

Effects of Ketamine on Ventricular Conduction, Refractoriness, and Wavelength

Potential Antiarrhythmic Effects: A High-resolution Epicardial Mapping in Rabbit Hearts

Antoine G. M. Aya, M.D., M.Sc.,* Emmanuelle Robert, M.Sc.,† Pascal Bruelle, M.D., M.Sc.,* Jean-Yves Lefrant, M.D., M.Sc.,* Jean-Marie Juan, M.D.,‡ Pascale Peray, M.D., M.Sc.,§ Jean-Jacques Eledjam, M.D.,|| Jean E. de La Coussaye, M.D., Ph.D. #

Background: The aims of the study were to verify the effects of ketamine on ventricular conduction velocity and on the ventricular effective refractory period, to determine its effects on anisotropy and on homogeneity of refractoriness, and to use wavelength to determine whether ketamine has antiarrhythmic or arrhythmogenic properties.

Methods: A high-resolution epicardial mapping system was used to study the effects of 50, 100, 150, and 200 μ M racemic ketamine in 15 isolated, Langendorff-perfused rabbit hearts. Five hearts were kept intact to study the effects of ketamine on spontaneous sinus cycle length (RR) interval and its putative arrhythmogenic effects. In 10 other hearts, a thin epicardial layer was obtained by an endocardial cryoprocure (frozen hearts) to study ventricular conduction velocity, ventricular effective refractory periods (five sites), and ventricular wavelength.

Results: Ketamine induced a concentration-dependent lengthening of the RR interval. Ketamine slowed longitudinal and transverse ventricular conduction velocity with no anisotropic change, and it prolonged the ventricular effective refractory period with no significant increase in dispersion. Ventricular longitudinal and transverse wavelengths tend to increase, but this was not statistically significant. Finally, no arrhythmia could be induced regardless of the ketamine concentration.

Conclusion: Ketamine slowed ventricular conduction and prolonged refractoriness without changing anisotropy or increasing dispersion of refractoriness. Although these effects should result in significant antiarrhythmic effects of ketamine, this should not be construed to suggest a protective effect in ischemic or other abnormal myocardium. (Key words: Electrophysiology: conduction; refractoriness; wavelength; anisotropy. Heart: epicardium. Animal: rabbit. Anesthetics, intravenous: ketamine.)

THE hemodynamic effects of ketamine in the clinical setting are complex and include direct cardiac action and activation of the autonomic nervous system. Ketamine has direct cardiac depressant effects, except in the rat, in which positive inotropic effects have been shown on papillary muscle¹ and the left atrium.² Studies performed in different experimental conditions in heart preparations,¹⁻³ in isolated hearts,⁴⁻⁶ in intact animals,⁷ and in humans⁸ showed that ketamine depresses myocardial contractility. The effects of ketamine on contractility, therefore, have been widely investigated, whereas its electrophysiologic effects, especially on ventricles, have been poorly documented. Available data show that ketamine inhibits ionic currents through sodium, potassium, and calcium channels. In guinea pig papillary muscle, investigators showed that ketamine induces a tonic block of cardiac sodium channels with a resulting decrease in maximum upstroke velocity of fast action potential (V_{max}) and in conduction velocity.⁹ Ketamine decreases the inward rectifier potassium current (I_{K1}) and the delayed rectifier current (I_{Kr}) in guinea pig ventricular myocytes.^{3,10} On single guinea pig ventricular myo-

* Staff Anesthesiologist, Department of Anesthesiology.

† Doctoral Student, Laboratory of Anesthesiology and Cardiovascular Physiology.

‡ Surgeon, Laboratory of Anesthesiology and Cardiovascular Physiology.

§ Department of Epidemiology and Biostatistics.

|| Professor and Chair of Anesthesiology.

Professor of Anesthesiology.

Received from the Laboratory of Anesthesiology and Cardiovascular Physiology, Medical School of Montpellier-Nîmes and Department of Anesthesiology, University Hospital of Nîmes, France. Submitted for publication November 21, 1996. Accepted for publication July 31, 1997. Supported by the Regional Council of Languedoc-Roussillon and General Council of the Department of Gard, France. Presented in part at the 38th National Congress of the French Society of Anesthesiology and Critical Care Medicine, September 26-29, 1996.

Address reprint requests to Dr. de La Coussaye: Départements d'Anesthésie-Réanimation et de l'Urgence, CHU Gaston Doumergue, 5 rue Hoche, 30029 Nîmes Cedex 4, France.

cytes, ketamine inhibits the transsarcolemmal calcium influx through voltage-gated calcium channels at clinically relevant concentrations.^{11,12} Based on all these data, we could infer that ketamine has depressant effects on electrophysiologic parameters, including the slowing of conduction velocity and the prolongation of refractoriness. Furthermore, it is established that the anisotropic conduction in the ventricular myocardium and effects of drugs on the anisotropic properties may facilitate the occurrence of reentrant arrhythmias around functional conduction blocks, which is called anisotropic reentry.¹³ It has also been shown that the dispersion of refractoriness may create conditions for reentrant arrhythmias.^{14,15} Although we can hypothesize, based on available data concerning the electrophysiologic effects of ketamine, that this agent might slow longitudinal (θ_L) and transverse (θ_T) ventricular conduction velocities, its effects on anisotropy, on dispersion of refractoriness, and on the possibility of anisotropic- or dispersion-based reentry have never been investigated. Thus our first aims were (1) to verify the effects of clinically relevant concentrations of ketamine on θ_L and θ_T and on the ventricular effective refractory period (VERP); (2) to evaluate the effects of ketamine on the anisotropic ratio and on the dispersion of refractory periods; and (3) to determine whether ketamine could facilitate or induce anisotropic or dispersion-based reentrant arrhythmias, or both.

Changes in conduction velocity, refractoriness, or both promote arrhythmias of the reentrant mechanism.¹⁶⁻¹⁸ Using atrial tissue, investigators showed that wavelength (λ) is a more reliable predictor of the initiation of reentrant dysrhythmias than is conduction velocity or the effective refractory period.^{19,20} Thus drug-induced changes in atrial λ are used to determine the arrhythmogenic or antiarrhythmic properties of drugs on atrial tissue.^{21,22} Drugs that increase λ tend to be antiarrhythmic, whereas agents that decrease λ tend to be arrhythmogenic on atria.²¹ Wavelength has been used to study ventricular reentrant tachycardia,²³ but no data exist concerning its use as an index of the arrhythmogenicity of drugs on ventricles. Because ventricular conduction is also anisotropic, our second aim was to use λ to evaluate the potential ventricular arrhythmogenic or antiarrhythmic properties of ketamine.

Methods

Heart Preparation

The principles for the care and treatment of experimental animals complied with the national guidelines

of the French Ministry of Agriculture. We used 15 New Zealand rabbits weighing 2.8–3.6 kg. After anesthesia with etomidate (1 mg/kg given intravenously followed by an infusion of $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), the trachea was intubated, and the lungs were mechanically ventilated with 100% oxygen (Logic 07; ATM Ohmeda, Coignières-Maurepas, France). The thorax was surgically opened by a midsternal incision. The aorta and the heart were exposed and, after anticoagulation with heparin (1,000 IU), they were rapidly removed and placed in cold perfusion fluid (10°C). The aorta was immediately cannulated and the heart connected to a Langendorff perfusion system using Tyrode's solution. The heart was perfused with a constant flow of 40–50 ml/min (Watson-Marlow 101U pump; Falmouth Cornwall, UK), resulting in a pressure of $70 \pm 10 \text{ mmHg}$ (Gould P23 transducer, Oxnard, CA; CGR monitor, St. Cloud, France). The Tyrode's solution consisted of 130 mM NaCl, 20.1 mM NaHCO_3 , 4 mM KCl, 2.2 mM CaCl_2 , 0.6 mM MgCl_2 , 1.2 mM NaH_2PO_4 , and 12 mM glucose. The solution was saturated with a mixture of 95% O_2 and 5% CO_2 and the pH was adjusted at 7.40 ± 0.02 .

Five Langendorff-perfused hearts were kept intact (nonfrozen heart). In 10 other hearts, an endocardial cryotechnique was used to freeze the complete right ventricle, the interventricular septum, and the endocardial and intramural layers of the free wall of the left ventricle (frozen heart).^{16,24,25} Briefly, a cryoprobe was inserted through the pulmonary artery into the right ventricle, filled with liquid nitrogen (-192°C), and maintained in place until the right ventricle was completely frozen. The heart was then immersed in a tissue bath containing perfusion fluid at 30°C . The cryoprobe was placed into the left ventricular cavity through the left atrium and the coronary circulation was temporary discontinued. The cryoprobe was filled with liquid nitrogen and maintained in place for 3 min. Thereafter, the coronary perfusion was restored, the probe was removed, and the heart withdrawn from the tissue bath. Then the temperature of the heart was kept constant at 37°C throughout the experiment. As a result of this procedure, only a thin epicardial layer of the free wall of the left ventricle, approximately 1 mm thick, survived because the endocardial and intramural layers were completely destroyed. Previous investigations showed that in this thin surviving layer, refractoriness and conduction velocity are not affected by the procedure and remained stable for many hours, suggesting adequacy of the circulation in the epicardial layer.^{13,24} This cryotechnique was used to avoid epicardial breakthrough

ELECTROPHYSIOLOGIC EFFECTS OF KETAMINE

of longitudinal wavefronts from deeper layers and to allow complete and bidimensional epicardial mapping of electrical activation. At the end of the experiments, the hearts were dissected to verify the efficacy of the cryoprocurement.

Protocol

Electrophysiologic and Antiarrhythmic or Arrhythmogenic Effects of Ketamine in Nonfrozen Hearts

Five nonfrozen hearts were perfused at 37°C in spontaneous sinus rhythm. After a 60-min stabilization period, they were given 50, 100, 150, and 200 μM racemic ketamine, with each concentration infused for 20 min. After the last concentration, ketamine was washed out for 40 min to verify the return to baseline values. Ketamine was obtained commercially (50 mg/ml) in water, with chlorobutanol (5 mg/ml) as a preservative (Panpharma, Fougères, France). We did not use a chlorobutanol-treated group because the highest concentration of chlorobutanol given with ketamine was 5.5 $\mu\text{g}/\text{ml}$, whereas others have shown that chlorobutanol has no significant cardiac effect at 15 $\mu\text{g}/\text{ml}$.²⁶ In nonfrozen hearts, the spontaneous sinus cycle length (RR interval, in milliseconds) and the occurrence of asystole or spontaneous arrhythmias were recorded at baseline, after each concentration of ketamine, and after washout. If sustained monomorphic tachycardias occurred, they were to be terminated by overdrive pacing, and atrial or ventricular fibrillation were to be stopped by administration of potassium chloride.

Electrophysiologic and Antiarrhythmic or Arrhythmogenic Effects of Ketamine in Frozen Hearts

Ten frozen hearts were treated with 50, 100, 150, and 200 μM ketamine.

Recording and Induction of Ventricular Dysrhythmias. High-resolution mapping of epicardial excitation was performed by applying to the epicardial surface a spoon-shaped electrode (fig. 1) containing 256 unipolar electrodes at regular distances of 2.25 mm. The computerized mapping system allows simultaneous recording, storage, and automatic analysis of all 256 electrograms and on-line presentation of color-coded activation maps (Maptech system, Maastricht, The Netherlands).^{27,28} Programmed electrical stimulation was performed using a programmable constant-current stim-

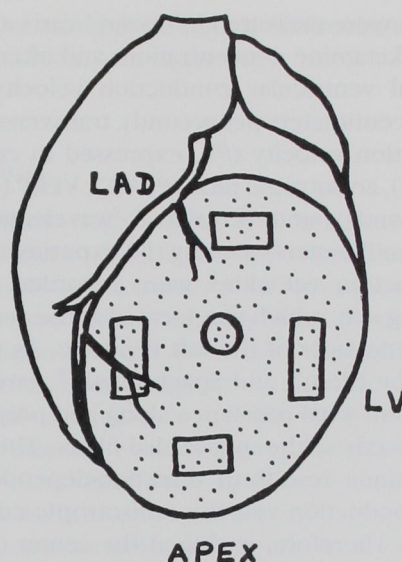


Fig. 1. The location of the spoon-shaped electrode on the left ventricle (LV). Unipolar electrograms were recorded from the mapping array (dotted area). The central circle indicates the main pacing site for the measurement of conduction velocity and VERP. Boxed areas on the left ventricle show the four other sites at which VERP was measured. LAD = left anterior descending coronary artery.

ulator that delivered square pulses lasting 2 ms at twice the diastolic threshold for both regular stimulation and induction of premature beats (Maptech system). Bipolar stimulation could be performed through any pair of electrodes in the spoon electrode. The stimulation protocol was only performed in frozen hearts and consisted of (1) application of one, two, and three premature stimuli (S2, S3, and S4, respectively) delivered with a decreasing coupling interval after 10 basic stimuli (S1-S1) at a 300-ms interval; and (2) application of trains of 10 stimuli at a regular cycle length, which was progressively decreased at 10-ms steps until 1-to-1 capture of the ventricle failed (F_{\max}). After the inducibility of ventricular dysrhythmias was assessed on baseline in the 10 frozen hearts, 50, 100, 150, and 200 μM ketamine were successively infused to the circuit for 20 min. Then the inducibility of dysrhythmias was tested again using the same protocol as during baseline. Once the protocol was completed, normal Tyrode solution was infused for approximately 40 min to return to baseline conditions to rule out the possibility of deterioration over time (washout). Thereafter, any occurrence of inducible ventricular dysrhythmias was also recorded and analyzed.

Electrophysiologic Measurements. The following

parameters were measured in frozen hearts at baseline, after each ketamine concentration, and after washout: longitudinal ventricular conduction velocity (θ_L , expressed in centimeters per second), transverse ventricular conduction velocity (θ_T , expressed in centimeters per second), anisotropic ratio (θ_L/θ_T), VERP (expressed in milliseconds), and ventricular wavelength (λ , expressed in millimeters). During the experiment, ventricular conduction velocities were recorded using the same pacing site, which was located at the center of the thin surviving layer of the left ventricle. As previously described by Clerc²⁹ and Spach *et al.*,³⁰ 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) at baseline. Therefore, pacing at the center of the thin surviving layer of the left ventricle produced an ellipsoidal spread of propagation. It has been shown that the long axis of this ellipsoid is parallel to the fiber orientation and has a fast conduction (longitudinal conduction, θ_L), whereas the short axis is perpendicular to the fiber orientation and has a slow conduction (transverse conduction, θ_T).¹³ Conduction velocity was defined as the distance traveled by the wavefront normal to the isochrones per unit of time. In each experiment, both longitudinal and transverse conduction velocities and anisotropic ratio were measured after 10 basic stimuli (S1-S1) at 1,000-ms intervals. In addition, to test the use dependency of ketamine, the longitudinal and transverse ventricular conduction velocities and anisotropic ratio were measured after 10 basic stimuli at 900-, 800-, 700-, 600-, 500-, 400-, 300-, 250-, and 200-ms intervals. Use dependency of ketamine is defined as the ketamine-induced changes in the rate-dependent ionic membrane properties, including conduction and refractoriness. The VERP was defined as the shortest S1-S2 interval that still resulted in a propagated premature impulse during regular pacing with a S1-S1 interval of 300 ms. The VERP was determined by decreasing the coupling interval of the premature stimulus in 1-ms steps. To test the spatial dispersion of refractoriness, VERP was measured on five different epicardial sites: center of left ventricular area (main pacing site), apex, near the free wall of the left ventricle, near the left anterior descending coronary artery, and near the base of the heart (fig. 1). Wavelength (λ) was defined as the product of the conduction velocity and the effective refractory period. Because ventricular conduction is anisotropic, λ was calculated for longitudinal (λ_L) and transverse (λ_T) di-

rections, using θ_L and θ_T , respectively, measured at a pacing cycle length (PCL) of 300 ms. This PCL was chosen because it is comparable to the normal rabbit heart rate.

Definition of Ventricular Arrhythmias. We defined ventricular arrhythmias as ventricular premature beats, ventricular fibrillation, and sustained and nonsustained ventricular tachycardia. Finally, monomorphic and polymorphic tachycardia were distinguished.

Statistical Analysis

Spontaneous sinus cycle length (RR) in the nonfrozen hearts, and VERP, longitudinal, and transverse ventricular conduction velocities and anisotropic ratio in frozen hearts were expressed as means \pm SD. Wavelengths were expressed as both the absolute value (in millimeters) and the percentage of change of mean values. All parameters were analyzed using a two-way analysis of variance for repeated measures followed by a Neuman-Keuls test and Bonferroni's correction. Variables used to determine the dispersion of refractoriness using analysis of variance were the dose and the site at which VERP was measured. In addition, we compared, in each heart, the area under the curve of VERP plotted for each site. This was designed to corroborate the results of analysis of variance. $P < 0.05$ was considered significant.

Results

Effects of Ketamine in Nonfrozen Hearts

Ketamine induced a dose-dependent lengthening of the spontaneous sinus cycle length (RR). The value of the RR interval was 325.6 ± 41.3 ms at baseline and increased to 374.6 ± 50.8 ms ($P < 0.01$), 427.6 ± 57.6 ms ($P < 0.01$), 464.6 ± 60.6 ms ($P < 0.005$), and 502.6 ± 70.1 ms ($P < 0.005$) after 50, 100, 150, and 200 μ M ketamine, respectively. After washout, all preparations returned to their baseline values (353.8 ± 56.5 ms). No dysrhythmia occurred spontaneously during and after ketamine administration.

Effects of Ketamine in Frozen Hearts

Conduction velocities, anisotropic ratio, and VERP were measured during ventricular pacing at a PCL ranging from 1,000–200 ms for the former and of 300 ms for the latter. During the study of conduction velocities and anisotropic ratio, all hearts could be paced until a PCL of 300 ms, whatever the dose of ketamine. At a

ELECTROPHYSIOLOGIC EFFECTS OF KETAMINE

Table 1. Dose Effect of Ketamine on Longitudinal (θ L) and Transverse (θ T) Conduction Velocity, and on Anisotropic Ratio (θ L/ θ T) (Frozen Hearts, N = 10)

	θ L (cm/s)	θ T (cm/s)	θ L/ θ T
Baseline	76.0 \pm 10.9	39.2 \pm 5.6	1.94 \pm 0.12
50 μ M	71.4 \pm 9.0*	35.1 \pm 7.7	2.08 \pm 0.36
100 μ M	66.8 \pm 12.7†	34.0 \pm 6.2*	1.97 \pm 0.23
150 μ M	62.0 \pm 13.7†	32.7 \pm 7.8†	1.91 \pm 0.24
200 μ M	58.6 \pm 12.7†	29.1 \pm 6.2‡	2.02 \pm 0.26
Washout	76.0 \pm 11.3	37.9 \pm 5.8	2.01 \pm 0.13

θ L, θ T, and θ L/ θ T were measured at a PCL of 1,000 ms. Pacing site was located at the center of the left epicardium (see fig. 1).

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ versus baseline values.

PCL of 250 ms, all hearts could be paced after 50 μ M ketamine, nine hearts after 100 and 150 μ M, and seven hearts after 200 μ M ketamine. At a PCL of 200 ms, seven hearts could be paced after 50 μ M ketamine, only three hearts after 100 and 150 μ M, and none after 200 μ M ketamine. After washout, all hearts recovered their ability to be paced until 200 ms.

No ventricular dysrhythmia could be induced at baseline and after increasing doses of ketamine. Table 1 reports the effects of ketamine on ventricular longitudinal and transverse conduction velocity and on anisotropic ratio. Ketamine induced a dose-dependent slowing of longitudinal conduction velocity that was significant from 50 μ M ($P < 0.05$). Transverse conduction velocity was also decreased in a dose-dependent manner, with statistical significance reached at 100 μ M ($P < 0.05$). No significant use dependency was observed, either on θ L or θ T (fig. 2). Anisotropic ratio was unchanged whatever the dose or the PCL (table 2).

The VERP was prolonged in a dose-dependent manner, which was significant from 50 μ M ketamine ($P < 0.05$; table 3). There was no significant intersite variability when assessed by the comparison of mean values of VERP (table 4) and the comparison of areas under the curves of VERP in each site. Figure 3 shows four different activation maps recorded during a regular pacing at 1,000 ms in the same heart on baseline, after 100 and 200 μ M ketamine, and after 200 μ M ketamine at a PCL of 400 ms.

In figure 4, ketamine-induced changes in ventricular λ are shown. Baseline values of λ L and λ T were 114.9 \pm 15.5 mm and 58.5 \pm 9.3 mm, respectively. Table 3 shows the dose effect of ketamine on the absolute value of λ L and λ T. Ventricular λ L was increased by 2.9% to 7.9%, whereas λ T was increased by 4.5% to 8.2% after

ketamine administration (fig. 4). However, this increase in λ L and λ T was not significant.

Discussion

The present study shows that ketamine induced a significant bradycardia in isolated intact hearts and did not facilitate the occurrence of spontaneous arrhythmias. In frozen hearts, ketamine slowed ventricular epicardial longitudinal and transverse conduction in a dose-dependent manner. Anisotropic ratio was unchanged, and no use dependency was observed. Furthermore, ketamine induced a dose-dependent prolongation of VERP, with no increased dispersion of refractoriness, whereas it did not significantly modify ventricular wavelength. Finally, no arrhythmia could be induced by pacing.

The first aim of the study was to verify the effects of clinically relevant concentrations of ketamine on ventricular θ L, θ T, and VERP. In the clinical setting, serum concentrations of ketamine are reported to range from 100 μ M, which corresponds to peak concentrations reached during induction of anesthesia, and 10 μ M, which is the concentration obtained during maintenance of anesthesia.³¹ Except for the concentration of 200 μ M, the other concentrations used in our study are clinically relevant. Previous studies showed that ketamine alters cardiac electrophysiologic parameters by interfering with the function of several ionic channels. In isolated guinea pig hearts, Stowe *et al.*⁵ showed that ketamine has little electrophysiologic effect at low doses. Indeed, in this study, heart rate was significantly decreased at 50 μ M, and atrioventricular conduction time was slowed only at 500 μ M. In guinea pig and rat papillary muscles and left atrial tissues, Endou *et al.*² found that 300 μ M ketamine decreases the maximum upstroke velocity of action potential (V_{max}), which is known to be correlated with the fast inward sodium current and conduction velocity in all tissues.³² This class 1 antiarrhythmic pattern of action was confirmed by the results of the study conducted by Hara *et al.*⁹ on guinea pig papillary muscle. However, these authors showed that this effect differs from that of pure class 1 antiarrhythmic agents by the absence of use dependency. These two studies investigated mainly the cellular or the longitudinal conduction, whereas ventricular conduction has been shown to be anisotropic. Indeed, in normal ventricular myocardium, conduction velocity is faster when parallel (longitudinal conduction) than

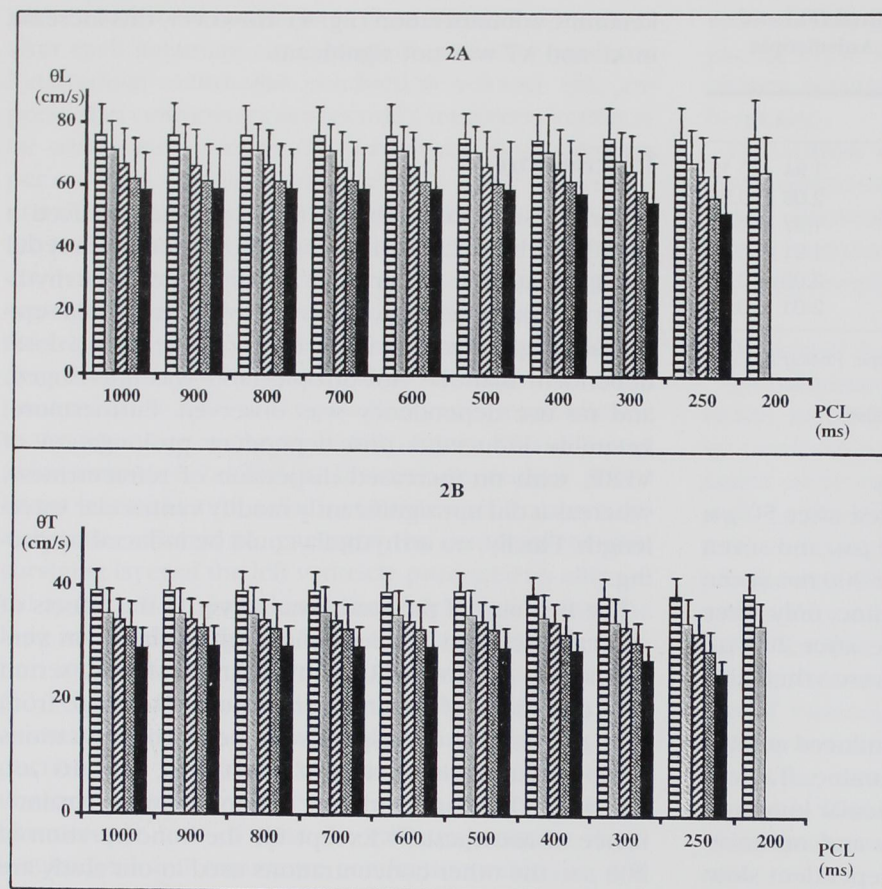


Fig. 2. Use-dependent effects on longitudinal (A) and transverse (B) conduction velocities of ketamine in frozen hearts. Data are expressed as means \pm SD bars. Control (horizontal striped box); 50 μ M ketamine (light gray box); 100 μ M ketamine (diagonal striped box); 150 μ M ketamine (black box). At a pacing cycle length (PCL) of 200 ms, data obtained after 100, 150, and 200 μ M ketamine were discarded because only a few hearts could be paced (see Results). θ_L = longitudinal ventricular conduction velocity (expressed as centimeters per second); θ_T = transverse ventricular conduction velocity (expressed as centimeters per second).

when perpendicular to the fibers orientation (transverse conduction) because of directional differences in effective axial resistance.^{29,33,34} Although longitudinal conduction is correlated to V_{\max} and to the fast inward sodium current, Brugada *et al.*²⁵ found that transverse conduction is an estimate of the cell-to-cell coupling.

In this regard, our study is the first to evaluate the effects of ketamine on both longitudinal and transverse conduction. Our results are in accord with previously described data, because ketamine induced a dose-dependent and a non-use-dependent slowing of epicardial conduction velocity, both in the longitudinal and

Table 2. Dose- and Frequency-dependent Effect of Ketamine on Anisotropic Ratio (θ_L/θ_T) in Frozen Hearts (N = 10)

PCL (ms)	Baseline	50 μ M	100 μ M	150 μ M	200 μ M	Washout
1000	1.94 \pm 0.12	2.08 \pm 0.36	1.97 \pm 0.23	1.91 \pm 0.24	2.02 \pm 0.26	2.01 \pm 0.13
900	1.94 \pm 0.12	2.07 \pm 0.33	1.95 \pm 0.24	1.90 \pm 0.25	2.01 \pm 0.27	2.01 \pm 0.13
800	1.94 \pm 0.12	2.07 \pm 0.33	1.96 \pm 0.22	1.91 \pm 0.24	2.01 \pm 0.26	1.98 \pm 0.15
700	1.93 \pm 0.13	2.06 \pm 0.34	1.94 \pm 0.25	1.91 \pm 0.23	2.01 \pm 0.26	1.98 \pm 0.15
600	1.94 \pm 0.12	2.07 \pm 0.33	1.96 \pm 0.23	1.91 \pm 0.24	2.01 \pm 0.26	1.98 \pm 0.15
500	1.92 \pm 0.14	2.06 \pm 0.34	1.96 \pm 0.23	1.89 \pm 0.25	2.02 \pm 0.26	1.98 \pm 0.15
400	1.94 \pm 0.17	2.08 \pm 0.34	1.95 \pm 0.27	1.95 \pm 0.19	1.99 \pm 0.27	1.96 \pm 0.21
300	1.97 \pm 0.18	2.05 \pm 0.31	1.98 \pm 0.22	1.94 \pm 0.24	2.01 \pm 0.27	1.89 \pm 0.18
250	1.97 \pm 0.25	2.04 \pm 0.34	1.99 \pm 0.27	1.97 \pm 0.30	2.06 \pm 0.34	1.89 \pm 0.26
200	1.96 \pm 0.22	1.98 \pm 0.18	2.19 \pm 0.07	2.35 \pm 0.05	—	1.97 \pm 0.23

ELECTROPHYSIOLOGIC EFFECTS OF KETAMINE

Table 3. Dose Effect of Ketamine on Longitudinal (θ L) and Transverse (θ T) Conduction Velocity, VERP, and Longitudinal (λ L) and Transverse (λ T) Wavelengths (Frozen Hearts, N = 10)

	θ L (cm/s)	θ T (cm/s)	VERP (ms)	λ L (mm)	λ T (mm)
Baseline	75.5 \pm 10.1	38.4 \pm 5.9	152.9 \pm 6.0	114.9 \pm 15.5	58.5 \pm 9.3
50 μ M	68.4 \pm 10.0*	34.1 \pm 7.9	178.3 \pm 8.7*	122.9 \pm 19.6	61.3 \pm 15.0
100 μ M	65.1 \pm 11.5†	33.2 \pm 6.2*	190.9 \pm 11.0*	124.2 \pm 18.9	63.5 \pm 11.9
150 μ M	58.7 \pm 13.7†	30.5 \pm 7.3†	204.2 \pm 16.2*	118.3 \pm 23.5	61.8 \pm 14.4
200 μ M	55.1 \pm 12.4†	27.4 \pm 5.0‡	225.2 \pm 16.6*	123.8 \pm 26.7	61.8 \pm 12.7
Washout	73.9 \pm 11.5	38.0 \pm 6.1	159.9 \pm 12.7	113.9 \pm 16.9	60.6 \pm 10.4

θ L, θ T, and VERP were measured at a PCL of 300 ms. Pacing site was located at the center of the left epicardium (see fig. 1).

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ versus baseline values.

the transverse directions. This corresponds with the results of Nigli *et al.*,³⁵ who showed that, unlike volatile anesthetics, ketamine does not impair cell-to-cell coupling.

In the present study, ketamine induced a dose-dependent prolongation of VERP. This effect is in accordance with the known effects of ketamine on the ionic currents involved in the recovery of excitability. Endou *et al.*² found that ketamine decreases the transient outward current (I_{to}) in a dose-dependent manner in rat single ventricular myocytes. These authors also showed that 100 μ M ketamine decreases the inward rectifier potassium current (I_{K1}) and the delayed rectifier current (I_K) in guinea pig ventricular cells. In the study by Baum,¹⁰ 100 μ M ketamine also inhibited I_{K1} but not I_K . The difference of effect on I_K between these two studies could not be explained, because 100 μ M ketamine was applied to guinea pig ventricular cells in both of them. This inhibitory effect of ketamine on the potassium currents might account for a delay in repolarization and the lengthening of action potential duration. However, it must be noted that action potential duration seems to be lengthened only at high concentrations of ketamine. Napolitano *et al.*²² showed that the guinea pig atrial effective refractory period was unchanged throughout

a ketamine concentration range of 0–50 μ M. Hara *et al.*⁹ showed that action potential duration at 90% repolarization was lengthened by 100 and 300 μ M ketamine in guinea pig papillary muscle. Endou *et al.*² found that action potential duration at –40 and –70 mV were also lengthened by 300 μ M ketamine in rat left atrium, rat papillary muscle, and guinea pig left atrium. In our study, VERP was prolonged from 50 μ M. Although our model does not allow the study of the ionic mechanisms of this effect, because rabbit ventricular myocytes have been shown to possess I_{to} , I_{K1} , and I_K , we can suggest that the prolongation of VERP is the result of the interference of ketamine with the early and the late phases of repolarization. In conclusion, ketamine slows ventricular conduction velocity in a dose-dependent manner, with no use dependency, and prolongs VERP.

We also aimed to evaluate the effects of ketamine on anisotropic ratio and on dispersion of the refractory period, and to evaluate the possible role of ketamine in the induction of anisotropic or dispersion-based reentry. It has been established that the anisotropic conduction in the ventricular myocardium and the effects of drugs on the anisotropic properties may facilitate the occurrence of reentrant arrhythmia around functional conduction blocks. However, anisotropic reentry oc-

Table 4. Dispersion of VERP in Frozen Hearts (N = 10)

	Site 1	Site 2	Site 3	Site 4	Site 5
Baseline	152.9 \pm 6.0	155.5 \pm 5.0	155.9 \pm 5.8	155.7 \pm 5.1	158.3 \pm 9.2
50 μ M	178.3 \pm 8.7	179.7 \pm 11.9	179.8 \pm 10.5	175.2 \pm 6.9	178.3 \pm 7.8
100 μ M	190.9 \pm 11.0	190.2 \pm 10.1	193.0 \pm 16.2	190.3 \pm 13.6	193.8 \pm 15.6
150 μ M	204.2 \pm 16.2	201.1 \pm 14.1	207.7 \pm 22.7	205.5 \pm 14.9	211.1 \pm 14.6
200 μ M	225.2 \pm 16.6	216.9 \pm 17.0	230.4 \pm 25.8	223.5 \pm 17.2	230.1 \pm 18.8
Washout	159.9 \pm 12.7	161.2 \pm 10.1	157.1 \pm 17.6	156.7 \pm 9.2	163.3 \pm 9.6

VERP was measured at PCL of 300 msec. In each site VERP values at all ketamine concentrations were significantly different from baseline (see table 3).

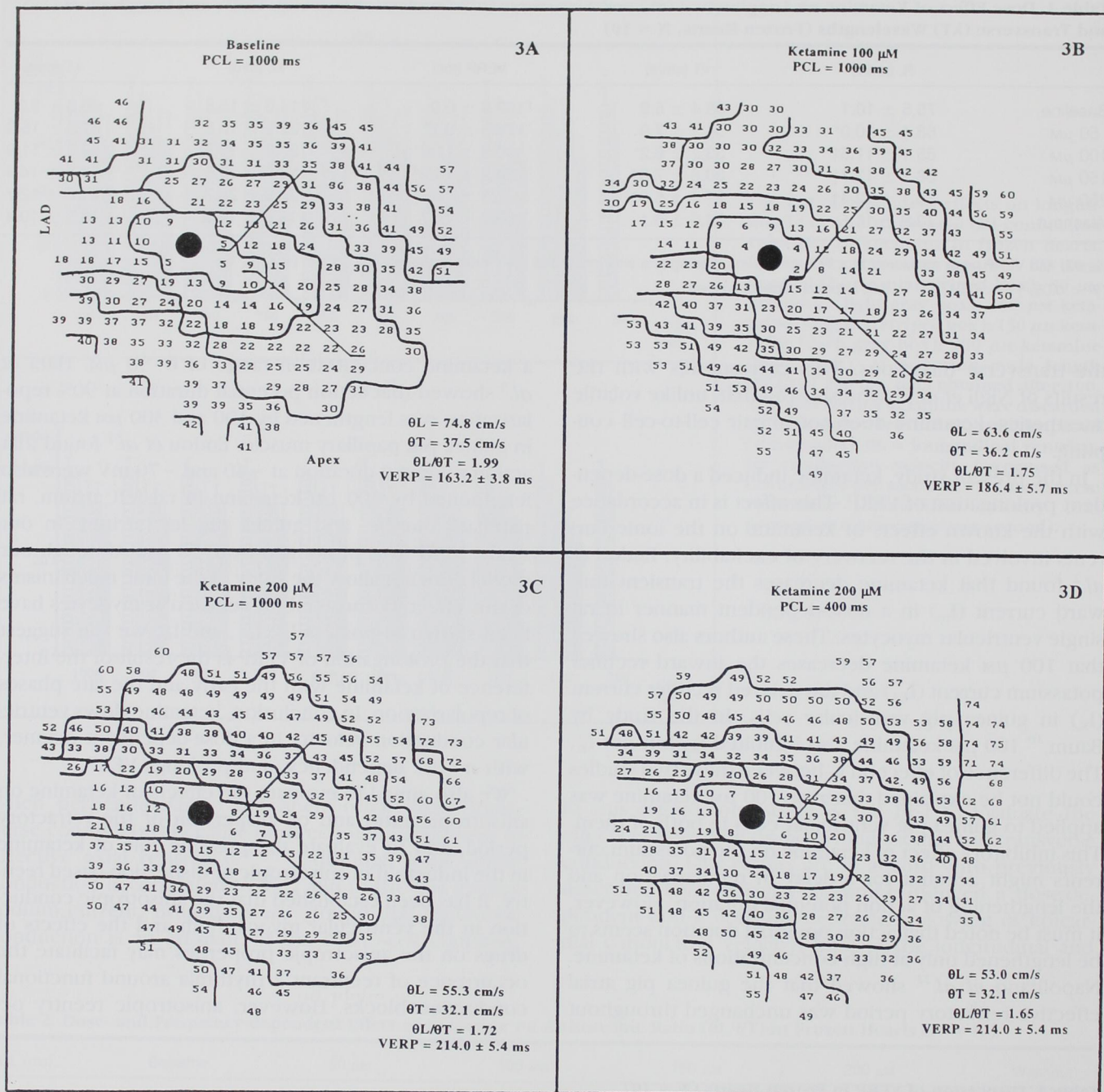


Fig. 3. Dose-dependent effects of ketamine in frozen hearts, on longitudinal and transverse ventricular conduction velocities at a pacing cycle length (PCL) of 1,000 ms (A, B, C). Panel D is designed to show that ketamine had no use-dependent effects (PCL of 400 ms). The closed circle represents the pacing site. Numbers indicate local activation times expressed in milliseconds. Isochrones are drawn at 10-ms intervals. The underlined activation times indicate the sites between which the longitudinal and transverse ventricular conduction velocities were measured in all panels. Increasing concentrations of ketamine progressively impaired longitudinal and transverse ventricular conduction velocity. The corresponding refractory periods are prolonged. Increasing the PCL did not enhance significantly the slowing of conduction velocities. No functional conduction block occurred, therefore no reentrant dysrhythmia could be induced. θL = longitudinal ventricular conduction velocity; θT = transverse ventricular conduction velocity. LAD = left anterior descending coronary artery.

ELECTROPHYSIOLOGIC EFFECTS OF KETAMINE

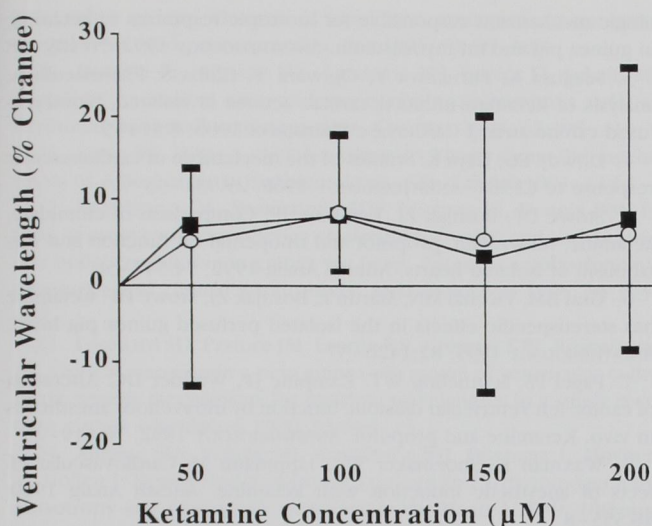


Fig. 4. Dose-dependent effects of ketamine on ventricular longitudinal (filled squares) and transverse (open circles) wavelength in frozen hearts. Data are expressed as percentages of the change of mean \pm SD.

curs when anisotropy is modified by a use-dependent block^{12,16,17} or by a selective or preferential slowing of conduction, or unidirectional conduction block.²⁵ In our study, anisotropic ratio was unchanged, suggesting that the slowing of the conduction was of similar extent in both longitudinal and transverse directions. Furthermore, there was no use dependency. Thus ketamine cannot induce ventricular arrhythmias due to anisotropic reentry, because no functional conduction block could be created. It has been shown that dispersion of refractoriness may also create conditions for reentrant arrhythmias.^{14,15} The results of our study show that ketamine did not induce any increase in dispersion of the refractory period. All these facts suggest that ketamine has no direct arrhythmogenic effect. Conversely, because selective prolongation of refractoriness has antiarrhythmic effects³⁶ and ketamine induces a uniform prolongation of VERP, we suggest that ketamine might possess genuine ventricular antiarrhythmic properties.

The second aim of the present study was to evaluate the antiarrhythmic or arrhythmogenic property of ketamine. In frozen hearts, we studied changes in ventricular wavelength as a possible index of the antiarrhythmic or arrhythmogenic properties of ketamine. Ketamine tended to increase wavelength (although the difference was not statistically significant), an effect that indicates an antiarrhythmic property. These results do not correspond with those of Napolitano *et al.*,²² who showed that, in guinea pig atrial tissue, ketamine significantly

decreased atrial λ . However, these authors studied the atria, another tissue species, and another range of ketamine concentrations than we did in our study. This disagreement is likely explained by small differences in the ionic mechanisms for atrial versus ventricular repolarization. For example, slow-inward currents (due to slow decay of Na^+ or Ca^{2+} plateau current) may play a more important role in determining ventricular action potential duration and refractoriness, whereas outward K^+ currents are more important in atrium.³⁷ The antiarrhythmic potency of ketamine has been previously described and was accounted for, at least in part, by its inhibitory effects on sodium channels.^{4,38} Our results show that the lengthening of the refractoriness, the absence of increase in its dispersion, and the homogeneous pattern of the slowing of conduction velocity with regard to anisotropy might play an important role in the antiarrhythmic property of ketamine. Further, from changes of λL and λT , we can postulate that the lengthening of VERP counteracts the effect of the slowing of conduction in longitudinal and transverse directions and prevents the occurrence of a circuit of reentry. Although the cellular and molecular grounds of this antiarrhythmic effect must be clarified, they might involve the effects of ketamine on various ionic currents on different structures of the heart.

Care must be taken before extrapolating these experimental result to the clinical setting. Although the concentrations of ketamine studied correspond to those used clinically, our results do not account for the complex interactions existing between the autonomic nervous system and the intrinsic cardiac electrophysiologic activity. Because of our choice of model, the sympathetic mediation of the cardiac effect of ketamine is not present and the hemodynamic influence and the possible cardiac pathologic conditions are ignored. It also appears that direct cardiac effects observed in the present study might be modified *in vivo*. In addition, the present study involves a thin epicardial layer. It is established that, from epicardium to endocardium, the ventricular wall is composed by at least three subtypes of myocardial cells with different electrophysiologic behaviors.³⁹⁻⁴¹ Thus the effects of ketamine on these different cell subtypes may vary qualitatively or quantitatively, so that the resulting effect may be unexpected based on our results. Finally, we measured VERP in five sites of epicardium. Therefore we cannot completely exclude possible VERP dispersion in other sites over the left ventricular epicardium.

Ketamine is usually selected for use as the sole or

adjunct anesthetic agent in patients with acute circulatory failure.⁴² The results of our study might have clinical relevance when these patients have healthy hearts, presuming that the other portions (M and endocardial regions) of the myocardium are affected similarly by ketamine. However, this cannot be extrapolated to situations of systemic imbalance such as hypoxia, hypocalcemia, or electrolyte disturbances. This limitation must be extended to patients with pathologic cardiac conditions such as ischemia or dilated or hypertrophic myopathy. In all these situations, the electrophysiologic behavior of the myocardial cells is modified. For example, conduction is slowed and refractoriness is shortened in ischemic compared with normal myocardial cells, and these cells might be affected differently by ketamine, as it has been demonstrated with halothane.^{43,44} Furthermore, Riou *et al.*⁴⁵ studied the effects of ketamine on the intrinsic mechanical properties of cardiac papillary muscle from healthy hamsters and those with cardiomyopathy. They showed that ketamine induces a positive inotropic effect on papillary muscle from the healthy hamsters, whereas this effect is markedly decreased or suppressed on cardiomyopathic muscles. Thus further studies are needed to investigate the cardiac effects of ketamine in the previously mentioned pathologic conditions.

In conclusion, using a high-resolution mapping system in rabbit hearts, the study shows that ketamine significantly slows longitudinal and transverse conduction velocity, without inducing conduction blocks at therapeutic concentrations. There was no significant use dependency, the VERP was prolonged in a spatial homogenous manner, and ventricular wavelength was not significantly modified. No dysrhythmia could be induced in cryotreated hearts with a thin surviving rim of epicardial tissue. No dysrhythmia was observed in nonfrozen hearts. The electrophysiologic effects of ketamine suggest, in the present rabbit heart model, that this agent is not arrhythmogenic and has antiarrhythmic properties on ventricles.

The authors thank Gilbert Saïssi, M.D. (Department of Anesthesiology), the entire pharmacy staff (especially Patrick Chartreux and Christian Francou), and Robert Sempéré (Medical School).

References

1. Riou B, Lecarpentier Y, Viars P: Inotropic effect of ketamine on rat cardiac papillary muscle. *ANESTHESIOLOGY* 1989; 71:116-25
2. Endou M, Hattori Y, Nakaya H, Gotoh Y, Kanno M: Electrophysiologic mechanisms responsible for inotropic responses to ketamine in guinea pig and rat myocardium. *ANESTHESIOLOGY* 1992; 76:409-18
3. Seagusa K, Furukawa Y, Ogiwara Y, Chiba S: Pharmacologic analysis of ketamine-induced cardiac actions in isolated, blood-perfused canine atria. *J Cardiovasc Pharmacol* 1986; 8:414-9
4. Dowdy EG, Kaya K: Studies of the mechanism of cardiovascular response to CI-581. *ANESTHESIOLOGY* 1968; 29:931-43
5. Stowe DF, Bosnjak ZJ, Kampine JP: Comparison of etomidate, ketamine, midazolam, propofol and thiopental on function and metabolism of isolated hearts. *Anesth Analg* 1992; 74:547-58
6. Graf BM, Vicenzi MN, Martin E, Bosnjak ZJ, Stowe DF: Ketamine has stereospecific effects in the isolated perfused guinea pig heart. *ANESTHESIOLOGY* 1995; 82:1426-37
7. Pagel PS, Schmeling WT, Kampine JP, Warltier DC: Alteration of canine left ventricular diastolic function by intravenous anesthetics in vivo. Ketamine and propofol. *ANESTHESIOLOGY* 1992; 76:419-25
8. Waxman K, Shoemaker WC, Lippmann M: Cardiovascular effects of anesthetic induction with ketamine. *Anesth Analg* 1980; 58:355-8
9. Hara Y, Tamagawa M, Nakaya H: The effects of ketamine on conduction velocity and maximum rate of rise of action potential upstroke in guinea pig papillary muscles: Comparison with quinidine. *Anesth Analg* 1994; 79:687-93
10. Baum VC: Distinctive effects of three intravenous anesthetics on the inward rectifier (I_{K1}) and the delayed rectifier (I_{Kr}) potassium currents in myocardium: Implications for the mechanism of action. *Anesth Analg* 1993; 76:18-23
11. Baum VC, Tecson ME: Ketamine inhibits transsarcolemmal calcium entry in guinea pig myocardium: Direct evidence by single cell voltage clamp. *Anesth Analg* 1991; 73:804-7
12. Baum VC, Wetzel GT, Klitzner TS: Effects of halothane and ketamine on activation and inactivation of myocardial calcium current. *J Cardiovasc Pharmacol* 1994; 23:799-805
13. Schlij MJ, Lammers WJEP, Rensma PL, Allesie MA: Anisotropic conduction and reentry in perfused epicardium of rabbit left ventricle. *Am J Physiol* 1992; 263:H1466-78
14. Kuo CS, Manakata K, Reddy CP, Surawicz B: Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. *Circulation* 1983; 67:1356-67
15. Di Diego J, Antzelevitch M: Pinacidil-induced electrical heterogeneity and extrasystolic activity in canine ventricular tissues. *Circulation* 1993; 88:1177-89
16. de La Coussaye JE, Brugada J, Allesie MA: Electrophysiologic and arrhythmogenic effects of bupivacaine: A study with high resolution ventricular epicardial mapping in rabbit hearts. *ANESTHESIOLOGY* 1992; 77:132-41
17. Robert E, Bruelle P, deLa Coussaye JE, Juan JM, Brugada J, Peray P, Dauzat M, Eledjam JJ: Electrophysiologic and proarrhythmic effects of therapeutic and toxic doses of imipramine: a study with high resolution ventricular epicardial mapping in rabbit hearts. *J Pharmacol Exp Ther* 1996; 278:170-8
18. Robert E, Delye B, Aya G, Péray P, Juan JM, Sassine A, de La Coussaye JE, Eledjam JJ: Comparison of proarrhythmogenic effects of two potassium channel openers, levromakalim (BRL 38227) and nicorandil (RP 46417): A high resolution mapping study on rabbit heart. *J Cardiovasc Pharmacol* 1997; 29:109-18
19. Smeets JL, Allesie MA, Lammers WJ, Bonke FI, Hollen J: The wavelength of the cardiac impulse and reentrant arrhythmias in iso-

ELECTROPHYSIOLOGIC EFFECTS OF KETAMINE

lated rabbit atrium. The role of heart rate, autonomic transmitters, temperature, and potassium. *Circ Res* 1986; 58:96-108

20. Rensma PL, Allesie MA, Lammers WJ, Bonke FI, Schalij MJ: Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. *Circ Res* 1988; 62:395-410

21. Janse MJ: What a clinician needs to know about the mechanisms of action of antiarrhythmic drugs. *Clin Cardiol* 1991; 14:65-7

22. Napolitano CA, Raatikainen MJP, Martens JR, Dennis DM: Effects of intravenous anesthetics on atrial wavelength and atrioventricular nodal conduction in guinea pig heart. Potential antidysrhythmic properties and clinical implications. *ANESTHESIOLOGY* 1996; 85:393-402

23. Girouard SD, Pastore JM, Laurita KR, Gregory KW, Rosenbaum DS: Optical mapping in a new guinea pig model of ventricular tachycardia reveals mechanisms for multiple wavelengths in a single reentrant circuit. *Circulation* 1996; 93:603-13

24. Allesie MA, Schalij MJ, Kirchhof CJHJ, Boersma L, Huybers M, Hollen J: Experimental electrophysiology and arrhythmogenicity: Anisotropy and ventricular tachycardia. *Eur Heart J* 1989; 10(Suppl E):8-14

25. Brugada J, Mont L, Boersma L, Kirchhof C, Allesie MA: Differential effects of heptanol, potassium and tetrodotoxin on reentrant ventricular tachycardia around a fixed obstacle in anisotropic myocardium. *Circulation* 1991; 84:1307-18

26. Arimura H, Ikemoto Y, Ito T, Yoshitake J: Lack of effects of d-tubocurarine and pancuronium on the slow action potential of the guinea pig papillary muscle. *Can Anaesth Soc J* 1985; 32:484-90

27. Brugada J, Boersma L, Kirchhof C, Brugada P, Havenith M, Wellens HJJ, Allesie MA: Double-wave reentry as a mechanism of ventricular tachycardia acceleration. *Circulation* 1990; 81:1633-43

28. Allesie MA, Hoeks APG, Schmitz GML, Reneman RS: On-line mapping system for the visualisation of the electrical activation of the heart. *Int J Cardiac Imaging* 1987; 2:59-63

29. Clerc L: Directional differences on impulse spread in trabecular muscle from mammalian heart. *J Physiol (Lond)* 1976; 255:335-46

30. Spach MS, Miller WT Jr, Geselowitz DB, Barr RC, Kootsey JM, Johnson EA: The discontinuous nature of propagation in normal canine cardiac muscle. Evidence for recurrent discontinuities of intracellular resistance that affect the membrane currents. *Circ Res* 1981; 48:39-54

31. Idvall J, Ahlgren I, Aronsen KF, Stenberg P: Ketamine infusion: Pharmacokinetics and clinical effects. *Br J Anaesth* 1979; 51:1167-73

32. Cohen CJ, Bean PB, Tsien RW: Maximum upstroke velocity (V_{max}) as an index of available sodium conductance: Comparison of

V_{max} and voltage clamp measurements of I_{Na} in rabbit Purkinje fibers. *Circ Res* 1984; 54:636-51

33. Roberts DE, Hersh LT, Scher AM: Influence of cardiac fiber orientation on wavefront voltage, conduction velocity and tissue resistivity in the dog. *Circ Res* 1979; 44:701-12

34. Spach MS, Dolber PC, Heidlage JF, Kootsey JM, Johnson EA: Propagating depolarisation in anisotropic human and canine cardiac muscle: apparent directional differences in membrane capacitance. A simplified model for selective directional effects of modifying the sodium conductance on V_{max} , t_{foot} , and the propagation safety factor. *Circ Res* 1987; 60:206-19

35. Niggli E, Rüdisüli A, Maurer P, Weingart R: Effect of general anesthetics on current flow across membranes in guinea-pig myocytes. *Am J Physiol* 1989; 256:C273-81

36. Sager PT, Nademanee K, Antimisiaris M, Pacifico A, Pruitt C, Godfrey R, Singh BN: Antiarrhythmic effects of selective prolongation of refractoriness. Electrophysiologic actions of sematilide HCl in humans. *Circulation* 1993; 88:1072-82

37. Giles WR, Imiazumi Y: Comparison of potassium currents in rabbit atrial and ventricular cells. *J Physiol* 1988; 405:123-45

38. Goldgerg AH, Keane PW, Phear WPC: Effects of ketamine on contractile performance and excitability of isolated heart muscle. *J Pharmacol Exp Ther* 1970; 175:388-94

39. Sicouri S, Antzelevitch C: A subpopulation of cells with unique electrophysiological properties in the deep subepicardium of the canine ventricle. The M cells. *Circ Res* 1991; 68:1729-41

40. Krishnan SC, Antzelevitch C: Sodium channel block produces opposite electrophysiological effects in canine ventricular epicardium and endocardium. *Circ Res* 1991; 69:277-91

41. Liu DW, Gintant GA, Antzelevitch C: Ionic bases for electrophysiological distinctions among epicardial, midmyocardial, and endocardial myocytes from the free wall of the canine left ventricle. *Circ Res* 1993; 72:671-87

42. White PF, Way WL, Trevor AJ: Ketamine—Its pharmacology and therapeutic uses. *ANESTHESIOLOGY* 1982; 56:119-36

43. Turner LA, Polic S, Hoffmann SG, Kampine JP, Bosnjak ZJ: Actions of halothane and isoflurane on Purkinje fibers in the infarcted canine hearts: Conduction, regional refractoriness, and reentry. *Anesth Analg* 1991; 72:596-603

44. Turner LA, Bosnjak ZJ, Kampine JP: Actions of halothane on electrical activity of Purkinje fibers from normal and infarcted canine hearts. *ANESTHESIOLOGY* 1987; 67:619-29

45. Riou B, Viars P, Lecarpentier Y: Effects of ketamine on the cardiac papillary muscle of normal hamsters and those with cardiomyopathy. *ANESTHESIOLOGY* 1990; 73:910-8