

Electrical Remodeling of the Human Atrium: Similar Effects in Patients With Chronic Atrial Fibrillation and Atrial Flutter

MICHAEL R. FRANZ, MD, PhD, FACC, PAMELA L. KARASIK, MD, CUILAN LI, PhD,
JEAN MOUBARAK, MD, MARY CHAVEZ, CVT
Washington, D.C.

Objectives. This study sought to determine whether chronic atrial fibrillation (AF) and atrial flutter in patients lead to electrical remodeling of the human atrial myocardium, manifested by an abnormal relation between atrial cycle length and action potential duration (APD).

Background. Experimental studies in goats and isolated human atrial tissue have shown that prolonged AF leads to persistent shortening of atrial refractoriness, a phenomenon referred to as electrical remodeling and which helps to explain why AF begets AF. Direct data on human in situ myocardium are still lacking.

Methods. Using monophasic action potential recordings at two right atrial sites simultaneously, we determined in 7 patients with chronic AF and 13 with chronic atrial flutter (3 weeks to 3 years in duration) the relation between paced cycle length and APD at 90% repolarization (APD90) 15 to 30 min after conversion to sinus rhythm. APD90 was measured during regularly paced cycle lengths (250 to 800 ms) to determine the steady state cycle length relation and during extrastimulus intervals (from 800 ms to refractoriness) at a basic cycle length of 600 ms to determine electrical restitution curves. The same pacing protocols and measurements were performed in nine control patients with sinus rhythm and no overt atrial disease.

Results. In control patients, steady state APD90 increased steadily with increases in cycle length from 250 to 800 ms,

reaching a maximal value of 325 ± 41 ms (mean \pm SD) at a cycle length of 800 ms. In patients with cardioversion from atrial flutter or AF, the steady state cycle length-APD90 relation was shifted downward and flattened at cycle lengths >400 ms, reaching only 219 ± 44 and 245 ± 39 ms, respectively, at the 800-ms cycle length ($p < 0.005$ vs. control). The early time course of electrical restitution (200- to 300-ms extrastimulus intervals) was similar between all three groups, but at extrastimulus intervals >350 ms, APD90 was shorter in both the AF and atrial flutter groups than in the control group ($p < 0.05$). There were no significant differences between patients with cardioversion from atrial flutter and those with cardioversion from AF. APD90 at a steady state cycle length of 600 ms showed no significant correlation with the duration of previous AF or atrial flutter.

Conclusions. AF and atrial flutter lead to marked, quantitatively similar decreases in the right atrial APD during steady state pacing and extrastimulation a considerable time after cardioversion. These data confirm that both AF and atrial flutter lead to electrical remodeling in the human atrium, with a preponderance at longer cycle lengths. It may be prudent to abort both types of arrhythmias early to prevent electrical remodeling.

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Clinical experience suggests that atrial fibrillation is a self-promoting electrical disease. Paroxysmal atrial fibrillation (AF) frequently progresses to chronic AF (1,2), and sinus rhythm becomes less sustainable after electrical or pharmacologic conversion of AF the longer AF lasts (3-5). Although underlying anatomic or pathophysiologic factors (2,6-10) may fuel the progression from paroxysmal to chronic AF, recent data suggest that AF itself may lead to its own progression and, eventually, chronic manifestation. Wijffels et al. (11) showed in

conscious goats that the more frequently AF is induced or the longer AF is maintained, the more easily inducible and the more sustained AF becomes. This finding led Wijffels et al. to coin the term "electrical remodeling." Their study (11) further demonstrated that the increased propensity for AF, conditioned by AF, was associated with an abnormal rate adaptation of the atrial effective refractory period compared with its pre-AF baseline state, thus providing a possible explanation for why "AF begets AF". Recently, Daoud et al. (12) showed in humans that just several minutes of electrically induced AF shortens the atrial effective refractory period for up to 8 min and that this shortening correlates with an increased propensity for the induction of secondary AF.

There has not yet been a systematic investigation of how

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Address for correspondence: Dr. Michael R. Franz, Cardiology Division, Veteran Affairs Medical Center, 50 Irving Street, NW, Washington, DC 20422. E-mail: mfranz@washington.va.gov.

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Abbreviations and Acronyms

AF	= atrial fibrillation
APD	= action potential duration
APD90	= action potential duration at 90% repolarization
AV	= atrioventricular
MAP	= monophasic action potential

chronic clinical AF may alter the normal relation between cycle length and action potential duration (APD) in the human atrium. The same information is lacking for chronic atrial flutter. Clinical data (1) suggest that atrial flutter if untreated may eventually lead to AF. It is plausible to assume that atrial flutter also leads to electrical remodeling and by doing so may facilitate degeneration into AF (13). Therefore, the present study sought to determine whether and to what extent atrial electrical remodeling develops in patients with either chronic AF or atrial flutter. To this end, we determined the relation between paced cycle length and right atrial monophasic APDs 15 to 30 min after cardioversion from either chronic AF or atrial flutter. These data were obtained over the entire range of regularly pacable cycle lengths as well as during extrastimulation to define both the steady state rate adaptation and electrical restitution curves. A control group with sinus rhythm and no overt atrial disease was studied for comparison.

Methods

Patients. The study was performed at the Veteran Affairs Medical Center, Washington, D.C. and included 29 consecutively enrolled male patients. The pertinent clinical and electrophysiologic features are presented in Table 1. All patients underwent electrophysiologic study after signing an informed consent form that was approved by our institution's committee on human investigation. No patient received antiarrhythmic drugs 5 half-times before the study. Nine patients were in sinus rhythm, had no known atrial or valvular disease and had structurally normal atria. These patients were evaluated for paroxysmal atrioventricular (AV) node reentrant tachycardias or ventricular tachycardia and constituted the control group. Seven patients had chronic AF known to have lasted from 3 weeks to 3 years, and 13 patients had atrial flutter 0.8 to 32 months in duration. These patients underwent electrical cardioversion in the electrophysiology laboratory, either by overdrive pacing or transthoracic shock. Preexisting anticoagulation therapy with Coumadin was replaced by heparin 1 to 3 days before the study. Data on left atrial diameter and left ventricular ejection fraction were obtained by echocardiography or angiography, respectively, 1 to 5 days before the electrophysiologic study.

All patients underwent instrumentation with two monophasic action potential (MAP) pacing catheters (EP Technologies, Inc.) (14), one placed at the high right atrium and the other at

the low right atrium. In all patients, MAPs were recorded during sinus rhythm (control patients) or during AF or atrial flutter before cardioversion to assess the average cycle length and APD for each group.

Cardioversion. In all patients with atrial fibrillation, cardioversion was performed with a transthoracic electrical shock of 200 to 360 J. In 3 of the 13 patients with atrial flutter, cardioversion was performed by rapid overdrive pacing that resulted in cardioversion within 1 to 2 min. In seven patients in whom overdrive pacing was unsuccessful despite attempts for 5 min (AF occurred in three of them), cardioversion was achieved by transthoracic shock. In the remaining three patients, atrial flutter was terminated by radiofrequency catheter ablation that targeted the isthmus between the inferior vena cava and the tricuspid valve ring.

Pacing protocols. After restoration of sinus rhythm, a 15-min waiting period was observed to allow short-term rate-dependent changes in APD to dissipate (15). Pacing with twice diastolic threshold stimuli was then begun from the MAP pacing catheter positioned in the high right atrium. Two pacing protocols were applied in the following sequence.

Steady state pacing. Pacing was begun at the longest cycle length that was not interrupted by escape beats. After 1 min of regular pacing, the cycle length was decremented by 100 ms without intermittent pause, and this sequence was repeated until a cycle length of 300 ms was reached. The last decrement was 50 ms, resulting in a minimal steady state cycle length of 250 ms.

Extrastimulation. The purpose of this protocol was to define the electrical restitution curve, which is known to characterize the short-term recovery of the APD from 1 beat to the next (15-17). The atrium was paced at a basic cycle length of 600 ms, and an extrastimulus was applied at varying coupling intervals to the last regular beat, starting with the longest S1-S2 interval possible without escape beats. The S1-S2 intervals were decremented in 50-ms steps until an S1-S2 interval of 400 ms. A subsequent decrement of 20 ms was used until an S1-S2 interval of 250 ms and a decrement of 10 to 5 ms until atrial refractoriness occurred. Each S1-S2 interval followed 12 regular stimuli at the basic cycle length of 600 ms with a subsequent 1-s pause and was repeated once to ensure data reproducibility. Both protocols were completed within 15 min without needing to change the catheter positions.

Measurements and data analysis. MAP recordings and a simultaneous 12-lead electrocardiogram were acquired continuously in digital format on a magneto-optical disk using a BARD electrophysiology system (USCI). An example of two simultaneous MAP recordings during pacing at three different steady state cycle lengths is shown in Figure 1. After the study, data were downloaded onto a Macintosh computer hard disk and converted into Macintosh binary format for off-line signal processing and data analysis. Signals during steady state and extrastimulus pacing were analyzed for cycle length and monophasic APD at 90% repolarization (APD90) with a custom-developed software algorithm written in LabVIEW language (National Instruments). This automated algorithm

Table 1. Selected Clinical and Electrophysiologic Features of Study Patients*

	Age (yr)	Arrhythmia Dx	LA Size (mm)	LVEF (%)	AF/Aflut Duration (mo)	Conv Mode	Sinus CL
Control Patients							
	60	VT					1,204
	73	VT	40	25			910
	67	VT	37	60			830
	66	VF	34	35			850
	81	VT	35	22			672
	70	Syncope	40	65			712
	61	AV block	32	20			752
	73	NSVT	38	45			614
	49	AVNRT	42	55			680
Mean	66.67		37.3	40.9			802.7
SD	9.26		3.4	17.9			178.2
Patients With Atrial Flutter							
	65	Typical	44	56	N/A	DCshock	680
	63	Typical	32	55	4	DC shock	600
	62	Atypical	40	55	12	DC shock	888
	63	Typical	40	45	8	Ablation	645
	48	Typical	50	25	24	Ablation	790
	82	Typical	31	45	4	DC shock	1,152
	62	Typical	51	38	1	Pace out	1,200
	65	Typical	39	50	9	Pace out	974
	82	Typical	37	45	32	DC shock	790
	66	Atypical	42	60	0.8	DC shock	640
	69	Typical	34	55	1	Ablation	740
	57	Typical	38	21	2	Pace out	670
	72	Atypical	37	50	4	DC shock	797
Mean	65.8		39.6	46.2	8.5		812.8
SD	11.0		6.8	13.1	11.4		202.0
Patients With Atrial Fibrillation							
	64		45	20	18	DC shock	830
	70		37	40	1	DC shock	600
	72		50	40	0.75	DC shock	615
	79		40	20	36	DC shock	804
	54		46	29	9	DC shock	1,030
	64		42	15	1	DC shock	800
	63		35	60	3	DC shock	655
Mean	66.6		42.1	32.0	9.8		762.0
SD	8.0		5.3	15.8	13.1		152.2

*Mean age, left atrial (LA) size and postcardioversion sinus cycle length (CL) were not significantly different between the three groups. AF = atrial fibrillation; Aflut = atrial flutter; Conv = conversion; DC = direct current; Dx = diagnosis; LVEF = left ventricular ejection fraction; N/A = not applicable; Pace out = termination of atrial flutter by overdrive pacing.

has been validated previously by two independent manual observers and shown to be accurate and reliable (18).

Effect on APD90 of duration of AF and atrial flutter before cardioversion. To examine the influence of the time during which patients had been in either AF or atrial flutter before cardioversion, the steady state APD90 at a paced cycle length of 600 ms (taken from the dataset of the first protocol) was plotted against the duration of the preexisting arrhythmia.

Statistical methods. Graphical representations of APD90 values are presented as mean value \pm SD. Both the steady state and S1-S2 APD90 values are presented for the three

groups for cycle lengths up to 800 ms because at longer cycle lengths, missing values due to escape beats prevented statistical comparison. To examine differences between patients with atrial flutter or AF and control subjects, repeated measures analysis of variance was performed with the diagnostic category as a three-level between-subjects factor and the pacing cycle length as a seven-level within-subjects factor (250, 300, 400, 500, 600, 700, 800 ms). Significant main and interaction effects were further examined with post hoc analyses of variance at each separate cycle length. A p value <0.05 was considered statistically significant. The effect of the duration of AF and atrial flutter on

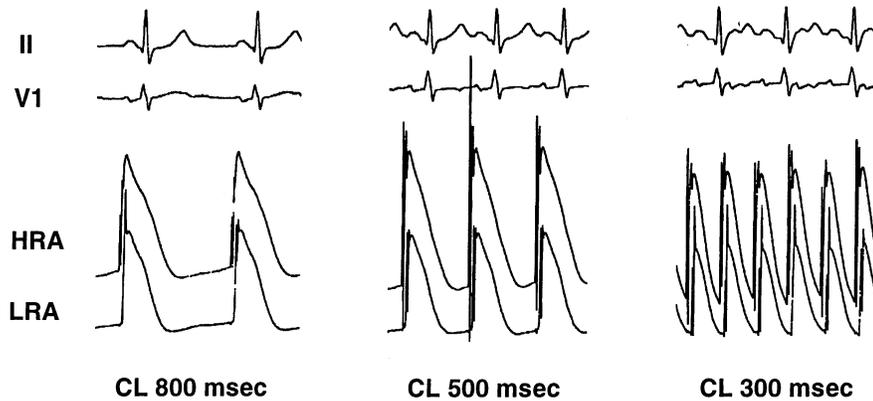


Figure 1. Example of original electrocardiographic (leads II and V₁) and MAP recordings obtained simultaneously at the high (HRA) and low (LRA) right atrium during steady state pacing at three different cycle lengths (CL).

the extent of APD₉₀ at a selected cycle length of 600 ms was evaluated by simple linear regression analysis.

Results

Clinical data. There were no significant differences in left ventricular ejection fraction and left atrial size between the three groups. Patients with previous AF had a nonsignificant trend toward a lower left ventricular ejection fraction than patients with previous atrial flutter and control patients.

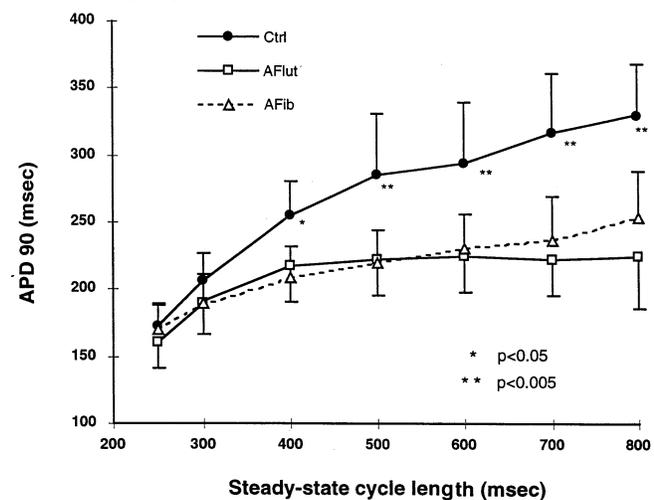
Spontaneous cycle length and APD₉₀ after cardioversion. All control patients had regular sinus rhythm with cycle lengths at the time of study, ranging from 672 to 1,204 ms. Spontaneous sinus cycle lengths in patients with conversion from AF or atrial flutter before the start of the steady state and extrastimulus pacing protocols were not significantly different from those in the control group (Table 1).

Steady state relation between cycle length and APD₉₀. After each 100-ms decrement in cycle length, APD₉₀ achieved a new steady state within ~30 to 40 s. The last 5 beats at each cycle length before switching to the next shorter cycle length at 60 s were analyzed to obtain a representative steady state for each cycle length. This analysis was done for both right atrial recordings, and the values for both atrial sites were averaged to produce steady state plots of APD₉₀ versus cycle length (Fig. 2). In control patients, APD₉₀ increased steadily with increases in the paced cycle length, reaching values of 325 ± 41 ms at a paced steady state cycle length of 800 ms. In contrast, in patients with cardioversion from AF or atrial flutter, the curve describing the relation between APD₉₀ and cycle length was shifted downward and flattened, exhibiting a markedly shorter APD₉₀ at cycle lengths between 400 and 800 ms. Statistically significant shortening of APD₉₀ started to occur at cycle lengths of 400 ms ($p = 0.015$) and was substantially greater at longer cycle lengths ($p < 0.005$). At the longest cycle length of 800 ms, APD₉₀ was approximately 130 to 150 ms shorter in the AF and atrial flutter groups than in the control group. There were no significant differences in APD₉₀ between patients with cardioversion from atrial flutter and those with cardioversion from AF at any of the paced cycle lengths.

Electrical restitution curves. APD₉₀ in response to variable extrastimulus intervals during the 600-ms basic cycle length pacing was plotted as a function of the respective S1-S2 interval. The longest S1-S2 coupling interval without escape beats ranged from 750 to 1,200 ms, and the shortest S1-S2 interval (effective refractory period) ranged from 185 to 210 ms. Each extrastimulus interval was repeated, and the respective responses of both right atrial sites were averaged to construct electrical restitution curves (Fig. 3). The early time courses of the electrical restitution curves were nearly identical for the three groups. However, significant separation occurred at S1-S2 intervals >350 ms, at which APD₉₀ was shorter in patients with previous atrial flutter or AF than in control subjects.

Effect of duration of AF or atrial flutter on postcardioversion steady state APD₉₀. To examine whether the length of time during which patients had been in either atrial flutter or AF before cardioversion had an impact on the extent of electrical remodeling, APD₉₀ at a paced steady state cycle

Figure 2. Average APD₉₀ \pm SD plotted as a function of steady state cycle length. Asterisks denote significant differences in average APD₉₀ of patients with AF (AFib) and atrial flutter (AFlut) versus control patients. There were no significant differences between the AF and atrial flutter groups.



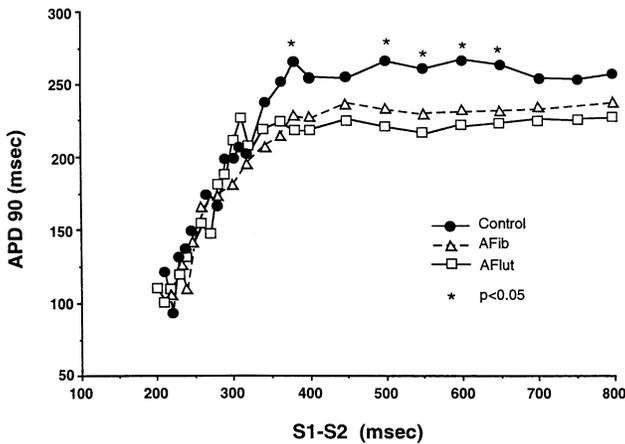


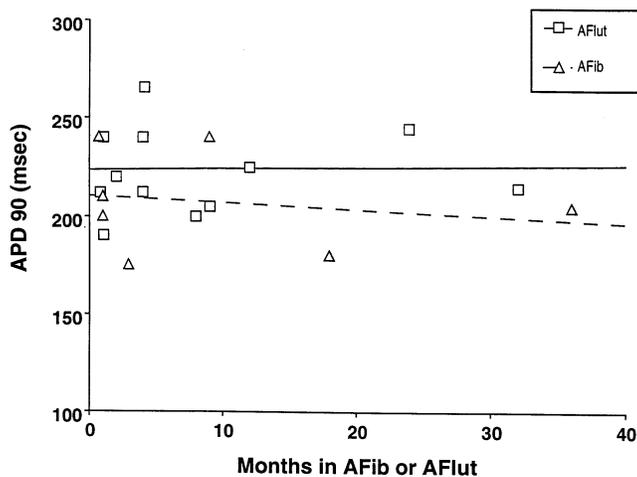
Figure 3. Average APD90 plotted as a function of S1-S2 intervals at a basic cycle length of 600 ms (electrical restitution curves). Standard deviation bars are omitted for clarity. Asterisks denote significant differences in average APD90 of patients with AF (AFib) and atrial flutter (AFlut) versus control patients. There were no significant differences between the AF and atrial flutter groups.

length of 600 ms was plotted against the duration of the preexisting atrial tachyarrhythmia (Fig. 4). There was no significant influence of the duration of either atrial flutter or AF on APD90.

Discussion

The present study produced the following main findings: 1) Sustained AF and atrial flutter both resulted in pronounced changes of the human in situ atrial APD measured during steady state pacing 15 to 30 min after cardioversion to sinus

Figure 4. Steady state APD90 at a cycle length of 600 ms plotted as a function of the duration of the preexisting AF (AFib) or atrial flutter (AFlut) (lines represent simple regression lines). For the study range of 3 weeks to 3 years, there was no significant influence of the duration of the preexisting atrial tachyarrhythmia on the extent of electrical remodeling.



rhythm. Patients with conversion from AF or atrial flutter had markedly depressed and flattened atrial APD-cycle length relations, which contrasted significantly with the APD-cycle length relation measured in the control patients (sinus rhythm) in whom the APD showed a continuous prolongation with each increase in cycle length. 2) Despite the slower rate of atrial flutter than AF, alterations in APD were similar in both the AF and atrial flutter groups. 3) The duration of previous AF or atrial flutter (range 3 weeks to 36 months) was found to have no significant impact on the extent of APD shortening after cardioversion.

Steady state adaptation of APD. It is well known that the APD and the associated refractory period bear a close relation to the cardiac cycle length. In most species, including humans, the APD increases linearly with cycle length, to reach a plateau at cycle length ≥ 800 ms (15,19). An abrupt decrease in cycle length leads to a rapid shortening of the APD and the associated refractory period, which reaches a new steady state within < 3 min. However, this short-term effect of cardiac rate memory dissipates equally rapidly on a return to the baseline cycle length (15,20,21). In contrast, in the study by Wijffels et al. (11) the refractory period shortening and flattening of the refractory period-cycle length relation curve caused by AF was still prevalent hours after conversion to sinus or regularly paced rhythm. This refractory period shortening was observed over the entire range of paced cycle lengths, resulting in a flat or even inverted curve of the refractory period-cycle length relation.

In the present study in patients, the normal rate adaptation curve of atrial action potentials (control patients) was very similar to that previously reported for ventricular action potentials in humans, which also showed a gradual and nearly linear increase in APD90 with increasing steady state cycle length (15). In contrast, patients with cardioversion from either AF or atrial flutter had nearly flat rate adaptation curves. The most marked lack of rate adaptation was observed during steady state pacing at long cycle lengths.

These human data correspond well with those reported by Wijffels et al. (11), who found that in conscious goats that had no previous atrial disease and were submitted to electrically induced AF, the atrial refractory period shortened, and the entire rate adaptation curve flattened or even inverted. Although we did not see inversion of the APD90-cycle length relation in human atria, the inversion of the refractory period-cycle length curves shown in several goats in the study by Wijffels et al. (11) may be explained by the fact that those individual animals had a less steep increase in the refractory period toward long cycle lengths compared with other animals or our control patients. Wijffels et al. (11) also showed that there was a fairly good correlation between the development of maladaptation of the atrial refractory period and the probability that a premature stimulus would provoke sustained AF. In an earlier clinical study Attuel et al. (22) found that patients in whom sustained atrial tachyarrhythmias could be induced by one to three extrastimuli had a poor or missing rate adaptation of the atrial refractory period as determined by pacing at three

or more different basic cycle lengths. Boutjdir et al. (23) measured the adaptation of the APD to changes in cycle length in isolated strips of human atrial myocardium and also found maladaptation in the myocardium of patients prone to AF. Clinical and experimental studies (23,24) have demonstrated that patients with recurrent AF have shorter atrial refractory periods than control patients and patients without recurrence of AF. These combined findings suggest that the shortening of the refractory period or APD and the loss of physiologic rate adaptation may be both the result and a mitigating factor of AF.

That the duration of either AF or atrial flutter was of no significance with regard to electrical remodeling may be explained by the fact that all patients in this study had had one of these atrial tachyarrhythmias continuously for at least 3 weeks. This duration may be sufficient or even exceed the time required to manifest the electrophysiologic changes by a sustained dramatic increase in atrial activation frequency. Goette et al. (25) showed that in conscious dogs submitted to rapid pacing, significant electrical remodeling occurs within 12 h.

Electrical restitution curves. It is well established that the electrical restitution curve (16) extracts information about short-term recovery processes of myocardial ion channels as opposed to long-term or steady-state changes (17,21,26). The early phase of electrical restitution (at S1-S2 intervals <180 to 300 ms) was not significantly different between patients with either previous AF, atrial flutter or sinus rhythm. This finding suggests that the processes that govern the short-term recovery of the APD at very short cycle lengths are unchanged by a history of either sustained atrial flutter or AF and that perhaps APD shortening at such short intervals has "bottomed out." However, at extrastimulus intervals >350 ms, electrical restitution curves in both AF and atrial flutter groups fell well below that of the control group (Fig. 4). Thus, electrical remodeling by either AF or atrial flutter is most notable at long cycle lengths.

Mechanisms underlying electrical remodeling. Adaptation of the APD or refractory period to increases in rate is physiologic and follows a rapid and fully reversible time course (15,19). In contrast, AF and atrial flutter lead to excessive shortening and delayed recovery. During rapid rates of depolarization, the proportion of depolarized state versus repolarized state shifts in favor of the depolarized state. This shift may cause a net increase in inward calcium current and subsequent intracellular calcium ion load, which in turn can accelerate repolarization by inhibiting the L-type calcium inward current (27) and enhancing the delayed rectifier current (I_K) (28). Chronic AF and atrial flutter and other forms of rapid atrial tachyarrhythmias (ectopic atrial tachycardia, AV node reentrant tachycardia) may cause this physiologic mechanism to overshoot or become irreversible. Direct evidence supporting the role of calcium ion overload as part of the electrical remodeling process was recently provided (25). Additional mechanisms may involve imbalance between perfusion and metabolic demand of the atrial myocardium, resulting in

ischemia-related action potential shortening (29), stretch of atrial myocardium (30) and electrolyte or yet unknown intrinsic cardiomyopathic changes. The slow time course of the development of and recovery from electrical remodeling might also suggest modulation of ion channel expression. Yue et al. (31) showed that after 1 to 7 days of rapid pacing in canine hearts, the transient outward current (I_{to}) and L-type Ca^{2+} current were greatly reduced, and Van Wagoner et al. (32) found that atrial myocytes excised from patients with chronic AF had decreased density of outward potassium channels.

We cannot exclude that in our patients with atrial flutter and AF, the underlying anatomic or pathophysiologic substrate caused the electrical problem to some extent. In studies of animals subjected to chronic atrial tachycardia, likewise, the electrophysiologic abnormality may have developed subsequent to an abnormal mechanical or ischemic myocardial state. Thus, it may not be entirely possible to resolve the chicken-egg problem in this area. However, marked electrical remodeling was found in previously healthy goats (11), and in our patients the underlying heart disease or duration of AF/atrial flutter (Fig. 4) was not a significant determinant of the extent of electrical remodeling, suggesting that the abnormally rapid rate of atrial depolarization itself was an important factor.

Atrial flutter versus AF. AF and atrial flutter are considered to be relatively disparate clinical entities in that particular, anatomically favored reentry mechanisms are thought responsible for both typical and atypical flutter (33), whereas AF may occur in enlarged atria that provide a greater opportunity for multiple wavelets to coexist or when the wavelength of atrial excitation is shortened by disease or autonomic and pharmacologic influences (34,35). The cycle length of atrial flutter is usually significantly longer than that of AF. Typical atrial flutter is characterized by cycle lengths of ~200 ms, whereas atypical atrial flutter has cycle lengths averaging 150 to 220 ms (36). AF in the human heart is characterized by even shorter (~136 to 174 ms) cycle lengths (37).

These differences in excitation cycle length between AF and atrial flutter might be expected to produce quantitatively different long-term effects on the APD of atrial myocardium. However, this was not evident from our study, which showed quantitatively similar abnormalities in APD after cardioversion in patients with conversion from either AF or atrial flutter. One possible explanation might be that the cycle length of atrial flutter is sufficiently short to induce these persistent changes in APD and that the shorter cycle length during AF adds no further challenge to the mechanism or mechanisms responsible for electrical remodeling of the atrial myocardium.

APD90 versus refractory period measurements. Most previous studies on the effect of AF or other atrial tachycardias (spontaneous or electrically induced or maintained) used measurements of the effective refractory period to assess the effect of electrical remodeling. For the following reasons we chose to measure instead the monophasic APD as a more direct method of assessing electrical remodeling of AF/atrial flutter: 1) Using the MAP pacing catheter, it was shown that the APD90 correlates very closely with the effective refractory

period over the entire physiologic cycle length range (45) and thus serves as a valid surrogate of the effective refractory period. 2) APD90 measurements with this method can be made continuously during the pacing protocol and do not require the introduction of a series of scanning extrastimuli, as is needed for determinations of the refractory period. Such repeated extrastimuli by themselves may perturb the measurement objective (38) or even risk unwanted induction of AF or atrial flutter that would require electrical cardioversion and further disturb steady state conditions. 3) Disease conditions (39,40) or antiarrhythmic drugs with sodium channel blocking activity (41-46) may result in postrepolarization refractoriness, which alters the normal relation between APD and refractoriness. Although the disparity between repolarization and refractoriness is of importance in many situations, we judged that measurements of APD90 would provide a "cleaner," more unperturbed measure of the effect of electrical remodeling.

Clinical implications. The present study demonstrates in patients that chronic AF or atrial flutter leads to electrical remodeling of the human atrial myocardium, as identified by markedly abbreviated APDs as late as 15 to 30 min after cardioversion. This finding may help to explain the high recurrence rate of atrial tachyarrhythmias in these patients. Persistent shortening of the atrial APD (and the associated refractory period) after cardioversion from chronic atrial flutter or AF has important clinical implications. A shorter refractory period results in a shorter wavelength of the atrial excitatory process and thereby allows an atrial premature depolarization to occur earlier and find reentry conditions more easily available than would otherwise be possible (34,35). It therefore seems desirable to counteract the process of atrial electrical remodeling caused by either AF or atrial flutter. This could be done by either preempting the process of electrical remodeling itself (potentially by calcium channel blockers or future molecular biologic interventions) or by prolonging the atrial action potential by class III drugs. Recent clinical trials (47,48) showed that pure class III drugs can terminate AF and atrial flutter and also help prevent their recurrence. Finally, our finding that atrial flutter produced electrical remodeling of the same magnitude as did AF suggests that it may be prudent to abort atrial flutter early so as to not pave the way for the development of chronic AF.

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