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Dispersion-based reentry: mechanism of initiation of ventricular tachycardia in isolated rabbit hearts

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Dispersion-based reentry: mechanism of initiation of ventricular tachycardia in isolated rabbit hearts. *Am. J. Physiol.* 276 (*Heart Circ. Physiol.* 45): H413–H423, 1999.—The aim of the study was to determine whether facilitation of reentry by potassium-channel openers is related to dispersion of refractoriness and/or modification of anisotropic properties of ventricular myocardium. The dispersion of ventricular effective refractory period (VERP), longitudinal and transverse ventricular conduction velocities (θ_L and θ_T , respectively), and wavelength [$\lambda = \text{VERP} \times \theta(L \text{ or } T)$] were studied in Langendorff-perfused left ventricular epicardium in 20 rabbits during infusion of incremental doses of levromakalim or nicorandil. Dispersion of refractoriness was assessed using standard deviation of VERP mean (SD-VERP), dispersion index (DI; SD-VERP/mean VERP), and maximum dispersion ($D_{\max} = \text{VERP}_{\max} - \text{VERP}_{\min}$). Ventricular conduction velocities and anisotropic ratio were not modified, whatever the dose used. VERP and λ were significantly shortened at high concentrations of levromakalim and nicorandil. At these doses, SD-VERP, DI, and D_{\max} were increased significantly. Analysis of ventricular tachycardia induction, performed using a high-resolution ventricular mapping system, confirmed that heterogeneity and shortening of VERP were factors inducing functional conduction block. Our data suggest that, in rabbit left ventricular epicardium, functional conduction block facilitating the occurrence of reentry could be initiated by shortening and, especially, by dispersion of refractoriness during infusion of potassium-channel openers.

heart; ventricular arrhythmia; epicardial mapping; potassium-channel openers

MOST CARDIAC ARRHYTHMIAS are due to reentrant mechanisms. It is well established that unidirectional conduction block is required for the initiation of a reentry (27). This conduction block can be anatomic (5–7) or functional. The occurrence of functional block is facilitated by anisotropic changes, especially those in the longitudinal direction (34, 37). Indeed, Clerc (11) and Spach et al. (36, 37) demonstrated that there are directional differences in the impulse propagation (i.e., longitudinal direction vs. transverse direction). In addition to this mechanism, functional conduction block can result from a marked slowing of conduction velocity, especially that due to use dependency (2), as has been

shown with class I antiarrhythmic agents and drugs such as imipramine (8, 12, 31). Another hypothesis is that increased dispersion of refractoriness could lead to functional conduction blocks and reentrant arrhythmias (1, 22). Using activation and refractory maps of the right ventricle in dogs 3–5 days postinfarction, Gough et al. (21) have shown that unidirectional conduction block can be induced as a result of heterogeneity of refractoriness. However, in this study, the nonuniform pattern of conduction and repolarization was anatomically determined, because it involved normal versus infarcted areas of heart. Thus, to our knowledge, the possibility of occurrence of unidirectional conduction block in ventricles with randomly heterogeneous refractoriness has never been directly demonstrated.

Potassium-channel openers are known to act on potassium ATP-dependent channels in cardiac tissue. The opening of this channel produces an acceleration of repolarization with shortening of action potential duration and effective refractory period (17). Moreover, the activation of this channel has deleterious consequences on cardiac rhythm in normoxic conditions, including ventricular fibrillation and tachycardia (13, 39). Using a microelectrode technique on canine ventricular myocardium, Di Diego and Antzelevitch (14) demonstrated that the activation of ATP-dependent potassium channel by pinacidil leads to a dispersion of repolarization and refractoriness in epicardium as well as between epicardium and endocardium. Consequently, an extrasystolic activity can occur, which is based on the mechanism that they called “*phase 2* reentry.” In a previous study (32) in isolated rabbit hearts, we demonstrated that both levromakalim and nicorandil produce reentrant ventricular tachycardia without changing either longitudinal or transverse ventricular conduction velocities. However, the precise mechanism leading to reentry was not fully investigated. We hypothesized that conduction block induced by potassium-channel openers is initiated by the shortening of ventricular effective refractory period and by an increased spatial dispersion of its value over the epicardium. Therefore, the aim of the present mapping study was to determine the role of potassium-channel opener-induced dispersion of refractoriness in the initiation of conduction block and reentry.

METHODS

Heart preparation. The principles for the care and treatment of animal experiments complied with the national guidelines of the French Ministry of Agriculture. Twenty New Zealand rabbits weighing 3.0 ± 0.5 kg were anesthetized with ketamine (50 mg/kg im). In each rabbit, the trachea was intubated and the lungs were mechanically ventilated with 100% O₂ (Logic 07, ATM, Maurepas, France). As previously described (32), the chest was surgically opened by a midsternal incision. After heparin (1,000 IU iv) was administered, the heart was quickly removed and placed in a cold perfusion fluid. The aorta was immediately cannulated, and the heart was connected to a Langendorff perfusion system using a Tyrode solution at a temperature of 37°C. The coronary arteries were perfused with a constant flow of 40–50 ml/min (Watson-Marlow 101U pump, Falmouth, UK), resulting in a perfusion pressure of 70 ± 10 mmHg (Gould P23 transducer, Oxnard, CA; CGR monitor, St-Cloud, France). Finally, all hearts underwent destruction of the pulmonary and mitral valves to allow the cryoprobe insertion. The composition of the Tyrode solution was 130 mmol/l NaCl, 20.1 mmol/l NaHCO₃, 4.0 mmol/l KCl, 2.2 mmol/l CaCl₂, 0.6 mmol/l MgCl₂, 1.2 mmol/l NaH₂PO₄, and 12 mmol/l glucose. The solution was saturated with a mixture of 95% O₂ and 5% CO₂, and pH was adjusted at 7.40 ± 0.02 .

In all hearts, an endocardial cryotechnique was used to completely destroy the right ventricle, the interventricular septum, and the endocardial and intramural layers of the free wall of the left ventricle. This cryotechnique was used to avoid epicardial breakthrough of longitudinal wave fronts from deeper layers and to allow complete mapping of electrical activation in two dimensions. Briefly, a cryoprobe was inserted through the pulmonary artery in the right ventricle and filled with liquid N₂ (–192°C). The probe was maintained in the ventricle until it was completely frozen. During freezing, the left ventricle was watered by the fluid perfusion to prevent the epicardium from freezing. The heart was then immersed in a tissue bath containing perfusion fluid at 30°C. The cryoprobe was placed in the left ventricle through the left atrium, and the coronary circulation was interrupted. The cryoprobe was filled with liquid N₂ for 3 min, and the coronary circulation was restored thereafter. The probe was removed and the heart withdrawn from the tissue bath. During the rest of the experiment, the temperature of the heart was kept constant at 37°C. As a result of this procedure, only a thin epicardial layer (~1 mm thick) of the free wall of the left ventricle survived, with the rest of the myocardium being completely destroyed (4). It was previously demonstrated that in this thin surviving layer, refractoriness and conduction velocities were not affected by the procedure and remained stable for many hours, suggesting that the circulatory condition was adequate (12, 31, 32). At the end of the experiment, the hearts were dissected to verify the efficacy of the cryoprocure. If the freezing was not adequate, the heart was excluded from the study.

Protocol. Twenty frozen hearts were randomly divided into two groups. One group ($n = 10$) was given incremental concentrations (1, 5, 10, and 50 μmol/l) of levromakalim (BRL-38227, a gift of SmithKline Beecham Laboratoires Pharmaceutiques, Unité de Recherche, Saint-Grégoire, France), and the other group ($n = 10$) received nicorandil infusion (RP-46417, a gift of Rhône-Poulenc Rorer, Centre de Recherche de Vitry-Alforville, Vitry-sur-Seine, France) at 1, 5, 10, 50, 100, and 500 μmol/l.

Recording and induction of ventricular arrhythmia. High-resolution mapping of epicardial excitation was performed by

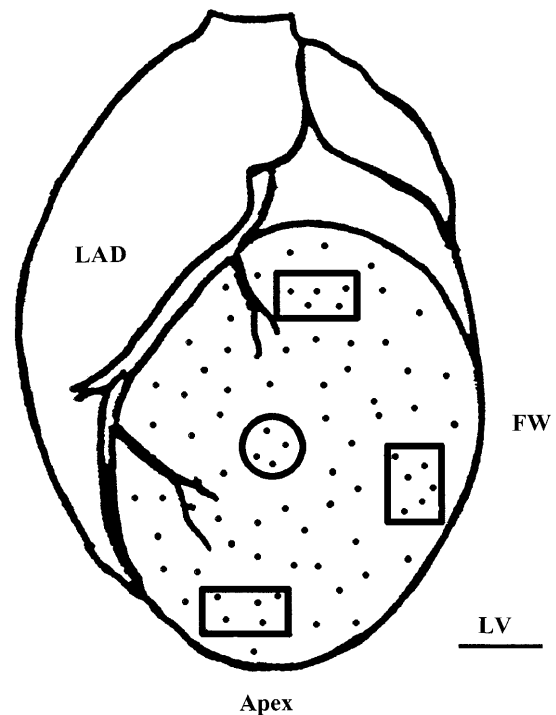


Fig. 1. Location of spoon-shaped electrode on left ventricle (LV). Unipolar electrograms were recorded from mapping array (dotted area). Central circle indicates main pacing site for measurement of conduction velocities and ventricular effective refractory period (VERP). Boxed areas on LV show 3 other sites at which VERP was measured. LAD, left anterior descending coronary artery; FW, ventricular free wall.

applying a spoon-shaped electrode containing 256 unipolar electrodes to the epicardial surface at a regular distance of 2.25 mm (Fig. 1). A computerized mapping system allowed simultaneous recording, storage, and automatic analysis of all 256 electrograms and on-line presentation of color-coded activation maps (Maptech System, Maastricht, The Netherlands) (3). Programmed electrical stimulation was performed using a programmable constant current stimulator. It delivered square pulses of 2 ms in duration at twice diastolic threshold for both regular stimulation and induction of premature beats (Maptech System). Induction of ventricular arrhythmia was performed with a bipolar stimulation protocol in all frozen hearts and consisted of 1) application of 1, 2, and 3 premature stimuli (S2, S3, and S4, respectively) delivered with decreasing coupling intervals after 10 basic stimuli (S1–S1) at 300-ms intervals, and 2) application of a train of 10 stimuli at a regular cycle length that was progressively decreased at 10-ms steps until one-to-one capture of the ventricle failed. After each concentration of levromakalim and nicorandil administered, the inducibility of ventricular arrhythmia was tested again using the same protocol as during the control. Once the protocol was completed, normal Tyrode solution was infused for an ~45-min period to allow a return to control conditions and to rule out the possibility of deterioration over time (washout). Any occurrence of ventricular arrhythmia was recorded and analyzed.

Electrophysiological measurements and data analysis. The following parameters were measured or calculated in the two groups at baseline, 20 min after each dose of levromakalim or nicorandil, and after washout: ventricular effective refractory period (VERP, in ms) at four sites, longitudinal ventricu-

lar conduction velocity (θ_L , in m/s), transverse ventricular conduction velocity (θ_T , in m/s), anisotropic ratio (θ_L/θ_T), longitudinal and transverse wavelength (λ , in mm), standard deviation of mean VERP (SD-VERP, in ms), index of dispersion (DI), and maximum dispersion (D_{\max} , in ms). As previously described by Clerc (11) and Spach et al. (37), cardiac tissue has a different axial resistance along and perpendicular to the fiber axis of the myocardial fibers. This different axial resistance results in direction-dependent differences in conduction velocity (anisotropic conduction). Therefore, pacing at the center of the thin surviving layer of the left ventricle produced an ellipsoidal spread of propagation with fast conduction parallel to the fiber axis (longitudinal conduction) and slow conduction perpendicular to the former (transverse conduction). Conduction velocity was defined as the distance traveled by the wave front per time unit. In each experiment, both longitudinal and transverse conduction velocities and anisotropic ratio were measured after 10 basic stimuli (S1–S1) at a 1,000-ms interval. In addition, to test the use dependence of the drug, these 3 parameters were measured after 10 basic stimuli at 900-, 800-, 700-, 600-, 500-, 400-, 300-, 250-, and 200-ms intervals. These parameters were also calculated after the last stimulation inducing ventricular tachycardia to exhibit a premature beat-induced slowing of conduction velocities.

VERP was defined as the shortest S1–S2 interval still resulting in a propagated premature impulse during regular pacing with an S1–S1 interval of 300 ms. VERP was determined by decreasing the coupling interval of the premature stimulus in steps of 1 ms. Measurement of VERP was done at the same four sites throughout the experiment (Fig. 1). The wavelength was calculated as the product of VERP, measured on the ventricular center site, and θ_L or θ_T , measured at a regular pacing of 300 ms. The dispersion was quantified by SD-VERP. Second, DI was defined as the quotient of SD-VERP and the mean of VERP after each dose of levocromakalim and nicorandil. D_{\max} was calculated as the difference between the maximum and the minimum values of VERP at each dose of the two drugs.

Definition of ventricular arrhythmia. We defined ventricular arrhythmia as ventricular fibrillation or sustained (SVT) or nonsustained ventricular tachycardia (NSVT). NSVT was defined as a ventricular tachycardia lasting more than three successive beats but <30 s before spontaneous termination. SVT was defined as a ventricular tachycardia that lasted >30 s. Finally, a separation into monomorphic (MVT) and polymorphic tachycardia (PVT) was made. The term "monomorphic" implied a uniform beat-to-beat QRS morphology. The term "polymorphic" was defined as the occurrence of continuous change in QRS configuration. When several types of arrhythmia occurred during administration of one concentration in one heart, the worst arrhythmia was taken into account.

Table 1. Effect of levocromakalim on longitudinal and transverse ventricular conduction velocities and on anisotropic ratio at a regular pacing of 1,000 ms

Concentration	<i>n</i>	θ_L , m/s	θ_T , m/s	θ_L/θ_T
Control	10	0.69 ± 0.01	0.35 ± 0.05	1.98 ± 0.24
1 $\mu\text{mol/l}$	10	0.75 ± 0.05	0.35 ± 0.05	2.13 ± 0.19
5 $\mu\text{mol/l}$	10	0.74 ± 0.05	0.35 ± 0.04	2.10 ± 0.14
10 $\mu\text{mol/l}$	10	0.72 ± 0.04	0.36 ± 0.05	2.02 ± 0.26
Washout	10	0.73 ± 0.07	0.36 ± 0.05	2.03 ± 0.21

Data are expressed as means ± SD; *n*, no. of hearts. θ_L , longitudinal conduction velocity; θ_T , transverse conduction velocities; θ_L/θ_T , anisotropic ratio.

Table 2. Effect of nicorandil on longitudinal and transverse ventricular conduction velocities and on anisotropic ratio at a regular pacing of 1,000 ms

Concentration	<i>n</i>	θ_L , m/s	θ_T , m/s	θ_L/θ_T
Control	10	0.69 ± 0.06	0.33 ± 0.04	2.11 ± 0.20
1 $\mu\text{mol/l}$	10	0.68 ± 0.06	0.34 ± 0.03	2.04 ± 0.30
5 $\mu\text{mol/l}$	10	0.69 ± 0.07	0.35 ± 0.05	1.99 ± 0.34
10 $\mu\text{mol/l}$	10	0.71 ± 0.06	0.35 ± 0.05	2.08 ± 0.33
50 $\mu\text{mol/l}$	10	0.71 ± 0.07	0.34 ± 0.03	2.06 ± 0.26
100 $\mu\text{mol/l}$	9	0.73 ± 0.07	0.36 ± 0.05	2.07 ± 0.31
500 $\mu\text{mol/l}$	9	0.71 ± 0.05	0.35 ± 0.05	2.09 ± 0.30
Washout	10	0.71 ± 0.07	0.35 ± 0.04	2.03 ± 0.25

Data are expressed as means ± SD; *n*, no. of hearts.

Statistical analysis. All parameters were expressed as means ± SD. Two-way analysis of variance for repeated measures followed by a contrast method, Newman-Keuls test, and Bonferroni's correction were used to list dose and/or frequency effect on the electrophysiological parameters. $P < 0.05$ was considered to be statistically significant.

RESULTS

Effects on ventricular conduction velocities and anisotropic ratio. The effects of levocromakalim and nicorandil on longitudinal and transverse ventricular conduction velocities and on the anisotropic ratio at the pacing cycle length (PCL) of 1,000 ms are reported in Tables 1 and 2. Neither levocromakalim nor nicorandil modified these three electrophysiological parameters. No use dependence was observed, and ventricular conduction velocities were not modified (Fig. 2). Consequently, the anisotropic ratio remained stable, regardless of the PCL and the dose of potassium-channel openers. Longitudinal and transverse conduction velocities were slightly slowed down during the stimulation inducing ventricular tachycardia compared with velocities during a regular pacing of 200 ms, from 0.71 ± 0.05 to 0.67 ± 0.07 m/s and 0.72 ± 0.04 to 0.67 ± 0.08 m/s and from 0.35 ± 0.06 to 0.33 ± 0.07 m/s and 0.35 ± 0.045 to 0.30 ± 0.06 m/s during infusion of levocromakalim and

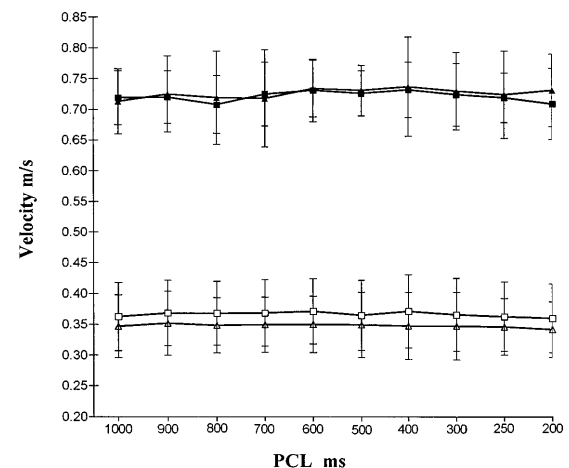


Fig. 2. Effects of 10 $\mu\text{mol/l}$ levocromakalim or 500 $\mu\text{mol/l}$ nicorandil at each pacing cycle length (PCL) on ventricular conduction velocities. Data are expressed as means ± SD; *n* = 10 for levocromakalim group; *n* = 9 for nicorandil group. ■, Longitudinal velocity (θ_L) in levocromakalim group; ▲, θ_L in nicorandil group; □, transverse velocity (θ_T) in levocromakalim group; △, θ_T in nicorandil group.

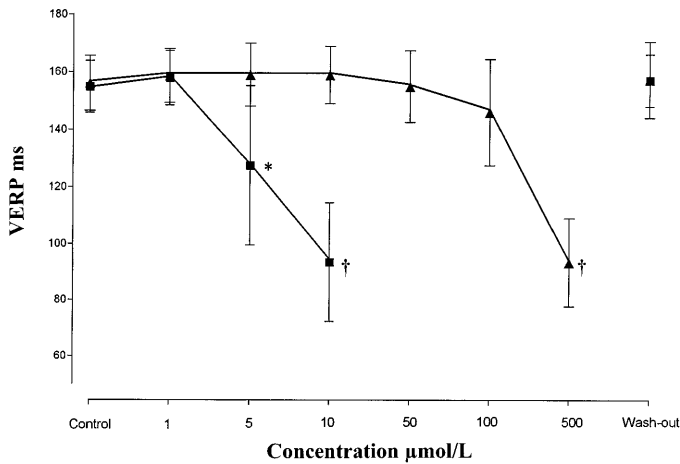


Fig. 3. Effects of levcromakalim (■) or nicorandil (▲) at each concentration on VERP. Data are expressed as means \pm SD; $n = 10$ at baseline, 1 and 5 $\mu\text{mol/l}$, and washout for both groups; $n = 7$ at 10 $\mu\text{mol/l}$ levcromakalim; $n = 9$ at 50 and 100 $\mu\text{mol/l}$ nicorandil; and $n = 6$ at 500 $\mu\text{mol/l}$ nicorandil. * $P < 0.05$; † $P < 0.01$.

nicorandil, respectively. However, the anisotropic ratio was not modified during this stimulation.

Effects on VERP and wavelength. Both levcromakalim and nicorandil modified VERP and wavelength. Figures 3 and 4 show changes of VERP and wavelength in each group. Levcromakalim shortened VERP from 5 $\mu\text{mol/l}$ ($P < 0.05$), whereas VERP was decreased from 100 $\mu\text{mol/l}$ of nicorandil with a significant effect at 500 $\mu\text{mol/l}$ ($P < 0.01$). Because VERP was shortened and ventricular conduction velocities were not modified, the

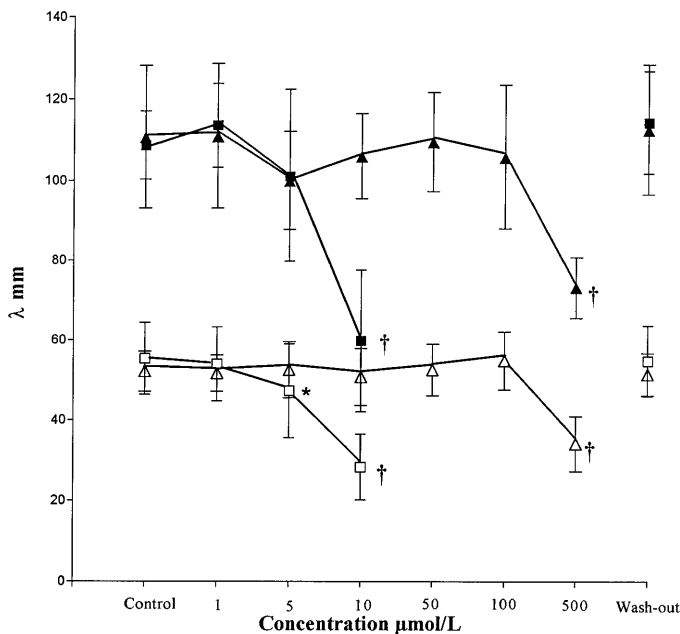


Fig. 4. Effects of levcromakalim or nicorandil at each concentration on wavelength (λ). Data are expressed as means \pm SD; $n = 10$ at baseline, 1 and 5 $\mu\text{mol/l}$, and washout for both groups; $n = 7$ at 10 $\mu\text{mol/l}$ levcromakalim; $n = 9$ at 50 and 100 $\mu\text{mol/l}$ nicorandil; and $n = 6$ at 500 $\mu\text{mol/l}$ nicorandil. ■, Longitudinal wavelength in levcromakalim group; ▲, longitudinal wavelength in nicorandil group; □, transverse wavelength in levcromakalim group; △, transverse wavelength in nicorandil group. * $P < 0.05$; † $P < 0.01$.

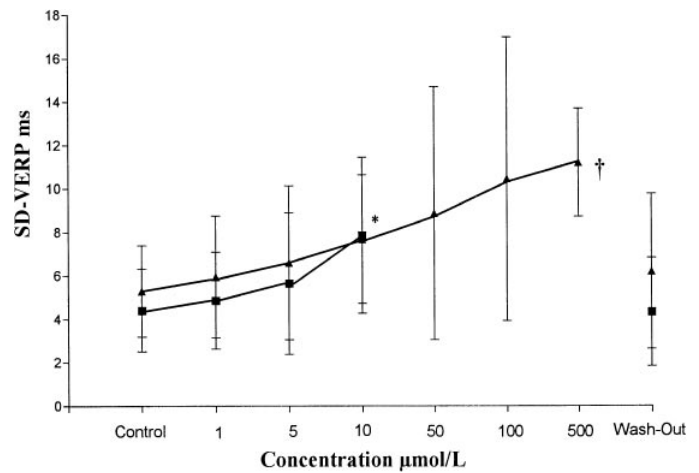


Fig. 5. Effects of levcromakalim (■) or nicorandil (▲) at each concentration on standard deviation of mean VERP (SD-VERP). Data are expressed as means \pm SD; $n = 10$ at baseline, 1 and 5 $\mu\text{mol/l}$, and washout for both groups; $n = 6$ at 10 $\mu\text{mol/l}$ levcromakalim; $n = 10$ at 50 $\mu\text{mol/l}$ nicorandil; $n = 9$ at 100 $\mu\text{mol/l}$ nicorandil; and $n = 4$ at 500 $\mu\text{mol/l}$ nicorandil. * $P < 0.05$; † $P < 0.01$.

longitudinal wavelength ($\theta\text{L} \times \text{VERP}$) was decreased from 108.7 ± 8.4 to 59.8 ± 17.8 mm ($P < 0.01$) and the transverse wavelength ($\theta\text{T} \times \text{VERP}$) was modified from 55.4 ± 9.1 to 28.3 ± 8.2 mm ($P < 0.01$) at 10 $\mu\text{mol/l}$ levcromakalim. Nicorandil had the same effect on the longitudinal and transverse wavelength, which decreased from 110.6 ± 17.6 and 52.1 ± 5.0 mm at baseline to 73.2 ± 7.6 ($P < 0.01$) and 34.1 ± 6.8 mm ($P < 0.01$), respectively, at 500 $\mu\text{mol/l}$.

To evaluate the refractoriness over the left epicardium, we calculated the standard deviation of the mean of VERP (Fig. 5), which was modified significantly at high doses of levcromakalim ($P < 0.05$) and nicorandil ($P < 0.01$). DI was also significantly increased at these same doses of levcromakalim ($P < 0.01$) and nicorandil ($P < 0.01$; Fig. 6). With regard to the modification of DI during nicorandil infusion, the same rise was observed ($P < 0.01$). Finally, D_{max} between values of VERP of each heart was modified from 8.0 ± 2.9 ms at baseline

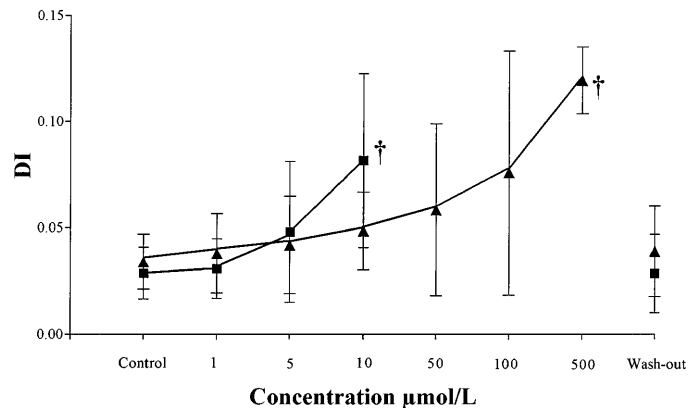


Fig. 6. Effects of levcromakalim (■) or nicorandil (▲) at each concentration on dispersion index (DI). Data are expressed as means \pm SD; $n = 10$ at baseline, 1 and 5 $\mu\text{mol/l}$, and washout for both groups; $n = 5$ at 10 $\mu\text{mol/l}$ levcromakalim; $n = 9$ at 50 and 100 $\mu\text{mol/l}$ nicorandil; and $n = 5$ at 500 $\mu\text{mol/l}$ nicorandil. † $P < 0.01$.

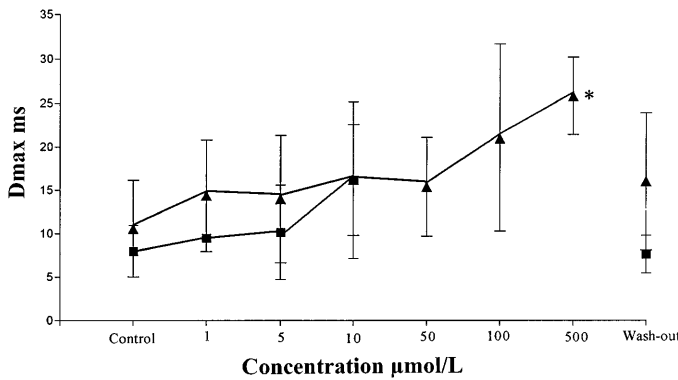


Fig. 7. Effects of levcromakalim (■) or nicorandil (▲) at each concentration on maximum dispersion (D_{max}). Data are expressed as means \pm SD; $n = 10$ at baseline, 1 and 5 $\mu\text{mol/L}$, and washout for both groups; $n = 6$ at 10 $\mu\text{mol/L}$ levcromakalim; $n = 9$ at 50 and 100 $\mu\text{mol/L}$ nicorandil; and $n = 5$ at 500 $\mu\text{mol/L}$ nicorandil. * $P < 0.05$.

to 16.2 ± 9.0 ms at 10 $\mu\text{mol/L}$ levcromakalim and from 10.6 ± 5.6 to 25.8 ± 4.4 ms at 500 $\mu\text{mol/L}$ nicorandil ($P < 0.05$) (Fig. 7).

Proarrhythmic effects. No spontaneous arrhythmia was observed after the administration of each concentration of levcromakalim and nicorandil. The inducibility of arrhythmia was tested. No arrhythmia was obtained at control, 1 and 5 $\mu\text{mol/L}$ of levcromakalim and nicorandil, and during washout. Levcromakalim induced ventricular arrhythmias from 10 $\mu\text{mol/L}$ (8 of 10), and all hearts had sustained ventricular tachycardia or ventricular fibrillation at 50 $\mu\text{mol/L}$ (6 of 6). One heart had a sustained MVT with 50 $\mu\text{mol/L}$ nicorandil. Ventricular arrhythmias occurred in all hearts treated with 500 $\mu\text{mol/L}$ of nicorandil (9 of 9). The types of arrhythmias and the results of their analysis are summarized in Table 3. Four ventricular fibrillations were induced at 50 $\mu\text{mol/L}$ levcromakalim. The analysis of their initiation was not performed because of their complexity ("no analysis"). The analysis of some sustained or nonsustained MVT or PVT did not allow us to

determine their mechanisms of initiation ("no conclusion"). Finally, most of the ventricular tachycardias induced were initiated consecutively to a reentry ("based on reentry"). Figures 8 and 9 show the initiation of two ventricular tachycardias, one that was a nonsustained polymorphic ventricular tachycardia (9 ventricular tachycardia beats) obtained after the application of one extrastimulus at 10 $\mu\text{mol/L}$ levcromakalim (Fig. 8) and one that was sustained and monomorphic, occurring at 50 $\mu\text{mol/L}$ nicorandil induced by three extrastimuli (Fig. 9). The upper left map of Fig. 8A describes the spread of ventricular depolarization after the extrastimulus (S2) during infusion of 10 $\mu\text{mol/L}$ levcromakalim. The stimulus was applied at the center of the ventricle, and the wave propagated in all directions. It encountered a line of conduction block near the apex and, because VERPs were shortened, reactivation occurred around a pattern of eight lines of functional conduction block at a time of 73 ms (VERP 40 ms). Subsequently, several beats of tachycardia occurred following the same pattern, although the position of the lines of block changed from beat to beat, leading to a polymorphic pattern (Fig. 8B). The ventricular tachycardia advancement is shown in Fig. 8B; an electrogram recorded on *site 3* shows the conduction block of the pacing influx and, therefore, the reexcitation of this area by the influx that had surrounded the area block.

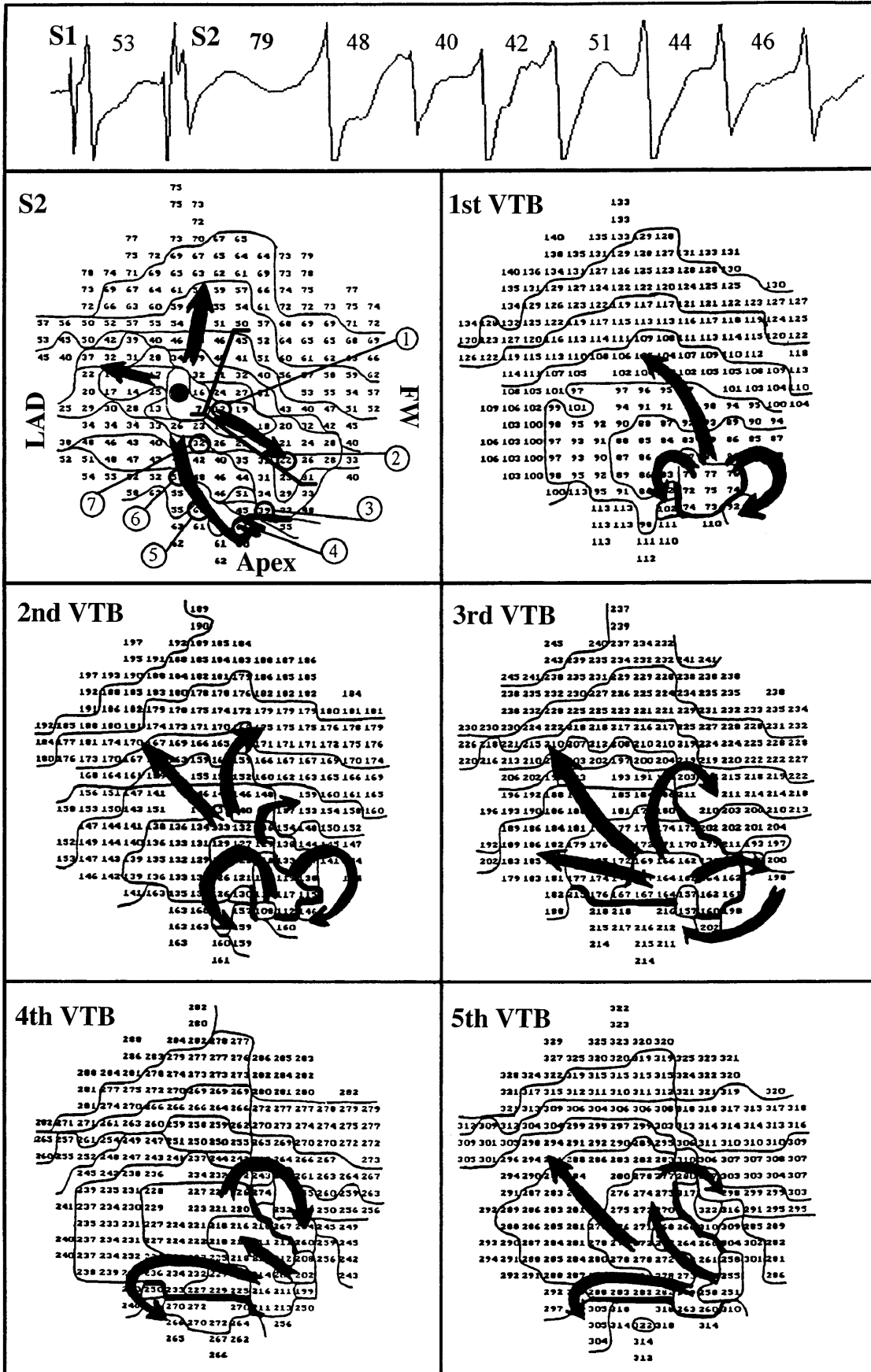
The second ventricular tachycardia, shown in Fig. 9, is a sustained MVT obtained during the infusion of 50 $\mu\text{mol/L}$ nicorandil. The upper left map of Fig. 9A shows the depolarization of the ventricle after the last extrastimulus (S4). The pulse was stopped by a wide line of conduction block in the direction of the apex and in the direction of the free wall. The excitation wave could propagate only in the direction of the base. The influx got around the block in the middle of the ventricle and activated the epicardium near the septum. The pulse could depolarize the area behind the line of block in the

Table 3. Type and analysis of ventricular arrhythmias after administration of levcromakalim or nicorandil

Concentration, $\mu\text{mol/L}$	Levcromakalim		Nicorandil	
	Type of arrhythmia	Analysis of arrhythmia	Type of arrhythmia	Analysis of arrhythmia
10	SPVT (5)	Based on reentry (3) No conclusion (2)		
	NSVT			
	Polymorphic (1) Monomorphic (2)	Based on reentry (1) No conclusion (2)		
50	VF (4)	No analysis (4)	SMVT (1)	Based on reentry (1)
	SMVT (1)	Based on reentry (1)		
	NSMVT (1)	No conclusion (1)		
500			SVT	
			Polymorphic (4)	Based on reentry (3) No conclusion (1)
			Monomorphic (2)	Based on reentry (2)
			NSVT	
			Polymorphic (1) Monomorphic (2)	No conclusion (1) No conclusion (2)

VF, ventricular fibrillation; NSVT, nonsustained ventricular tachycardia; SVT, sustained ventricular tachycardia; M, monomorphic; P, polymorphic. "No analysis" indicates that ventricular fibrillations are not analyzed because of complexity of analysis; "no conclusion" indicates that some analysis of ventricular tachycardias could not determine a mechanism of initiation; and "based on reentry" indicates that ventricular tachycardias were consecutive to a reentry. When sustained tachycardia was terminated by KCl administration, no further concentration was administered.

A



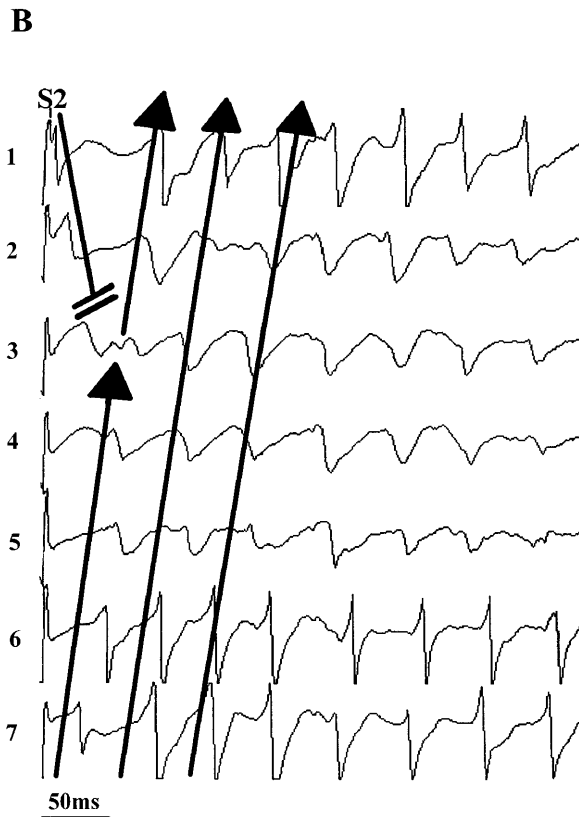


Fig. 8. *A*: initiation of nonsustained polymorphic reentrant ventricular tachycardia during administration of 10 $\mu\text{mol/l}$ levocromakalim in frozen LV epicardium. *Top*: electrogram recorded during induction of ventricular tachycardia using 1 extrastimulus (S2). Numbers above electrogram indicate time interval (in ms) between 2 ventricular activations. Six consecutive activation maps show spread of depolarization. Numbers indicate local activation times (in ms). Isochrones are drawn at 10-ms intervals. Thick isochrones indicate local conduction blocks. Arrows indicate direction of activation. Double bars indicate stop of influx propagation in direction considered, and ● represents pacing site. Circled activation times indicate recording sites of electrograms shown in *B*. Upper left map shows conduction blockade resulting from the extrastimulus (S2). Upper right map shows first beat of sustained ventricular tachycardia (1st VTB). Pattern of depolarization during sustained monomorphic ventricular tachycardia (2nd, 3rd, 4th, and 5th VTB) is shown consecutively in lower maps. Underlined activation times (S2 map) indicate sites between which conduction velocity was measured. Conduction velocities were measured in transverse and longitudinal directions. At a regular PCL of 300 ms, $\theta_L = 0.68$ m/s and $\theta_T = 0.30$ m/s; at PCL = 200 ms, $\theta_L = 0.62$ m/s and $\theta_T = 0.31$ m/s; and with premature pacing (S2), $\theta_L = 0.60$ m/s and $\theta_T = 0.28$ m/s. All maps present same frontal view of heart; see text for further description. *B*: 7 different electrograms recorded (at sites indicated in S2 map in *A*) during initiation of nonsustained polymorphic reentrant ventricular tachycardia with administration of 10 $\mu\text{mol/l}$ levocromakalim in frozen LV epicardium using 1 extrastimulus (S2). Study of these 7 electrograms shows functional conduction block on *site 3* and polymorphism of reentrant ventricular tachycardia.

direction of the free wall (Fig. 9A, upper right map) and reactivated the area close to the base in a counterclockwise direction, initiating reentrant tachycardia around a line of functional conduction block (1st and 2nd VTB). This path of depolarization was possible because of dispersion of the left ventricular refractoriness as confirmed by VERP measurements. VERP was shorter at the base (139 ms) than near the septum (151 ms) and

then at the free wall (162 ms). Recorded electrograms show the conduction block and the initiation of this ventricular tachycardia on *site 4* (Fig. 9B). Finally, the monomorphism of this tachycardia was shown on this pattern (Fig. 9B).

DISCUSSION

The present study demonstrates that, in homogeneous left ventricular epicardium, potassium-channel openers induce shortening and increase dispersion of refractoriness without changing conduction velocities and anisotropy. This leads to occurrence of functional conduction blocks and reentrant ventricular arrhythmias.

Unidirectional block. Unidirectional block is essential for the initiation of reentry. In previous studies, its occurrence has been associated with different mechanisms, including changes in anisotropic properties of the myocardium (34, 36) and use dependency (2, 8, 12, 31). However, these two mechanisms are not involved in potassium-channel opener-induced conduction blocks. Indeed, we previously demonstrated that these agents do not modify ventricular conduction velocities or anisotropic ratio and that there is no use dependency (32). These results are confirmed in the present study. On the other hand, one could argue that during rapid pacing or premature stimuli, conduction velocities may be affected (20, 21, 30), and this could have played a role in the occurrence of conduction block in our experiments. Thus we calculated conduction velocities and anisotropic ratios during the propagation of premature stimuli and rapid pacing that induced arrhythmias. Because these parameters did not significantly differ from those obtained during baseline pacing, we can infer that changes in conduction velocities are not involved in the initiation of unidirectional block in our study, even during programmed stimulation.

Heterogeneity of refractoriness has been suggested as another putative mechanism of initiation of functional conduction block and reentry. Han and Moe (22) found differences of up to 30 ms between the longest and the shortest refractory period in ventricular muscle and suggested that dispersion might play a role in the initiation of tachycardia. In open-chest dogs, Kuo et al. (24) reported that an increase in dispersion of repolarization induced by hypothermia and regional warm blood is arrhythmogenic. These authors demonstrated that an increased dispersion enhances conduction delay, facilitating the occurrence of arrhythmia when a premature stimulus is applied in the area with the shortest repolarization. However, in their model, conduction velocities were also modified. In microelectrode studies performed in epicardial and endocardial sheets, investigators have shown that some drugs and simulated ischemia produce a marked dispersion of repolarization and refractoriness (14, 23, 26) in the epicardium and between the epicardium and endocardium and that the resulting extrasystolic activity is based on the

A

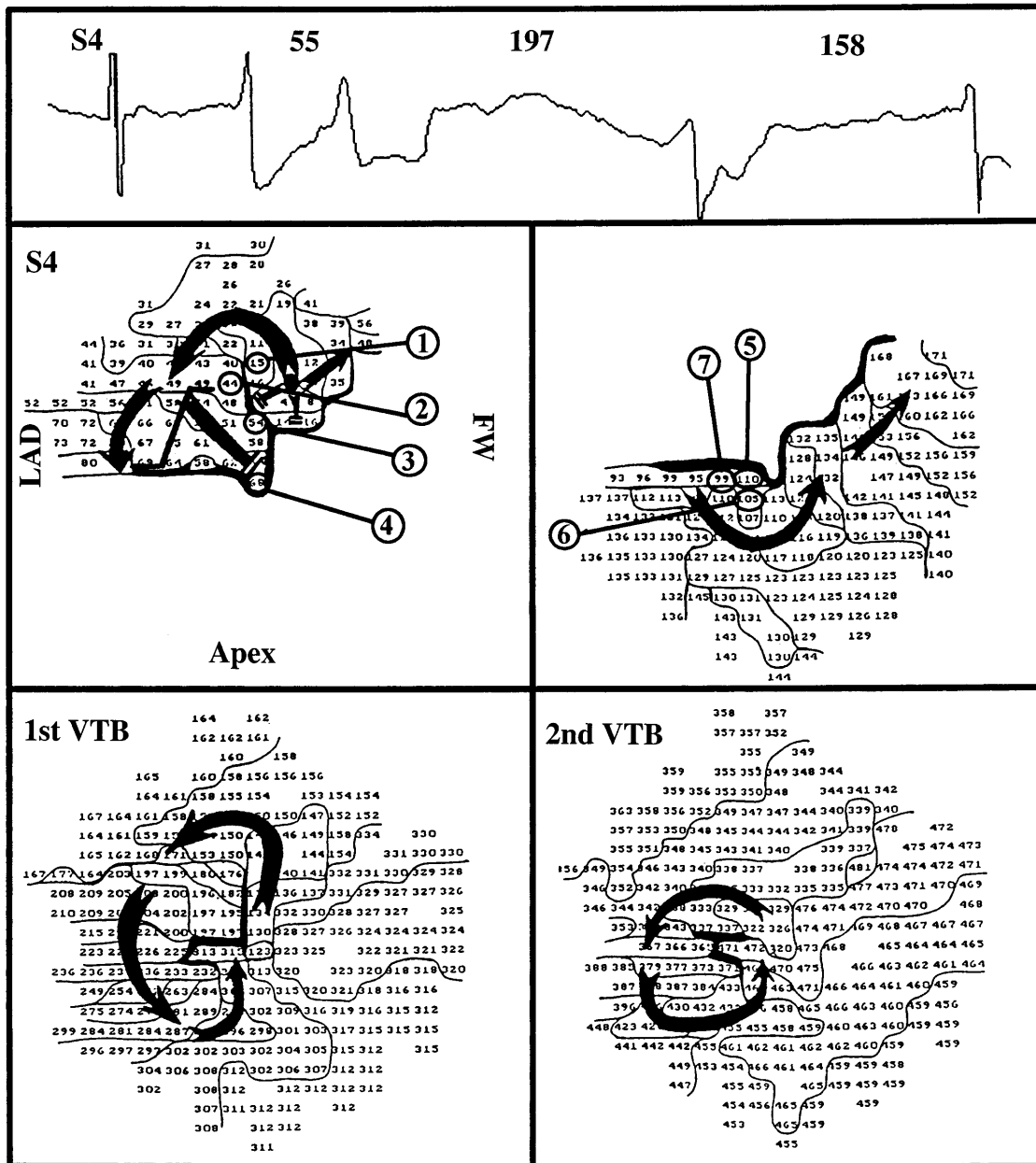


Fig. 9. *A*: initiation of sustained monomorphic reentrant ventricular tachycardia during administration of 50 $\mu\text{mol/l}$ nicorandil in frozen LV epicardium. *Top*: electrogram recorded during induction of ventricular tachycardia using 3 premature stimuli (S2, S3, S4). Numbers above electrogram indicate time interval (in ms) between 2 ventricular activations. Four consecutive activation maps show spread of depolarization. Numbers indicate local activation times (in ms). Isochrones are drawn at 10-ms intervals. Thick isochrones indicate local conduction blocks. Arrows indicate direction of activation. Double bars indicate stop of influx propagation in direction considered, and ● represents pacing site. Circled activation times indicate recording sites of electrograms in *B*. Upper maps show conduction blockade resulting from last stimulus (S4). Lower left map shows 1st VTB. Pattern of depolarization during sustained monomorphic ventricular tachycardia (2nd VTB) is shown in lower right map. Underlined activation times (S4 map) indicate sites between which conduction velocity was measured. Conduction velocity was not strictly in transverse or longitudinal direction; at S1 (regular pacing at 300 ms), $\theta = 0.56$ m/s; at S2, $\theta = 0.59$ m/s; at S3, $\theta = 0.48$ m/s; and at S4, $\theta = 0.50$ m/s. A slight slowing was observed during premature stimulation, but it was not responsible for the functional block. All maps present same frontal view of heart. See text for further description. *B*: 7 different electrograms recorded (at sites indicated in S4 maps in *A*) during initiation of sustained monomorphic reentrant ventricular tachycardia with administration of 50 $\mu\text{mol/l}$ nicorandil in frozen LV epicardium using 3 extrastimuli (S2, S3, S4). Study of these 7 electrograms shows initiation, advancement, and monomorphism of reentrant ventricular tachycardia observed during analysis of tachycardia initiation.

B

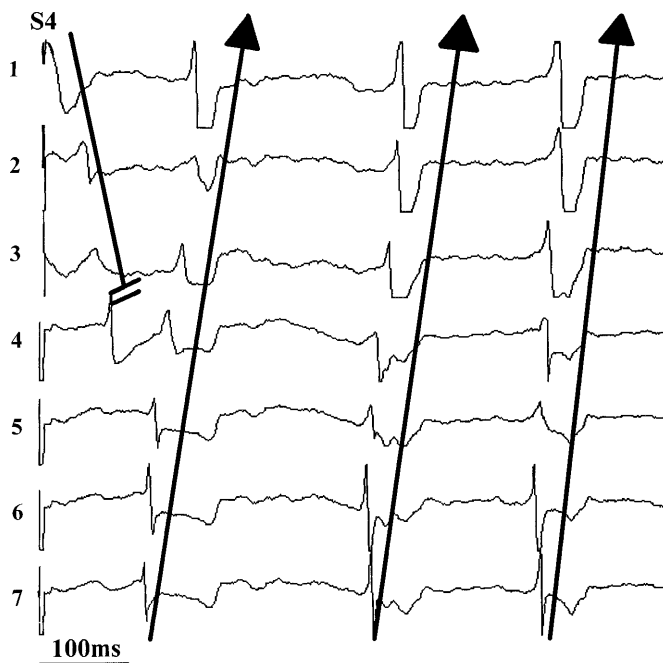


Fig. 9—Continued.

so-called *phase 2* reentry. However, in dog atrium, Spach et al. (35) observed that neither repolarization heterogeneity nor anisotropic propagation is the sole mechanism responsible for reentrant tachycardia. These authors suggested that factors leading to a reentrant tachycardia might be a combined mechanism due to spatial repolarization and discontinuities of anisotropic propagation. Because the anisotropic pattern of epicardial propagation was not affected in our study, we can state that unidirectional conduction block results from both the shortening and the increased dispersion of VERP.

Dispersion of refractoriness. To test the heterogeneity of epicardial refractoriness, SD-VERP, DI, and D_{\max} were determined. These three parameters reflected a great spatial inhomogeneity of the epicardial repolarization after infusion of high doses of levcromakalim and nicorandil. DI values obtained were in accordance with those observed by Ogawa et al. (28) in a canine model of myocardial infarction. These authors found that the value in the group in which ventricular fibrillation or tachycardia was induced was 13.6%, whereas the value for the control group was 6.2%. They reported that this increase in DI should be associated with the creation of epicardial functional block and the induction of ventricular fibrillation and tachycardia. In our study, SD-VERP increased significantly at the dose associated with arrhythmia, as shown by Ogawa et al. (28). The occurrence of arrhythmia is associated with an increased dispersion of VERP. Current data do not allow us to specify the respective part of each factor (i.e., shortening and dispersion) in the arrhythmogenicity. We are not aware of a study in which the role of shortening of VERP without dispersion, or dispersion of VERP with-

out prolongation or shortening, has been determined. Nevertheless, because the homogeneous prolongation of VERP is considered to be antiarrhythmic (10, 33), since arrhythmias are usually observed in the case of both prolongation and dispersion of refractoriness (16), we can suggest that the dispersion of refractoriness could probably play a major role in the initiation of reentry in our study.

Wavelength. In the present study, we also demonstrated that the wavelength concept, which is a good predictive parameter of arrhythmia inducibility in the atrium (30), could also be useful in the ventricular epicardium. The decrease in wavelength occurs in the same manner as that of VERP because of ventricular conduction velocity stability. The maximum proarrhythmogenic effect of potassium-channel openers is reached at 10 $\mu\text{mol/l}$ levcromakalim and 500 $\mu\text{mol/l}$ nicorandil; at these doses, wavelengths are also the shortest. Similar to the manner in which the atrial impulse wavelength in normal conscious dogs allows the correlation between modification of electrophysiological parameters and the inducibility of atrial arrhythmia (30), the wavelength determined in the left ventricular epicardium could be used as an indicative parameter of proarrhythmogenic effect. The decrease of the wavelength exhibits that the initiation of a circuit would require a small area of functional conduction block. Therefore, a little dispersion of VERP could easily lead to a reentry. However, because VERPs are dispersed, the wavelength calculated could vary according to the VERP considered.

Study limitations. It would have been useful to know the VERP value near the functional block. In the present study, we measured VERP in four sites located in four different regions of the left epicardium. Given the spatial resolution achieved and the fact that conduction block could occur anywhere over the left epicardium, it is currently impossible for us to know the VERP near the conduction block. Moreover, VERP could not be measured in all sites, because the shortening of the coupling interval performed by pacing in some sites could lead to the initiation of a sustained arrhythmia.

Another difficulty was in the analysis of ventricular tachycardias. Because wavelengths were significantly reduced by potassium-channel openers, and because the thin epicardial rim yielded some cellular layers, a reentrant circuit initiated in the transmural dimension could not be excluded. This type of reentry cannot be mapped with our technique, and in this case we cannot determine the real initiation mechanism.

Care must be taken in extrapolating our results to the clinical setting. We studied solely the ventricular epicardium of isolated rabbit hearts, and some studies demonstrated that a dispersion of refractoriness exists within the ventricular wall. The presence of prominent transient outward currents in the epicardium, but not in the endocardium, and the differential ATP sensitivity of potassium channels between these tissues could explain the difference in their response to drugs and ischemia, and then in the repolarization dispersion (14,

19, 23). A difference in the responsiveness to potassium-channel openers is also observed between atria and ventricles (29). These different effects on different cardiac tissues could lead to a disparity in refractoriness and, as demonstrated in this study, could contribute to reentrant arrhythmias. Moreover, the concentrations used in our study were in a toxic range with the exception of the concentration of 1 $\mu\text{mol/l}$ nicorandil, which is considered a clinical dose (18). Levromakalim is not available for clinical use in humans.

Brugada and Wellens (9) postulated that the mechanism called prolonged repolarization-dependent reexcitation is due to a dispersion of repolarization between contiguous structures. Early afterdepolarization at low membrane potentials could induce a difference in refractoriness and should be considered as a mechanism of torsade de pointes with a long Q-T interval. Initiation of this arrhythmia could be due to triggered activity resulting from early afterpotential, but perpetuation of the arrhythmia is considered a reentrant mechanism related to dispersion of refractoriness, despite a long wavelength associated with an increase in action potential duration, VERP, and Q-T interval (15, 38). In contrast, Leenhardt et al. (25) reported some cases of unusual torsade de pointes with a short coupling interval of the first beat of the arrhythmia. We could therefore hypothesize that large doses of potassium-channel openers could facilitate such polymorphic arrhythmias with a decrease in Q-T duration and a rise in dispersion of repolarization.

In conclusion, the present study highlights on the mechanism of initiation of potassium-channel opener-induced ventricular reentrant tachycardia, which is based on both shortening of VERP and refractoriness dispersion with no change of ventricular conduction velocities and anisotropic ratio. This allows conditions for functional conduction blocks, facilitating the occurrence of arrhythmia by reentry.

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