Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Alteration of Ventricular Fibrillation by Flecainide, Verapamil, and Sotalol
An Experimental Study

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Background—The purpose of this study was to determine whether the myocardial electrophysiological properties are useful for predicting changes in the ventricular fibrillatory pattern.

Methods and Results—Thirty-two Langendorff-perfused rabbit hearts were used to record ventricular fibrillatory activity with an epicardial multiple electrode. Under control conditions and after flecainide, verapamil, or *d,l*-sotalol, the dominant frequency (FrD), type of activation maps, conduction velocity, functional refractory period, and wavelength (WL) of excitation were determined during ventricular fibrillation (VF). Flecainide (1.9±0.3 versus 2.4±0.6 cm, $P<0.05$) and sotalol (2.1±0.3 versus 2.5±0.5 cm, $P<0.05$) prolonged WL and diminished FrD during VF, whereas verapamil (2.0±0.2 versus 1.7±0.2 cm, $P<0.001$) shortened WL and increased FrD. Simple linear regression revealed an inverse relation between FrD and the functional refractory period ($r=0.66$, $P<0.0001$), a direct relation with respect to conduction velocity ($r=0.33$, $P<0.01$), and an inverse relation with respect to WL estimated during VF ($r=0.49$, $P<0.0001$). By stepwise multiple regression, the functional refractory periods were the only predictors of FrD. Flecainide and sotalol increased the circuit size of the reentrant activations, whereas verapamil decreased it. The 3 drugs significantly reduced the percentages of more complex activation maps during VF.

Conclusions—The activation frequency is inversely related to WL during VF, although a closer relation is observed with the functional refractory period. Despite the diverging effects of verapamil versus flecainide and sotalol on the activation frequency, WL, and size of the reentrant circuits, all 3 drugs reduce activation pattern complexity during VF. (*Circulation*. 2000;101:1606-1615.)

Key Words: ventricular fibrillation ■ mapping ■ antiarrhythmic agents ■ electrophysiology

M odification of cardiac electrophysiological properties and analysis of its repercussions on the activation patterns have provided useful information for furthering our knowledge of atrial fibrillatory processes.[1–5] Interpretation of antiarrhythmic drug action on ventricular fibrillation (VF) entails the added difficulty of myocardial metabolic impairment secondary to the interruption of coronary perfusion.[6–10] The use of experimental models in which myocardial perfusion is maintained during VF[8,10–12] facilitates analysis of the characteristics of the arrhythmia and its relation to the electrophysiological properties of the ventricular myocardium, as in studies of atrial fibrillation.[2–5,13–16] The present study investigates the pharmacological modifications of the VF activation pattern induced by 3 antiarrhythmic drugs (flecainide, verapamil, and *d,l*-sotalol) in the isolated rabbit heart using both time- and frequency-domain techniques and analysis of the epicardial activation maps. The purpose of the study is to analyze the variations in activation frequency and

the complexity of the fibrillatory pattern produced by these drugs and to determine whether the modifications in myocardial electrophysiological properties are useful for predicting changes in the ventricular fibrillatory processes.

Methods

Experimental Preparation

The procedures followed in this study conformed to institutional and NIH guidelines for the care and use of laboratory animals (NIH publication 85-23, revised 1985).

Thirty-two California rabbits (mean weight, 3.9±0.6 kg) were used. After anesthesia with ketamine (25 mg/kg IM) and heparinization, the hearts were removed and immersed in cold (4°C) Tyrode's solution. After isolation, the aorta was connected to a Langendorff system for perfusing the Tyrode's solution at a pressure of 50 mm Hg and a temperature of 37±0.5°C. The millimolar composition of the perfusion fluid was NaCl 130, $NaHCO_3$ 24.2, KCl 4.7, $CaCl_2$ 2.2, NaH_2PO_4 1.2, $MgCl_2$ 0.6, and glucose 12. Oxygenation was carried out with a mixture of 95% O_2 and 5% CO_2.
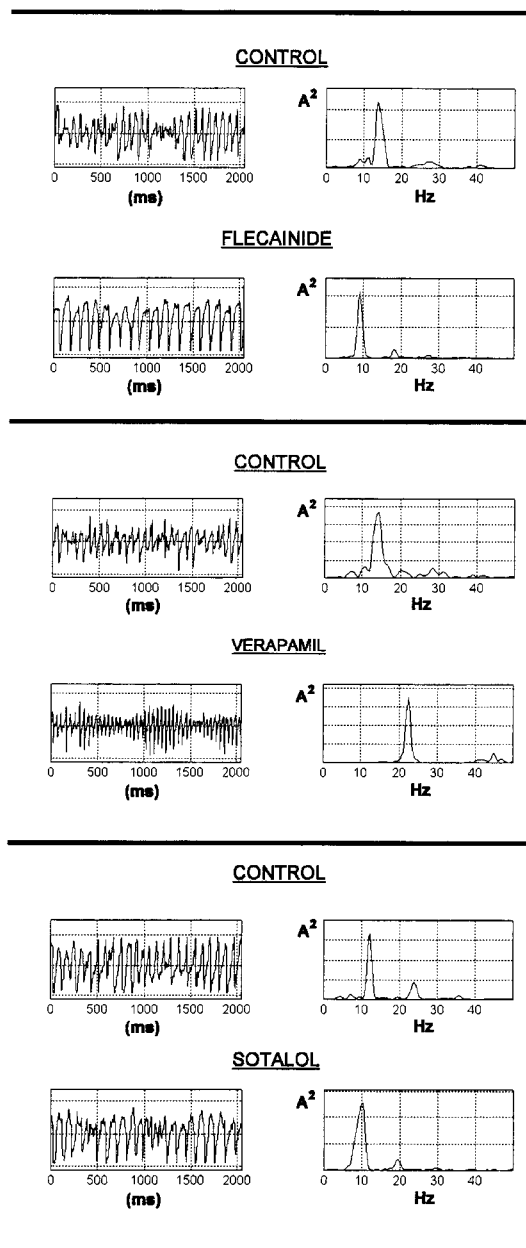
Figure 1. Power spectrum (right) and recordings obtained during 2-second time window beginning at 30th second of VF onset with 1 epicardial electrode (left) under control conditions and after drug administration. FrD decreases with flecainide and *d,l*-sotalol and increases with verapamil.

A plaque with 121 unipolar stainless steel electrodes (diameter, 0.125 mm; interelectrode distance, 1 mm) was positioned at the epicardial surface of the lateral wall of the left ventricle. The indifferent electrode was a 4×6-mm silver plaque located over the cannulated aorta. Ventricular pacing was performed with bipolar electrodes (diameter, 0.125 mm; interelectrode distance, 1 mm) located in the upper or central zone of the multiple electrode. Pacing (2-ms rectangular pulses, intensity twice the diastolic threshold) was carried out with a GRASS S88 stimulator with a stimulus isolation unit (SIU5). Recordings were obtained with a cardiac electrical activity mapping system (MAPTECH). The electrograms were amplified with a gain of 100 to 300, broadband (1 to 400 Hz) filtered, and multiplexed. The sampling rate in each channel was 1 kHz.

Experimental Protocol

Thirty minutes after the electrodes were positioned, the extrastimulus test with 2 extrastimuli was applied. The basic cycle (S_0S_0) was fixed at 250 ms. The first extrastimulus (S_1) was fixed at the minimum S_0S_1 interval that captured the ventricles when this interval was reduced in steps of 10 ms from 200 ms. The second extrastimulus (S_2) was delivered at increasing S_1S_2 intervals in steps of 2 ms until an interval 10 ms longer than the minimum S_1S_2 that captured the ventricles. VF was induced by pacing at increasing frequencies from 4 to 20 Hz, and coronary perfusion was maintained during the arrhythmia. Recordings were analyzed 30 seconds after the onset of VF. The heart was defibrillated 5 minutes after VF induction by a DC shock (5 J). After 15 minutes, the protocol was repeated when the antiarrhythmic drug was added to the Tyrode's solution: flecainide (1 μmol, n=10), verapamil (0.2 to 0.8 μmol, n=12), or *d,l*-sotalol (20 μmol, n=10). The concentrations of flecainide,[17–19] *d,l*-sotalol,[20,21] and verapamil[22,23] were selected from the range in which their characteristic electrophysiological effects are observed. In the case of verapamil, dose adjustment was also made according to the effect elicited on the AV Wenckebach cycle length, choosing the concentration that produced a prolongation of this parameter of ≥50%.

## Data Analysis

Constant Pacing at the Basic Train (250 ms)

The following parameters were determined: (1) Effective ventricular refractory period (EVRP) for S_2, or the maximum S_1S_2 interval that failed to induce ventricular activation. (2) Functional ventricular refractory period (FVRP), or the minimum V_1V_2 interval. (3) Ventricular conduction velocity, determined at the minimum V_1V_2 interval in both the longitudinal (VELG) and transverse (VELTR) direction of propagation. It was estimated by dividing the distance between 2 electrodes positioned 5 interelectrode spaces apart in the direction of maximum velocity as indicated by the isochrones or perpendicular to the former by the time interval between them. (4) Wavelength of the ventricular activation process (WL), or the product of the FVRP and the longitudinal conduction velocity.

Ventricular Fibrillation

Spectral analysis: Welch's method[24] was used to obtain the power spectrum of the signals recorded with 5 electrodes: 4 located in the midzone of each of the sides of the multiple electrode, and the fifth positioned in its central zone. The analysis was performed involving a data block of 2048 points (sampling rate, 1 kHz) (Figure 1). This 2-second window of the VF recordings began at the 30th second after the onset of the arrhythmia. The dominant frequency (FrD) and the energy contained in the segment of the periodogram corresponding to FrD±1 Hz was obtained for each block. Data processing was performed with Matlab software on a Hewlett-Packard 712/80 platform.

Time-domain Analysis: Activation times in each electrode were determined by identifying the moment of maximum negative slope of the electrograms. The minimal threshold for dV/dt to be judged as a local deflection was a percentage (20%) of the maximal negative slope in each channel. The fibrillation interval (VV) histograms and the median (MN) of the consecutive VV intervals were determined during the same 2-second time windows.

Analysis of the Epicardial Activation Maps During VF: The maps were constructed every 100 ms in the 2-second time windows of the VF recordings. Isochrones were drawn semiautomatically at 5-ms intervals, and each map was classified into 3 categories based on its complexity[13]: type I, single broad wave fronts propagating uniformly without significant conduction delay; type II, 2 wave fronts or 1 wave front with areas of conduction block or slow conduction; and type III, ≥3 wave fronts associated with areas of slow conduction and conduction block (Figure 2). Likewise, for each map, the presence of activation patterns corresponding to complete reentry was analyzed (Figure 3). In these maps, the electrodes activated on the internal portion of the reentrant wave front were identified by
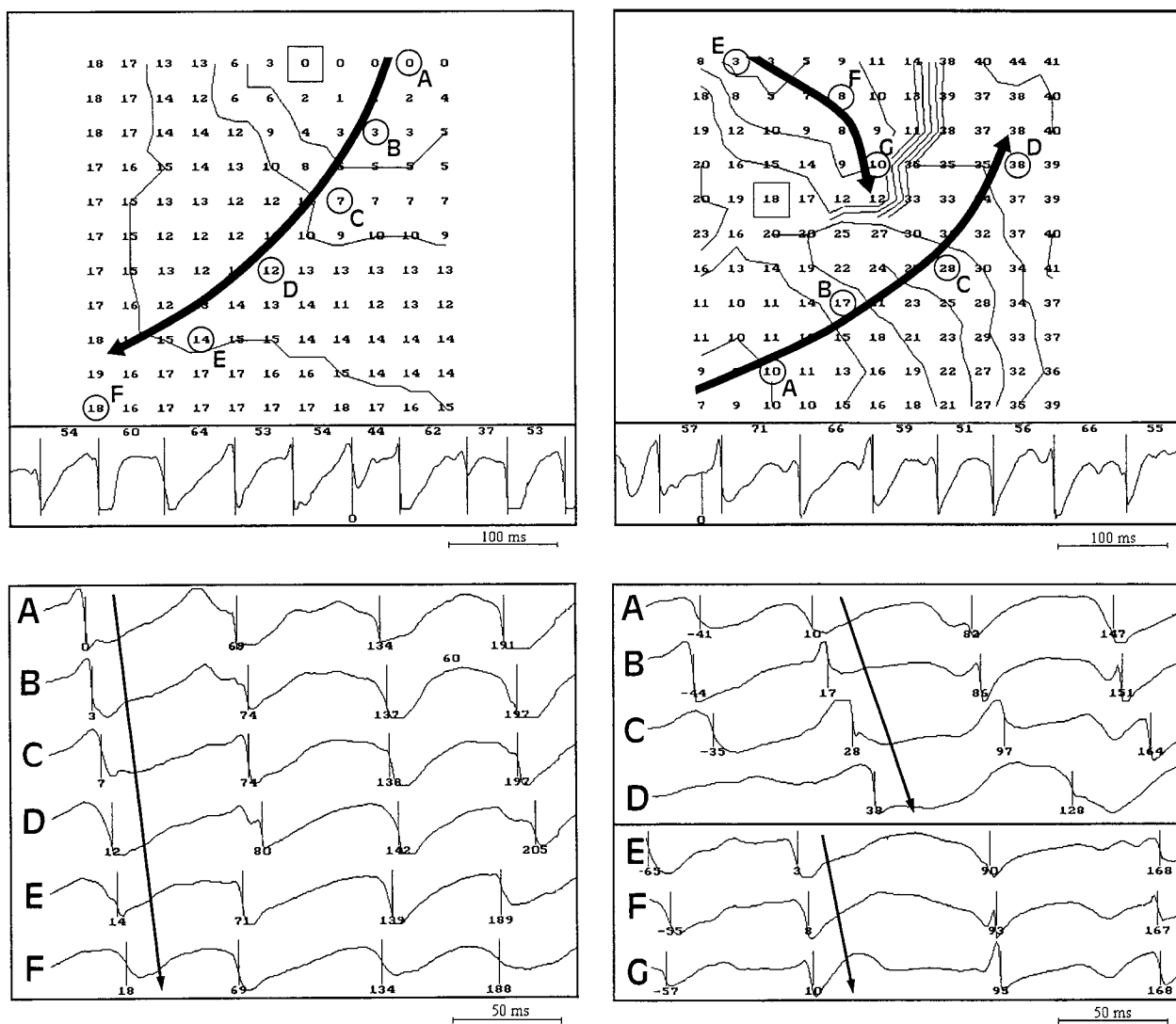
Figure 2. Types of activation maps according to complexity. Left, Type I; center, type II; and right, type III. Top, Activation maps. Bottom, Selected electrograms along trajectory of wave fronts.
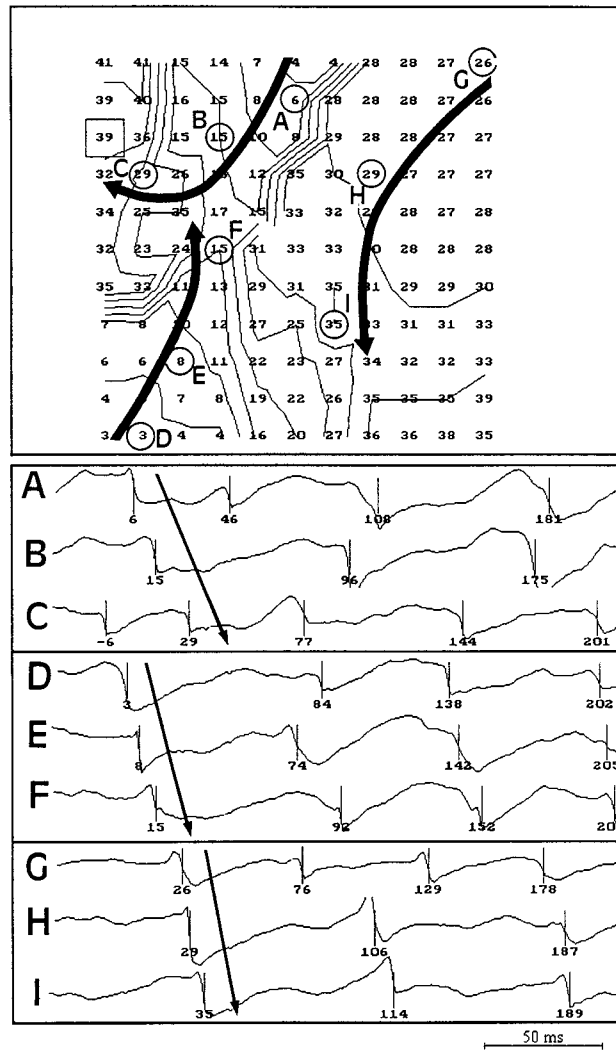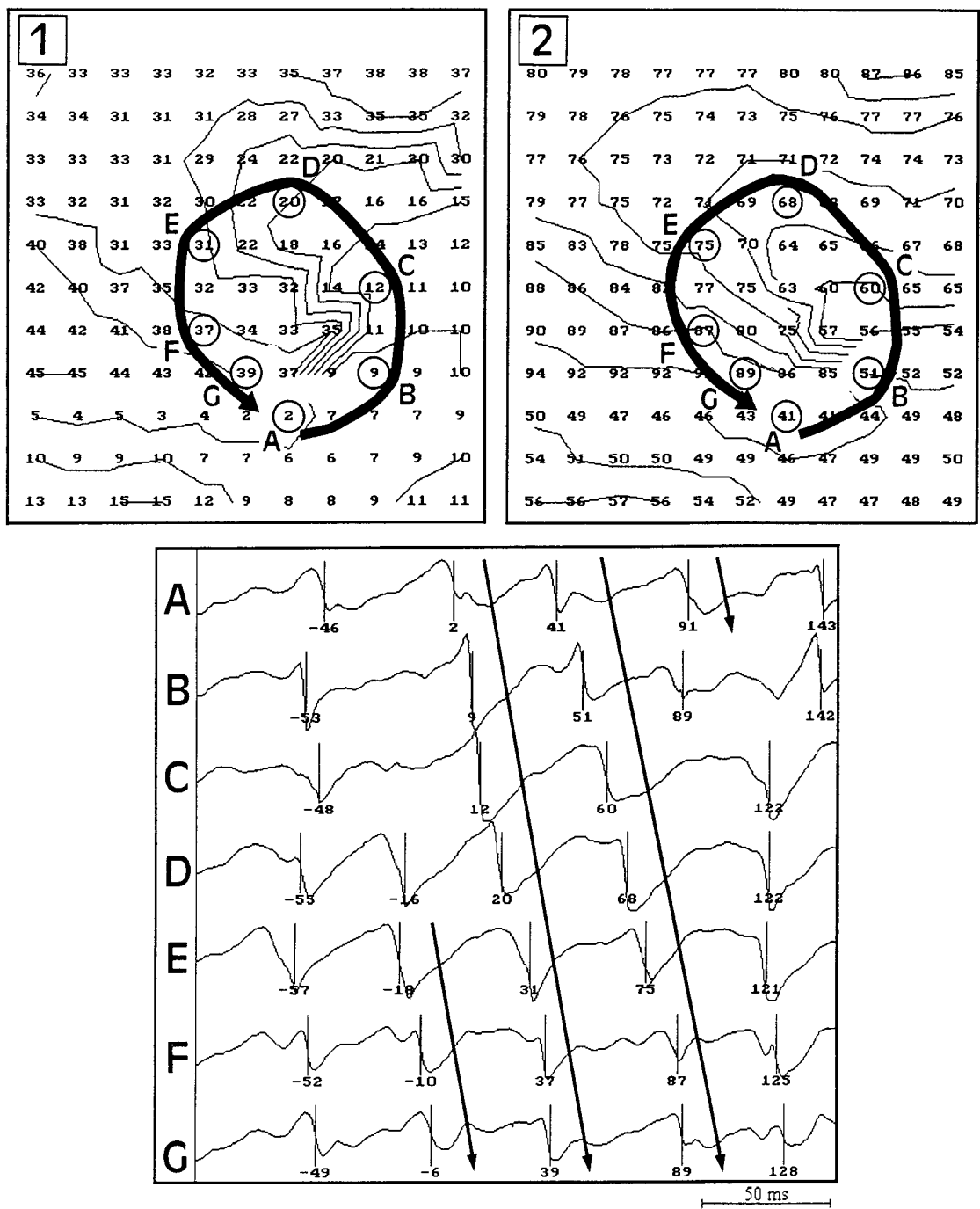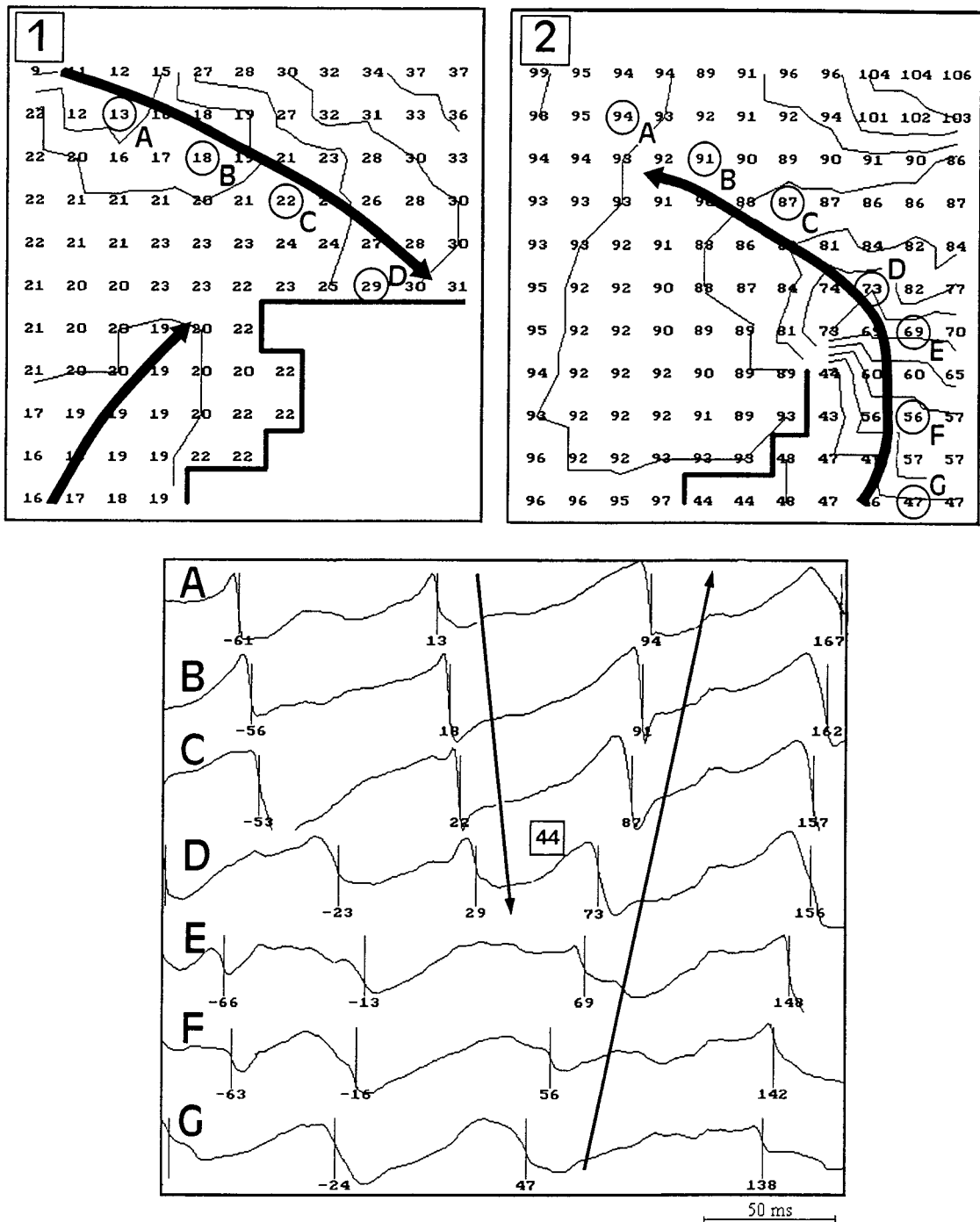
Figure 2. Continued

Figure 3. Consecutive activation maps (1 and 2) obtained during VF showing complete reentry activation pattern. Locations of electrodes A to G are indicated, selected along trajectory of reentrant waveform; corresponding recordings are shown at bottom.

Figure 4. Consecutive ventricular activation maps obtained during VF, showing how zone activated by wave front entering from upper left of map 1 to conduction block on reaching middle zone at right (electrodes A to D) is activated immediately after by another, different wave front entering from lower right in map 2 (electrodes G to A). Time between 2 successive activations of electrode D is 44 ms. FRPVF was taken as average of 5 smallest intervals obtained on analysis of all maps in which this activation pattern was repeated.

display of successive 10-ms time windows. These electrodes delimited the central core, whose maximum diameter (ie, length of the central core) was measured with the grid electrode matrix as reference. The area encompassed by the central core plus 2 electrodes recording the reentrant activation and the number of consecutive rotations were also determined.

Conduction Velocity During VF (VELVF): In the maps in which the activation front entered the area encompassed by the electrode, without

evidence of breakthrough, velocity was calculated by dividing the distance between 2 electrodes positioned 5 interelectrode spaces apart in a direction perpendicular to the isochrones by the difference between their activation times (average of 5 determinations).

Functional Refractory Period During VF (FRPVF): The minimum intervals between 2 successive activations by 2 different wave fronts were determined (Figure 4). FRPVF was regarded as the average of the 5 smallest values.

TABLE 1.   Electrophysiological Parameters (Mean±SD) Obtained in Each Group of Experiments

	Flecainide		Verapamil		Sotalol	
	Control	Drug	Control	Drug	Control	Drug
EVRP, ms	114±14	131±18*	120±13	111±15	129±16	143±20*
FVRP, ms	123±12	143±16†	130±11	118±15*	139±16	154±18*
VELG, cm/s	59.2±16.0	47.6±14.5‡	56.3±15.4	60.9±12.5	56.2±6.7	51.6±8
VELTR, cm/s	23.3±9.9	16.4±4.8*	19.4±3.2	20.6±2.7	23.2±3.3	22.4±4.6
WL, cm	7.3±2.3	6.8±2.1	7.3±2.1	7.1±1.5	7.8±1.1	7.9±1.8
FRPVF, ms	41±4	70±7‡	47±5	39±2‡	47±5	66±11‡
VELVF, cm/s	47.2±6.6	34.6±7.4‡	43.1±4.3	43.3±4.7	45.4±5.1	39.0±5.8*
WLVF, cm	1.9±0.3	2.4±0.6*	2.0±0.2	1.7±0.2‡	2.1±0.3	2.5±0.5*

Significance of the control vs drug differences: *$P<0.05$, †$P<0.01$, ‡$P<0.001$.

WL During VF: WLVF, or the product of FRPVF and VELVF, was analyzed.

Statistical Calculations

Data are presented as mean±SD. Comparisons between 2 sets of data were made with Student's *t* test for paired and unpaired data. The differences between qualitative variables were analyzed by χ^2 test. Differences were considered significant for $P<0.05$. The linear regressions between pairs of variables were made by the least-squares method. Stepwise regression was used for multiple linear regression analysis.
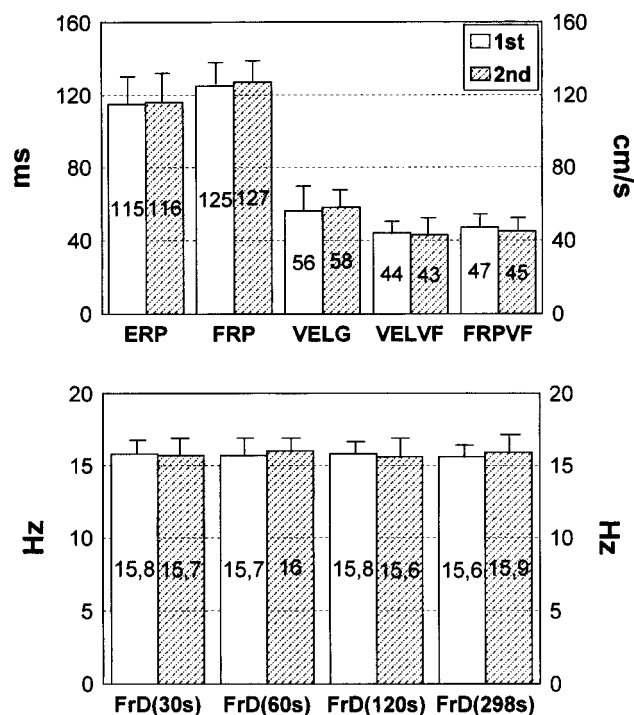
Figure 5. Reproducibility of determinations after repeated induction of VF without any drug (n=7). 1st and 2nd indicate first and second determinations; 30s, 60s, 120s, and 298s, 2-second time windows of VF recordings analyzed at 30, 60, 120, and 298 seconds from onset of VF.

Results

Effects on Electrophysiological Parameters During Constant Pacing (250 ms)

Both flecainide and *d,l*-sotalol significantly prolonged FVRP and EVRP, and flecainide reduced the conduction velocity (VELG and VELTR) (Table 1). Verapamil produced a slight shortening of the FVRP, without significant variations in EVRP or conduction velocity. None of the 3 drugs modified WL. Reproducibility of the determinations after a repeated induction of VF without adding any drug was tested, and no significant differences were found (Figure 5).

Drug Effects on the Fibrillatory Pattern

Electrophysiological Parameters During VF

Flecainide and *d,l*-sotalol significantly prolonged FRPVF and WLVF and reduced VELVF (Table 1). Verapamil reduced FRPVF and WLVF, although without changes in VELVF.

Spectral Analysis

Flecainide and *d,l*-sotalol produced a decrease in the FrD determined by the 5 selected electrodes, without significant variations in the energy contained in the interval FrD±1 Hz, whereas verapamil increased both parameters (Table 2).

Analysis in the Time Domain

Flecainide and *d,l*-sotalol produced an increase in the median of the VV intervals (MN) determined in each of the 5 selected electrodes or in the combined electrodes (Table 3). Verapamil produced a decrease in this parameter.

Analysis of the Activation Maps

In all 3 study groups, the most frequent activation maps under control conditions corresponded to type II (type I: flecainide control, 15%; verapamil control, 19%; sotalol control, 11%; type II: flecainide control, 46%; verapamil control, 49%; sotalol control, 52%; type III: flecainide control, 39%; verapamil control, 32%; sotalol control, 37%), and patterns exhibiting complete reentry were recorded in 18 maps (9%) of the flecainide group, in 14 maps (7%) of the verapamil group, and in 12 maps (6%) of the *d,l*-sotalol group.

TABLE 2.   Parameters (Mean±SD) Obtained by Spectral Analysis of the Fibrillatory Signal

	Flecainide		Verapamil		Sotalol	
	Control	Drug	Control	Drug	Control	Drug
FrD, Hz						
E1	14.7±1.5	9.4±1.9‡	14.4±1.4	20.4±2.1‡	12.6±1.4	10.7±1.3‡
E2	14.8±2.1	9.3±2.8‡	14.4±2.7	20.4±1.8‡	12.9±1.1	10.3±1.7‡
E3	15.8±1.9	9.6±2.0‡	14.7±2.2	20.4±1.6‡	13.2±1.4	11.5±1.8†
E4	15.9±2.8	9.8±1.9‡	14.5±2.4	20.3±1.9‡	12.5±1.2	10.9±1.9†
E5	16.2±2.2	10.3±1.9‡	14.9±2.2	19.9±2.8‡	12.3±1.4	11.2±1.3*
EG, Nu						
E1	0.25±0.03	0.25±0.04	0.25±0.05	0.30±0.04*	0.29±0.04	0.26±0.04
E2	0.26±0.03	0.24±0.04	0.24±0.03	0.30±0.05†	0.24±0.05	0.25±0.05
E3	0.25±0.04	0.26±0.05	0.25±0.05	0.32±0.04†	0.26±0.05	0.27±0.02
E4	0.24±0.04	0.25±0.04	0.26±0.05	0.31±0.05*	0.27±0.06	0.26±0.04
E5	0.25±0.03	0.24±0.06	0.22±0.05	0.29±0.06*	0.25±0.04	0.26±0.03

E1 to E5 indicate electrodes; Nu, normalized units.
Significance of the control vs drug differences: *$P<0.05$, †$P<0.01$, ‡$P<0.001$.

There were significant variations in the percentage of activation maps after administration of the 3 drugs ($P<0.001$), with a decrease in type III maps and an increase in maps of types I and II (type I: flecainide, 36%; verapamil, 24%; sotalol, 28%; type II: flecainide, 51%; verapamil, 58%; sotalol, 58%; type III: flecainide, 13%; verapamil, 18%; sotalol, 14%).

The number of activation maps with complete reentry patterns was 12 (6%) under the influence of flecainide, versus 14 (7%) and 12 (6%) with verapamil and *d,l*-sotalol, respectively. During flecainide perfusion, the number of consecutive rotations of reentrant activation did not vary (control, 1.4±0.6; flecainide, 1.3±0.5), whereas the length of the central core increased (control, 5±1; flecainide, 7±1 mm; $P<0.001$), as did the area encompassed by the central zone and the 2 electrodes recording the reentrant activation (control, 45±6; flecainide, 64±6 mm²; $P<0.001$).

Verapamil produced an increase in the number of consecutive rotations in the maps exhibiting reentry patterns (control, 1.3±0.4; verapamil, 2.1±1.1; $P<0.02$), with a significant decrease in the length of the central core (control, 5±1; verapamil, 4±1 mm; $P<0.02$) and the calculated area (control, 49±4; verapamil, 37±5 mm²; $P<0.001$).

d,l-Sotalol produced no significant variation in the number of consecutive rotations (control, 1.2±0.3; sotalol, 1.0±0.1), although increments were observed both in the length of the central core (control, 5±1; sotalol, 7±1 mm; $P<0.001$) and in area (control, 43±6; sotalol, 57±7 mm²; $P<0.001$).

Relation Between FrD and Electrophysiological Parameters

When the data corresponding to the control condition and after drug administration were considered jointly, the regression lines obtained on relating FrD (in Hz) to the MN (in ms) or its inverse (IMN, in Hz) were as follows: FrD=0.19 MN+28.6; $r=0.88$; n=64; $P<0.0001$; SEE=1.9 Hz; SE of the constant=1; SE of the coefficient=0.01. FrD=1.0 IMN−0.02; $r=0.92$; n=64; $P<0.0001$; SEE=1.6 Hz; SE of the constant=0.82; SE of the coefficient=0.06.

Simple regression analysis yielded significant results with the following parameters: EVRP ($r=0.51$, $P<0.0001$), FVRP ($r=0.59$, $P<0.0001$), FRPVF ($r=0.66$, $P<0.0001$), VELG ($r=0.31$, $P<0.01$), VELVF ($r=0.33$, $P<0.01$), and WLVF ($r=0.49$, $P<0.0001$). By stepwise multiple regression, the independent variables entered in the function were in first place FRPVF, and in second place FVRP ($r=0.71$, $P<0.0001$).

TABLE 3.   Median of VV Intervals (Mean±SD) During Ventricular Fibrillation

	Flecainide		Verapamil		Sotalol	
Median, ms	Control	Drug	Control	Drug	Control	Drug
E1	69±11	95±10*	75±8	52±5*	83±9	100±11*
E2	68±10	97±14*	73±8	52±6*	77±12	99±13*
E3	63±6	95±12*	75±6	51±5*	80±8	94±13*
E4	63±9	95±9*	73±7	50±5*	83±12	99±21†
E5	62±9	94±11*	73±6	51±5*	79±9	96±14*
All	64±8	95±10*	74±7	51±5*	80±8	96±13*

E1 to E5 and All indicate electrodes.
Significance of the control vs drug differences: *$P<0.001$, †$P<0.01$.

Conclusions

(1) Flecainide and *d,l*-sotalol prolong WLVF, whereas verapamil shortens it. (2) An inverse relation exists between FrD and WLVF, although this relation is more accentuated when ventricular refractoriness is considered. (3) The drug-induced modifications in activation frequency and WL are accompanied by significant changes in reentrant wave-front size, with increments induced by flecainide and *d,l*-sotalol and decrements under the action of verapamil. (4) Despite the divergent effects on activation frequency, WL, and reentrant circuit size of verapamil with respect to flecainide and *d,l*-sotalol, all 3 antiarrhythmic drugs diminish the complexity of the activation patterns during VF.

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