Anesthesiology
1997; 87:327–34

Effect of Intravenous Anesthetics on Inward Rectifier Potassium Current in Rat and Human Ventricular Myocytes

Cynthia A. Carnes, Pharm.D., Ph.D., William W. Muir, III, D.V.M., Ph.D.,† David R. Van Wagoner, Ph.D.‡*

***Background*: Inhibition of the inward rectifying potassium current (I_{K1}) may cause cardiac dysrhythmias by decreasing resting membrane potential or prolonging action potential.**

***Methods*: The effects of thiopental, ketamine, and propofol on I_{K1} conductance were evaluated in rat ventricular myocytes. The effect of thiopental on I_{K1} conductance was also evaluated in human ventricular myocytes. Currents were recorded using the nystatin-perforated whole-cell patch-clamp technique (holding potential, −50 mV; test potentials, −140 to −40 mV). Pipette solution contained 130 mM KCl, 5 mM $MgCl_2$, 5 mM HEPES, and 5 mM EGTA, *p*H 7.2. Bath solution (32°C) contained 134 mM NaCl, 4 mM KCl, 1 mM $MgCl_2$, 1 mM $CaCl_2$, 0.3 mM $CdCl_2$, 5 mM HEPES, and 5 mM d-glucose, *p*H 7.4. Drug concentrations examined encompassed the range of clinically relevant unbound plasma concentrations. Currents were normalized for cell capacitance. Conductance was calculated as current density/ΔmV from −140 to −100 mV. Analysis of variance was used to test for changes in conductance as a function of drug concentration.**

***Results*: Thiopental reduced I_{K1} conductance in a concentration-dependent manner ($P < 0.0001$). Thiopental-induced changes in I_{K1} conductance in rat ventricular myocytes were fit to an inhibitory E_{max} model, with a median inhibitory concentration of 10.5 μM. The effect of thiopental on I_{K1} conductance in human ventricular cells was comparable to that observed in rat ventricular myocytes. Neither ketamine nor propofol altered I_{K1} conductance.**

***Conclusions*: Thiopental reduces I_{K1} conductance in a concentration-dependent manner at clinically relevant concentrations in both rat and human ventricular myocytes. (Key words: Anesthetics, intravenous: ketamine; propofol; thiopental. Heart: electrophysiology. Ions: potassium. Species: human, rat.)**

CARDIAC dysrhythmias are due to changes in the electric activity of individual myocytes or groups of myocardial cells; this activity is determined by cellular ionic currents. Inhibition of one of these currents, the inward rectifier potassium current (I_{K1}), causes diastolic depolarization.[1] A reduction in resting potential decreases the time to threshold and can increase cardiac excitability, which may potentially contribute to a greater likelihood of cardiac dysrhythmias.[2,3] In addition, I_{K1} contributes to the final stages of membrane repolarization; inhibition of I_{K1} may result in modest prolongation of action potential.[3] Thus a drug-induced reduction in I_{K1} may cause action potential and QT prolongation. Changes in cardiac repolarization may also contribute to the development of reentrant dysrhythmias.[3]

Thiopental (30 μM) has been shown to inhibit I_{K1} in guinea pig ventricular myocytes.[2] The effects of ketamine were examined in guinea pig ventricular myocytes in two different studies.[4,5] Endou *et al.*[4] found that ketamine (30 and 300 μM) inhibited I_{K1}. Baum[5] found that ketamine at a concentration of 100 μM inhibited I_{K1}. In contrast, propofol (28 μM) had no effect on I_{K1} amplitude in guinea pig ventricular myocytes.[5] Interestingly, these previous evaluations of thiopental, ketamine, and propofol on I_{K1} did not include the range of usual free drug concentrations that occur clinically. We evaluated the hypothesis that thiopental, ketamine, and propofol block I_{K1} in ventricular myocytes at clinically relevant concentrations.

Materials and Methods

All procedures involving animals were approved by the Ohio State University Institutional Laboratory Animal Care and Use Committee. The procedures for isolat-

* Assistant Professor of Pharmacy.

† Professor of Veterinary Clinical Sciences.

‡ Assistant Professor of Pharmacy, The Ohio State University and the Cleveland Clinic Foundation.

Received from the College of Pharmacy, The Ohio State University, Columbus, and the Cleveland Clinic, Cleveland, Ohio. Submitted for publication August 9, 1996. Accepted for publication March 18, 1997. Supported by a National Research Service Award from the National Institute of General Medical Sciences. Presented at the American College of Clinical Pharmacy annual meeting, Nashville, Tennessee, August 6, 1996.

Address reprint requests to Dr. Carnes: 500 W. 12th Avenue, The Ohio State University, Columbus, Ohio 43210. Address electronic mail to: Carnes.4@osu.edu

ing rat ventricular cells were modified from a previously described method.[6] Male Sprague-Dawley rats (200–250 g) were used for all studies. Rats were decapitated; this method was chosen to eliminate the possibility of residual anesthetic effects. The heart and lungs were rapidly removed and placed in iced incubation buffer composed of 118 mM NaCl, 4.8 mM KCl, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 1 mM $CaCl_2$, 0.68 mM glutamine, 11 mM dextrose, 25 mM HEPES, 5 mM pyruvate, 0.001 mM insulin, basal medium eagle and minimum essential medium nonessential amino acids (GIBCO, Grand Island, NY), *p*H 7.35. The heart was perfused in a retrograde manner using a Langendorff apparatus with 50 ml Krebs-Henseleit (KH) buffer of 118 mM NaCl, 4.8 mM KCl, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 0.68 mM glutamine, 11 mM dextrose, 25 mM $NaHCO_3$, and 5 mM pyruvate. The perfusate was warmed to 37°C, oxygenated with 95% oxygen and 5% carbon dioxide, and maintained at a *p*H of 7.30–7.35 throughout the isolation procedure. The initial perfusion was followed by perfusion with 70 ml of a nominally calcium-free EGTA-containing KH buffer. Subsequently, 1 mg/ml collagenase (Type II, 144 U/mg; Worthington Biochemical, Freehold, New Jersey) and 1 mg/ml bovine serum albumin were added to the EGTA-containing KH buffer; the buffer was recirculated for the rest of the perfusion period. Protease XIV (0.55 U/ml; Sigma Chemical, St. Louis, MO) was added to the perfusate 20 min after the collagenase; additional calcium was gradually added every 5 min to produce a final concentration of 1 mM. When the heart was soft, the ventricles were removed, minced, and placed in a beaker with 5 ml of the perfusate (final collagenase concentration, 2 mg/ml). The beaker was placed in a shaking water bath at 37°C. Cells were collected after washing the cells with a series of bovine serum albumin–containing incubation buffers (composition as noted before). The cells were maintained in incubation buffer with 1 mM $CaCl_2$. This isolation procedure generally produced 70–90% rod-shaped cells. The cells were placed under an oxygen hood at room temperature until used for study. Only rod-shaped cells with sharp margins and clear striations were used for all studies. All studies were conducted within 8 h of cell isolation.

Human Ventricular Myocyte Isolation

Procedures for obtaining human cardiac tissue were approved by the Institutional Review Board of the Cleveland Clinic Foundation. Human ventricular myocytes were isolated from two failing hearts, explanted from transplant recipients at the Cleveland Clinic Foundation (from men ages 49 and 65 yr who had ischemic cardiomyopathy). The hearts were perfused with cardioplegic solution before explantation. After removal, the heart was stored in cold cardioplegic solution until it was brought back to the laboratory (less than 30 min). A 1-g segment of right ventricular free wall was excised and rinsed in a dissection buffer containing 140 mM NaCl, 5.4 mM KCl, 1.2 mM $MgCl_2$, 5 mM HEPES, 5 mM glucose, 30 mM butanedione monoxime, *p*H 7.0. The tissue was cut into small chunks (<1 mm^3) with scissors. Tissue chunks were transferred to a 25-ml Erlenmeyer flask containing 10 ml dissection buffer. The flask was placed in a water bath (30–32°C) mounted over a magnetic stirrer. The tissue chunks were washed three times for 4 min with the dissection buffer and then placed in 10 ml of solution of identical composition but supplemented with 2% bovine serum albumin, collagenase (Worthington type II, 125 U/ml), and protease (Sigma Type XXIV, 0.4 mg/ml). After 30 min of collagenase exposure, the supernatant was aspirated from the tissue and discarded. Fresh collagenase solution (75 U/ml, without protease) was added for an additional 10-min digestion period. The tissue was triturated at the end of the period and the chunks were allowed to settle. The digestion buffer was aspirated with a transfer pipette and centrifuged for 1 min at 300 rpm (approximately 18*g*). The resulting supernatant was discarded and the myocyte pellet was resuspended in an incubation buffer containing 118 mM NaCl, 4.8 mM KCl, 1.2 mM $MgCl_2$, 0.5 mM $CaCl_2$, 1.2 mM KH_2PO_4, 0.68 mM glutamine, 11 mM glucose, 5 mM pyruvate, 10 mM butanedione monoxime, 1 mM insulin, *p*H 7.2, and 1% bovine serum albumin. The undigested tissue was placed in a fresh aliquot of collagenase solution for further digestion. This procedure was repeated five times. After the final collection, the pooled myocytes were again centrifuged to remove residual collagenase/protease and resuspended in fresh incubation buffer. The myocytes were kept in an open plastic beaker under a 100% oxygen hood, at room temperature, until used. Yields from this procedure ranged from 5% to 10% for viable, calcium-tolerant myocytes. Only well-striated, rod-shaped myocytes were used in the electrophysiologic studies.

Electrophysiologic Recordings

The nystatin-perforated, whole-cell, patch-clamp technique was used for all ventricular myocyte recordings.[7,8] Patch pipettes (2–4 MΩ) were made from Corning 8161

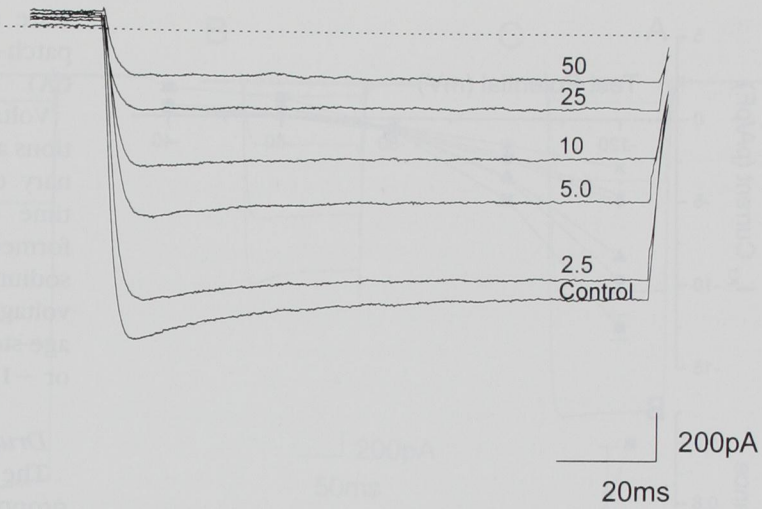

Fig. 1. Thiopental causes a concentration-dependent suppression of I_{K1} current. Currents were recorded at a test potential of −120 mV in a single rat ventricular myocyte exposed to increasing thiopental concentrations. The dashed line indicates zero current. Cell capacitance is 88 pF, and series resistance is 14.2 MΩ.

glass (World Precision Instruments, Sarasota, FL), and the shank of each pipette was coated with Sylgard (World Precision Instruments). Pipette solution contained 130 mM KCl, 5 mM $MgCl_2$, 5 mM HEPES, 5 mM EGTA, *p*H adjusted to 7.25 with potassium hydroxide.

Nystatin stock solution was prepared each day and added to the pipette solution to a final concentration of 240 μg/ml. Pipette tips were filled with nystatin-free solution by capillary action. Pipettes were backfilled with nystatin-containing buffer immediately before use. After seal formation, changes in the capacitative response to a −10 mV step were used to monitor for nystatin perforation of the patch. The access resistance and cell capacitance were monitored throughout each experiment by tuning the patch-clamp amplifier with repeating −10 mV steps from a holding potential of −50 mV. Only cells with stable (less than 10% change) and low access resistance (less than 20 MΩ) were included in the data analysis.

The bath solution contained 134 mM NaCl, 1 mM

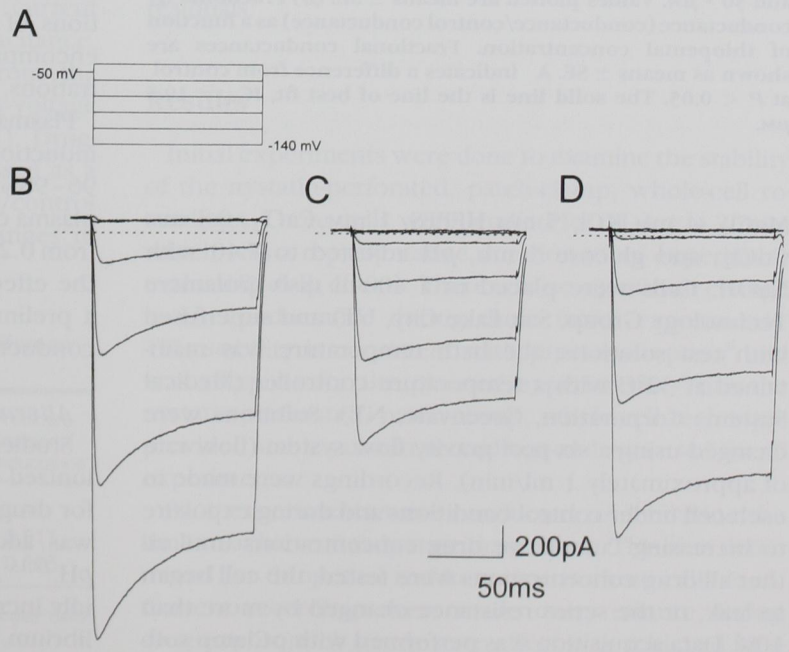

Fig. 2. Currents recorded in a rat ventricular myocyte exposed to 10 μM thiopental. (*A*) Voltage-clamp protocol. (*B*) Control current tracing. (*C*) Thiopental, 10 μM. (*D*) Ten-minute washout. The dashed line indicates zero current. Cell capacitance is 108 pF, and series resistance is 13.9 MΩ.

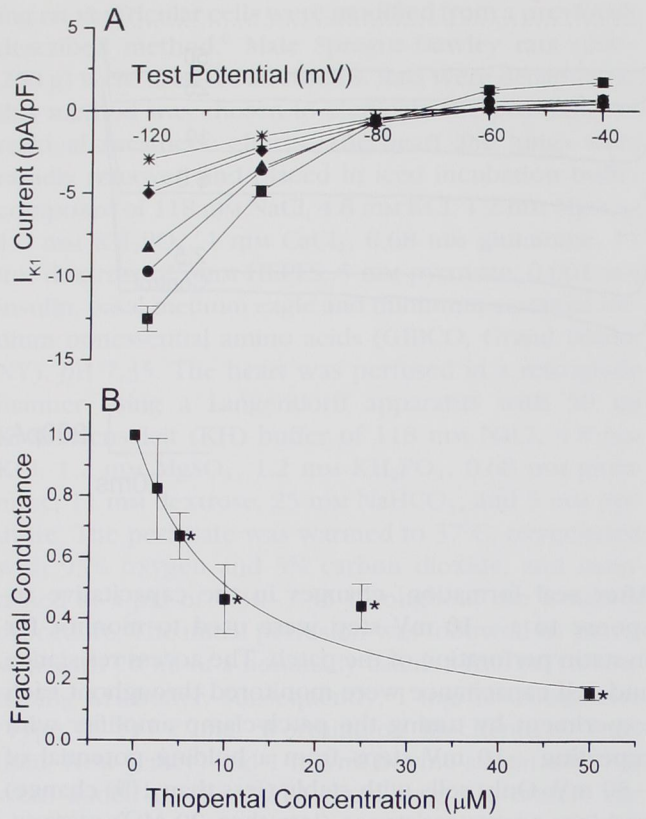

Fig. 3. (*A*) Concentration-dependent effect of thiopental on I_{K1} current density-voltage relation in rat ventricular myocytes. Mean current density-voltage relations were recorded in control bath solution (n = 18) and during thiopental exposure (n = 6 per concentration). Control ■, 2.5 •, 5.0 ▲, 10 ♦, 25 +, and 50 * μM. Values plotted are means ± SE. (*B*) Fractional I_{K1} conductance (conductance/control conductance) as a function of thiopental concentration. Fractional conductances are shown as means ± SE. A indicates a difference from control at $P < 0.05$. The solid line is the line of best fit, IC_{50} = 10.5 μM.

$MgCl_2$, 4 mM KCl, 5 mM HEPES, 1 mM $CaCl_2$, 0.3 mM $CdCl_2$, and glucose 5 mM, *p*H adjusted to 7.40 with NaOH. Cells were placed in a 400-μl dish (Solamere Technology Group, Salt Lake City, UT) and superfused with test solutions; the bath temperature was maintained at 32°C with a temperature controller (Medical Systems Corporation, Greenvale, NY). Solutions were changed using a six-port gravity flow system (flow rate of approximately 1 ml/min). Recordings were made in each cell under control conditions and during exposure to increasing cumulative drug concentrations until either all drug concentrations were tested, the cell began to leak, or the series resistance changed by more than 10%. Data acquisition was performed with pClamp software and either an Axopatch-1C or Axopatch 200A patch-clamp amplifier (Axon Instruments, Foster City, CA).

Voltage clamp recordings were made in control solutions and at the time of steady-state drug effect. Preliminary experiments were conducted to determine the time to steady-state effect. Experiments were performed from a holding potential of −50 mV to inactivate sodium current. Adding $CdCl_2$ to the bath suppressed voltage-gated calcium current. A series of 100-ms voltage steps, in 20-mV increments, starting at either −140 or −120 mV, were applied at 3-s intervals.

Drug Concentrations

The drug concentrations of thiopental, ketamine, and propofol selected encompassed the range of unbound plasma concentrations reported to occur during anesthesia induction.[9-11] Usual plasma concentrations of thiopental during induction range from 41-83 μM (10-20 μg/ml), of which 72-86% is bound to albumin in the plasma.[9] The unbound thiopental concentrations during induction were therefore assumed to range from 5.8-23.8 μM. Concentrations of 2.5, 5, 10, 25, and 50 μM were examined to encompass the range of clinically relevant concentrations.

Usual plasma concentrations of ketamine during induction are 2.6-14.6 μM (0.7-4.0 μg/ml), with an unbound fraction in plasma of 0.465.[9,10] The unbound ketamine concentrations during induction therefore were assumed to range from 1.2-6.8 μM. Concentrations of 0.5, 1, 2.5, 5, and 10 μM were examined to encompass the range of clinically relevant drug concentrations.

Plasma concentrations of propofol reported during induction range from 11.2-44.9 μM (2-8 μg/ml), with 96-98% bound to plasma proteins.[9,11] The unbound plasma concentrations therefore were assumed to range from 0.22-1.8 μM. Because a previous report examining the effect of 28 μM propofol on I_{K1} found no effect,[5] a preliminary series of experiments on six cells were conducted at a concentration of 2.5 μM.

Alterations in Internal p*H*

Studies were conducted to determine whether the ionized or un-ionized form of thiopental is responsible for drug effects by altering internal *p*H. NH_4Cl (20 mM) was added to the perfusate to increase intracellular *p*H.[12,13] Application of external NH_4Cl is known to rapidly increase intracellular *p*H and achieve a stable equilibrium.[12,13] Measurements were taken after 2 min,

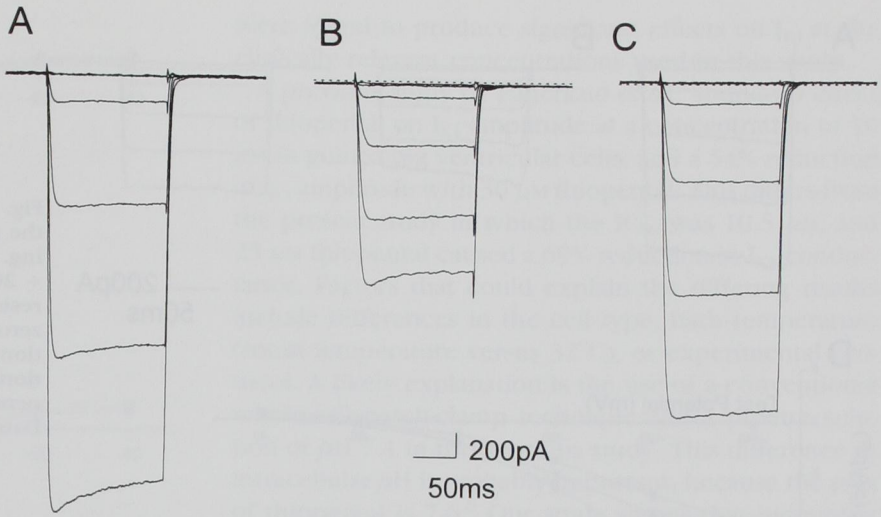

Fig. 4. Effect on 10 μM thiopental in a representative human right ventricular myocyte. (*A*) Control current tracing. (*B*) Thiopental, 10 μM. (*C*) Ten-minute washout. Cell capacitance, 253 pF; series resistance, 8.0 MΩ. The dashed line indicates zero current.

when the intracellular *p*H was expected to be 7.6–7.8.[12,13]

Chemicals

Thiopental sodium was produced by Abbott Laboratories. Ketamine and all other reagents were obtained from Sigma Chemical Company unless otherwise noted. Propofol was obtained from Aldrich Chemical Company.

Data Analysis

The measured currents were expressed as current density (pA/pF) after normalization for cell capacitance. I_{K1} conductance (mS/cm^2) was calculated from the slope of the linear portion of the current density-voltage relation (test potentials of −140 to −100 mV). Drug-induced changes in conductance were expressed as a fraction of control conductance (conductance/control conductance) for statistical comparisons. Changes in conductance were tested using analysis of variance with a *post hoc* least-significant difference test (SAS Inc., Cary, NC) to determine which concentrations differed from control. Probability values less than 0.05 were considered significant for all comparisons.

Statistically significant changes in conductance were fit using PCNONLIN (Statistical Consultants, Lexington, KY). The best fit was determined using the Akaike Information Criterion, as well as examination of the condition number, standard error of the estimates, correlation of the estimates, and the random distribution of the residuals.

Table 1. Effect of Thiopental on I_{K1} Conductance in Human Ventricular Cells

Concentration (μM)	Conductance (mS/cm^2) (mean ± SE)	Fractional Conductance	Predicted Fractional Conductance*
0	0.136 ± 0.0290	—	—
10 (n = 5)	0.0634 ± 0.0137	0.466	0.511
25 (n = 3)	0.0422 ± 0.0110	0.310	0.295

* Predicted from fitted reduction in I_{K1} conductance in rat ventricular cells. See figure 3B.

Results

Initial experiments were done to examine the stability of the nystatin-perforated, patch-clamp, whole-cell recordings. Three cells were studied for 11.3 ± 4.2 min, which was a representative duration of an experiment evaluating drug effects. There was no significant change in I_{K1} conductance during these initial experiments. This stability is consistent with previous reports[8] and was adequate for the planned experiments. Thus the nystatin-perforated, patch-clamp, whole-cell technique provided stable current recordings and was used for all experiments.

Pilot experiments were conducted to determine the time to achieve steady-state drug effect. This was determined for thiopental and ketamine in three cells each. Current recordings were made every minute during drug exposure. A steady-state effect was achieved by 4

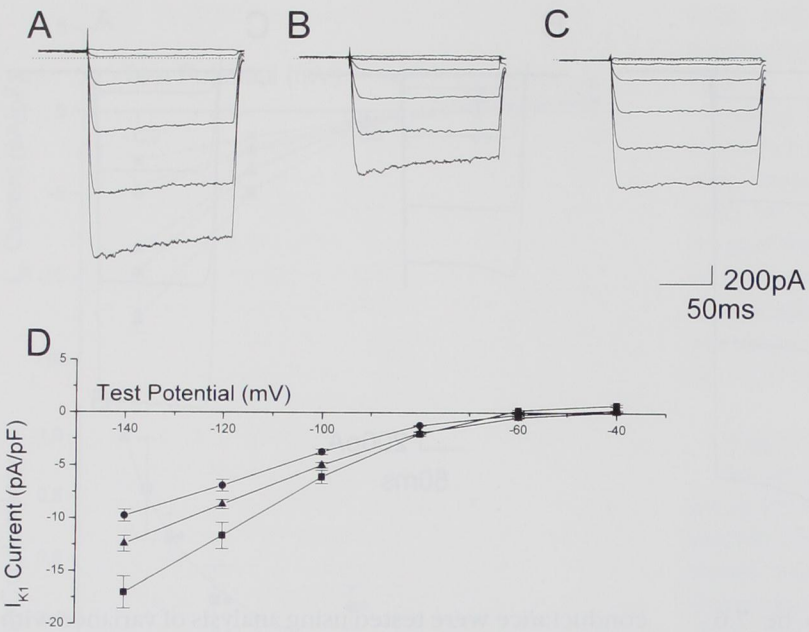

Fig. 5. Reversal of thiopental inhibition of I_{K1} by the addition of NH_4Cl. (*A*) Control current tracing. (*B*) Thiopental, 10 μM. (*C*) 10 μM Thiopental + 20 mM NH_4Cl. Cell capacitance, 95 pF; series resistance, 18.5 MΩ. The dashed line indicates zero current. (*D*) Reversal of thiopental inhibition by NH_4Cl. Mean current density-voltage relations were determined in control ■, 10 μM thiopental •, and 10 μM thiopental + 20 mM NH_4Cl ▲. Data are means ± SE.

min for thiopental and ketamine. No drug effect was detected during propofol exposure (n = 6). All drug effects were determined after 4 min of exposure to the test concentration.

Thiopental

The effects of thiopental were examined in 18 cells; six cells were studied at each concentration (see fig. 3). The data in figure 1 were obtained in one cell exposed to all concentrations tested. Each trace demonstrates the steady-state drug effect. The effect of 10 μM thiopental in a single rat ventricular myocyte is shown in figure 2.

The mean effect of each thiopental concentration on the normalized current-voltage relation is plotted in figure 3A. Thiopental decreased I_{K1} conductance in a concentration-dependent manner ($P < 0.0001$; fig. 3B). The conductance data were best fit using an inhibitory effect model $E = 1 - C/(C + IC_{50})$, where E is the fractional conductance, C is the drug concentration, and IC_{50} is the concentration producing one half of the maximal inhibitory effect.[14] This model assumes that the effect in the absence of drug is equal to 1, and that the maximum achievable effect is complete suppression of conductance. The estimated IC_{50} was 10.5 μM (95% confidence interval, 9.53–11.4).

The effect of thiopental on I_{K1} conductance in human ventricular myocytes was examined at concentrations of 10 (n = 5) and 25 μM (n = 3). Thiopental suppressed I_{K1} in the human ventricular myocytes with a dose-related response very similar to that obtained from the rat ventricular myocyte experiments (fig. 4 and table 1).

NH_4Cl was added to the perfusate to increase intracellular *p*H; this resulted in a significant reduction in the effect of thiopental ($P < 0.05$). Data from these experiments (n = 3) are shown in figure 5.

Thiopental washout data was acquired in eight myocytes (five rat and three human). The I_{K1} conductance returned to at least 80% of baseline in all cells between 4 and 6 min of washout.

Ketamine

The effects of ketamine were studied in 18 cells; six cells were studied at each concentration (fig. 6A). Error bars were omitted from the figure for clarity. Ketamine produced no significant effect on I_{K1} conductance ($P = 0.66$).

Propofol

Dimethylsulfoxide was used to solubilize propofol, because it is so poorly soluble in aqueous solutions. Pilot studies confirmed that dimethylsulfoxide at the highest possible bath concentration of 0.0025% had no detectable effects on I_{K1} conductance (n = 3). Propofol

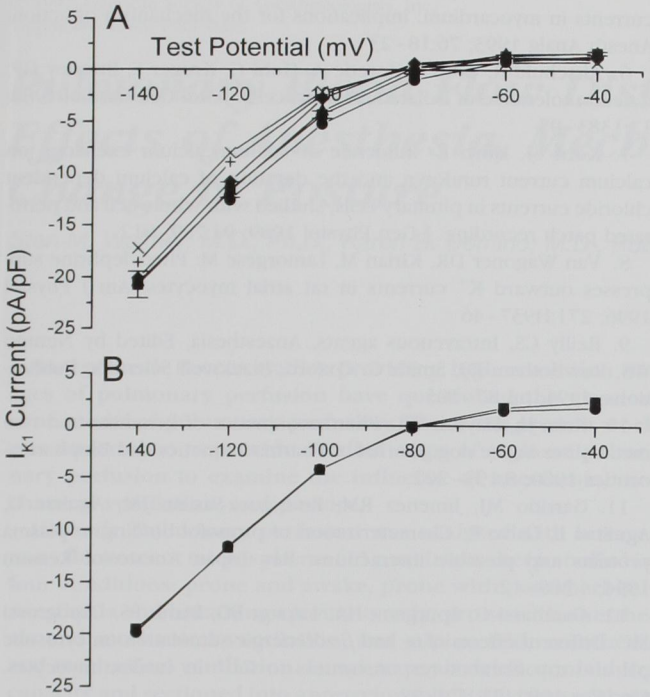

Fig. 6. (*A*) Ketamine concentration-dependent effect on the current density-voltage relation. Mean current density-voltage relations were recorded in control bath solution (n = 18) and during thiopental exposure (n = 6 per concentration). Control ■, 0.5 μM •, 1.0 μM ▲, 2.5 μM ▼, 5.0 μM +, and 10 μM ×. (*B*) Effect of 2.5 μM propofol. Mean current density-voltage relations were recorded in control (■) and during 2.5 μM propofol (•) exposure (n = 6).

(2.5 μM) produced no effect on I_{K1} conductance (fig. 6B).

Discussion

The inward rectifier potassium current is the primary current contributing to the resting membrane potential in ventricular cardiac myocytes. Inhibition of I_{K1} causes diastolic depolarization, which can result in increased cardiac excitability[1] and contribute to the development of dysrhythmias due to abnormal automaticity.[3] In addition to inward current, I_{K1} also contributes to the terminal phase of repolarization *via* outward current at potentials between −50 and −40 mV.[15,16] Drug-induced inhibition of I_{K1} would result in prolongation of the action potential duration and potentially may result in early after-depolarizations and triggered dysrrhythmias.[3]

This study has shown that thiopental inhibits I_{K1} at clinically relevant concentrations in both rat and human ventricular myocytes. Neither ketamine nor propofol were found to produce significant effects on I_{K1} at the clinically relevant concentrations used in this study.

A previous study by Pancrazio *et al.*[2] found no effect of thiopental on I_{K1} amplitude at a concentration of 10 μM in guinea pig ventricular cells, and a 54% reduction in I_{K1} amplitude with 30 μM thiopental. This differs from the present study in which the IC_{50} was 10.5 μM, and 25 μM thiopental caused a 69% reduction in I_{K1} conductance. Factors that could explain the differing results include differences in the cell type, bath temperature (room temperature versus 32°C), or experimental protocol. A likely explanation is the use of a conventional whole-cell patch-clamp technique and a pipette solution of *p*H 7.4 in the previous study. This difference in intracellular *p*H is probably important, because the pKa of thiopental is 7.6.[9] Our study shows that increasing the intracellular *p*H (with NH_4Cl) significantly reduces the effect of thiopental on I_{K1}, as expected if the active form of thiopental is un-ionized.

The observed reduction in I_{K1} is also consistent with the prolongation of action potential duration, which has been reported in *in vitro* experiments.[17,18]

Ketamine was found to produce no effect on I_{K1} conductance in our studies. This differs from two previous reports of I_{K1} inhibition by ketamine in guinea pig ventricular cells.[4,5] The discrepant results may be attributed to species differences or, more likely, to the range of concentrations studied. In the present study, only clinically relevant concentrations, corrected for protein binding, were examined, with 10 μM being the highest concentration studied. The two previous studies examined concentrations of 30, 100, and 300 μM. Thus although ketamine may inhibit I_{K1} at supratherapeutic concentrations, it does not do so at clinically relevant concentrations.

Propofol, at a concentration of 2.5 μM, was found to have no significant effect on I_{K1} conductance. This corresponds to a previous report that propofol (28 μM) had no effect on I_{K1}.[5]

Potential Limitations

The present study was conducted primarily in rat ventricular myocytes. There are clearly interspecies variations in potassium current distribution. However, there was a very good concordance in our study between the rat myocyte data and the human ventricular myocyte data, with respect to the dose-related suppression of I_{K1} by thiopental.

The nystatin-perforated, patch-clamp technique was used for all studies. When compared with conventional whole-cell techniques, this method has the advantage of minimiz-

ing the dialysis of intracellular regulatory components by the pipette solution. This may be particularly important when measuring I_{K1}, because diffusible intracellular polyamines are known to contribute to its rectification.[1]

Clinical Implications

Drug-induced alterations in potassium currents may be responsible for prodysrhythmic effects.[3] Data from the present study show that thiopental inhibits I_{K1} current at clinically relevant concentrations. Inhibition of I_{K1} increases cardiac excitability and prolongs repolarization, both of which may predispose hearts to dysrhythmias.[1,2] Thiopental has been reported to prolong the QT_c interval of the electrocardiograph, indicating an increased time for ventricular repolarization.[19] Thiopental also potentiates epinephrine-induced dysrhythmias produced by halogenated inhalational anesthetics.[20]

Neither ketamine nor propofol produced a significant effect on I_{K1} at clinically relevant concentrations. Ketamine does not appear to affect the results of electrocardiograph but has been reported to sensitize the heart to epinephrine-induced dysrrhythmias.[21] Propofol prolongs the QT_c interval of the electrocardiograph in patients with normal baseline QT_c interval. In patients with prolonged baseline QT_c intervals, propofol causes no change in the QT_c interval.[22,23] This differential response based on baseline QT_c interval may reflect differences in K^+ channel distribution or autonomic tone.

The direct effects of drugs on cardiac repolarization may be mediated by several ionic currents including I_{K1}, the delayed rectifier K^+ currents, or the transient outward current. In addition to direct cardiac effects, these drugs may alter ventricular repolarization indirectly by alterations in autonomic tone.

References

1. Nichols CG, Nakhina DN, Pearson WR, Sha Q, Lopatin AN: Inward rectification and implications for cardiac excitability. Circ Res 1996; 78:1-7

2. Pancrazio JJ, Frazer MJ, Lynch C III: Barbiturate anesthetics depress the resting K^+ conductance of myocardium. J Pharmacol Exp Ther 1993; 265:358-65

3. The Task Force of the Working Group on Arrhythmias of the European Society of Cardiology: The Sicilian Gambit. Eur Heart J 1991; 12:1112-31

4. Endou M, Hattori Y, Nakya H, Gotoh Y, Kanno M: Electrophysiologic mechanisms responsible for inotropic responses to ketamine in guinea pig and rat myocardium. ANESTHESIOLOGY 1992; 76:409-18

5. Baum VC: Distinctive effects of three intravenous anesthetics on the inward rectifier (I_{K1}) and the delayed rectifier (I_K) potassium currents in myocardium: implications for the mechanism of action. Anesth Analg 1993; 76:18-23

6. Altschuld R, Gibb L, Zoretic A, Hohl C, Kruger F, Brierley GP: Calcium tolerance of isolated rat heart cells. J Mol Cell Cardiol 1980; 12:1383-95

7. Korn SJ, Horn R: Influence of sodium-calcium exchange on calcium current rundown and the duration of calcium dependent chloride currents in pituitary cells, studied with whole cell and perforated patch recording. J Gen Physiol 1989; 94:789-812

8. Van Wagoner DR, Kirian M, Lamorgese M: Phenylephrine suppresses outward K^+ currents in rat atrial myocytes. Am J Physiol 1996; 271:H937-46

9. Reilly CS, Intravenous agents, Anaesthesia, Edited by Nimmo WS, Rowbotham DJ, Smith G. Oxford, Blackwell Scientific Publications, 1994, pp 87-105

10. Kaka JL, Hayton WL: Pharmacokinetics of ketamine and two metabolites in the dog. Journal of Pharmacokinetics and Biopharmaceutics 1980; 8:193-202

11. Garrido MJ, Jimenez RM, Rodriguez-Sasiain JM, Aguirre C, Aguilera L, Calvo R: Characterization of propofol binding to plasma proteins and possible interactions. Rev Espan Anestesiol Reanim 1994; 4:308-12

12. Gambassi G, Spurgeon HA, Lakatta EG, Blank PS, Capogrossi MC: Different effects of α- and β-adrenergic stimulation on cytosolic pH and myofilament responsiveness to Ca^{2+} in cardiac myocytes. Circ Res 1992; 71:870-82

13. Blank PS, Silverman HS, Chung OY, Hogue BA, Stern MD, Hansford RG, Lakatta EG, Capogrossi MC: Cytosolic pH measurements in single cardiac myocytes using carboxy-seminaphthorhodafluor-1. Am J Physiol 1992; 263: H276-84

14. Holford NHG, Sheiner LB: Pharmacokinetic and pharmacodynamic modeling in vivo. CRC Crit Rev Bioeng 1981; 5:273-322

15. Kass RS, Freeman LC. Potassium channels in the heart: Cellular, molecular, and clinical implications. Trends Cardiovasc Med 1993; 3:149-59

16. Koumi S, Wasserstrom JA, Ten Eick RE: β-Adrenergic and cholinergic modulation of the inwardly rectifying K^+ current in guinea-pig ventricular myocytes. J Physiol 1995; 486:647-59

17. Park WK, Lynch C III. Propofol and thiopental depression of myocardial contractility. Anesth Analg 1992; 74:395-405

18. Frankl WS, Poole-Wilson PA: Effects of thiopental on tension development, action potential, and exchange of calcium and potassium in rabbit ventricular myocardium. J Cardiovasc Pharmacol 1981; 3:554-65

19. Saarnivaara L, Lindgren L: Prolongation of QT interval during induction of anaesthesia. Acta Anaesthesiol Scand 1983; 27:126-30

20. Bednarski RM, Majors LJ, Atlee JL: Epinephrine-induced ventricular arrhythmias in dogs anesthetized with halothane: potentiation by thiamylal and thiopental. Am J Vet Res 1985; 46:1829-31

21. Bednarski RM, Sams RA, Majors LJ, Ashcraft S: Reduction of the ventricular arrhythmogenic dose of epinephrine by ketamine administration in halothane-anesthetized cats. Am J Vet Res 1988; 49:350-4

22. McConachie I, Keaveny JP, Healy TE, Vohra S, Million L: Effect of anaesthesia on the QT interval. Br J Anaesth 1989; 63:558-60

23. Saarnivaara L, Hiller A, Oikkonen M: QT interval, heart rate and arterial pressures using propofol, thiopentone or methohexitone for induction of anaesthesia in children. Acta Anaesthesiol Scand 1993; 37:419-23