High-Density Mapping of Electrically Induced Atrial Fibrillation in Humans

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Background Mapping studies in animals have suggested that atrial fibrillation (AF) is based on multiple reentering wavelets. Little information is available about the patterns of activation during AF in humans. The objective of the present study was to reconstruct and classify the patterns of human right atrial (RA) activation during electrically induced AF.

Methods and Results AF was induced by rapid atrial pacing in 25 patients with Wolff-Parkinson-White syndrome undergoing surgery for interruption of their accessory pathway(s). The free wall of the RA was mapped using a spoon-shaped electrode containing 244 unipolar electrodes. The activation of the RA during AF showed large interindividual differences. Based on the complexity of atrial activation, three types of AF were defined. In type I (40% of patients), single broad wave fronts propagated uniformly across the RA. Type II (32%) was characterized by one or two nonuniformly conducting wavelets, whereas in type III (28%), activation of the RA was highly fragmented and showed three or more different wavelets that frequently changed their direction of propagation as a result of numerous arcs of functional conduction block. There were significant differences ($P<.05$) among the three types of AF in median intervals (174±28, 150±14, and 136±16 milliseconds), variation in AF intervals (P_{5-95}) (54±25, 94±21, and 104±22 milliseconds), incidence of electrical inactivity (42±11%, 21±4%, and 8±4%) and reentry (3±7%, 36±28%, and 99±36%), and average conduction velocity during AF (61±6, 54±4, and 38±10 cm/s).

Conclusions During pacing-induced AF in humans, the RA is activated by one or multiple wavelets propagating in different directions. Three types of RA activation during AF were identified. From type I to type III, the frequency and irregularity of AF increased, and the incidence of continuous electrical activity and reentry became higher. These various types of AF in humans appear to be characterized by different numbers and dimensions of the intra-atrial reentrant circuits. (***Circulation.* 1994;89:1665-1680.**)

Key Words • atrium • fibrillation • pacing • Wolff-Parkinson-White syndrome • mapping

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The mechanisms underlying atrial fibrillation in humans are not yet fully understood. In the beginning of this century, it was believed that the irregular contractions of the atria were caused by either single or multiple ectopic foci.[1,2] This concept was first challenged in 1920 by Lewis,[3] who stated that during atrial fibrillation, "the incoordination of the contracting fibers may be held to result from the impact of contraction waves and the production of localized areas of block." Also, Garrey[4] concluded that reentry had to be the mechanism of atrial fibrillation. The debate about ectopic foci versus reentry continued, and on the basis of computer simulations, Moe[5] hypothesized in 1962 that a "grossly irregular wavefront becomes fractionated as it divides about islets or strands of refractory tissue, and each of the daughter wavelets may now be considered as independent offspring. Fully developed fibrillation would then be a state in which many such randomly wandering wavelets coexist." Experimental evidence for this multiple wavelet hypothesis was provided by a number of studies in which the excitation of the atria during atrial fibrillation was actually mapped.[6-14] These studies showed multiple wavelets wandering around natural anatomic obstacles and functional arcs of conduction block. In some cases, the wavelets appeared to be offsprings of a single reentrant circuit.[10] However, until now mapping of atrial fibrillation in humans has been limited to a small number of patients, and no systematic analysis of mapping data has been done.[10,12]

With the use of the surface ECG, atrial fibrillation has been divided clinically into "coarse" and "fine" fibrillation.[15,16] Wells et al[17] identified four different types of atrial fibrillation based on the characteristics of the bipolar atrial electrogram.

The objective of the present study was to systematically analyze the patterns of activation using high-resolution mapping during electrically induced atrial fibrillation in a relatively large group of young patients being operated on for transection of an accessory atrioventricular pathway.

Methods

Patient Population

The study included 25 patients with Wolff-Parkinson-White (WPW) syndrome who were undergoing surgery for symptomatic or drug-refractory tachycardia at the Academic Hospital of Maastricht between March 1988 and June 1990. Mean age of the patients was 32±11 years (range, 12 to 57 years). Sixteen patients were male and 9 were female. In none of the patients were cardiac abnormalities other than WPW syndrome found by evaluation of the chest radiograph and coronary catheterization. The left atrial size as determined by echocardiography

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TABLE 1. Characteristics of Patients Who Had Atrial Fibrillation Induced Electrically

Patient no.	Age, y	Sex	Location of Pathway	AERP, ms	LA Size, mm	Documented AF	Duration of Analyzed Episode of AF, s
1	18	F	RL+LL	NA	39	−	>120
2	27	M	LL	230	NA	−	420
3	23	M	RL	260	NA	−	40
4	16	M	RL	NA	NA	−	60
5	28	F	LP	190	28	−	>120
6	27	M	LL	220	43	−	>120
7	45	M	LL	230	40	+	540
8	20	M	LP	260	38	−	>120
9	57	M	LL	200	42	+	30
10	18	M	LL	210	40	−	60
11	36	F	LL	NA	32	−	35
12	43	M	LL	220	36	+	>120
13	45	M	LL	200	36	+	>300
14	25	M	LL	220	NA	+	>60
15	27	M	LL	NA	43	−	>180
16	37	M	LL	250	NA	−	60
17	29	M	LP	180	30	−	180
18	34	M	LL	160	44	−	>180
19	12	F	PS	260	37	+	>600
20	31	F	RP	200	NA	−	>60
21	52	F	LL	240	32	−	300
22	38	F	PS	200	45	−	>260
23	34	M	LL	260	50	+	>110
24	44	F	LP	NA	NA	−	180
25	33	F	LL	220	46	−	>60
Mean±SD	32±11	16 M, 9 F		221±29	39±6	7+	>173±154

AERP indicates atrial effective refractory period during pacing at a cycle length of 500 milliseconds; NA, not available; LA size, left atrial size as determined by echocardiography (normal value, ≤40 mm); AF, atrial fibrillation; F, female; M, male; PS, posteroseptal; LP, left posteroseptal; RP, right posteroseptal; LL, left lateral; and RL, right lateral.

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was normal in most patients. In 3 patients (22, 23, and 25), the left atrium was moderately enlarged.

In all patients, an invasive electrophysiological study was performed before surgery. During this study, circus movement tachycardia was induced (except in patients 5 and 19), and the location of the accessory pathway(s) was determined. A left lateral accessory pathway was present in 15 patients, a left posteroseptal pathway in 4, a right lateral pathway in 2, a posteroseptal pathway in 2, and a right posteroseptal pathway in 1. In 1 patient, two accessory pathways existed—one located in the right free wall and one located left laterally. The atrial refractory period during pacing at 500-millisecond intervals was normal. In 7 patients, paroxysms of atrial fibrillation were documented by ECG or Holter recordings. These 7 patients did not have significantly different atrial refractory periods or left atrial sizes ($P>.462$). In Table 1, clinical characteristics of the patients are given. Antiarrhythmic medication was discontinued 4 to 5 days before surgery. None of the patients were taking amiodarone. Informed consent for induction of atrial fibrillation and mapping was obtained before surgery.

Experimental Protocol

The patients were anesthetized with fentanyl (50 to 100 μg/kg), alfentanil (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and propofol (2 $mg \cdot kg^{-1} \cdot h^{-1}$). The chest was opened by median sternotomy, and a pericardial cradle was made. Four bipolar electrodes were attached to the right and left atria and to each of the ventricles for bipolar recording and stimulation. Epicardial mapping of the free wall of the right atrium was performed during sinus rhythm, rapid atrial pacing, and induced atrial fibrillation before the patients were put on cardiopulmonary bypass and before cryoablation of the accessory pathway(s). A spoon-shaped electrode (diameter, 3.6 cm) was used that consisted of 244 unipolar electrodes (silver wires; diameter, 0.3 mm) arranged in a regular octagonal array (interelectrode distance, 2.25 mm) (Fig 1). A silver plate (diameter, 2.5 cm) positioned in the thoracic cavity was used as an indifferent electrode. The mapping electrode was positioned in the middle of the right atrial free wall and was kept in place manually by the surgeon applying light constant pressure to the atrium. In this way, usually more than 90% of the electrodes recorded adequate electrograms of sufficient amplitude without motion artifacts. At the edge of the mapping electrode, some electrodes sometimes yielded low-amplitude signals either because of fat at the atrioventricular sulcus or because the edge of the electrode did not make good contact with the atrium. Because this occurred only at the edge of the electrode, the only consequence was that the map became slightly smaller than

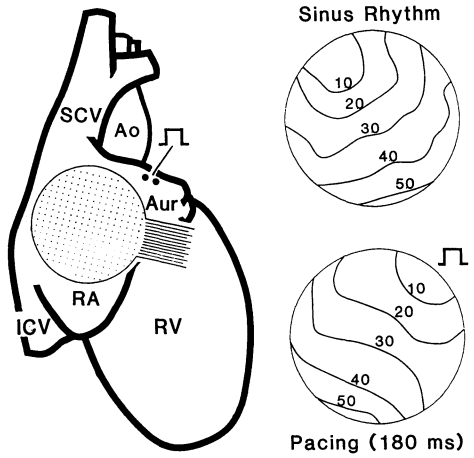

FIG 1. Mapping of the free wall of the right atrium using a 244-lead epicardial mapping electrode (interelectrode distance, 2.25 mm). Atrial pacing was performed through a separate pair of electrodes sutured to the right auricle (Aur). The electrograms recorded by five electrodes—one in the center and four in the middle of each quadrant of the mapping area—were used for making fibrillation interval histograms. Right panels, Activation maps during sinus rhythm and right atrial pacing (interval, 180 milliseconds). No areas of slow conduction or conduction block were present. Isochrones are drawn at 10-millisecond intervals. Ao indicates aorta; ICV, inferior caval vein; SCV, superior caval vein; RV, right ventricle; and RA, free wall right atrium.

the electrode array. We also tried to record from the free wall of the left atrium. However, because of the poor exposure of the left atrium, the left atrial recordings were of sufficient quality in only 8 of 25 patients. All electrograms were individually amplified (gain, 150 to 1000), filtered (bandwidth, 2 to 500 Hz), multiplexed (sampling rate, 1 kHz), and AD converted (8 bits). Bipolar reference electrograms from the right and left atria and the right and left ventricles and ECG leads I, II, III, and aVR were recorded simultaneously. All recordings were stored on videotape (Sony SL-C9ES) for subsequent analysis.

Atrial fibrillation was induced either by incremental atrial pacing or by introduction of one to three early atrial premature beats. Constant current pulses of 2-millisecond duration and twice-diastolic threshold were used. The duration of electrically induced atrial fibrillation varied from less than 3 seconds to more than 10 minutes. In all patients, atrial fibrillation terminated spontaneously, except in 1 patient, in whom it was terminated by cardioversion. Only episodes of atrial fibrillation lasting longer than 30 seconds were used for analysis. In most patients (20), only one episode of "sustained" atrial fibrillation was induced. In case of multiple inductions of atrial fibrillation, the longest episode was selected for analysis. The average duration of the analyzed episodes was more than 3 minutes.

Activation Maps and Interval Histograms

During off-line analysis, time windows of 12 seconds of atrial fibrillation were selected from tape, and the signals were transferred to a personal computer (Olivetti 386) for detailed analysis. In 3 patients, only 4 seconds were analyzed because of the short duration of atrial fibrillation. Because it is feasible that both during initiation and before termination of fibrillation transients may occur between more or less complex patterns of fibrillation, the first and last 12 seconds of atrial fibrillation were excluded from analysis. During the sample of 12 seconds of fibrillation selected for analysis, the pattern of atrial fibrillation appeared to be stable as judged from the cycle length and degree of irregularity of the different electrograms. The software used for analysis of the 244 recorded unipolar electrograms included an algorithm for automatic detection of the intrinsic negative deflections of the electrograms,[18] generation of color-coded activation maps, and interactive editing of local activation times. Isochrones of 10-millisecond intervals were drawn by hand. Intra-atrial conduction block was defined as an apparent local conduction velocity of less than 7.5 cm/s associated with a change in direction of propagation distal to the line of block.[19] A detailed description of the mapping system has been given.[20,21] Fibrillation interval histograms of the right atrium were made using five electrograms of the mapping area—one recorded at the center and the others at the middle of each quadrant of the mapping electrode. The variation in local fibrillation interval was expressed as the difference between the 5th and 95th percentiles in the fibrillation histogram (P_{5-95}). The conduction velocity of uniformly propagating wave fronts during sinus rhythm, rapid pacing, and atrial fibrillation were calculated from the total conduction time across the mapping electrode. The average conduction velocity during atrial fibrillation in the free wall of the right atrium was measured as follows. During each beat, a conduction velocity map was calculated from the local activation times of four neighboring electrodes. The distribution of local conduction velocities was plotted in a histogram. The average of the median conduction velocities during a period of at least 4 seconds of fibrillation was used as a measure of average intra-atrial conduction velocities during atrial fibrillation.

Statistical Analysis

Results are expressed as mean±SD. Bonferroni's modification of the t test was used to compare differences between groups. The χ^2 test was used to compare the characteristics of patients and the incidence of atrial fibrillation. Spearman's rank correlation test was used to test the correlation between median interval and variation of fibrillation with the degree of complexity of atrial activation. A value of $P<.05$ was considered statistically significant.

Results

Activation During Sinus Rhythm and Atrial Pacing

Both during sinus rhythm and during rapid atrial pacing (330 beats per minute), the free wall of the right atrium was activated uniformly by a single broad activation wave (Fig 1). No areas of slow conduction or conduction block were found. Activation of the right atrial free wall was always completed within 65 milliseconds, and only a minor beat-to-beat variation in the spread of activation was observed. The average conduction velocity during sinus rhythm was 73±5 cm/s (n=25), and during rapid pacing, it was 68±5 cm/s (n=18) ($P=.002$).

Characteristics of Electrically Induced Atrial Fibrillation

An example of electrically induced atrial fibrillation is given in Fig 2. The surface ECG showed an irregular ventricular rhythm with preexcited QRS complexes without regular P or F waves. The unipolar right atrial electrogram showed a rapid irregular rhythm with a continuous beat-to-beat variation in electrogram morphology and cycle length. The atrial fibrillation interval histogram showed a considerable variation in cycle length (P_{5-95}, 96 milliseconds) with a median value of 155 milliseconds. In this patient, the ventricular rhythm had a median interval of 301 milliseconds, varying from 256 milliseconds (P_5) to 352 milliseconds (P_{95}). In all patients (n=25), the median fibrillation interval was 155±26 milliseconds with a P_{5-95} of intervals of 81±31 milliseconds. The RR intervals varied between 249±81

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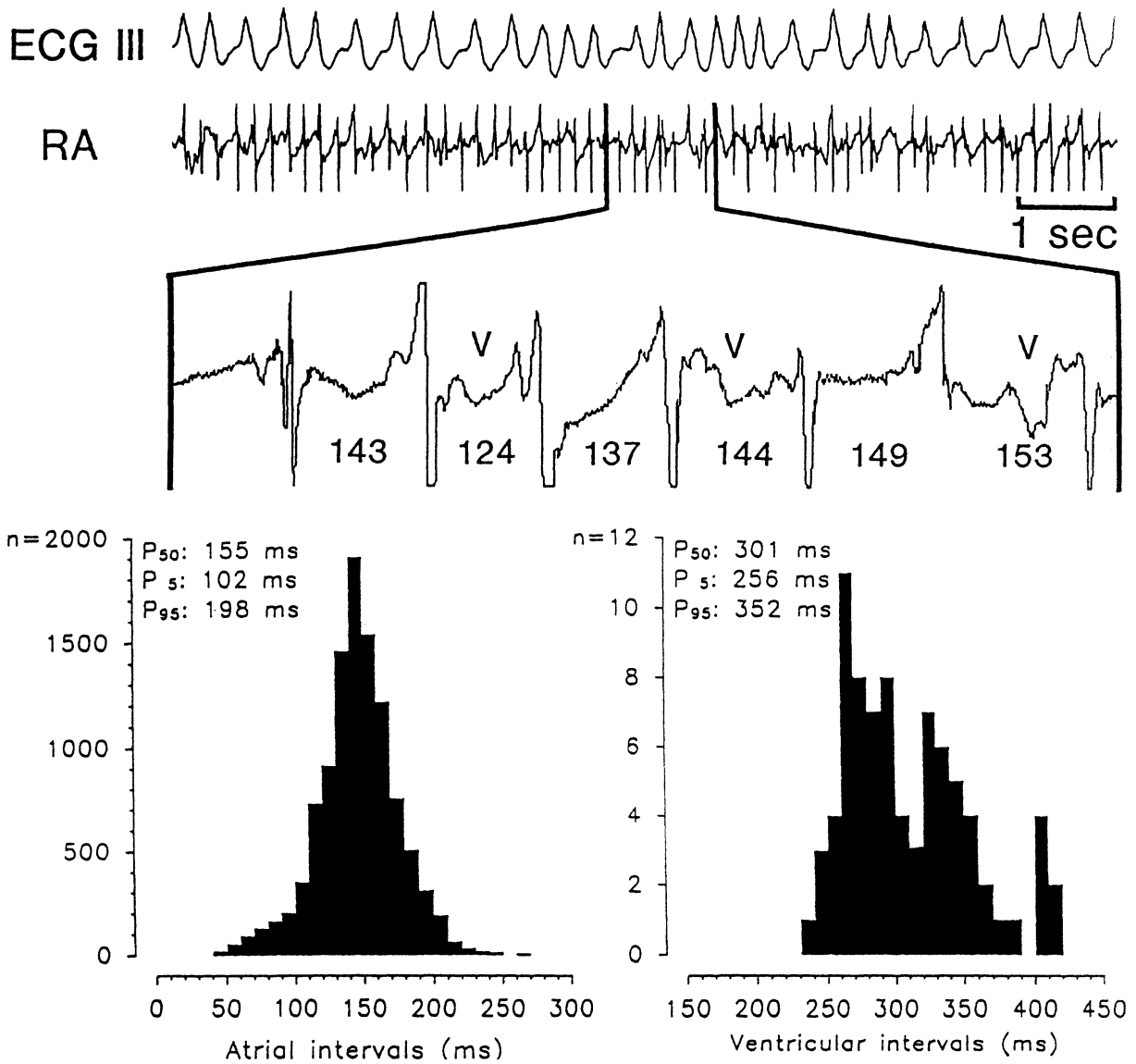

FIG 2. ECG (lead III) and a single unipolar right atrial electrogram (RA) during an episode of electrically induced atrial fibrillation lasting for longer than 2 minutes (patient 12). Bottom, Histograms are plotted of the atrial fibrillation intervals (left) and the RR intervals (right). Atrial fibrillation interval histogram was made from the intervals of five electrograms recorded from the mapping area (see Fig 1). In this patient, the median fibrillation interval was 155 milliseconds (P_5, 102 milliseconds; P_{95}, 198 milliseconds). The ventricular interval histogram showed a median value of 301 milliseconds (P_5, 256 milliseconds; P_{95}, 352 milliseconds). V indicates ventricular response.

milliseconds (P_5) and 468±67 milliseconds (P_{95}) (median, 379±51 milliseconds).

Mapping of Atrial Fibrillation

In contrast to the uniform activation during sinus rhythm and atrial pacing, during atrial fibrillation the free wall of the right atrium was activated by more or less fragmented wave fronts. Although in all cases the right atrium was activated nonuniformly, the *degree* of fragmentation showed large interindividual variations. In some patients, the right atrium was activated by single broad wave fronts exhibiting only a minimal degree of intra-atrial conduction block. In others, activation of the right atrium was highly fragmented by various arcs of intra-atrial conduction block dividing the depolarization wave into multiple wavelets.

In Figs 3 through 5, three cases of atrial fibrillation are shown with an increasing degree of complexity in

FIG 3. Facing page. ECG (lead I), a right atrial unipolar electrogram (RA), activation maps of the free wall of the right atrium, and atrial and ventricular interval histograms during atrial fibrillation (patient 4). Atrial fibrillation intervals in this patient ranged from 157 milliseconds (P_5) to 195 milliseconds (P_{95}), with a median value of 174 milliseconds. The median ventricular interval was 354 milliseconds ($P_{5\text{-}95}$, 72 milliseconds). The 12 activation maps of the free wall of the right atrium were taken at 1-second intervals. Because the median fibrillation interval in this patient was 174 milliseconds, the maps of about one of six beats are plotted. Isochrones have been drawn at 10-millisecond intervals. Thick lines represent arcs of conduction block. Arrows indicate the main directions of activation. In this case of atrial fibrillation, the right atrium was activated rather uniformly. Single broad waves entered the free wall from the atrial appendage, and only small arcs of block were found. The total conduction time of the myocardium under the mapping electrode varied between 70 and 130 milliseconds.

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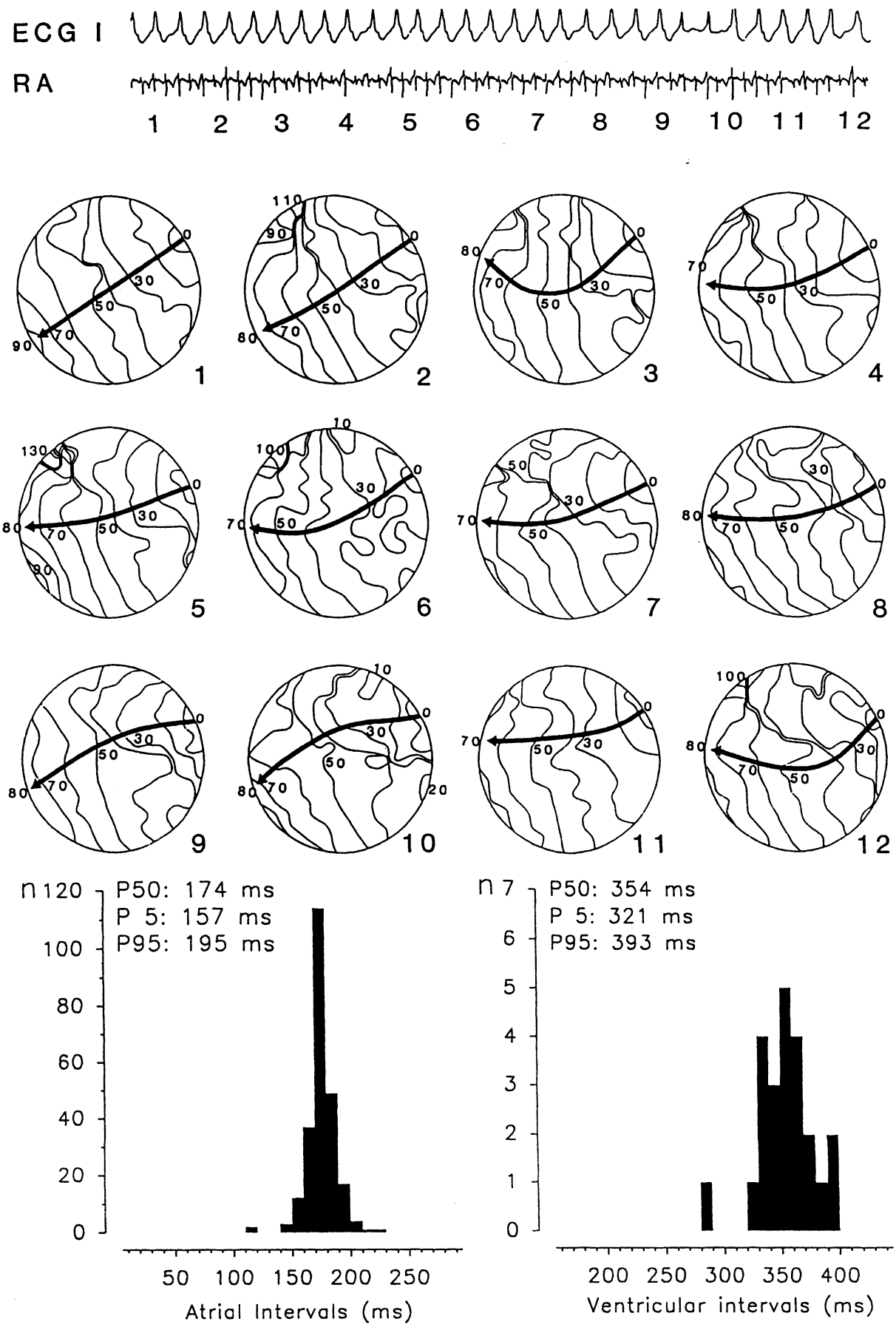

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the pattern of activation. A relatively simple pattern of activation is illustrated in Fig 3 (patient 4). In this case, the median fibrillation interval was 174 milliseconds, with a P_{5-95} of 38 milliseconds. During fibrillation, the right atrium was repeatedly activated by a single activation wave entering the mapped area from the right atrial appendage (at 2 o'clock in the map). During sinus rhythm, the sinus impulse entered the mapped area at 12 o'clock (not shown). Because of beat-to-beat variations in conduction velocity during fibrillation, the conduction time across the mapping area varied between 50 and 90 milliseconds, representing a conduction velocity between 40 and 72 cm/s. Only small arcs of intra-atrial conduction block were present (ie, maps 2, 4 through 7, 10, and 12). Because of delayed activation of areas distal to these arcs of conduction block, the total conduction time of the mapped area could be prolonged up to 130 milliseconds (beat 5).

In Fig 4, another case of atrial fibrillation is shown (patient 19) in which the median fibrillation interval was 147 milliseconds with a variation of 78 milliseconds (P_{5-95}). In contrast to the case shown in Fig 3, this patient showed a continuously changing pattern of excitation of the right atrium. The site of entrance of the fibrillation waves (t=0) differed from beat to beat, whereas most of the time the right atrium was activated by two wavelets (maps 1, 3 through 5, 7, and 11). During some beats, three different wave fronts could be identified (maps 10 and 12). Frequently, long arcs of conduction block were present when depolarization waves encountered areas still refractory from activation by a previous wavelet. Also, many examples of collision or fusion of wavelets (maps 3 through 5, 7, and 10) and local slowing of conduction (crowding of isochrones) can be seen (maps 2, 4, and 9). Only occasionally was the mapped area activated by a single depolarization wave (maps 6 and 8). In that case, the conduction time across the area was still relatively short (70 to 80 milliseconds), indicating that the intrinsic conduction properties of the atrium were not markedly depressed. The prolonged activation times of the right atrium were caused either by the turning of wave fronts around local arcs of conduction block (map 9) or by different wavelets entering the right atrium out of phase (map 1).

In Fig 5, the maps of atrial fibrillation are shown from a patient (3) in whom the activation of the right atrium was extremely complex. Also, during sinus rhythm or rapid pacing (interval, 180 milliseconds), no signs of slow conduction or intra-atrial conduction block were found. During atrial fibrillation, only 1 of 12 maps showed a more or less uniform activation pattern with a conduction time across the mapping area of about 60 milliseconds (map 2). Thus, even in this case of highly complex atrial fibrillation, the intrinsic conduction properties of the atrium were still normal (60 cm/s). Most of the time, the right atrium was activated by multiple narrow wavelets entering and leaving the mapping area at different sites. The conduction velocity of these wavelets varied considerably, as can be seen from the varying distances between isochrones. Crowding of isochrones (conduction velocity, <10 cm/s) and multiple arcs of conduction block can be found in almost every map. After collision and fusion of wavelets, branching of a wave front into two separate wavelets occurred most frequently (maps 1 and 7 through 11). Often, areas that had been activated by one of these wavelets were reexcited by another wavelet (random reentry). In this patient, the fibrillation intervals varied widely between 75 milliseconds (P_5) and 191 milliseconds (P_{95}), with a median interval of 143 milliseconds.

Continuous Electrical Activity

In Fig 6, the percentage of the mapped area activated during atrial fibrillation for the three patients shown in Figs 3 through 5 is plotted for each 10-millisecond time window. These graphs express the temporal variation of right atrial tissue mass that is being depolarized during fibrillation. In patient 4 (top), electrical activation of the right atrium clearly alternated with periods during which no depolarization waves were present under the mapping electrode (39% of the time). In patient 19 (middle), no electrical activity was recorded during 23% of the time, whereas in patient 3 (bottom), only the right atrium was free of depolarization waves 7% of the time. In this patient, during atrial fibrillation long episodes of continuous electrical activity were recorded from the right atrium. One of these episodes of continuous electrical activity is analyzed in Fig 7. At the top, the main trajectory of the fibrillation waves is plotted, and at the bottom, individual isochrone maps are given. In the first map, the right atrium was activated by a single wave entering the mapping area from below and leaving it at the top at t=140 milliseconds. While this activation wave was still present, a new wave entered the mapping area at t=120 milliseconds (map 2). As can be seen from the trajectory diagram, this wave started to circulate in the mapping area for a period of longer than 1 second. Maps 2 through 10 show the details of this continuously shifting leading circuit. Frequently, offsprings from this wandering circuit propagated away from the mapping area toward the remainder of the atria. At the same time, other fibrillation waves entered the mapping area and fused with the wandering leading circuit. At t=1200 milliseconds, the circulating wave front was blocked (double bar), and the circuit was interrupted. However, continuous electrical activity persisted because at t=1130 another wavelet had already entered the mapping area. Thus, continuous electrical activity during atrial fibrillation was based on two mechanisms: (1) the presence of a continuously reentering impulse (shifting leading circuit) and (2) temporal overlap of different waves entering the mapping area at different times.

FIG 4. Facing page. ECG (lead III), a right atrial unipolar electrogram (RA), activation maps of the right atrial free wall, and a right atrial and ventricular interval histogram during atrial fibrillation (patient 19). Atrial fibrillation intervals in this patient ranged from 93 milliseconds (P_5) to 171 milliseconds (P_{95}), with a median value of 147 milliseconds. The median ventricular interval was 281 milliseconds (P_{5-95}, 175 milliseconds). The 12 activation maps were taken at 1-second intervals. Compared with the activation patterns in Fig 3, in this case, the activation of the right atrium was more complex. During most beats, two wavelets entered the mapping area from different directions. Frequently, areas of slow conduction, as indicated by crowding of isochrones, were present. Only incidentally was the right atrium activated by a single wave front conducting at high speed (map 6).

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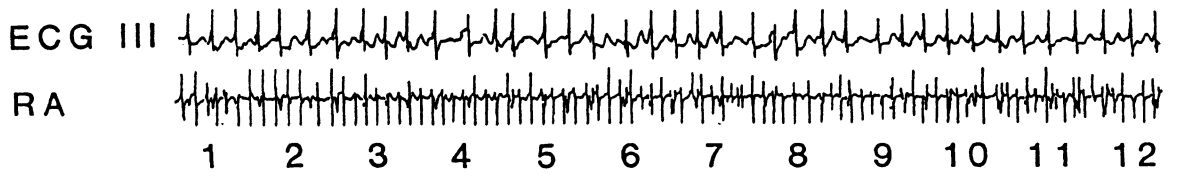

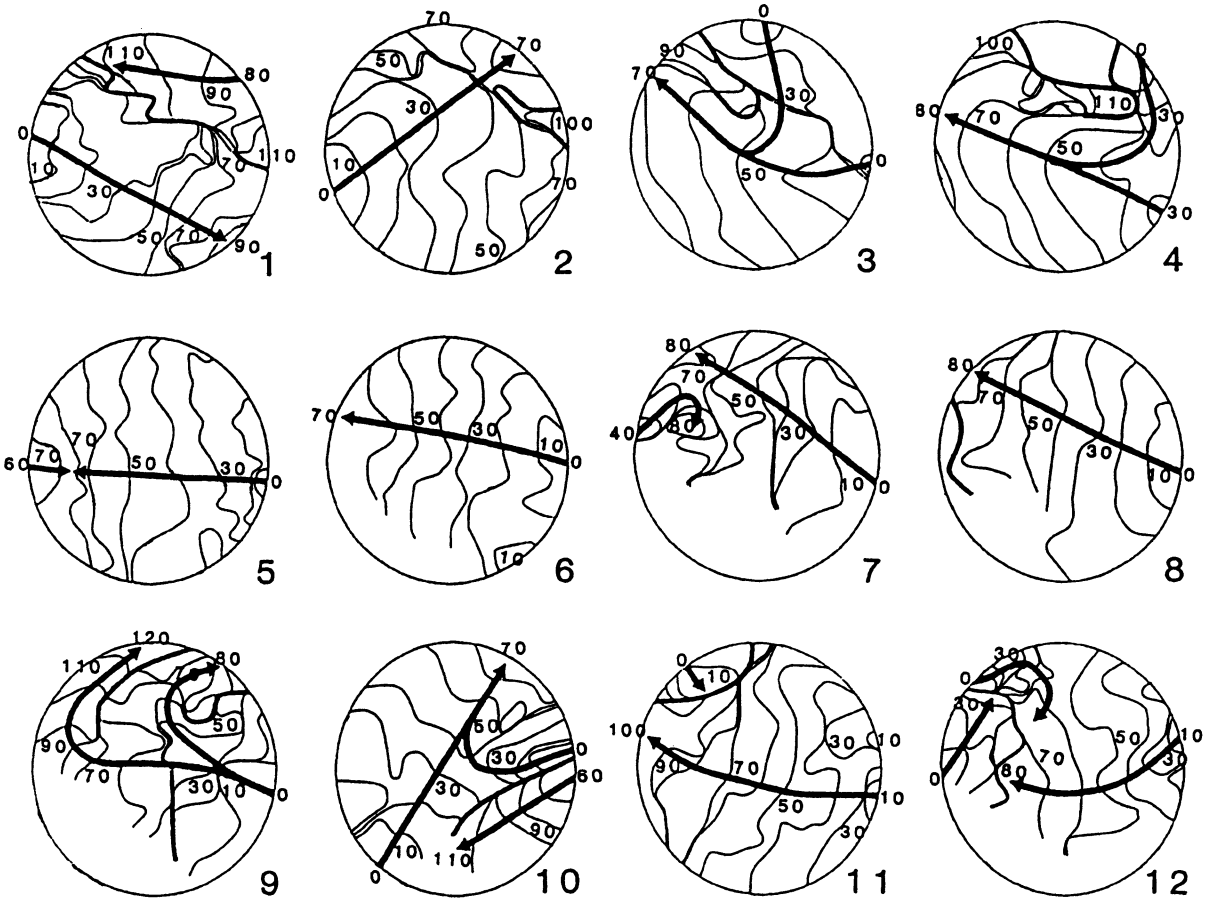

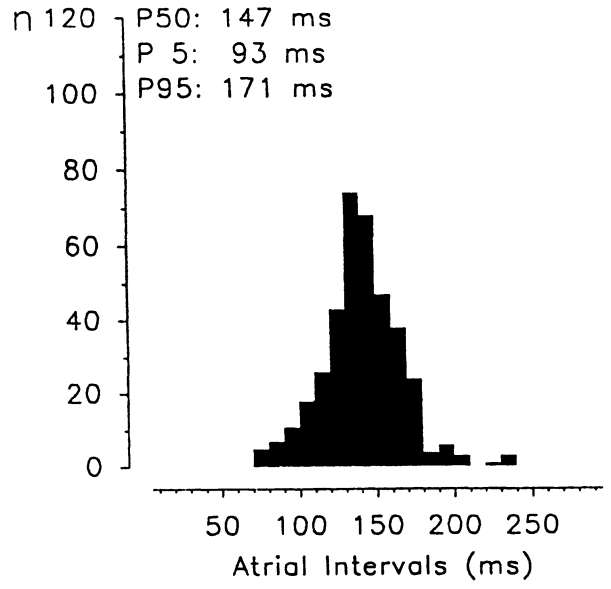

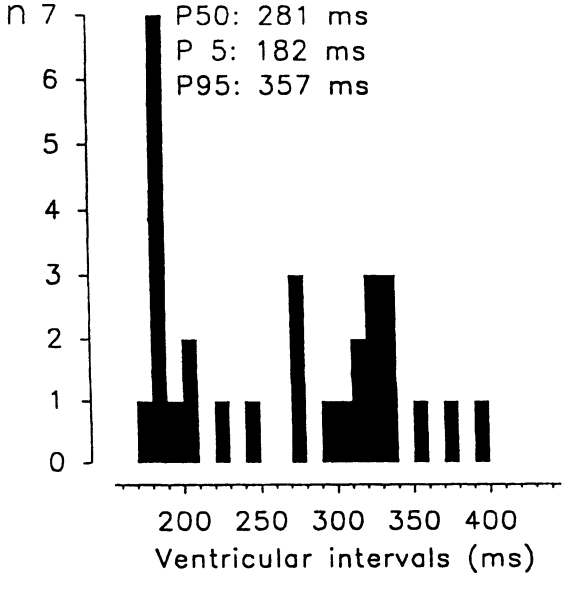

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Classification of Atrial Fibrillation

In an attempt to quantify the degree of complexity of atrial activation during fibrillation, all maps (n=1500) were classified into three categories. The criteria used for classification were as follows (Fig 8).

Type I

Single broad wave fronts propagating without significant conduction delay, exhibiting only short arcs of conduction block or small areas of slow conduction not disturbing the main course of propagation, were considered to describe type I.

Type II

Activation patterns characterized either by single waves associated with a considerable amount of conduction block and/or slow conduction or the presence of two wavelets were considered to describe type II.

Type III

The presence of three or more wavelets associated with areas of slow conduction (<10 cm/s) and multiple arcs of conduction block were considered to describe type III.

In Table 2, the 25 patients are classified according to the degree of complexity of atrial fibrillation. An incidence of more than 50% of type I or type III beats was chosen as the boundary between the types of fibrillation. In this way, 10 patients (40%) were classified as having type I, 8 patients (32%) as having type II, and 7 patients (28%) as having type III fibrillation.

No statistically significant difference was found among the three groups of patients with respect to age ($P>.897$), sex ($P>.417$), location of the accessory pathway(s) ($P>.199$), atrial refractory period ($P>.859$), left atrial size ($P>.455$), incidence of documented atrial fibrillation ($P>.165$), and duration of electrically induced atrial fibrillation ($P>.184$). However, because of the small sample size and the large variation of the various parameters in each group, the confidence limits were rather wide, and consequently the ability to discern differences was limited. Thus, in this case, the absence of statistical significance does not necessarily mean that no clinical differences exist between patients with different types of atrial fibrillation.

The conduction properties of the right atrium during sinus rhythm ($P=.371$), rapid atrial pacing ($P=.478$), and uniform propagation of fibrillation waves ($P=.381$) did not differ in patients with type I, II, or III fibrillation (Table 2). Because the standard deviations of these parameters were small, the confidence limits were quite narrow, and in this case, the statistical analysis indicates a true absence of differences between the groups.

Compared with sinus rhythm, during atrial fibrillation intra-atrial conduction was clearly depressed (53±12 compared with 73±5 cm/s). In patients with type I fibrillation, the average median conduction velocity was still relatively high (61±6 cm/s). During type II fibrillation, average conduction velocity was 54±4 cm/s ($P<.02$), whereas during type III fibrillation, conduction velocity decreased to 38±10 cm/s ($P<.001$).

The type of fibrillation was correlated to the fibrillation interval. In type I, the average median interval was 174±28 milliseconds, whereas in types II and III, the median fibrillation intervals were 150±14 and 136±16 milliseconds ($P<.05$). When the median fibrillation interval was shorter, the variation in fibrillation intervals was larger. In type I fibrillation, the P_{5-95} of the fibrillation intervals was 54±25 milliseconds, whereas in types II and III, these values were 94±21 and 104±22 milliseconds, respectively ($P<.005$).

Also, the time during which no propagating waves were present in the mapped area became shorter with increasing complexity of fibrillation. In type I, most beats were separated by a clear period of electrical inactivity, and during about half of the time (42±11%), no propagating waves were detected in the free wall of the right atrium. Electrical inactivity was still frequently observed in type II fibrillation (21±4%, $P<.001$), although short periods of continuous electrical activity also were observed. In contrast, during type III fibrillation, episodes of continuous right atrial activity were predominant, and propagating wavelets were absent during only 8±4% of the time ($P<.001$).

Although the above classification of atrial fibrillation may be useful, we want to emphasize that the three types of fibrillation should not be regarded as separate entities. The different types of fibrillation should rather be regarded as part of a continuous spectrum of increasing complexity. This is illustrated in Fig 9, in which the 25 patients are ranked according to the degree of complexity of atrial fibrillation. On the ordinate, the median fibrillation interval and the variation in fibrillation interval (P_{5-95}) are plotted. As can be seen, in going from the simplest type I to the most complex type III patient, the median interval gradually shortens from 212 to 120 milliseconds, whereas the P_{5-95} increases from 21 to 123 milliseconds. No clear separation exists between the different types of atrial fibrillation.

FIG 5. Facing page. ECG (lead I), a right atrial unipolar electrogram (RA), activation maps of the right atrial free wall, and a right atrial and ventricular interval histogram during atrial fibrillation in patient 3. The varying morphology of the QRS complex is caused by a varying degree of preexcitation. The activation maps were taken at 1-second intervals. In this case, the right atrium showed highly fragmented activation by multiple wavelets.

Differences Between Right and Left Atria

In 8 patients, we mapped the free wall of the left atrium and the right atrium simultaneously during the same episode of atrial fibrillation. In Table 3, the type of fibrillation in each atrium is compared. In 5 of 8 patients, the right and left atrial free walls showed the same type of atrial fibrillation. In 2 patients, the left atrium showed a more disorganized activation pattern, whereas in 1 patient, the left atrium was more organized than the right. No differences in fibrillation interval or variation in fibrillation intervals (P_{5-95}) were found between the right and left atria ($P>.492$).

Incidence of Reentry

During atrial fibrillation, two kinds of reentrant excitation were observed in the free wall of the right atrium. One type of reentry (random reentry) was defined by Hoffman and Rosen[22] as "depending on multiple areas in which the impulse blocks in a unidirectional manner [although the sites of block change from moment to moment] and on the continuous propagation of the

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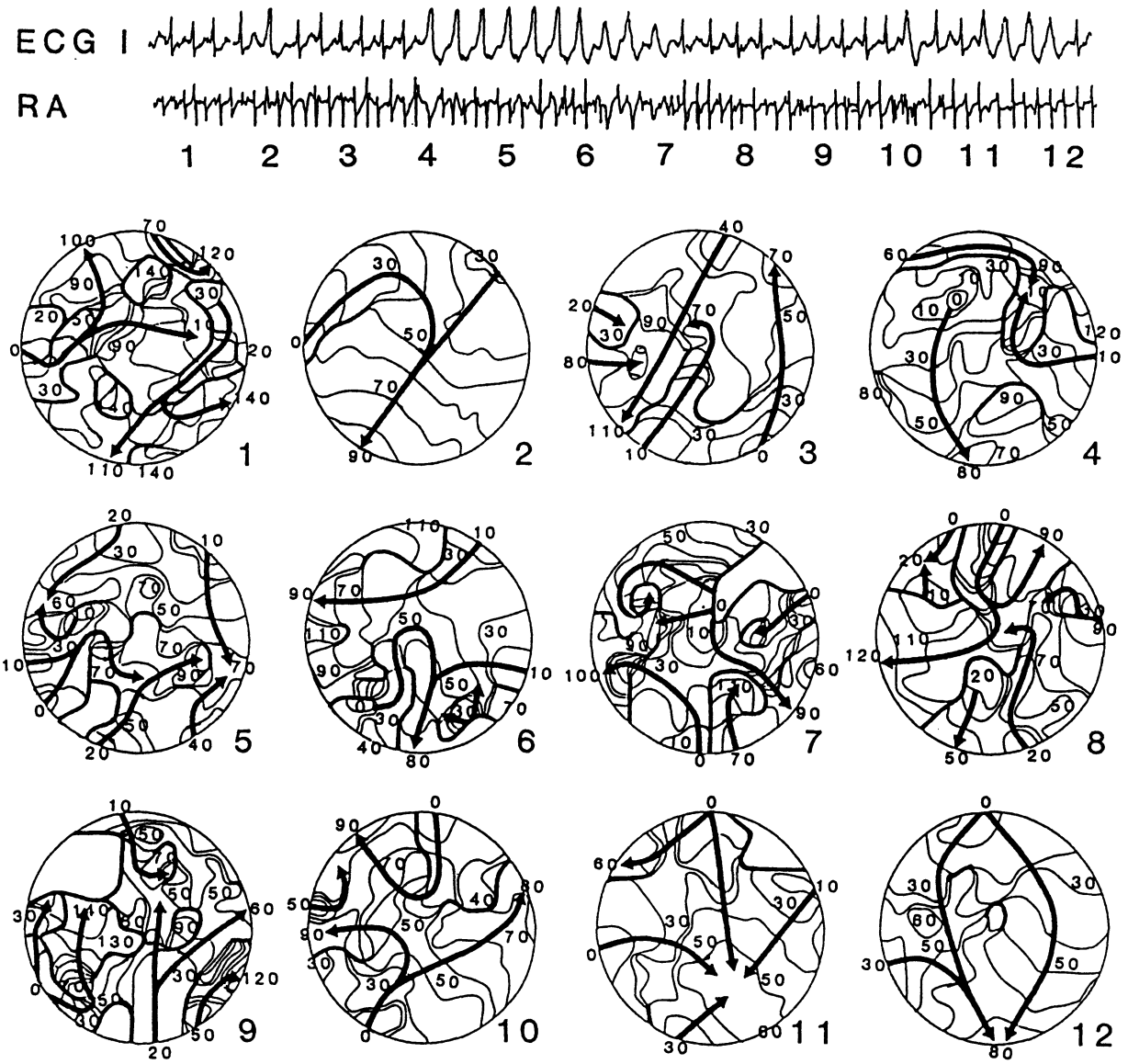

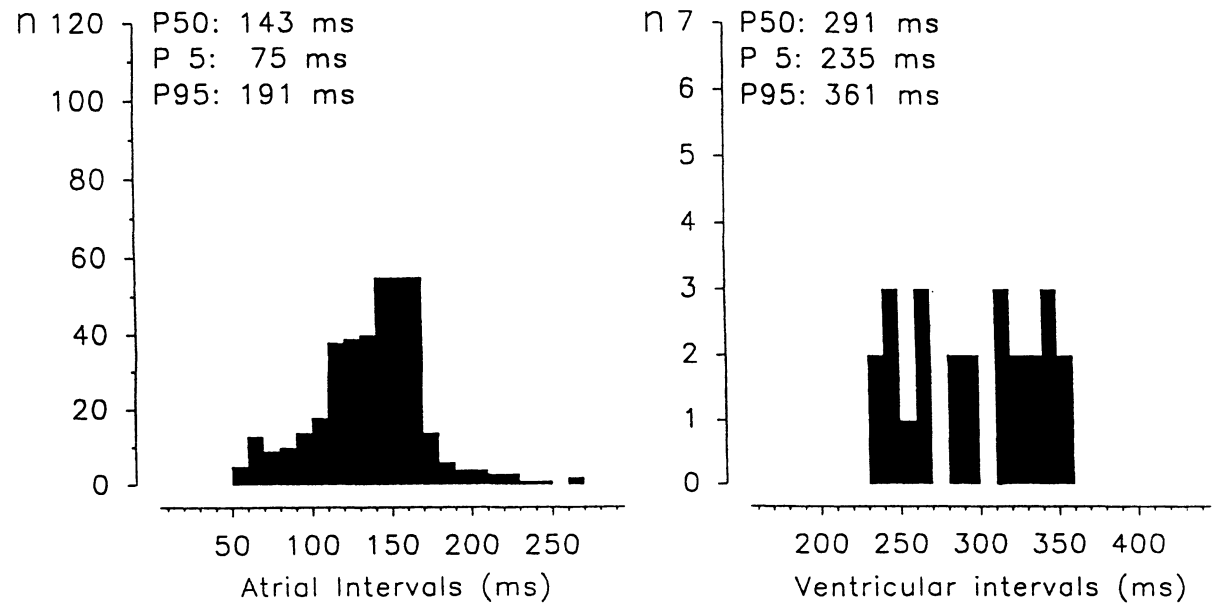

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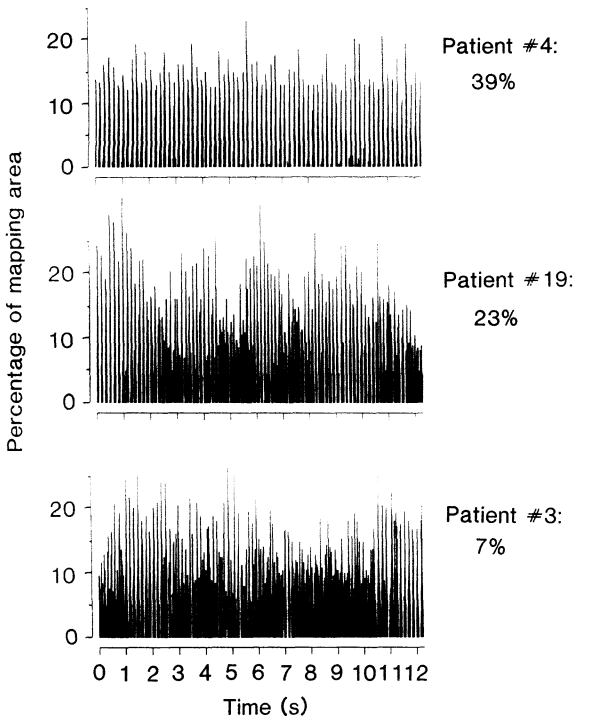

FIG 6. Temporal variation in right atrial tissue mass activated during atrial fibrillation in the three patients shown in Figs 3 through 5. In each diagram, the percentage of the mapping area (ordinate) depolarized during each isochrone of 10 milliseconds is plotted sequentially (abscissa). Going from the simplest case of atrial fibrillation (top) to a more complex one (bottom), the time that no electrical activity was present in the free wall of the right atrium decreased from 39% to 7%. During complex fibrillation, frequently periods of continuous electrical activity occurred that lasted for several seconds.

impulse [over random paths] so that individual groups of fibers are excited repetitively." We narrowed the definition of random reentry to the phenomenon of a propagating wavelet reexciting an area that shortly before had been activated by another present wavelet. An example of random reentry is given in Fig 10 (left panels). In the upper map, a fibrillatory wavelet is entering the mapping area from the left (t=0), activating electrodes 1, 2, and 3, in that order. This wavelet was blocked between electrodes 3 and 4. Later (t=70 milliseconds), another wavelet entered the mapping area at electrode 6 and propagated all the way from right to left from electrodes 6 to 1. Thus, sites 3 to 1, which were previously activated from left to right, were now reentered by the second wave from right to left. As a result, at the site of unidirectional block, a short interval of 76 milliseconds was found that gradually became longer at more distant electrodes (105 and 136 milliseconds at electrodes 2 and 1). An example of the other type of reentry is illustrated in the middle panels of Fig 10 (leading circle reentry). In this case, the impulse circulated in a clockwise direction from electrodes 1 to 6 around a central arc of functional conduction block about 2 cm long. While the revolution time of the first beat was 138 milliseconds, during the next beat (lower map) the central arc of conduction block shifted slightly, resulting in a revolution time of 127 milliseconds. Fixed reentrant circuits were never observed in the free wall of the right atrium.

The incidence of both random reentry and leading circle reentry was different in the three types of fibrillation (Table 2). In type I, random reentry was not observed, and leading circle reentry occurred in only 2 patients. The number of beats that a leading circle persisted in the free wall of the right atrium was small (2.4±1.4 beats). In type II fibrillation, random reentry occurred in 8±8%, and shifting leading circles were more common (28±25%). In type III fibrillation, random reentry occurred in 33±10% of the beats, whereas a shifting leading circle was observed during 66±29% of the fibrillation cycles. During type III, the average persistence of a shifting leading circle in the free wall of the right atrium was 5.4±3.1 beats. The incidence of both shifting circles and random reentry was significantly different in all groups ($P<.005$).

Epicardial Breakthrough

Incidentally, a "new" wavelet appeared to originate from somewhere in the free wall of the right atrium. The right panels in Fig 10 give an example of this phenomenon. The upper map shows a focal pattern of activation starting at the site indicated by the asterisk. From the mapping data, no evidence could be obtained for epicardial propagation toward this earliest site of activation. It appears unlikely that these focal patterns of activation originated from the sinus node because during normal sinus rhythm, the sinus impulses always originated at a point outside the mapping area. Although abnormal automaticity cannot be completely excluded, the most likely explanation for this excitation pattern is epicardial breakthrough of a fibrillation wave propagating in a free running endocardial trabecula.[13] In agreement with this explanation is the fact that the electrograms at the earliest sites of activation usually exhibited a small r wave before the intrinsic negative deflection. In addition, epicardial breakthrough occurred only at different sites as solitary events. Repetitive focal responses were never observed. In Table 2, the incidence of epicardial breakthrough is given for the three types of atrial fibrillation. In type I, a focal pattern was never seen. Also, in types II and III, epicardial breakthrough was a rare event, occurring in 1.4±1.8% and 3.5±3.6% of the beats, respectively.

Discussion

Classification of Atrial Fibrillation

Based on the morphology of a single *bipolar* atrial electrogram (electrode distance, 0.5 to 1.0 cm), Wells et al[17] distinguished four types of atrial fibrillation. In type I, the electrogram showed discrete complexes of variable morphology separated by a clear isoelectric baseline. Type II was also characterized by discrete atrial beat-to-beat complexes of variable morphology but differed from type I in that the baseline showed continuous perturbations of varying degrees. During type III fibrillation, highly fragmented atrial electrograms were recorded that showed no discrete complexes or isoelectric intervals. Type IV fibrillation was characterized by alternation between type III and the other types. In our opinion, this should not be regarded as a separate type of fibrillation but rather indicates the general property of atrial fibrillation to exhibit temporal variations in both rate and irregularity.

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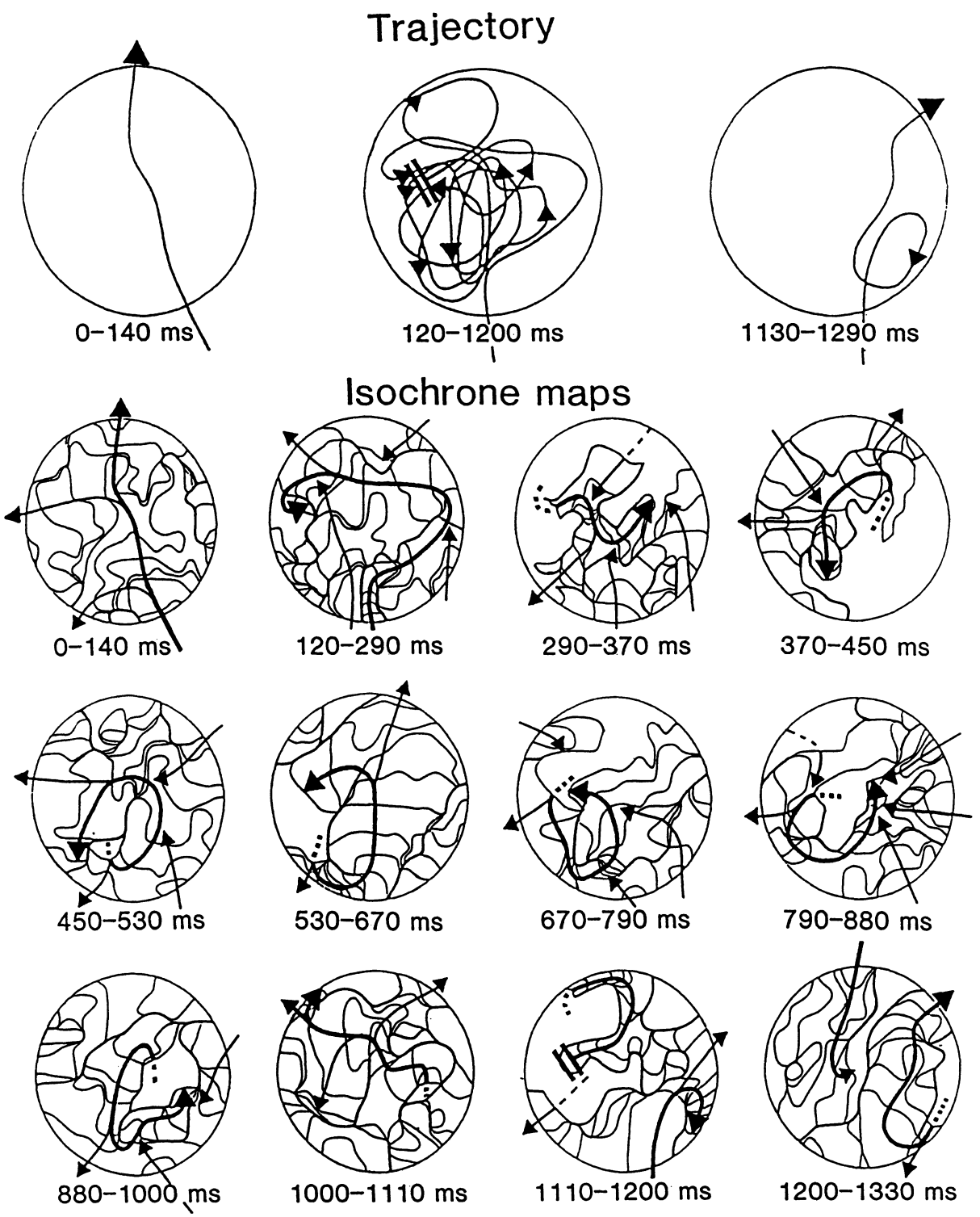

FIG 7. Right atrial activation during a period of continuous electrical activity (patient 3). The diagrams at the top show the trajectory of the main fibrillatory wave fronts. Below, the corresponding isochrone maps during this period of continuous electrical activity are given. The first trajectory and isochrone map 1 show a single wave activating the mapping area from t=0 to t=140 milliseconds. While this activation wave was still present, another wave entered the mapping area at t=120 milliseconds. As can be seen from the second trajectory diagram and isochrone maps 2 through 10, this wave started to circulate in the mapping area for more than 1 second. At t=1200 milliseconds, this wave was blocked (double bar), and the wandering circuit was interrupted (map 11). However, continuous electrical activity persisted because at the same time (t=1130), another wave entered the mapping area (right trajectory and maps 11 and 12).

Although we used the same terminology for classification as that of Wells et al[17] (ie, types I, II, and III), our criteria for classification of atrial fibrillation were completely different. Instead of the morphology of a single bipolar atrial electrogram, we used the complete pattern of activation of the free wall of the right atrium

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TABLE 2. Classification of Atrial Fibrillation

Type of AF	Patient no.	Type of Beat, %			Conduction Velocity, cm/s				Interval, ms	
		I	II	III	SR	Pacing	AF_{uni}	AF_{avg}	Median	P_{5-95}
I	24	100	0	0	76	73	71	69	212	21
	8	100	0	0	75	. . .	72	70	204	19
	21	100	0	0	73	70	60	59	193	42
	17	100	0	0	62	. . .	51	51	184	80
	4	96	4	0	79	69	65	56	174	38
	14	93	7	0	76	65	61	59	155	79
	10	91	9	0	76	. . .	62	55	132	46
	11	90	10	0	77	71	69	66	150	59
	15	79	21	0	76	69	66	62	140	87
	9	84	10	6	78	69	68	65	191	69
Mean±SD		93±7	6±7	1±2	75±5	69±3	64±6	61±6*	174±28*	54±25*
II	5	27	69	4	66	65	60	57	140	115
	19	33	50	17	78	73	54	50	147	78
	12	31	49	20	63	. . .	55	51	155	96
	7	20	68	12	75	70	69	59	138	73
	6	36	33	31	71	66	63	50	139	105
	23	0	89	11	79	. . .	70	58	172	63
	25	0	65	35	70	66	60	53	169	125
	20	0	56	44	77	. . .	64	56	141	93
Mean±SD		18±16	60±17	22±14	72±6	68±3	62±6	54±4*	150±14†	94±21†
III	18	3	28	69	75	71	60	53	118	65
	3	6	10	84	78	68	64	32	143	116
	2	2	8	90	74	70	55	50	148	97
	13	0	6	94	70	. . .	53	35	145	125
	16	0	5	95	66	62	61	38	121	87
	22	0	4	96	69	63	66	34	155	115
	1	0	1	99	72	66	60	25	120	123
Mean±SD		2±2	9±9	90±10	72±4	67±4	60±5	38±10*	136±16†	104±22†
Total mean±SD					73±5	68±3	62±6	53±12	155±26	81±31

SR indicates sinus rhythm; AF, atrial fibrillation; AF_{uni}, conduction velocity of uniform beats during atrial fibrillation; and AF_{avg}, average median conduction velocity during atrial fibrillation.

*$P<.05$ compared with both other types of AF.

†$P<.05$ compared with type I AF.

‡$P<.05$ compared with type III AF.

as obtained by high-resolution mapping (244 points). In type I fibrillation, the right atrium was activated by broad wave fronts propagating rapidly and without significant conduction delay. The activation during type II was more complex, showing a higher degree of delayed conduction and intra-atrial conduction block. During type III, activation was highly complex, with the right atrium activated by three or more wavelets that frequently reentered either themselves (leading circle reentry) or each other (random reentry).

In both studies, the mean atrial rate increased from type I to type III. Wells et al[17] measured a mean atrial cycle length of 179 milliseconds in type I and 151 milliseconds in type II fibrillation, whereas in our patient population the different types of fibrillation showed an average median fibrillation interval of 174, 150, and 136 milliseconds with a mean range of 54, 94, and 104 milliseconds, respectively (P_{5-95}).

Because of the totally chaotic nature of the bipolar recordings in the study of Wells et al, the atrial rate

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TABLE 2. Continued

Electrical Inactivity, % of time	Incidence of Reentry, % of beats: Random	Incidence of Reentry, % of beats: Leading Circle	Incidence of Epicardial Breakthrough, % of beats
60	0	0	0
55	0	0	0
32	0	0	0
42	0	0	0
39	0	0	0
35	0	20	0
24	0	13	0
45	0	0	0
39	0	0	0
52	0	0	0
42±11*	0±0*	3±7*	0±0‡
15	4	10	0
23	7	82	0
22	13	0	4.5
23	15	8	1.8
15	23	31	1.4
20	0	33	0
24	13	24	0
26	3	3	3.3
21±4*	8±8*	28±25*	1.4±1.8
14	21	14	0
7	85	30	2.4
11	38	56	4.8
10	31	54	3.7
7	48	93	3.3
8	21	64	0
2	42	95	10.6
8±4*	33±10*	66±29*	3.5±3.6†
26±16	14±21	25±31	1.4±2.5

during type III fibrillation could not be accurately determined. This points to an important limitation of using widely spaced bipolar electrodes for the characterization of atrial fibrillation. As shown by our activation maps, during type III fibrillation atrial activation is highly dissociated. Consequently, two distant electrodes will frequently record from different activation waves rather than record a differential signal of a single depolarization wave. Under these circumstances, a widely spaced bipolar electrogram should be regarded as a dual unipolar electrogram representing two irregular dissociated rhythms that cannot be used to determine the fibrillation rate. Thus, for the recording of endocardial or epicardial electrograms of atrial fibrillation, either unipolar or closely spaced bipolar electrodes (<1 mm) should be used.

Mapping of Atrial Fibrillation

Mapping of atrial fibrillation has been performed in a number of studies.[6-14] In some of the studies, atrial fibrillation was sustained by cholinergic stimulation,[6,7,11] hypokalemia,[8] or atrial enlargement resulting from mitral valve incompetence.[10] These studies indicate that atrial fibrillation is based on reentry. The various cases disclose a wide spectrum of activation patterns, ranging from a single macroreentrant circuit to numerous mutually reentering wavelets.

In our studies of cholinergic fibrillation in canine hearts[6,7] and in those by Wang et al,[11] total mapping of both atria exhibited complex activation patterns resulting from the interference of an average of about six individual wavelets. Obviously, "fine" atrial fibrillation as present during vagal or cholinergic stimulation is associated with the most complex activation patterns classified in this study as type III fibrillation.

In humans, only one other mapping study of atrial fibrillation has been reported.[10] This study described findings in 13 patients with WPW syndrome (age, 15 to 36 years) who were operated on for division of an accessory atrioventricular connection. In all patients, atrial fibrillation was induced by burst atrial pacing. In 6 patients, atrial activation patterns were found that were suggestive of reentry in the right atrium. In some of them, functional conduction block appeared to be associated with an underlying structure such as the crista terminalis. The cycle length of right atrial reentrant circuits ranged between 180 and 210 milliseconds. The left atrium was activated nonuniformly by wave fronts emerging from either the right atrial reentrant circuit or the accessory atrioventricular pathway. Documentation of complete left atrial reentry was rare. In the remaining 7 patients, reentry could not be conclusively demonstrated, but the repetitive sequence of activation of the atria was compatible with a large reentrant atrial pathway partly through the interatrial septum.[10]

When we compare our results with the fibrillation maps in the article of Cox et al,[10] we conclude that in all of their cases, the pattern of activation of the right atrial free wall was consistent with type I fibrillation. This implicates that during type I fibrillation, the broad uniform wave fronts propagating across the free wall of the right atrium may be part of a large reentrant circuit around one of the natural anatomic obstacles present in the atria, with dimensions considerably larger than the diameter of our mapping electrode (3.6 cm). In contrast, during type III fibrillation, we frequently observed shifting leading circle reentry in the right atrium with a diameter of only 1 to 2 cm. The fact that in the study of Cox et al[10] no maps of type III fibrillation were shown might be the result of the lower spatial resolution used in that study, in which a total of 156 electrodes were divided over the total epicardial surface of both atria. The resulting relatively large interelectrode distance of about 1 cm makes it difficult to reconstruct the more complex activation patterns of type III fibrillation, and the underlying shifting microreentrant circuits might easily be missed.

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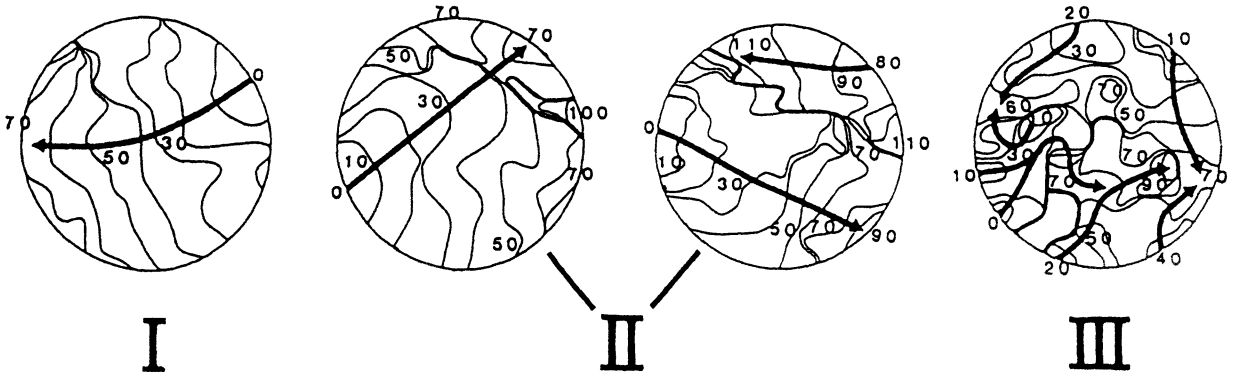

FIG 8. Mapping criteria for classification of atrial fibrillation. Type I is characterized by single uniformly propagating waves. During type II, single nonuniformly conducting waves or two wavelets are present. Type III is characterized by the presence of three or more wavelets associated with multiple areas of slow conduction and arcs of conduction block.

Types I, II, and III Fibrillation: Do They Represent Different Mechanisms?

Atrial fibrillation is a clinical diagnosis based on the absence of regular P or F waves and the presence of irregular RR intervals. However, as emphasized by the present study, from a pathophysiological point of view, it is likely that atrial fibrillation is not a homogeneous arrhythmia. The electrocardiographic characteristics of atrial fibrillation can be caused by several different electrophysiological mechanisms: (1) a single fixed source of rapid impulses that are not followed in a regular 1:1 fashion by all parts of the atrial myocardium (fibrillatory conduction), (2) a single shifting source of rapid impulses (wandering circuit), (3) two or more asynchronous sources of rapid impulses (parasystolic fibrillation), and (4) multiple propagating wavelets reentering each other or/and themselves (multiple wavelets).

The recent mapping studies in both humans and dogs have failed to demonstrate a significant role of automatic foci in the perpetuation of atrial fibrillation and, with the exception of its initiation, have been shown to be entirely based on abnormalities in intra-atrial conduction. Our present study shows that type III fibrillation in humans is based on multiple reentering wavelets. On the other hand, type I fibrillation might be more consistent with a single macroreentrant circuit giving rise to irregular activation of other parts of the atria. From a pathophysiological point of view, type I fibrillation actually might also be regarded as a case of atrial flutter (possibly type III flutter) with such a high rate that it cannot be followed in a 1:1 fashion by all parts of the atria. If this were true, type I atrial fibrillation might be a good candidate for termination by rapid pacing.[23]

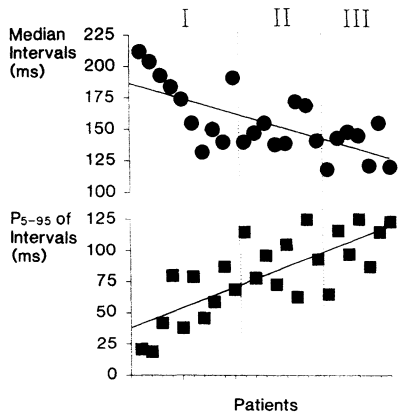

FIG 9. Three types of atrial fibrillation as a continuous spectrum of atrial fibrillation. On the abscissa, the 25 patients are ranked in order of increasing complexity of their activation patterns of atrial fibrillation. On the ordinate, the median fibrillation interval and the variation in fibrillation interval (P_{5-95}) are plotted. Going from the most simple case (type I) to type III fibrillation, both the interval and the variation in fibrillation intervals changed progressively. There were no abrupt changes in these variables between the different types of fibrillation.

Study Limitations

In the present study, atrial fibrillation was mapped in a group of young patients (average age, 32 years) with WPW syndrome. In these patients, the atria are apparently normal and showed a normal spread of activation during sinus rhythm and rapid atrial pacing. Thus, the patient population of the present study is not representative for the group of patients with clinical paroxysmal or chronic atrial fibrillation. The incidence of atrial fibrillation largely increases with age and is reported to be about 4% in the general population older than 60 years of age.[24] Also, the conduction properties of the atrium have been shown to change with age because of the development of intra-atrial fibrous septa, thus providing numerous anatomic substrates for conduction block and reentry.[25] Although it has recently been demonstrated that the presence of an accessory atrioventricular connection does not affect the vulnerability of the atria to fibrillate in response to rapid atrial pacing,[26] it is unknown to what extent the existence of an accessory pathway affects the characteristics of the fibrillation process. In addition, the mechanisms underlying spontaneous atrial fibrillation in the elderly or in cardiac patients may be different from electrically induced self-terminating atrial fibrillation as studied in our group of patients.

Another important limitation of this study is that in most patients, recordings were made of only one area (the right atrial free wall) during one episode of atrial fibrillation and that only one sample of 12 seconds was analyzed. Obviously, this makes it hazardous to extrapolate our findings both to other parts of the atria and to other episodes of atrial fibrillation. In 8 of 25 patients, we were able to analyze the patterns of excitation of

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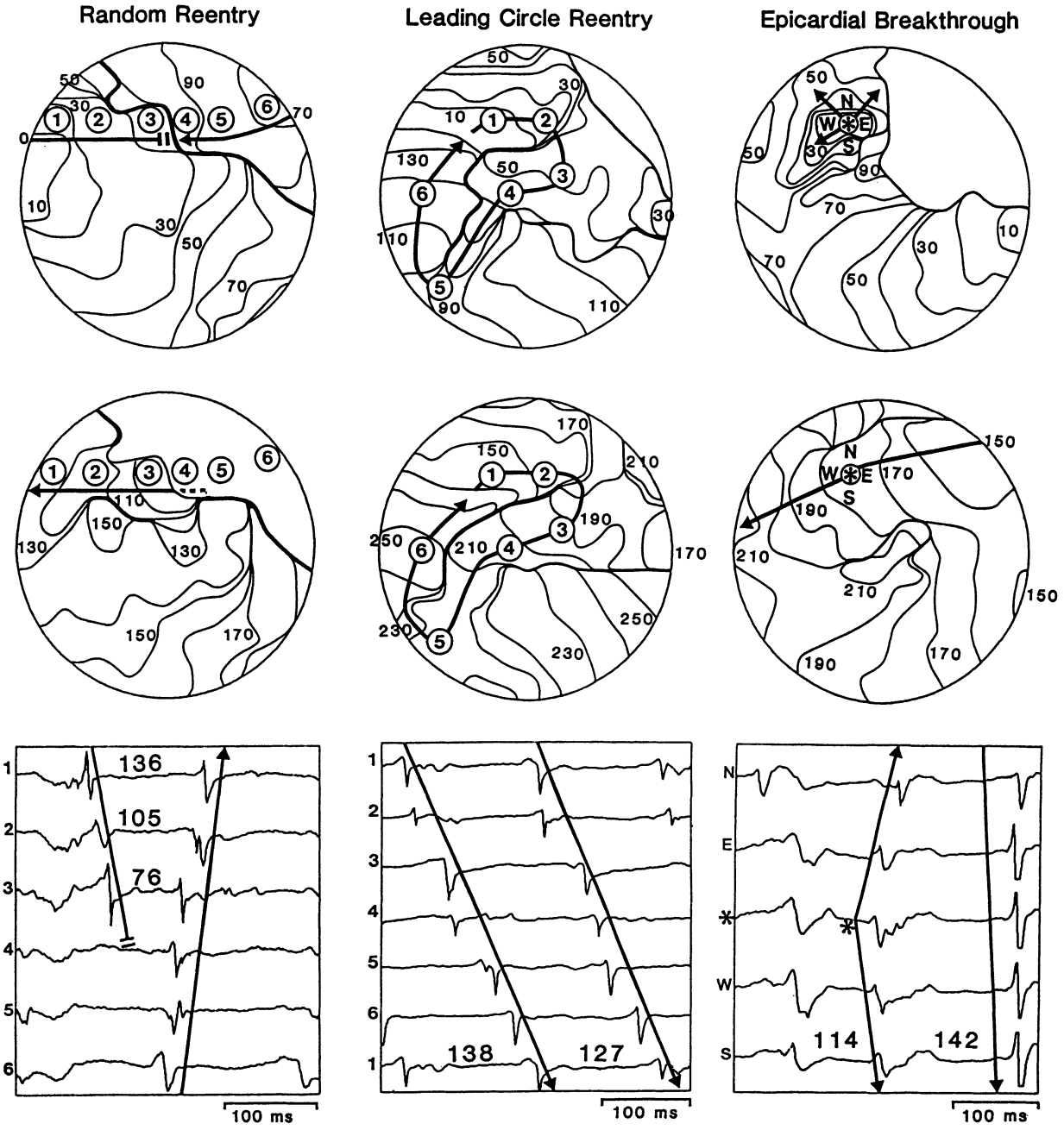

FIG 10. Two different types of reentry (random reentry and leading circle reentry) and a focal type of activation during atrial fibrillation. The sites of the unipolar electrograms given below the maps are indicated on the maps. During random reentry, a wavelet reexcites tissue that shortly before has been activated by another simultaneously present wavelet. During leading circle reentry, the impulse circulates around a shifting central line of functional conduction block. A focal activation pattern (right) was preceded by a small r wave at the earliest electrogram (*) and was never observed during more than one beat. See text for discussion.

both the right and left atrial free wall during the same episode of atrial fibrillation. In these patients, no major differences were found between the right and left atria in type of fibrillation, local fibrillation intervals, and variation in fibrillation intervals. However, because the group of patients is rather small, general conclusions cannot be drawn about *spatial* differences in activation patterns during atrial fibrillation. Because we analyzed only a single episode of atrial fibrillation in each patient, we cannot address the question of whether *temporal* variations among the three types of fibrillation may occur.

Clinical Implications

At present, the clinical relevance of our observations is not clear. Is the pacing-induced arrhythmia the same as spontaneously occurring atrial fibrillation, or is it more comparable to polymorphic ventricular tachycardia, which can be induced in the normal ventricle during aggressive ventricular pacing? In this respect, it is important that in 15 of the 25 patients the induced arrhythmia lasted for more than 2 minutes, suggesting a sustained and stable nature of the arrhythmia. In the 7 patients who had clinical documentation of atrial fibrillation, no preference for one of the three types of induced atrial fibrillation was

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TABLE 3. Comparison of Right and Left Atria

	Right Atrium			Left Atrium		
		Interval, ms			Interval, ms	
Patient no.	Type of AF	Median	P_{5-95}	Type of AF	Median	P_{5-95}
4	I	174	38	I	197	84
14	I	155	79	I	167	24
9	I	191	69	II	167	92
12	II	155	96	II	150	109
6	II	139	105	III	133	126
25	II	169	125	II	156	107
2	III	148	97	II	154	112
16	III	121	87	III	143	126
Mean±SD		157±22	87±26		158±19	98±31

AF indicates atrial fibrillation.

found, suggesting that during spontaneous atrial fibrillation, different numbers and dimensions of intra-atrial circuits may be present. The question remains of how often during atrial fibrillation fluctuations in number and dimension of intra-atrial circuits occur in the same patient. This might be relevant to ablative procedures to prevent those circuits from occurring. It is also of importance when pacing techniques are considered for termination and prevention of atrial fibrillation. Observations during spontaneously occurring episodes of atrial fibrillation are required to answer these questions.

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