different sites (high lateral [HL], mid lateral [ML], high posterior, mid posterior [MP], high septal [HS] and mid septal) of the right atrium. The position of the MAP electrode was adjusted until an acceptable MAP signal was obtained. Electrocardiographic leads II and V_1 and the MAP output were displayed on an oscilloscope and recorded at a paper speed of 100 mm/s (Prucka Engineering, Inc., Houston, Texas). The MAP electrogram was filtered from 0.05 to 500 Hz. After AF had been converted to sinus rhythm, a 15-min wait was allowed to enable short-term, rate-dependent changes in the APD. Atrial pacing was performed using the MAP catheter at twice the diastolic threshold. The APD at each site was measured at 90% repolarization (APD_{90}) during pacing at a basic cycle length (BCL) of 600 ms.

Construction of the APDR curve. The restitution of APD_{90} was determined using a single S_2 delivered after every eighth S_1 at a BCL of 600 ms. The S_1S_2 interval was started at 400 ms and was decreased in 20-ms steps until an S_1S_2 of 300 ms was reached. Subsequently, it decreased every 10 ms until atrial capture failed. It was then increased by 8 ms and finally decreased in 2-ms steps until the atrial effective refractory period (ERP) was reached. After each S_2, S_1 pacing was interrupted for 5 s. The MAP signals were analyzed with a custom-developed software algorithm, which had been validated by previous studies (12,13). The APDR curve was constructed by plotting the APD_{90} as S_2 versus the preceding DI, which was obtained by subtracting the APD_{90} of the eighth S_1 from the S_1S_2 interval.

The restitution of APD_{90} was also determined using rapid pacing at the high right atrium, which is the best site to acquire a stable S_1S_2 recording. After 50 stimuli had been delivered at an initial BCL of 400 ms, the BCL was shortened in steps of 50 ms for BCLs >250 ms, and in steps of 10 ms for BCLs <250 ms until APD alternans or 2:1 block occurred. Fifty stimuli were given at each BCL. Pacing was interrupted for 5 s when the BCL was changed.

The time course of restitution obtained by S_1S_2, and rapid pacing was fit using the monoexponential equation:

$$y\ (APD_{90}) = y_0 + A_1\ (1 - e^{-DI/\tau_1})$$

where A_1 is the free-fitting variable. With each A_1 and τ_1 at the correspondent DI, the slope was calculated using equation:

$$\text{slope} = (A_1/\tau_1)\cdot[\text{Exp}\ (-DI_1/\tau_1)]$$

The slope of the shortest DI was defined as the maximal slope of the APDR curve (4,14,15).

Spatial dispersion of ERP and MAP recordings. The spatial dispersion of the ERP and APD_{90} during pacing at a BCL of 600 ms was determined from the difference between the maximal and minimal values recorded at six different sites. The spatial dispersion of the maximal slope of the APDR curve was calculated.

Statistical analysis. Results are presented as the mean value ± SD. The Student *t* test was used when appropriate. Analysis of variance with the Newman-Keuls test was used to perform multiple comparisons. A p value <0.05 was considered significant.

RESULTS

Patient characteristics. In patients with CAF (mean age 53 ± 6 years; 14 men and 4 women), the mean left ventricular ejection fraction (LVEF) and left atrial diameter were 62 ± 12% and 43 ± 4 mm, respectively. In patients with PAF (mean age 51 ± 7 years; 11 men and 3 women), the mean LVEF and left atrial diameter were 65 ± 8% and 40 ± 3 mm, respectively. In the control subjects (mean age 50 ± 15 years; 6 men and 3 women), the mean LVEF and left atrial diameter were 67 ± 4% and 38 ± 3 mm,

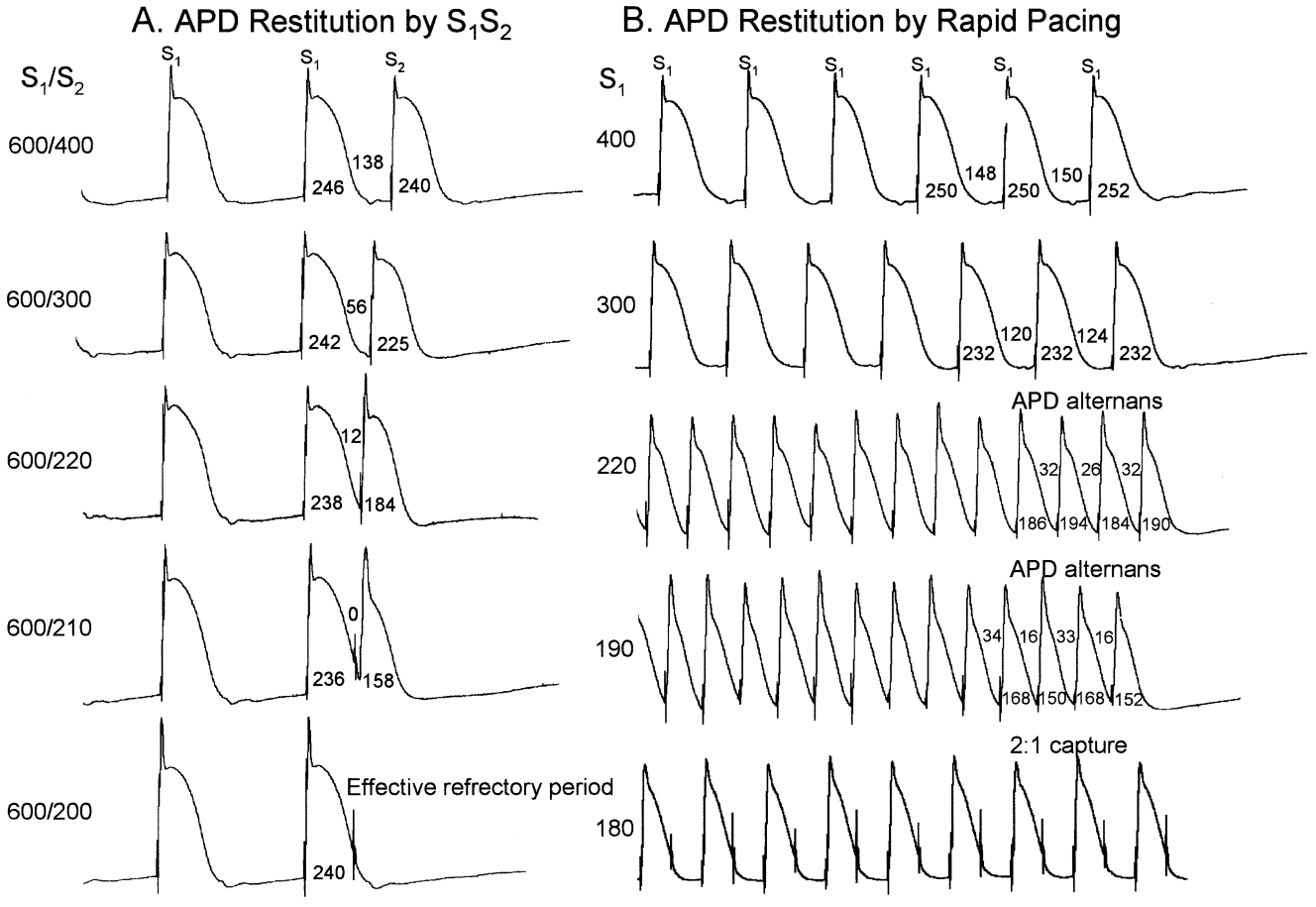

Figure 1. (A) Examples of monophasic action potentials recorded at the high lateral wall of the right atrium by S_1S_2 in patients with chronic atrial fibrillation. A single extrastimulus (S_2) was given at progressively shorter S_1S_2 intervals. As diastolic interval decreased from 138 to 0 ms, the action potential duration (APD) at 90% repolarization decreased from 240 to 158 ms, and then reached the effective refractory period with a coupling interval of 200 ms. **(B)** The right atrium was paced at progressively shorter S_1S_1 intervals until APD alternans and then 2:1 atrial capture failure occurred. Pacing with cycle lengths of 220 and 190 ms resulted in APD and diastolic interval alternans.

respectively. The patients with CAF had a significantly larger left atrial diameter, as compared with patients with PAF or control subjects. There was no significant difference in the left atrial diameters of patients with PAF and control subjects. Hypertension was present as an underlying disease in 10 patients with CAF (56%) and in 3 patients with PAF (21%). The energy requirement for cardioversion in patients with CAF was significantly higher than that in patients with PAF ($p < 0.01$).

Differences between APD_{90} and ERP and their spatial dispersions. The APD_{90} during pacing at a BCL of 600 ms in those with CAF (225.9 ± 15.6 ms) was significantly ($p < 0.05$) shorter than that in patients with PAF (250.3 ± 34.6 ms) or control subjects (258.4 ± 25.1 ms). The APD_{90} values at all of the recording sites, except the HS, were shorter in patients with CAF than in those with PAF or control subjects ($p < 0.05$). The spatial dispersion of APD_{90} values in patients with CAF (26.8 ± 22.2 ms) was no greater than that in patients with PAF (30.1 ± 18.9 ms) or control subjects (29.5 ± 23.6 ms).

The ERP in patients with CAF (211.0 ± 23.8 ms) was shorter than that in patients with PAF (232.5 ± 29.2 ms) or control subjects (227.6 ± 19.4 ms; $p < 0.05$). The spatial dispersions of the ERP in each group were similar (32.4 ± 30.3 ms in patients with CAF, 41.7 ± 27.4 ms in patients with PAF and 32.7 ± 19.2 ms in control subjects).

Properties of APDR and spatial dispersion. Figure 1 shows a representative example of MAPs obtained from the HL by a single S_2 (left panel) and rapid pacing (right panel) in a patient with CAF. As the DI decreased from 138 to 0 ms, the APD_{90} decreased from 240 to 158 ms, and then reached the ERP with a coupling interval of 200 ms. In the right panel of Figure 1, straight pacing with a cycle length of both 220 and 190 ms resulted in APD alternans, and 2:1 block occurred with pacing at a cycle length of 180 ms. Figure 2 shows an example of APDR by a single S_2 in each group. In the patients with PAF, as the DI decreased from 142 to 0 ms, the APD_{90} decreased from 256 to 156 ms and resulted in a change in APD_{90} of 100 ms (middle panel), which was similar to that of patients with CAF (left panel). In the control subjects, the change in APD_{90} was 55 ms as DI decreased from 147 to 0 ms (right panel).

Representative examples of APDR curves by S_1S_2 at the same site of each group are shown in Figure 3. In patients

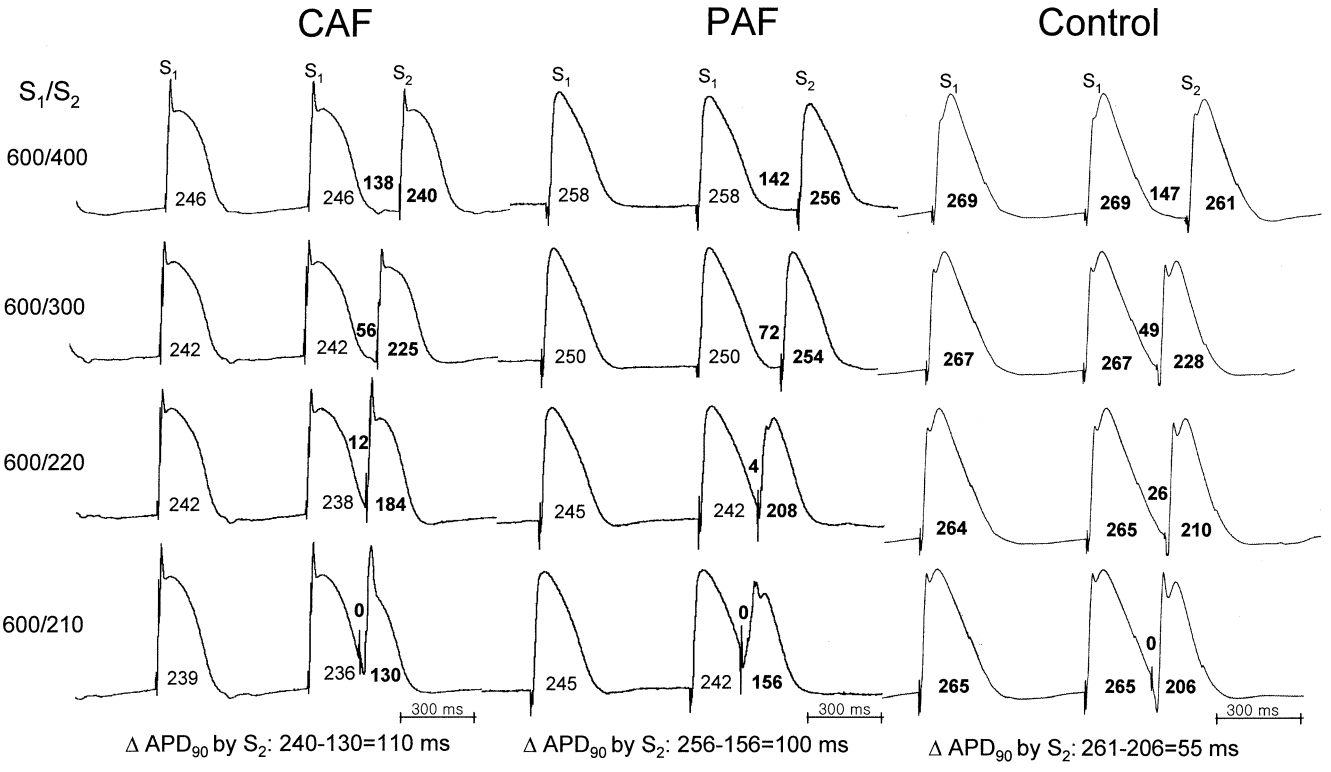

Figure 2. Monophasic action potentials recorded at the high lateral wall of the atrium by S_1S_2 in each group (patients with chronic atrial fibrillation [CAF] in the **left panel**; patients with paroxysmal atrial fibrillation [PAF] in the **middle panel**; and control subjects in the **right panel**). In the patients with CAF and PAF, as the diastolic interval progressively decreased to 0 ms, the changes in action potential duration at 90% repolarization (ΔAPD_{90}) were 110 and 100 ms, respectively. In the control subjects, the change in APD_{90} was 55 ms as the diastolic interval decreased from 147 to 0 ms.

with CAF, the APD_{90} shortened with increasing prematurity of the extrastimulus. As the DI decreased to <30 ms, the APD_{90} shortened by 30 ms, and the maximal slope of the curve was 1.6. In patients with PAF, the change in APD_{90} was 31 ms, and the maximal slope was 1.4. In contrast, in the control subjects, the decrease in the APD_{90} with increasing prematurity was small, which resulted in a flat APDR curve. As the DI decreased to <30 ms, the change in APD_{90} was 23 ms, and the maximal slope was 0.8. Figure 4 shows a representative example of APDR by S_1S_2 and rapid pacing in each patient. The slopes of the APDR curve by rapid pacing in patients with CAF (1.7 ±

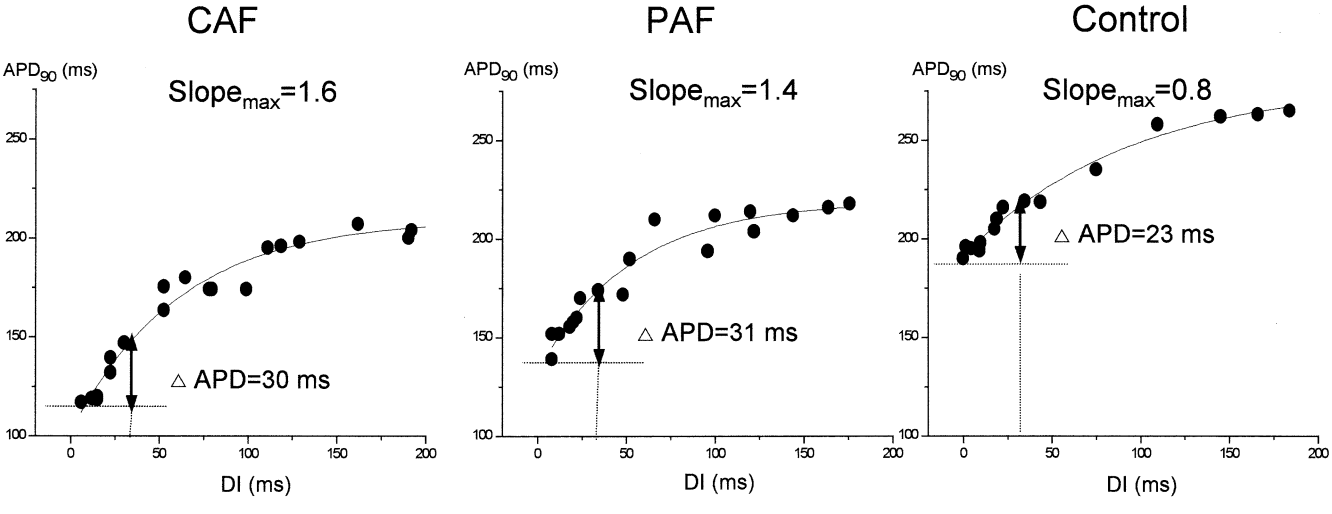

Figure 3. The action potential duration restitution (APDR) curves by S_1S_2 in each group (patients with chronic atrial fibrillation [CAF] in the **left panel**; patients with paroxysmal atrial fibrillation [PAF] in the **middle panel**; and control subjects in the **right panel**). In patients with CAF, action potential duration at 90% repolarization (APD_{90}) shortening became 30 ms as the diastolic interval (DI) decreased to <30 ms (ΔAPD_{90}) and the maximal slope ($Slope_{max}$) was 1.6. In patients with PAF, the change in APD_{90} was 31 ms, and the maximal slope was 1.4. In contrast, the decrease in APD_{90} with increasing prematurity was small in the control group, which resulted in a flat APDR curve ($Slope_{max}$ = 0.8).

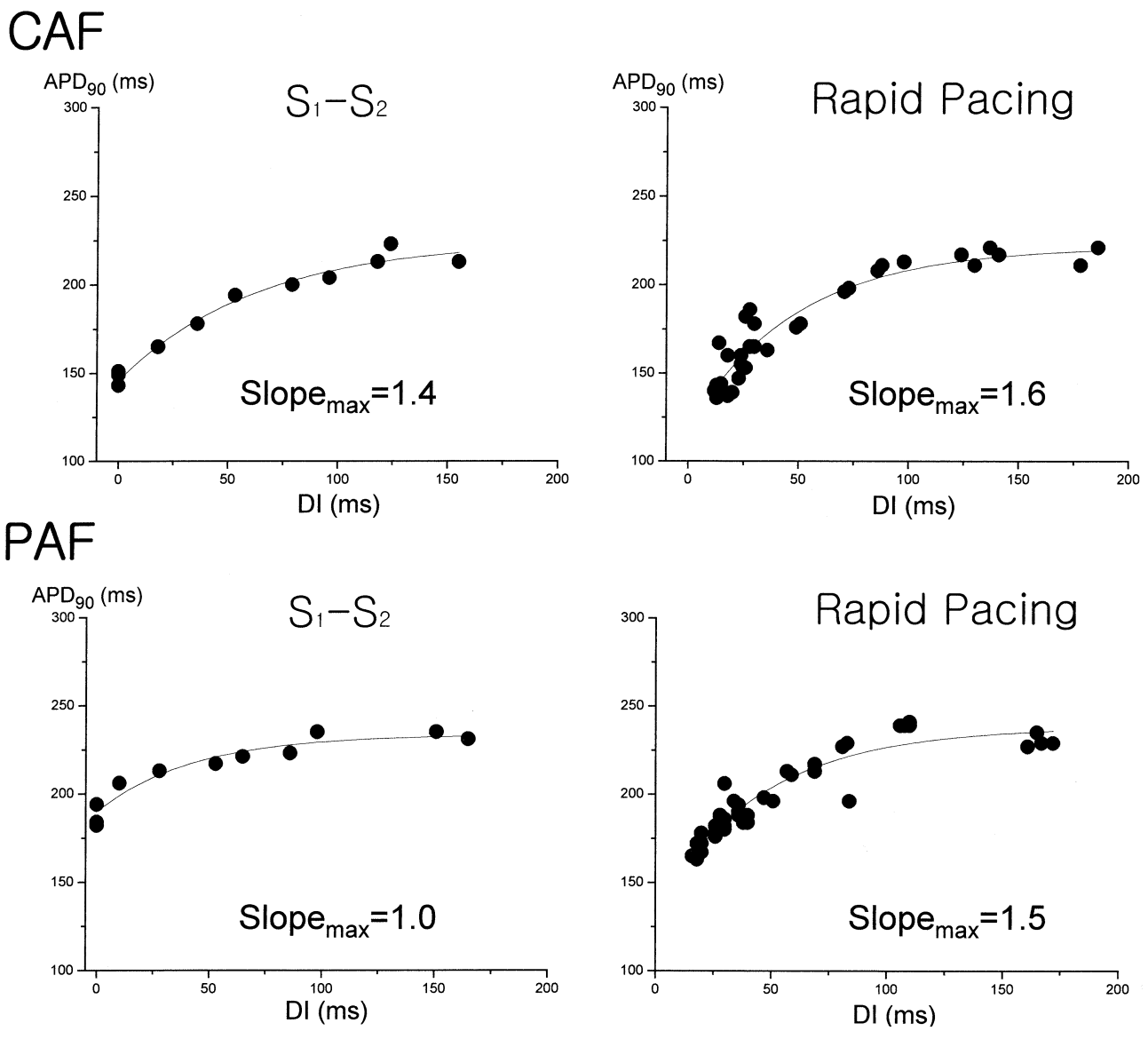

Figure 4. Representative examples of action potential duration restitution (APDR) by S_1S_2 **(left panels)** and rapid pacing **(right panels)**. The slope of APDR by rapid pacing was slightly steeper than that of restitution by S_1S_2 in each patient. APD_{90} = action potential duration at 90% repolarization; CAF = chronic atrial fibrillation; DI = diastolic interval; PAF = paroxysmal atrial fibrillation; $Slope_{max}$ = maximal slope.

0.2) and PAF (1.3 ± 0.4) were steeper that those obtained by S_1S_2, but there was no statistical significance. Overall, the mean slope of the APDR curve by S_1S_2 both in patients with CAF (1.4 ± 0.3) and PAF (1.1 ± 0.4) was significantly greater than that of the control subjects (0.5 ± 0.3, $p < 0.01$). No significant difference was evident between the CAF and PAF groups.

The APDR curves obtained at four different sites (HL, HS, MP and ML) are shown in Figure 5. Shortening of the APD_{90} with a decreasing DI in patients with CAF was greater in the HL and ML regions than in the MP and HS regions, resulting in a spatial dispersion of the maximal slope of 2.1 (lower panel), which was greater than that in patients with PAF (1.7) or control subjects (0.8). Mean spatial dispersion of the maximal slope in patients with CAF (1.6 ± 0.4) was greater than that in patients with PAF (1.2 ± 0.3) or control subjects (0.4 ± 0.2; $p < 0.05$). These observations indicate that the spatial dispersion of APDR in patients with CAF may form the substrate for the persistence of AF.

Validation of APDR by two independent observers. The APDR curves were validated by two independent observers in both the patients with AF and control subjects. There was a measurement error of approximately <10 ms in the APDR curve, and the regional differences in the slope were minimal (≤0.02).

DISCUSSION

Changes in atrial refractoriness of AF. Shortening of the atrial ERP (16–18) and increased dispersion of ERP (11,18–20) have been described in patients with AF. Evi-

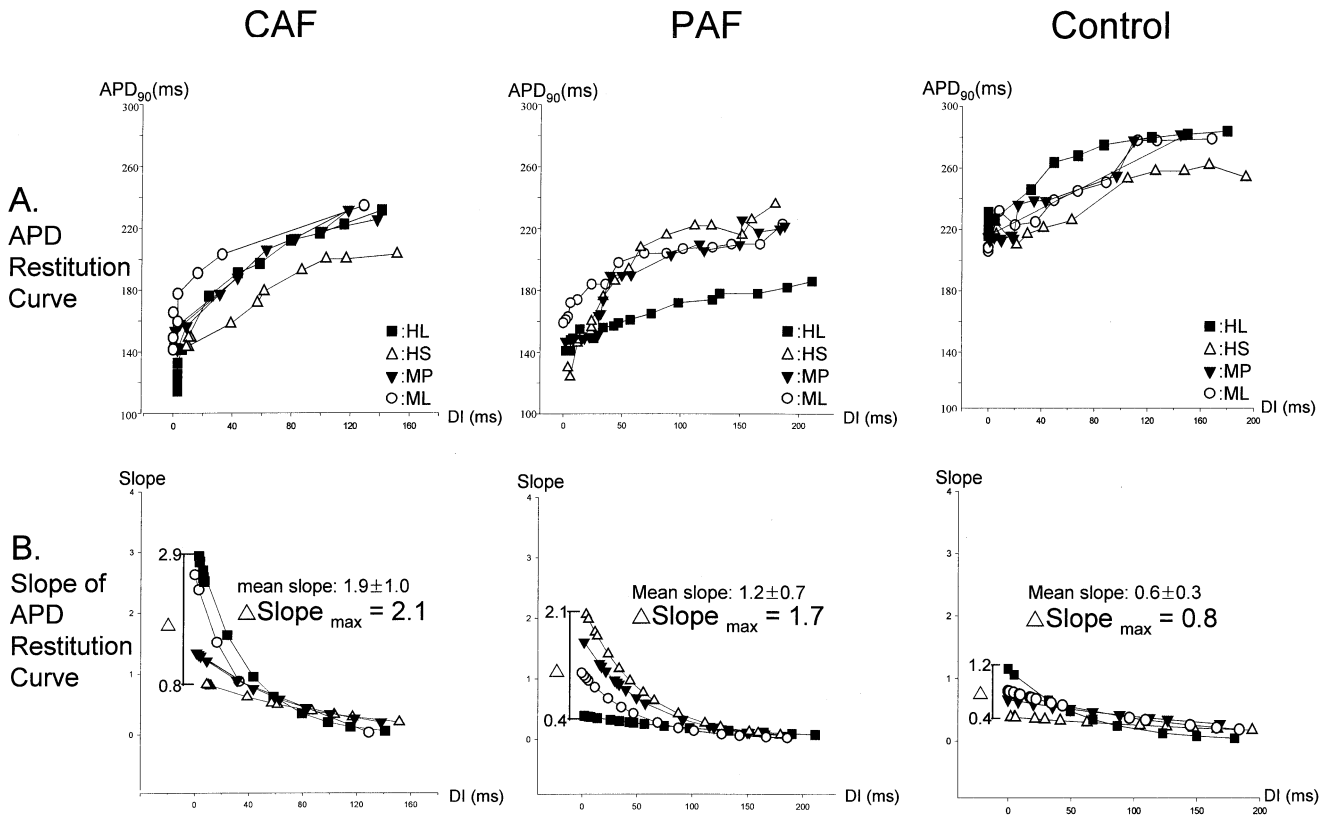

Figure 5. (A, top row) The action potential duration restitution (APDR) curves. **(B, bottom row)** Corresponding nonlinear slopes plotted as a function of DI obtained at four sites of the right atrium (high lateral [HL], high septal [HS], mid posterior [MP] and mid lateral [ML]). Shortening of action potential duration at 90% repolarization (APD_{90}) with decreasing diastolic interval (DI) in patients with chronic atrial fibrillation (CAF) **(left panels)** was greater at the HL and ML sites than at the MP and HS sites, resulting in a change in the maximal slope ($Slope_{max}$) of 2.1. In patients with paroxysmal atrial fibrillation (PAF) **(middle panels)**, $\Delta Slope_{max}$ was 1.7. Regional differences of the APDR curve were not evident in the control subjects **(right panels)**, and resulted in a $\Delta Slope_{max}$ of 0.8.

dence for AF-induced remodeling in the human atrium has been presented (21–23). These studies demonstrated that the monophasic APD_{90} or ERP in patients who had cardioversion of CAF was significantly shorter than that in control subjects. Furthermore, abnormal adaptation of the ERPs in relation to a change in the cycle length has been observed (18,24,25). Fareh et al. (11) reported that an increase in the regional heterogeneity of the ERP in the different parts of the atrium played an important role in enhancing vulnerability to AF, whereas the ERP, per se, was not a significant determinant. The ionic mechanisms responsible for the alterations in atrial ERP have been demonstrated in a canine model of AF (26), but regional variations in the ERP of patients with AF, as well as their mechanisms, are still unclear.

The present study has shown that the dispersion of atrial refractoriness in patients with CAF was not greater than that in patients with PAF or control subjects. This finding is in agreement with the results of previous studies (11,24) and may be due to a general shortening of the ERP in patients with CAF.

Electrical restitution properties in the atrium. A wave break is known to be one of the important mechanisms responsible for the maintenance of fibrillation and is associated with steeply sloped (>1) restitution kinetics (4,27). In contrast, if the slope is <1, perturbations in the APD and DI are damped, rather than amplified, which resists a wave break.

The present study has shown that the maximal slope of the APDR curve is significantly steeper in patients with CAF and PAF than in control subjects. These results are inconsistent with the results of a study by Hara et al. (14), who found that the slope of the APDR curves in canine atria with sustained and nonsustained AF was smaller (<1) than that of normal atria. These conflicting results can be explained: First, Hara et al. (14) recorded action potentials at only two sites—Bachmann's bundle and the trabeculae. In this study, the slope of the APDR curve was found to show inter-regional variation, indicating that the APDR obtained at a single site or two sites does not represent the whole atria. Second, there are important differences between the pacing model of the fibrillating canine atria (pacing for 5 weeks) and that of the chronically fibrillating human atria. In the pacing model of AF, there are no differences in the steady-state action potentials or APDR between sustained and nonsustained AF, suggesting that it is less likely that alteration of the cellular electrophysiologic mechanisms with pacing is associated with chronic remodeling of the cellular structure.

We suggest that a steep slope of the APDR curve in patients with AF may be associated with frequent occurrence of a wave break, resulting in the initiation or perpetuation of fibrillation, or both. In contrast, in the ring model of atrial re-entry, Frame and Simson (28) described that a steep slope (>1) favored large cycle length oscillations and termination of re-entry, whereas a flat slope decreased oscillations and improved the stability of re-entry. If stable re-entry is an important mechanism by which fibrillation perpetuates, a chronically fibrillating atrium may show a flat slope, as shown in the study by Hara et al. (14). However, it remains to be determined whether stable re-entry plays an important role in the maintenance of fibrillation, or whether the fibrillation is terminated if this re-entry is halted.

Restitution of the APD during pacing at a cycle length of 600 ms might not account for APD dynamics during AF, because it is difficult to extrapolate the slope of the restitution curve from the lower rates to the ultra-high rates present during AF. It is demonstrated that dynamic pacing (pacing at progressively faster rates until 1:1 capture fails) is relevant to fibrillation and is superior to the S_1S_2 method in terms of estimating restitution (15). The time course of changes in APD after a sudden, sustained change in the cycle length is "rate adapted," rather than "restituted" (29). During APD alternans induced by rapid pacing, a short DI sequence generates a short APD sequence, which is also linked to the slope of the restitution relationship. In this study, the maximal slope of the restitution curve by S_1S_2 was lower than that obtained using the dynamic protocol, but there was no statistical difference. Therefore, our findings indicate that APD dynamics in patients with AF can be explained by a single extrastimulus in the restitution relationship, as well as by dynamic pacing that induced APD alternans.

Heterogeneity of restitution in the atrium. Laurita et al. (30) reported that restitution properties vary when measured at hundreds of sites across the ventricle. This spatial heterogeneity creates critical gradients or a dispersion of repolarization and results in the modulation of the electrophysiologic substrate for re-entrant arrhythmias and vulnerability to fibrillation.

In the present study, inter-regional differences in the APDR curves were greater in patients with CAF than in those with PAF or control subjects. Thus, spatial dispersion of APDR may relate to the perpetuation of AF. However, the electrophysiologic basis of the nonuniform APDR properties remains unclear and requires further study.

Study limitations. First, the limitations of fluoroscopic guidance for electrode placement, as well as the difficulties of electrode manipulation, did not allow us to record the numerous MAPs from a precisely defined region of the endocardial surface. Second, in patients with CAF, the total energy required for cardioversion was higher than that in patients with PAF. We cannot exclude the possibility that the electrophysiologic changes might be related to the amount of direct current energy. Third, the episodes of AF in the PAF group lasted from 1 to 48 h, and this wide range of AF persistence may have affected the results. Fourth, the number of patients in each group was too limited to allow our findings to be uncritically extrapolated to all patients with AF. Finally, whether normalization of the spatial heterogeneity of APDR in the atrium can have an antifibrillatory effect, and thus prevent or terminate AF, remains unclear.

Conclusions. The slope of APDR in patients with CAF and PAF is steeper than that of control subjects. The APDR in patients with CAF is spatially nonuniform, and this contributes to the perpetuation of AF.

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