Ionic Mechanisms Mediating the Differential Effects of Methohexital and Thiopental on Action Potential Duration in Guinea Pig and Rabbit Isolated Ventricular Myocytes

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Background: Commonly used barbiturate anesthetics may significantly influence cardiac electrophysiological characteristics. The authors evaluated thiopental (a thiobarbiturate) and methohexital (an oxbarbiturate), two compounds with similar physicochemical properties but different structures, to determine whether they have distinct effects on the major ionic currents that determine action potential duration (APD) in ventricular myocytes.

Methods: The effects of thiopenal and methohexital (50 μM) on APD at 50% (APD50) and 90% (APD90) repolarization were measured in guinea pig and rabbit single ventricular myocytes using the patch-clamp technique in a whole-cell configuration. The ionic mechanisms underlying the APD changes were evaluated by measuring the anesthetics’ effects on the L-type calcium inward current, the inward rectifier potassium current, and the delayed rectifier potassium current in guinea pig cells and on the transient outward potassium current in rabbit cells.

Results: Thiopental and methohexital caused opposite effects on APD. Whereas thiopental prolonged APD50 and APD90 in guinea pig and rabbit ventricular myocytes, methohexital shortened them. Thiopental markedly depressed both the inward and outward components of the inward rectifier potassium current, whereas methohexital caused minimal inhibition of the inward component and no change in the outward component.

Discussion: The delayed rectifier potassium current was inhibited by thiopental but significantly potentiated by methohexital. Neither thiopental nor methohexital significantly affected the transient outward potassium current or the L-type calcium inward current.

Conclusions: Despite their similar lipid solubilities, molecular weights, and pK values, thiopental increased and methohexital decreased the APD in ventricular myocytes by predominantly inhibiting the inward rectifier potassium current and the delayed rectifier potassium current and by increasing the delayed rectifier potassium current, respectively. These characteristics suggest distinct structure-specific actions of barbiturates on the function of myocardial ionic channels. (Key words: Anesthetics; calcium current; cardiac electrophysiology; potassium current.)

ANESTHETIC agents may contribute to cases of dysrhythmias, cardiac arrests, and death during the perioperative period. 1 Ideally, the selection of anesthetics for patients with a history of or a susceptibility to develop dysrhythmias should be based on a detailed knowledge of the electrophysiological properties of the drugs (i.e., the Sicilian Gambit approach). 2 For example, despite several case reports of intraoperative torsades de pointes, 3-5 few studies have investigated the prodysrhythmic potential of anesthetics in the setting of prolonged ventricular repolarization. 6

Thiopental and methohexital are commonly used thiobarbiturates and oxbarbiturates, respectively, that may have important effects on cardiac electrophysiological characteristics. Recently, we showed that clinically relevant concentrations of thiopental significantly prolong ventricular repolarization duration in hearts with either normal or delayed (erythromycin-induced) ventricular repolarization. 6 Consistent with this observation, thiopental (5 mg/kg) significantly prolongs the corrected QT interval in patients undergoing surgery who have normal repolarization. 7,8 On the other hand, clinical evidence indicates that methohexital (2 mg/kg) tends to shorten
the corrected QT interval (>440 ms) in patients undergoing surgery who have preexisting delayed repolarization.9

We hypothesize that methohexitol and thiopental, because of small but potentially important structural differences of the barbituric acid moiety, may cause distinct effects on myocardial repolarization by specifically modulating voltage-regulated ionic channels. Therefore, we studied the effects of thiopental and methohexitol on action potential duration (APD), and on the L-type calcium inward current (I_{Ca,L}), and on several potassium (inward rectifier, I_{K}; delayed rectifier, I_{Kd}; and transient outward, I_{to}) currents that underlie APD in guinea pig and rabbit isolated ventricular myocytes.

**Methods**

**Chemicals**

Sodium thiopental and methohexitol were purchased from Abbott Laboratories (North Chicago, IL) and Eli Lilly & Co. (Indianapolis, IN), respectively. Collagenase (type I) was obtained from Worthington Biochemical (Freehold, NJ). Protease (type XIV) and bovine serum albumin (fraction V) were purchased from Sigma Chemical (St. Louis, MO). Halothane, pentobarbital, and heparin were purchased from Halocarbon Laboratories (River Edge, NJ), Veterinary Laboratories (Lenexa, KA), and Elkins-Sinn (Cherry Hill, NJ), respectively.

**Isolation of Ventricular Myocytes**

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 and weighing 300 to 400 g were anesthetized with halothane and killed by cervical dislocation. New Zealand white rabbits of either sex weighing 2.0 to 2.5 kg were given 1,000 U porcine-derived, sodium heparin for anticoagulation and killed with 50 mg/kg sodium pentobarbital administered via a single injection to an ear vein.

Single ventricular myocytes were obtained from guinea pig and rabbit hearts by enzymatic and mechanical dispersion of tissue, as previously described.6,10 Briefly, the heart was quickly removed and retrogradely perfused with oxygenated solution (100% oxygen, 36.0 ± 0.5°C) at a constant flow rate of 6 ml·min⁻¹·g⁻¹ 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, 0.75 mM CaCl₂, pH 7.25. After 5 min of perfusion with this solution, the perfusate was changed to a nominally Ca²⁺-free solution for 5 min. The hearts were perfused for 10 to 20 min with the Ca²⁺-free solution (80 ml) containing 0.8 mg/ml collagenase and 0.08 mg/ml protease.

Thereafter, the heart was removed from the cannula. The ventricles were chopped coarsely with scissors and placed into a beaker containing 5 ml Ca²⁺-free solution used for heart perfusion, the enzymes, and 6.4 mg/ml bovine serum albumin. The tissue was shaken in this solution for 3 min to disperse the cells mechanically. The cell suspension was filtered through a sterile gauze sponge and poured into 3.75 ml high-K⁺, low-Na⁺ solution containing 50 mM L-glutamic acid, 40 mM KCl, 10 mM HEPES, 0.5 mM EGTA, 20 mM taurine, 10 mM glucose, 3 mM MgCl₂, 70 mM KOH, 20 mM KH₂PO₄, and 6 mg/ml (100 mg/5 ml) bovine serum albumin; pH 7.2. The suspension was centrifuged for 2 min, the supernatant replaced with 2 ml of high-K⁺, low-Na⁺ solution, and kept at room temperature until it was needed.

**Electrophysiologic Techniques**

Aliquots of the cell suspension were transferred to a recording chamber mounted on the stage of an inverted microscope (Axiovert 10; Carl Zeiss, Thornwood, NY). A pipette connected to multiple temperature-controlled superfusion lines was positioned over the cell being studied to allow rapid (<1 s) solution changes. The HEPES-buffered Tyrode’s solution contained 130 mM NaCl, 5 mM KCl, 1.8 mM CaCl₂, 1 mM MgCl₂, 10 mM glucose, 10 mM HEPES; pH 7.25. Fresh solutions of the drugs were prepared immediately before experimentation by dissolving the substances in the superfusion solution. Depending on the experimental protocol, other compounds or anesthetics were added (or substituted) into the solution. Each cell was treated with only one anesthetic. The temperature of the superfusing solution was maintained at 36.0 ± 0.5°C.11 The gigaseal technique for whole-cell patch-clamp recordings was used.12 The patch microelectrodes had resistances of 3 to 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 Na₂-ATP, and 0.4 mM GTP; pH 7.25. Current- and voltage-clamp experiments were performed using an Axopatch 1D amplifier and pClamp 6.1 software (Axon Instruments, Foster City, CA). Data were monitored on an oscilloscope (5A26, Tektronix, Beaverton, OR), digitized on-line using a DigiData 1200A digitizing system (Axon Instruments, V 90, No 1, Jan 1999).
Instruments), and stored on the hard drive of an IBM-compatible personal computer (P5-166; Gateway 2000, North Sioux City, ND).

**Current- and Voltage-clamp Protocols**

Depolarizing currents of suprathreshold amplitudes (0.6 to 0.7 nA) that lasted 5 ms were applied to record action potentials from guinea pig and rabbit isolated myocytes in the current-clamp mode. In most cells, current- and voltage-clamp protocols were alternated, which allowed us to take measurements of membrane potentials and ion currents in the same cell.

In guinea pig ventricular myocytes, the I-type calcium current (\( I_{\text{ca,L}} \)) was elicited by voltage-clamp steps that lasted 100 ms and were 50 mV in amplitude from a holding potential of -40 mV (to inactivate \( I_{\text{ca}} \)) to +10 mV in one step at a frequency of 0.1 Hz. Peak inward current was measured in relation to the holding current. In the set of experiments that examined potassium conduction, \( I_{\text{ca,L}} \) was blocked by adding 200 \( \mu \)M CdCl\(_2\) to the extracellular solution. In guinea pig cells, recordings of the inward rectifier potassium current (\( I_{\text{K}} \)) were obtained using a voltage ramp protocol in which cells were held at -40 mV before their membrane potential was changed linearly from -120 to +50 mV in 6 s. In guinea pig ventricular myocytes, the delayed rectifier potassium current (\( I_{\text{K}} \)) was studied in cells held at -40 mV and depolarized for 600 ms to test potentials of -30 to +60 mV in 10-mV increments. The \( I_{\text{K}} \) was measured at the end of the 600-ms depolarizing pulses. The transient outward potassium current (\( I_{\text{o}} \)) present in human ventricular myocytes but poorly developed in guinea pig ventricular myocytes, was recorded in rabbit ventricular myocytes during depolarizing steps from -30 to +60 mV from a holding potential of -90 mV and lasted 200 ms. The \( I_{\text{o}} \) was measured as the initial outward peak current. All data were adjusted for a liquid junction potential of -10 mV.

**Data Analysis**

The APDs at 50% (\( \text{APD}_{50} \)) and 90% (\( \text{APD}_{90} \)) repolarization were measured using a custom-made computer template written for Microsoft Excel (Microsoft, Redmond, WA), as previously described.\(^{1,5}\) Current data were analyzed using pClamp 6.1 (Axon Instruments). Values are presented as mean ± SD. Differences among means were analyzed using two-way repeated measures analysis of variance followed by Student–Newman–Keuls testing. In all cases of parametric testing, the assumption of normality was validated using the Kolmogorov–Smirnov test.

**Results**

**Changes in Action Potential Duration**

At concentrations of 50 \( \mu \)M, thiopental and methohexital caused opposite effects on APD. The mean \( \text{APD}_{50} \) and \( \text{APD}_{90} \) of 14 guinea pig ventricular myocytes bathed in standard saline solution were 199.0 ± 40.7 ms and 223.5 ± 41.1 ms, respectively. (The baseline values for \( \text{APD}_{50} \) and \( \text{APD}_{90} \) of the thiopental- and methohexitol-treated myocytes were not statistically different \( P = 0.62 \)). Thiopental (\( n = 6 \)) significantly prolonged \( \text{APD}_{50} \) and \( \text{APD}_{90} \) to 110.5 ± 12.3% and 112.7 ± 7.6% of the control value, respectively (fig. 1). In contrast, methohexital (\( n = 4 \)) significantly shortened \( \text{APD}_{50} \) and \( \text{APD}_{90} \) to 84.5 ± 8.0% and 89.8 ± 4.7% of the control value, respectively (fig. 1). The effects of the anesthetics were partially reversible (i.e., 31.5 ± 6.0% of thiopental-induced \( \text{APD}_{90} \) prolongation; 53.0 ± 14.2% of methohexital-
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A. Thiopental

B. Methohexital

![Graphs showing effects of thiopental and methohexital on cardiac ionic currents.]

Fig. 2. Effects of (A) 50 μM thiopental and (B) 50 μM methohexital on the inward rectifier ($I_{K,i}$) and delayed rectifier ($I_{K,d}$) potassium currents in guinea pig isolated ventricular myocytes. Currents were recorded in response to a linear voltage ramp protocol ($B$, inset) in controls and in the presence of anesthetic.

Induced APD$_{90}$ shortening was reversed with washout. Similar changes in APD$_{90}$ and APD$_{90}$ were observed in ventricular myocytes isolated from the rabbit hearts after application of thiopental or methohexital (data not shown). To determine which ionic currents mediate these changes in APD, several currents ($I_{K,i}$, $I_{K,d}$, $I_{Ca,L}$, and $I_{A,Ca}$) were measured before and after thiopental or methohexital application.

Inward Rectifier Potassium Current

Changes in the inward and outward components of the ramp current at membrane potentials negative to −20 mV are associated with modulation of $I_{K,i}$ channels. As shown in figure 2, the peak control amplitudes of the inward (measured at a $V_m$ of −120 mV) and the outward (measured at a $V_m$ of −80 mV) components of $I_{K,i}$ were −2.89 ± 2.00 nA and 0.46 ± 0.13 nA, respectively (n = 19). Thiopental (n = 12) significantly attenuated the inward and outward components of $I_{K,i}$ to 52.6 ± 13.3% and 19.9 ± 15.6%, respectively, of control values. On the other hand, methohexital (n = 7) significantly inhibited the inward component of $I_{K,i}$ to 84.9 ± 8.1% of the control value and caused no significant changes in the outward component (92.2 ± 11.0% of the control value, P = 0.14).

Delayed Rectifier Outward Potassium Current

The current-voltage relations presented in figure 2 show that the outward current recorded at membrane potentials positive to −20 mV, which primarily represents $I_{K_o}$, was also sensitive to thiopental and methohexital. More detailed study of the effects of these barbiturates on the time-dependent $I_{K_o}$ was undertaken by measuring the amplitude of $I_{K_o}$ at the end of step depolarizations. Thiopental (fig. 3) partially blocked $I_{K_o}$ whereas methohexital augmented this current (fig. 4). That is, the control value at +60 mV for $I_{K_o}$ of 0.84 ± 0.23 nA (n = 12) was attenuated to 52.6 ± 6.6% by thiopental (n = 7, P < 0.001) but was increased to 135.1 ± 13.8% by methohexital (n = 5, P < 0.02).

Transient Outward Potassium Current

Because $I_{Ca,L}$ is poorly developed in the guinea pig,

the effects of the barbiturates on this current were measured in rabbit isolated ventricular myocytes. Neither thiopental nor methohexital caused significant changes in the amplitude of $I_{Ca,L}$ (fig. 5). At membrane potentials of +60 mV, the control value of $I_{Ca,L}$ was 2.1 ± 0.9 nA (n = 10). After thiopental and methohexital, $I_{Ca,L}$ was 96.9 ± 6.2% (n = 5, P = 0.4) and 101.0 ± 10.4% (n = 5, P = 0.9) of the control value, respectively.

L-type Calcium Current

In guinea pig ventricular cells, the mean peak $I_{Ca,L}$ at +10 mV measured under control conditions was 2.2 ± 2.1 nA (n = 11). As shown in figure 6, neither thiopental (94.1 ± 29.0% of control, n = 5, P = 0.69) nor methohexital (93.9 ± 10.3% of control, n = 6, P = 0.21) caused any significant effect on $I_{Ca,L}$. The holding cur-

![Graph showing effect of thiopental on delayed outward potassium current ($I_{K_o}$) in guinea pig ventricular myocytes. Examples are shown of current records recorded in response to a voltage step from −30 to +50 mV in controls and after application of thiopental (left). Dashed lines in the current records denote zero current. The corresponding current-voltage relations of $I_{K_o}$ are shown in controls and in the presence of thiopental (right).]

Fig. 3. Effect of thiopental on the delayed outward potassium current ($I_{K_o}$) in guinea pig ventricular myocytes. Examples are shown of current records recorded in response to a voltage step from −30 to +50 mV in controls and after application of thiopental (left). Dashed lines in the current records denote zero current. The corresponding current-voltage relations of $I_{K_o}$ are shown in controls and in the presence of thiopental (right).

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Fig. 4. Effect of methohexital on the delayed outward potassium current (I_K) in guinea pig ventricular myocytes. Examples of currents are shown recorded in response to a voltage step from −30 to +50 mV in controls and after application of methohexital (left). Corresponding current-voltage relations of I_K are shown in controls and in the presence of methohexital (right). Dashed lines in the current records denote zero current.

The APD_{50} and APD_{90} before barbiturate administration were 128 and 163 ms, respectively (fig. 7). Adjustment of values for I_{Ca,L}, the outward component of I_{Kl}, and I_K to values observed after administration of methohexital (93.9%, 92.2%, and 135.1% of control currents, respectively) shortened both APD_{50} and APD_{90} to 84.0% and 82.7% of control values. Changes in I_{Ca,L}, the outward component of I_{Kl}, and I_K to values recorded after thiopental treatment (94.1%, 19.9%, and 52.6% of control currents, respectively) prolonged APD_{50} and APD_{90} to 125% and 170% of control values. In addition, the resting model cell slightly depolarized in response to thiopental but not methohexital administration.

Discussion

The results of this study show for the first time that unique structure-activity relations may exist among barbiturates to modulate ventricular repolarization via different effects on myocardial ionic channels. Two barbiturate anesthetics commonly used at the higher range of their clinically relevant free concentrations (7-60 μM for thiopental and 10-100 μM for methohexital) have opposite effects on APD in isolated ventricular cardiomyocytes of the guinea pig and rabbit. Although thiopental prolonged ventricular APD_{50} and APD_{90}, methohexital hastened repolarization in these cells. These differences appear to result from the distinct effects of thiopental and methohexital on the inward rec-
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A. Thiopental

![Graph showing the effects of thiopental on calcium current (I_{Ca,L})](image)

B. Methohexital

![Graph showing the effects of methohexital on potassium current (I_{K})](image)

Fig. 6. Typical examples of the effects of (A) 50 μM thiopental and (B) 50 μM methohexital on the L-type calcium current (I_{Ca,L}) and the holding current in guinea pig isolated ventricular myocytes. Each symbol represents the peak of an individual current record. Horizontal bars denote the period when an anesthetic was applied. (Insets) Examples of individual currents recorded in the presence of (A) thiopental (B) and methohexital. The data gaps in B occurred when action potentials were recorded under current-clamp conditions in the same cell.

tifier (I_{K1}) and delayed rectifier (I_{K}) potassium currents. That is, thiopental markedly suppressed I_{K1} and I_{K}, whereas methohexital did not affect I_{K} and significantly enhanced I_{K}.

Effects on Action Potential Duration

Our finding that thiopental markedly prolonged ventricular APD is supported by the findings of several previous investigations. Others have shown that not only thiopental but also other thiobarbiturates prolong ventricular APD. Thiopental (30–100 μM) prolonged APD 10–15% in guinea pig20 and canine21 isolated ventricular papillary muscle. Similarly, Azuma et al.22 found that thiamylal (300 μM) lengthened APD_{50} and APD_{90} in rat ventricular papillary muscle. In guinea pig papillary muscle, 100 μM thiamyl slightly prolonged APD, but a higher concentration (300 μM) antagonized calcium channel current and shortened repolarization.22 Frankl and Poole-Wilson23 observed APD_{90} prolongation, but APD_{50} shortening, in rabbit ventricular myocardium in response to thiopental (227 μM).

In the only other study to investigate the effect of methohexital on action potential of which we are aware, methohexital (1,000–5,000 μM) prolonged APD in leech Retzius cells.24 This discrepancy, compared with our data on the effect of methohexital on APD, may be related to differences in species, cell type, and to the 20- to 100-fold differences in anesthetic concentrations.

Effects of Thiopental and Methohexital on Potassium Currents

**Inward Rectifier Potassium Current.** The thiopental-induced changes in APD described here appeared to be caused, at least in part, by depression of I_{K1}. Thiopental, but not methohexital, markedly suppressed both the inward and outward components of I_{K1}. This finding that thiopental blocks I_{K1} in guinea pig and rabbit ventricular myocytes is similar to previous observations in frog atrial myocytes25 and in guinea pig,26 rat,27 and human ventricular myocytes.28

In our experiments, the effect of methohexital on I_{K1} was markedly different from that of thiopental. Although methohexital slightly diminished the inward component of I_{K1}, it did not cause any significant changes in the

![Graph showing simulated guinea pig ventricular action potentials](image)

Fig. 7. Simulated guinea pig ventricular action potentials. After control measurements, each value for L-type calcium current, the inward rectifier potassium current, and the delayed outward potassium current was adjusted appropriately to a fraction of each respective control current as determined from experimental data. See the Methods section for more details of the current measurement and action potential modeling.
outward component of \( I_{Ko} \). In support of this finding, Baum\textsuperscript{16} observed no significant effect of methohexital (100 \( \mu M \)) on \( I_{Ko} \) in guinea pig ventricular myocytes. On the other hand, Pancrazio et al.\textsuperscript{25} found that 30 \( \mu M \) methohexital depressed \( I_{Ko} \) in frog atrial myocytes. The discrepancies between these studies may be accounted for by different species (guinea pig vs. frog), cell types (ventricular vs. atrial), and temperature at which experiments were conducted (36 vs. 25°C).\textsuperscript{11}

**Delayed Rectifier Outward Potassium Current.** Our results clearly showed that thiopental suppressed \( I_K \) in guinea pig and rabbit ventricular myocytes, whereas methohexital significantly augmented this current. This finding is consistent with previous observations that 10 \( \mu M \) thiopental suppressed \( I_K \) to 21.7%\textsuperscript{15} of control, whereas higher concentrations (100 \( \mu M \)) may completely abolish this current.\textsuperscript{15,27} Arhem and Kristjansson\textsuperscript{28} also observed that thiopental reduced \( I_K \) at all voltages, but methohexital enhanced \( I_K \) at membrane potentials greater than +10 mV in myelinated nerve membrane. At higher concentrations (100–1,000 \( \mu M \)), methohexital reduced the \( I_K \) in invertebrate and vertebrate neurons\textsuperscript{29} and caused no change in guinea pig ventricular myocytes.\textsuperscript{19}

**Transient Outward Potassium Current.** To our knowledge, no investigators have evaluated the effects of barbiturates on \( I_o \). Although the effect of \( I_o \) inhibition on prolonging ventricular APD is less predictable than that caused by reductions in \( I_{Ko} \) or \( I_K \) currents, \( I_o \) has been associated with increased repolarization in humans with heart failure.\textsuperscript{30} Neither thiopental nor methohexital caused any significant effect on \( I_o \).

**Effects on L-type Calcium Current**

Although potassium currents primarily determine APD, changes in calcium conductance may also alter the duration of the ventricular action potential. In our experiments, neither 50 \( \mu M \) thiopental nor methohexital produced any significant effect on the L-type calcium current (\( I_{Ca,L} \)). Similarly, Pancrazio et al.\textsuperscript{25} observed that 30 \( \mu M \) thiopental did not affect \( I_{Ca,L} \) in guinea pig ventricular myocytes, although other investigators\textsuperscript{20} found that higher concentrations of thiopental (100–227 \( \mu M \)) reduced \( I_{Ca,L} \).

**Concordance of Changes in Currents and Action Potential Duration**

Cardiac APD is determined by a balance between inward and outward membrane currents. Any change in the balance between these currents results in shortening or prolongation of APD. Inward currents during the plateau phase of the ventricular APD are carried mainly through the L-type calcium current (\( I_{Ca,L} \)). As the major repolarizing current for cardiomyocytes, \( I_K \) activation initiates repolarization near the end of the ventricular AP plateau, which can be assessed by APD\textsubscript{50}. In contrast, not only is \( I_{Ko} \) the main determinant of resting conductance (phase 4 of the ventricular AP) but it also plays an important role during late repolarization of the ventricular action potential (phase 3) and is reflected by changes in APD\textsubscript{50}. In most species, \( I_o \) is responsible for the initial phase of repolarization, and its reduction has been associated with APD prolongation in failing hearts.\textsuperscript{31} Interestingly, thiopental tended to prolong APD\textsubscript{50} more than APD\textsubscript{80}, but methohexital caused a greater change in APD\textsubscript{50} compared with APD\textsubscript{80}, although this difference was not significant.

Given these facts, we can conclude that the changes caused by methohexital and thiopental on cardiac potassium conductance (i.e., \( I_K \) and \( I_{Ko} \)) accurately predicted the effects of these agents on ventricular APD. That is, methohexital, which augments \( I_K \) and has no effect on \( I_{Ko} \), would predictably shorten APD\textsubscript{50} more than APD\textsubscript{80}, and thiopental, which primarily inhibits \( I_{Ko} \), would prolong APD\textsubscript{50} more than APD\textsubscript{80}. Indeed, we observed these effects in single ventricular myocytes in which both action potential and currents were measured in the same cell.

**Action Potential Modeling**

The use of computer-generated models of action potentials allows direct comparison of experimental and simulated results (fig. 7) and identifies gaps in current knowledge of cardiac electrophysiology when discrepancies exist. On the one hand, the simulated action potential changes after methohexital administration corresponded closely with the data measured in real guinea pig ventricular myocytes (with differences of <6\% between simulated and measured APD\textsubscript{50} and APD\textsubscript{80}). However, differences in the magnitude of change, but not direction, were noted between the modeled and experimental data after thiopental treatment. This discrepancy may be attributed to difficulties in modeling action potentials with a plateau phase. In contrast to the species (such as the rat) in which repolarization is comprised of rapid initial and late slow phases, repolarization in guinea pig and human ventricular cells begins slowly, produces a plateau “square” wave, and then rapidly returns to phase 4.\textsuperscript{32} Modeling of these more complex wave forms depends on several assumptions (internal
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[Na], concentration, a direct relation between [Ca], and the sodium–calcium exchange current) that may not be true. Similarly, other investigators noted that use of older models of I_K that falsely manifest outward currents at positive membrane potentials may cause erroneous delays in the repolarization of simulated action potentials.

The Structure–Activity Relation of Thiopental and Methohexital

The underlying causes of the different effects of thiopental and methohexital on I_K and I_BK are not readily apparent. Both thiopental and methohexital are barbiturate anesthetics with similar molecular weights (264.3 and 284.3, respectively), pKa values (7.5 and 7.9, respectively), and lipid solubility (octanol–water partition coefficients of 390 and 333, respectively). Thus, it is unlikely that the observed differences in the electrophysiologic actions of these drugs would result from nonspecific membrane effects. In addition, if these changes (APD, I_K, and I_K variations) were mediated by general membrane effects, then both the effects of apnea were highly unlikely to cause alteration in the same direction, although the magnitude of variation might differ. An alternative explanation is that the differences in the chemical structure of the agents render structure–activity relations that modulate cardiac membrane ionic currents. Thiopental varies from methohexital by substitution of sulfur for oxygen at the second carbon atom of the barbituric acid ring, demethylation of the nitrogen atom, and truncation of the alky side chain. Given the markedly different myocardial electrophysiologic effects of two enantiomers, d- and l-sotalol, it would not be surprising that such small structural differences may significantly and selectively alter the effects of barbiturates on cardiac membrane currents. Indeed, Hattori et al. suggested that oxybarbiturates (pentobarbital and secobarbital) reduce extracellular calcium influx, whereas thiobarbiturates (thiopental and thiamylal) reduce sarcoplasmic uptake and transport in rat papillary muscle. The suggested differences in the structure–activity relations of oxybarbiturates and thiobarbiturates on ion channel activity may have clinical implications not only for perioperative management of patients but also for future anesthesia and antiarrhythmic drug development strategies.

In conclusion, thiopental inhibits I_K and I_BK with corresponding lengthening of the APD, and methohexital shortens APD by augmenting I_K in guinea pig and rabbit isolated ventricular myocytes. These differences indicate that rather than causing generalized membrane effects, these oxy- and thiobarbiturates may exert structure-specific actions on cardiac ion channels underlying ventricular repolarization. When considered with preliminary clinical results indicating that methohexital accelerates repolarization in patients having surgery who have delayed repolarization, these data suggest that methohexital may be beneficial for this cohort of patients. In contrast, the inhibition of potassium conductances by thiopental could contribute to cardiac excitability and dysrhythmogenesis. However, correlative clinical studies are necessary before any definitive recommendations can be made about anesthetic management.

References

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