Ionic Basis of the Differential Effects of Intravenous Anesthetics on Erythromycin-induced Prolongation of Ventricular Repolarization in the Guinea Pig Heart

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Background: Dysrhythmias and death occur in patients with acquired long QT syndrome (LQTS). Little information exists regarding interactions between anesthetics and drugs that prolong ventricular repolarization. Therefore the effects of three commonly used intravenous anesthetics on ventricular repolarization were investigated in the setting of drug-induced long QT syndrome.

Methods: The effects of increasing concentrations of propranolol, ketamine, and thiopental on ventricular repolarization were evaluated by measuring the monophasic action potential duration at 90% repolarization (MAPD90) in guinea pig Langendorff-perfused hearts in the absence or presence of erythromycin (100 µM). If an anesthetic enhanced erythromycin-induced prolongation of MAPD90, its effects on the delayed rectifier (Ikr) and inward rectifier (IK1) potassium currents were measured using the whole-cell patch-clamp technique.

Results: At clinically relevant concentrations, only thiopental significantly modulated erythromycin’s effect on MAPD90. Thiopental at 10, 25, and 50 µM prolonged MAPD90 from a control of 163 ± 6 ms by 18 ± 4, 30 ± 3, and 31 ± 4 ms, respectively. In a separate group, erythromycin prolonged MAPD90 from 155 ± 2 ms to 171 ± 2 ms (n = 21, P < 0.001). In the presence of erythromycin, thiopental at 10, 25, and 50 µM caused significantly greater prolongation from a control of 171 ± 2 ms by 39 ± 2, 58 ± 3, and 72 ± 6 ms, respectively. Whole-cell patch-clamp experiments indicated that thiopental inhibited Ikr and IK1.

Conclusions: Intravenous anesthetics caused markedly different effects on ventricular repolarization. Thiopental, unlike propranolol and ketamine, potentiated the effects of erythromycin on ventricular repolarization by inhibiting Ikr and IK1. (Key words: Anesthetics: propranolol; ketamine; thiopental. Arrhythmias: long QT syndrome; torsades de pointes.)

DYSRHYTHMIAS, cardiac arrest, and death have been observed in patients with idiopathic (congenital) or acquired long QT syndrome (LQTS) during general anesthesia.1 2 Although some clinical and experimental data indicate that under conditions of normal ventricular repolarization intravenous anesthetics may prolong the QT interval in patients5 6 and lengthen action potential duration in isolated guinea pig hearts,7 papillary muscle,8 and cardiomyocytes,9 little information exists regarding the interactions between intravenous anesthetics and drugs known to prolong ventricular repolarization.

Drugs that prolong the QT interval and cause torsades de pointes are being used more frequently.5 If repolarization is sufficiently prolonged by drugs and electrolyte imbalance (e.g., hypokalemia or hypomagnesemia), a condition of acquired (rather than idiopathic) LQTS may develop (i.e., corrected QT interval, or QTc, >440 ms). In some cases, the concurrent use of drugs that delay ventricular repolarization (e.g., potassium channel inhibitors) and prolong action potential duration may have synergistic effects and increase the risk for torsades de pointes to develop.10 Therefore it is important to know not only the effects of anesthetics on action potential duration but also the interactions between anesthetic and drugs, which prolong ventricular repo-
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larization. For example, an anesthetic that blocks both the delayed rectifier (I_k) and the inward rectifier (I_{Kr}) potassium currents would likely cause additional prolongation of the action potential duration in the presence of a drug such as erythromycin that selectively blocks the rapid component of I_k (I_{Kr}).\(^{11}\) However, the additional effects of an anesthetic that produces only selective block of I_k would markedly depend on the magnitude of the preexisting, concomitant I_{Kr} block. Although it has been shown that ketamine inhibits I_{Kr} at 100 \(\mu M\),\(^{12}\) propofol inhibits I_k at 28 \(\mu M\),\(^{12}\) and thiopental inhibits I_{Kr} at 30–100 \(\mu M\)\(^8\) and I_k at 100 \(\mu M\)\(^6\) in ventricular myocytes, no previous study has investigated these effects in the setting of preexisting potassium channel blockade. Thus an understanding of the interactions between anesthetics and drugs that prolong ventricular repolarization and their effects on the ionic currents underlying cardiac repolarization may provide a framework whereby anesthesiologists can rationally select intravenous anesthetics for patients with drug-induced LQTS.

The purposes of this study were (1) to determine the effects of three commonly used intravenous anesthetics (propofol, ketamine, and thiopental) on the ventricular action potential duration in hearts treated with erythromycin, a drug known to prolong ventricular repolarization by inhibiting the rapid component of the delayed rectifier potassium current (I_{Kr}),\(^{11}\) and (2) to identify the ionic mechanisms whereby anesthetic(s) enhance the effects of erythromycin on ventricular repolarization.

Materials and Methods

Chemicals

Erythromycin (molecular weight, 733.9) was purchased from Fisher Scientific (Fair Lawn, NJ) and dissolved on the day of an experiment in the perfusion solution to a concentration of 100 \(\mu M\). Propofol (2,6-dipropylphenol; molecular weight, 178.3) was obtained commercially from Zeneca Pharmaceuticals (Wilmington, DE) as a sterile nonpyrogenic emulsion containing 10 mg/ml propofol. Intralipid 10% (Kabi Pharmacia, Clayton, NC), was obtained to exclude any effects attributable to propofol's vehicle. Ketamine (molecular weight, 274.2) was obtained commercially from Fort Dodge Laboratories (Fort Dodge, IA) as a 1:1 racemic mixture of 100 mg/ml ketamine. Sodium thiopental (molecular weight, 264.3) was purchased from Abbott Laboratories (North Chicago, IL) as a powder and mixed in sterile water to obtain a 25 mg/ml solution. Anesthetics were dissolved in the perfusion media to make 100 mm stock solutions and infused into the perfusion line to achieve the desired concentrations.

Isolated Perfused Hearts

Isolation and Perfusion of Hearts. All protocols were reviewed and approved by the Animal Use Committee of the University of Florida Health Sciences Center. Hartley guinea pigs of either sex weighing 300–400 g were anesthetized with halothane (Halocarbon Laboratories, Rivers Edge, NJ) and killed by cervical dislocation. The hearts were rapidly removed and rinsed in ice-cold Krebs-Henseleit solution containing 117.9 mm NaCl, 4.8 mm KCl, 2.5 mm CaCl\(_2\), 1.18 mm MgSO\(_4\), 10 mm KH\(_2\)PO\(_4\), 1.2 mm KHPO\(_4\), 0.5 mm Na\(_2\) EDTA, 2 mm ascorbic acid, 5.5 mm glucose, 2 mm pyruvic acid (sodium salt), and 25 mm NaHCO\(_3\). The ascending aorta was cannulated for perfusion of the coronary arteries at a constant flow of 8 ml/min with Krebs-Henseleit solution gassed continuously with 95% oxygen and 5% carbon dioxide. The oxygen tension, temperature, and pH of the Krebs-Henseleit solution were maintained at 500–600 mmHg, 36 ± 0.5°C, and 7.3–7.4, respectively. After dissection and instrumentation, the hearts were allowed to equilibrate for 30 min before experiments commenced.

Pacing and Electrophysiologic Measurements. Hearts were paced using an interval generator (A310 Accupulsar, World Precision Instruments, Sarasota, FL) that delivered stimuli \(via\) a stimulus isolation unit (A360R, World Precision Instruments) as square-wave pulses lasting 3 ms and of twice the threshold intensity. The stimuli were delivered at a basic cycle length of 300 ms \(via\) a stainless steel, teflon-coated, bipolar electrode placed on the epicardium of the right ventricle.

Monophasic action potentials were recorded using pressure contact silver-silver chloride electrodes (Langendorff probe; EP Technologies, Sunnyvale, CA) placed on the epicardial surface of the left ventricle, as previously described.\(^{13}\) The signals were amplified and filtered using an isolated biological amplifier (IsoDam, World Precision Instruments), and displayed in real time on a digital oscilloscope (model 2201; Tektronix Inc., Beaverton, OR). The amplitudes of the monophasic action potentials were determined from the diastolic baselines to the plateaus. Signals were considered adequate if they were stable for 10 min and their amplitudes exceeded 10 mV. Data were digitized using a DigiData

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1200A digitizing system (Axon Instruments, Foster City, CA) and stored using the pClamp 6.1 data acquisition program (Axon Instruments) at 2 kHz for later analysis. Each data set was acquired as a group of 20 consecutive monophasic action potentials and subsequently averaged. The duration of the average monophasic action potential at 90% repolarization (MAPD90) was measured using pClamp 6.1.

**Experimental Protocols.** After the control monophasic action potentials were recorded, the infusion of one of three randomly selected intravenous anesthetics (propofol, ketamine, or thiopental) was started. Each heart was treated with only one anesthetic. Anesthetics were infused for 20 min at 10, 25, and 50 μm concentrations using a syringe infusion pump (sp 100i syringe pump, World Precision Instruments), and steady-state monophasic action potentials were recorded at each anesthetic concentration. After treatment of the hearts with all anesthetic concentrations, the anesthetic was discontinued and washed out for 60 min and monophasic action potentials recorded again. In a separate series of parallel experiments, drug-induced acquired LQTS was simulated by pretreating the hearts with erythromycin. After control monophasic action potentials were recorded, the hearts were perfused with Krebs-Henseleit solution containing erythromycin (100 μm). Monophasic action potentials were recorded every 5 min, until steady-state effect was reached (fig. 1). Once the effects of erythromycin reached steady state (60 min), hearts were subjected to the same anesthetic drug administration protocol previously described.

**Single Cell Experiments**

**Isolation of Ventricular Myocytes.** Single ventricular myocytes were obtained from guinea pig hearts by enzymatic and mechanical dispersion, as previously described. Briefly, the heart was quickly removed and perfused in a retrograde manner with oxygenated solution (100% oxygen at 36 ± 0.5°C) at a constant flow rate of 6 ml/min per gram of heart tissue. The perfusion solution contained 130 mM NaCl, 4.5 mM KCl, 3.5 mM MgCl2, 0.4 mM NaH2PO4, 5 mM HEPES, 10 mM glucose, 20 mM taurine, 10 mM creatine, and 0.75 mM CaCl2; pH 7.25. After 5 min of perfusion with this solution, the perfusate was switched to a nominally Ca2+ free solution for 5 min. The hearts were then perfused for 10–20 min with the Ca2+ free solution (80 ml) containing 0.8 mg/ml collagenase (type I; Worthington Biochemical Corp., Freehold, NJ) and 0.08 mg/ml protease (type XIV; Sigma Chemical Co., St. Louis, MO).

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![Fig. 1. Time course of the effects of erythromycin on ventricular repolarization. After 35 min, erythromycin did not cause any further significant prolongation of the monophasic action potential duration at 90% repolarization (MAPD90). Data are mean ± SEM of 21 hearts. P < 0.05, MAPD90 compared with MAPD90 at 0 min. The inset shows a representative example of a monophasic action potential for measurement of MAPD90 (arrows; see text for further details).](image)
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MgCl₂, 10 mm glucose, and 10 mm HEPES; pH 7.25. CdCl₂ (0.5 mm) was added to the external solution to eliminate the inward calcium current. Depending on the experimental protocol, solutions were modified by the appropriate addition (or substitution) of compounds, anesthetics, or both. To eliminate the known effects of nonphysiologic temperatures on current measurements, the temperature of the superfusing solution was monitored using a digital thermometer (BAT-12; Physitemp Instruments, Clifton, NJ) and maintained at 36 ± 0.5°C.

The gigaseal technique for whole-cell patch-clamp recordings was used. The patch microelectrodes were pulled from 1.5-mm KIMAX borosilicate capillary glass (Kimble-Kontes, Vineland, NJ) using a two-stage vertical puller (PP-83; Narishige USA, New York, NY). The patch microelectrodes had resistances of 3–5 MΩ when filled with the pipette-filling solution containing 107 mm potassium aspartate, 20 mm KCl, 1 mm MgCl₂, 5 mm HEPES, 5 mm EGTA, 1 mm CaCl₂, 4 mm Na₂ATP, and 0.4 mm GTP; pH 7.25. The voltage-clamp experiments were performed using an Axopatch 1D amplifier (Axon Instruments). Data were monitored using an oscilloscope (5A26; Tektronix, Beaverton, OR), digitized online using a DigiData 1200A digitizing system (Axon Instruments), and stored on the hard drive of an IBM-compatible PC (P5-166, Gateway 2000, North Sioux City, ND). Voltage clamp protocols and off-line data analysis were performed using pClamp 6.1 software (Axon Instruments).

Recordings of Iₖ were obtained using a voltage ramp protocol wherein cells were held at −40 mV before their membrane potential was changed from −130 to 50 mV over 6 s in a linear manner. The Iₖ was studied in cells held at −40 mV (to inactivate Iₖ) and depolarized by 600 ms pulses using 10 mV voltage steps to test potentials from −30 to 60 mV. The Iₖ was measured at the end of the 600 ms-long depolarizing pulses. All data were adjusted for a liquid junction potential of −10 mV.

Table 1. Effects of Anesthetics on Monophasic Action Potential Duration at 90% Repolarization (MAPD₉₀)

<table>
<thead>
<tr>
<th></th>
<th>MAPD₉₀ (ms)</th>
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<tr>
<td></td>
<td>Proposition (n = 6)</td>
</tr>
<tr>
<td>Control</td>
<td>161 ± 2</td>
</tr>
<tr>
<td>Anesthetic 10 μM</td>
<td>157 ± 5</td>
</tr>
<tr>
<td>Anesthetic 25 μM</td>
<td>153 ± 6</td>
</tr>
<tr>
<td>Anesthetic 50 μM</td>
<td>134 ± 7‡‡</td>
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<tr>
<td>Washout</td>
<td>135 ± 6</td>
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</table>

Values are mean ± SEM for the number of experiments in parentheses. Boldface values represent measurements at clinically relevant anesthetic concentrations.

* P < 0.05 versus control for a given drug.
† P < 0.05 versus ketamine or propofol at a given concentration (control, anesthetic [10, 25, 50 μM], or washout).
‡ P < 0.05 versus previous concentration for a given drug.

Results

Changes in Monophasic Action Potential Duration

In hearts not treated with erythromycin, thiopental significantly prolonged MAPD₉₀ in a concentration-dependent manner. The MAPD₉₀ values after thiopental administration at 0, 10, 25, and 50 μM were 163 ± 6 ms, 180 ± 7 ms, 193 ± 7 ms, and 194 ± 5 ms, respectively. The effect observed at 50 μM thiopental was not significantly greater than that at 25 μM. In contrast, propofol at lower concentrations (10 and 25 μM) did not significantly affect MAPD₉₀. However, the highest concentration of propofol (50 μM) significantly shortened MAPD₉₀ (161 ± 2 ms to 134 ± 7 ms; P < 0.05). Ketamine had no significant effect. At all concentrations, differences between the effects of thiopental compared with those of propofol and ketamine on MAPD₉₀ were statistically significant (table 1). The MAPD₉₀ changes were completely reversible for thiopental but only partially reversible for propofol. In four separate hearts, intralipid alone (propofol's vehicle) did not affect MAPD₉₀ at rates corresponding to those of the highest concentration (50 μM) of propofol (155 ± 3 ms [control] vs. 158 ± 2 ms [intralipid]; P = 0.22).

As shown in figure 1, the effect of erythromycin on MAPD₉₀ reached steady state slowly. Erythromycin (100

Data Analysis

All measurements are reported as means ± SEM. Differences among multiple group means were made using univariate three-way repeated measures analysis of variance with one-way replication followed by Student-Newman-Keuls testing using SPSS version 7.5 statistical analysis software (SPSS Inc., Chicago, IL). Single mean comparisons were made using two-tailed, paired t test-

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Erythromycin-induced prolongation of the monophasic action potential duration at 90% repolarization (MAPD_{90}). The circles are data from individual hearts treated with 100 M M erythromycin for 60 min. The squares represent means ± SEM of 21 hearts (P < 0.001). The inset shows a representative example of a monophasic action potential at control and after 100 M M erythromycin (Erythro) treatment.

µM prolonged MAPD_{90} in all hearts (n = 21, fig. 2). The MAPD_{90} increased from 155 ± 2 ms to 171 ± 2 ms during the 60-min erythromycin infusion (P < 0.001). No statistical difference in MAPD_{90} values before and after the 60-min erythromycin treatment, but before anesthetic administration, was noted among the three anesthetic groups.

In the continuous presence of erythromycin, thiopental further prolonged ventricular MAPD_{90} in a concentration-dependent manner (P < 0.05). The MAPD_{90} during treatment of the hearts with thiopental at 0, 10, 25, and 50 µM was 168 ± 4 ms, 191 ± 5 ms, 210 ± 6 ms, and 225 ± 8 ms, respectively. Similar to hearts not treated with erythromycin, propofol (10 and 25 µM) did not significantly affect MAPD_{90} in erythromycin-treated hearts, whereas the highest concentration of propofol (50 µM) significantly shortened MAPD_{90} (171 ± 4 ms to 163 ± 5 ms, P < 0.05). Ketamine had no significant effect. At 25 µM and 50 µM concentrations, differences among the effects of thiopental, propofol, and ketamine on MAPD_{90} were statistically significant. The changes caused by erythromycin and the anesthetics were completely reversed during the 60-min washout period (table 2). The MAPD_{90} for all drug groups after washout (156 ± 4 ms) was not significantly different from the grand mean of control MAPD_{90} (155 ± 2 ms), indicating complete reversal of drug effects on ventricular repolarization. Similarly, no differences in the washout values were observed among the anesthetic groups in hearts treated with erythromycin (table 2).

After adjusting baseline values to account for the prolongation of MAPD_{90} caused by erythromycin, thiopental (25 and 50 µM) caused greater lengthening of MAPD_{90} in the presence than in the absence of erythromycin (P = 0.018; fig. 3). In contrast, the shortening of MAPD_{90} caused by supraclinical concentrations of propofol (25 µM and 50 µM) were smaller in the presence than in the absence of erythromycin (P = 0.015; fig. 3).

**Changes in Potassium Currents**

Figure 4 shows whole-cell voltage-clamp recordings of quasi-steady-state currents in guinea pig ventricular myocytes in response to a voltage ramp protocol. There was a large inward current shift at membrane potentials negative to −90 mV and a smaller outward current shift between −90 and −20 mV (primarily outward conduction through channels of the inward rectifier current.

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**Table 2. Effects of Anesthetics on Monophasic Action Potential Duration at 90% Repolarization (MAPD_{90}) in Erythromycin-treated Hearts**

<table>
<thead>
<tr>
<th>MAPD_{90} (ms)</th>
<th>Propofol (n = 8)</th>
<th>Ketamine (n = 5)</th>
<th>Thiopental (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>155 ± 3</td>
<td>158 ± 4</td>
<td>152 ± 4</td>
</tr>
<tr>
<td>Erythromycin 100 µM</td>
<td>171 ± 4⁺</td>
<td>176 ± 5⁺</td>
<td>168 ± 4⁺</td>
</tr>
<tr>
<td>+ Anesthetic 10 µM</td>
<td>175 ± 3⁺</td>
<td>177 ± 5⁺</td>
<td>191 ± 5⁺†</td>
</tr>
<tr>
<td>+ Anesthetic 25 µM</td>
<td>175 ± 5⁺</td>
<td>177 ± 4⁺</td>
<td>210 ± 6⁺††</td>
</tr>
<tr>
<td>+ Anesthetic 50 µM</td>
<td>163 ± 5⁺†</td>
<td>181 ± 5⁺</td>
<td>225 ± 8⁺††</td>
</tr>
<tr>
<td>Washout</td>
<td>152 ± 8†</td>
<td>150 ± 3†</td>
<td>152 ± 9†</td>
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</table>

Values are mean ± SEM for number of experiments in parentheses. Boldface values represent measurements at clinically relevant anesthetic concentrations.

* P < 0.05 versus control for a given drug.
† P < 0.05 versus erythromycin for a given drug.
‡ P < 0.05 versus propofol or ketamine at a given concentration (control, anesthetic [10, 25, 50 µM], or washout).

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**A.**

<table>
<thead>
<tr>
<th>Anesthetic 10 µM</th>
<th>Not treated with Erythromycin</th>
<th>Erythromycin</th>
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<tbody>
<tr>
<td>ΔMAP_90 (ms)</td>
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**B.**

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<th>Anesthetic 25 µM</th>
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<td>ΔMAP_90 (ms)</td>
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**C.**

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<th>Anesthetic 50 µM</th>
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<tr>
<td>ΔMAP_90 (ms)</td>
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Fig. 3. Effects of anesthetics on the monophasic action potential duration at 90% repolarization (MAPD_90) in hearts either treated (solid bar) or not treated (open bar) with 100 µM erythromycin. Each heart was treated with propofol, ketamine, or thiopental at 10, 25, and 50 µM concentrations. Control MAPD_90 values for hearts either treated or not treated with erythromycin were not significantly different (159 ± 3 ms vs. 154 ± 2 ms, respectively). Prolongation of MAPD_90 caused by erythromycin was subtracted when calculating differences in the presence of erythromycin. Data are mean ± SEM, P < 0.05: *MAPD_90 in hearts treated with erythromycin vs. MAPD_90 in hearts not treated with erythromycin for a given drug and anesthetic concentration; †difference in MAPD_90 in hearts, either treated or not treated with erythromycin, among the different drugs at a given anesthetic concentration.

At more positive membrane potentials, there was a larger delayed outward current (I_k). Thiopental (50 µM) significantly depressed inward I_k at −120 mV and outward I_k at −80 mV from −2,509 ± 187 pA to −1,293 ± 116 pA (53 ± 4% of control) and from 500 ± 44 pA to 108 ± 29 pA (20 ± 5% of control), respectively (n = 12). In addition, thiopental significantly inhibited the outward component of the ramp current at membrane potentials positive to −20 mV. For example, thiopental reduced potassium currents recorded at +40 mV (primarily representing I_k) from 901 ± 120 pA to 524 ± 73 pA (P < 0.05, n = 12). In contrast to isolated hearts, the effect of thiopental on the potassium currents in single ventricular myocytes was only partially reversible. As a typical example, the inward (−120 mV) and outward (−80 mV) I_k current on washout was −1966 ± 265 pA (68 ± 10% of control) and 140 ± 76 pA (35 ± 11% of control), respectively.

The effects of thiopental on I_k were further investigated by measuring the amplitude of I_k at the end of 10-mV incremental, step depolarizations applied from a holding potential of −40 mV to potentials ranging from −30 to +60 mV (fig. 5). The results of the step protocol, a more sensitive method to assess time-dependent currents than the ramp protocol, confirmed the findings of the voltage ramp experiments. In seven cells, thiopental (50 µM) changed the net I_k in a similar manner as in the voltage ramp protocol. That is, thiopental (50 µM) significantly decreased the amplitude of I_k from 828 ± 96 pA to 421 ± 53 pA (55 ± 3% of control) and from 154 ± 31 pA to 60 ± 13 pA (44 ± 4% of control) at +50 and +10 mV, respectively (n = 7). Thus propor-

![Fig. 4](image.png)
Fig. 5. Effect of thiopental on the delayed outward rectifier potassium current (I_K) recorded using the voltage step protocol. (A) A typical example of currents recorded in response to 10-mV voltage steps from −30 mV at control and after application of 50 μM thiopental in the same cell. The thiopental-blocked currents were obtained by subtracting currents in the presence of thiopental from control currents. The dashed line denotes zero current. (Inset A) Voltage step protocol used in this experiment. (B) A typical example of the current voltage relations in the absence of thiopental (control), in the presence of 50 μM thiopental, and after washout in the same cell.

Discussion

This study was designed specifically to investigate the effects of intravenous anesthetics in the setting of drug-induced, acquired LQTS. A major finding was that intravenous anesthetics caused different effects on ventricular repolarization in hearts treated with erythromycin, a drug known to cause QT prolongation and torsades de pointes by inhibiting the rapid component of the delayed rectifier potassium current (I_K). Coincident with erythromycin administration, thiopental at clinically relevant, free concentrations (i.e., 7.2–60 μM), unlike those of propofol or ketamine, further lengthened ventricular MAPD90 in a concentration-dependent manner by a mechanism involving inhibition of not only the inward rectifier current (I_K), primarily between membrane potentials between −90 to −20 mV) but also of the delayed rectifier potassium current (I_K, mainly at membrane potentials > −20 mV). The magnitude of the lengthening of MAPD90 caused by thiopental was significantly greater in the presence of erythromycin than in its absence, even after subtracting the lengthening caused by erythromycin alone.

Effects of Anesthetics on Ventricular Repolarization

Our findings are consistent with the results of other studies that have examined the effects of anesthetics on ventricular repolarization using isolated hearts or tissues. For example, thiopental (10–100 μM) has been found to reversibly increase the action potential duration in isolated guinea pig perfused heart, guinea pig papillary muscle, and rabbit ventricular muscle. In the present study, propofol shortened the action potential duration, but only at concentrations greater than the clinically relevant range of 1–10 μM. This finding is supported by previous studies in which propofol (≥ 50 μM) did not significantly change action potential duration. On the other hand, the report of Baum showing that propofol at 28 μM blocks I_K in guinea pig ventricular myocytes is difficult to explain in light of the results of previous studies and the data presented here. We would expect an increase in MAPD90 if propofol blocked only I_K. However, this paradox may be explained by the fact that anesthetics may simultaneously modulate the activity of several currents, and drug-induced changes in action potential duration reflect the net effect on several different individual currents. For example, propofol is also known to inhibit the cardiac L-type calcium channels (I_{Ca,L}) In the present study, ketamine (≤ 50 μM) did not affect MAPD90. This corresponds to the results of previous studies showing that ketamine affects action potential duration and diminishes I_{Ca,L} only at concentrations greater than the clinically relevant range of 3–90 μM.

Compared with the effects of anesthetics alone, erythromycin potentiated the prolongation of MAPD90 caused by thiopental (25 and 50 μM) and attenuated the shortening caused by supraclinical concentrations of propofol (25 and 50 μM), even after accounting for the prolongation caused by erythromycin treatment alone. The previous observation is in keeping with our finding that thiopental inhibits not only I_K, the mechanism by which erythromycin delays repolarization, but also depresses I_K in isolated ventricular myocytes. Inhibition of both ionic currents may prolong MAPD90 synergistically.

In addition to these experimental studies, several clinical investigations have assessed the effects of thiopental

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and propofol on the QT interval duration. The results of these studies show that induction of anesthesia with either thiopental (5.0-7.5 mg/kg) or propofol (1.5-2.5 mg/kg) prolongs the corrected QT interval (QTc) by approximately 10-36 ms. The results for thiopental correspond well with our and others' experimental data, whereas the propofol-induced lengthening of the QTc is not fully supported by data of the present and previous studies. The differences between the clinical and experimental propofol data may be attributable to several factors. First, we simulated LQTs by treating the hearts with erythromycin, whereas the clinical investigators almost exclusively examined patients with normal repolarization. Of note, however, propofol (2 mg/kg) did not affect QTc in a subset of patients with prolonged QTc intervals. Second, given the inaccuracy of Bazett's formula to adjust the QT interval for changes in heart rate, the negative chronotropic effects of propofol, purportedly secondary to its direct actions (e.g., activation of M2 muscarinic cholinergic receptors and inhibition of the L-type calcium current and indirect effects on autonomic nervous tone (e.g., gamma-aminobutyric acid receptor-mediated anxiolysis leading to sympatoexcitatory actions, parasympathomimetic effects may have affected the clinical measurements of ventricular repolarization. Third, the measurement of the monophasic action potential duration used in the present study provides superior precision and accuracy for assessing changes in ventricular repolarization compared with the conventional measurements of the QT interval.

Cellular Mechanisms of Thiopental-induced Prolongation of Ventricular Repolarization

In this study, we found that the thiopental-induced prolongation of ventricular repolarization is mediated, at least in part, by inhibition of outward potassium currents. Our results showed that both the inward rectifier IK and delayed rectifier IK were markedly suppressed by thiopental. Although the effect of thiopental on IK has been reported, ours is the first study to show that thiopental also affects IK at clinically relevant concentrations. This finding may have important clinical implications in the context of drug-induced LQTS. That is, by depressing both IK and IK thiopental is likely to cause additional prolongation of the action potential duration, particularly at higher concentrations, even in the presence of a drug that produces only selective IK or IK block. On the other hand, many previous studies have shown that thiopental inhibits the L-type calcium channel. Antagonism of the L-type calcium channel effectively terminates early afterdepolarizations, the putative electrophysiologic substrate of torsades de pointes. This finding, combined with preliminary results from our laboratory showing that thiopental prolongs ventricular repolarization in a frequency-independent manner, may reduce the risk for the development of torsades de pointes related to thiopental-induced action potential prolongation. Frequency-independence refers to a phenomenon whereby drug-induced lengthening of the action potential duration does not depend on the underlying heart rate. Usually drugs that prolong the action potential by selectively blocking a potassium channel (e.g., IK block by d-sotalol) exhibit greater effects on ventricular repolarization at slow heart rates (i.e., reverse frequency-dependence behavior). The lack of effect of heart rate on thiopental-induced lengthening of action potential duration is in keeping with the findings of previous studies that more electrophysiologically complex drugs such as amiodarone and AT1-2001 exhibit frequency-independent behavior on ventricular repolarization.

Although our results corresponded mainly with those of Pancrazio et al., there were some differences. First, we found that the outward component of IK was more sensitive to thiopental than the inward component was. They showed that thiopental (30 μM) caused a slightly greater inhibition of the outward component of IK (66% of control) compared with the inward component of IK (54% of control). Second, the onset of the effect of thiopental on IK was faster in our experiments and reached maximum changes in 2-5 min, whereas previous investigators pretreated cells for 20 min with thiopental. Third, we observed that thiopental inhibited not only IK but also IK. These differences can be explained by different experimental conditions and drug concentrations. Most importantly, our experiments were performed at 36°C, whereas other researchers did their experiments at 22°C.

Limitations

When the results of our study are interpreted, some potential limitations should be noted. First, the results from guinea pig heart may not be directly extrapolated to humans. For example, the guinea pig heart does not possess the transient outward potassium current (Ito), which is partly responsible for ventricular repolarization in humans. Second, any supposition that thiopental may be more dysrhythmogenic than propofol or ketamine in hearts with delayed ventricular repolarization...
must be tempered by the fact that effects of anesthetics on innervated (in vivo) hearts may differ from those on denervated (in vitro) Langendorff hearts. For example, although we found that clinically relevant concentrations of propofol did not affect MAPD$_{90}$ in isolated hearts paced at a constant rate, the phenol-derivative may delay repolarization in vivo by slowing heart rate not only via several direct mechanisms previously described$^{27,28,54}$ but also by modulating autonomic tone.$^{35-57}$ On the other hand, by using an isolated heart model and controlling heart rate, we could directly assess the effects of anesthetics on ventricular repolarization without the confounding influences of autonomic nervous tone on heart rate and ventricular action potential duration. Third, we chose to simulate acquired LQTS in the guinea pig heart by treating the hearts with erythromycin. Whether these results are directly applicable to delayed ventricular repolarization caused by different agents such as drug-induced I$_{Kr}$ block (e.g., terfenadine)$^{44}$ is not known. Fourth, the effects of anesthetics on action potentials in patients with congenital LQTS (ts. acquired LQTS) remains to be established. Several genetic mutations cause distinct subtypes of congenital LQTS, including SCN5A (persistent inward sodium current), KVLQT1, and HERG (inhibition of the potassium currents).$^{35}$ The acquired and congenital forms of LQTS vary dramatically with respect to aggravating factors and treatment. For example, enhanced sympathetic innervation to the heart may precipitate torsades de pointes in patients with congenital LQTS.$^{45}$ In contrast, isoproterenol is used to treat acquired LQTS. Therefore, anesthetics known to increase sympathetic drive to the heart should be used cautiously in patients with congenital LQTS.

Implications

Prolongation of ventricular repolarization (QT interval) is a well known risk factor for the development of malignant ventricular dysrhythmias and sudden death.$^{59,45}$ Anesthetics that further prolong ventricular repolarization in patients with acquired LQTS may predispose patients to the development of torsades de pointes-type ventricular tachydysrhythmias during the perioperative period. Therefore, the selection of an anesthetic induction agent may be an important consideration with regard to dysrhythmogenesis and clinical outcome. Although our data suggest that thiopental should be used cautiously in the setting of acquired (drug-induced) LQTS, additional correlative clinical studies are warranted before definitive recommendations can be made.

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