Effects of Intravenous Anesthetics on Atrial Wavelength and Atrioventricular Nodal Conduction in Guinea Pig Heart

Potential Antidysrhythmic Properties and Clinical Implications

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Background: Supraventricular tachydysrhythmias such as atrial fibrillation frequently complicate the perioperative period. Two electrophysiologic factors critical to the pathogenesis of supraventricular tachydysrhythmias are: 1) atrial wavelength, the product of atrial conduction velocity (CV) and effective refractory period (ERP), and 2) atrioventricular nodal conduction. Modulation of these factors by drugs has important clinical ramifications. The authors studied the effects of propofol, thiopental, and ketamine on atrial wavelength and atrioventricular nodal function in guinea pig isolated atrial trabeculae and hearts, respectively.

Methods: Electrocardiogram recordings in superfused atrial tissue were obtained using hanging microelectrodes. A stimulating and two recording electrodes were placed on a single atrial trabecula, and the interelectrode distance was measured. Atrial ERP determinations were made using a premature stimulus protocol. The time (t) required for a propagated impulse to traverse the interelectrode distance (d) was measured. Conduction velocity was calculated as d/t. Langendorff-perfused guinea pig hearts were instrumented for low atrial pacing (cycle length = 300 ms) and for measurements of stimulus-to-His bundle interval, an index of atrioventricular nodal conduction. To investigate the frequency-dependent behavior of the atrioventricular node, computer-based measurements were made of Wenckebach cycle length (WCL) and atrioventricular nodal ERP.

Results: Thiopental significantly prolonged atrial ERP in a concentration-dependent manner, whereas propofol and ketamine had no significant effect on atrial refractoriness. In contrast, ketamine caused a dose-dependent decrease in atrial CV, but propofol and thiopental had no significant effect on CV. Therefore, thiopental, ketamine, and propofol caused an increase, a decrease, and no change, respectively, in atrial wavelength. All anesthetics caused a concentration-dependent prolongation of the stimulus-to-His bundle interval, atrioventricular nodal ERP, and WCL. However, on an equimolar basis, significant differences in potencies were found. The concentrations of drug that caused a 20% increase in ERP (ERP20) and WCL (WCL20) for propofol, thiopental, and ketamine were 1.8 ± 2 μM, 26 ± 5 μM, and 62 ± 11 μM, and 17 ± 2 μM, 50 ± 1 μM, and 123 ± 19 μM (mean ± SEM), respectively. Therefore, the rank order of potency for frequency-dependent atrioventricular nodal effects is propofol > thiopental > ketamine.

Conclusion: The authors' results indicate that propofol would be most effective at filtering atrial impulses during supraventricular tachydysrhythmias, whereas thiopental would be most effective at preventing atrial reentrant dysrhythmias. In contrast, ketamine may be most likely to promote atrial reentry while having minimal effect on atrioventricular nodal conduction. (Key words: Anesthetics, intravenous: propofol, thiopental, ketamine. Heart: atrial wavelength, atrioventricular nodal conduction.)

SUPRAVENTRICULAR tachydysrhythmias (SVTs) frequently complicate the perioperative period.¹ Their prevalence and potential for causing hemodynamic instability has prompted a decade of work that indicates that most paroxysmal SVTs involve a reentrant mechanism rather than an automatic mechanism.² Although atrioventricular nodal reentry tachycardia and atrioventricular reciprocating tachycardia are common forms of SVTs, the most prevalent SVTs are the reentrant atrial dysrhythmias (e.g., atrial fibrillation and atrial...
flutter). In viewing reentrant dysrhythmias as a “circus movement” in a ring of excitable tissue, it can be predicted that if the conduction velocity (CV) is too rapid, or the effective refractory period (ERP) too long, the circulating impulse will return to its point of origin before the fibers have restored their excitability. Consequently, the wave of excitation will be extinguished after one circuit around the pathway. In contrast, if the CV is too slow or the ERP too short, the region of initial excitation will have sufficient time to restore its excitability and the impulse may continue to circulate as a sustained reentrant tachydysrhythmia. Therefore, two electrophysiologic factors critical to the pathogenesis of reentrant SVTs are CV and ERP. By taking into account both parameters, atrial wavelength (λ), the product of CV and ERP, was found to predict the initiation of reentrant dysrhythmias more reliably than either CV or ERP alone. Therefore, modulation of λ by drugs has important clinical ramifications. Drugs that increase λ tend to prevent reentry and are antidysrhythmic (e.g., antiarrhythmic), whereas those agents that decrease λ tend to promote the development of atrial reentry tachydysrhythmias and are proarrhythmic (e.g., proarrhythmic).

By regulating the rate of ventricular response, the atrioventricular node plays an important role in determining the hemodynamic consequences of SVTs. An important physiologic characteristic of atrioventricular nodal conduction is the phenomenon of frequency dependence, whereby atrioventricular nodal conduction is modulated by atrial rate. As atrial rate increases, conduction of electrical impulses through the atrioventricular node becomes progressively slower (i.e., conduction time is prolonged), until conduction fails. In this manner, failure of impulse conduction through the atrioventricular node protects the ventricles from excessive atrial activity. As a result, drugs that depress atrioventricular nodal conduction (i.e., exert a negative dromotropic effect) in a frequency-dependent manner will effectively filter rapid supraventricular atrial impulses while having minimal-to-no effect on atrioventricular nodal conduction during sinus rhythm.

To our knowledge, no prior studies have addressed the direct effects of intravenous anesthetics on both atrial wavelength and atrioventricular nodal conduction. To test the hypothesis that intravenous anesthetics impact on the pathogenesis of SVTs, we studied the effects of propofol, thioental, and ketamine on atrial conduction and refractoriness and on the frequency-dependent behavior of atrioventricular nodal conduction.

Materials and Methods

Chemicals

Propofol (Diprivan, 2,6 diisopropylphenol; molecular weight = 178.3), a sterile nonpyrogenic emulsion that contains 10 mg/ml propofol, was a gift of Zeneca Pharmaceuticals (Wilmington, DE). Thioental Sodium (Pentothal; sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate; molecular weight = 264.3), a powder mixed in sterile water to make a 25 mg/ml solution, was purchased from Abbott Laboratories (North Chicago, IL). Ketamine hydrochloride (Ketalar; dl 2-(O-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride; molecular weight = 274.2), a 1:1 racemic mixture, at a concentration of 100 mg/ml was purchased from Parke-Davis (Morris Plains, NJ). Solutions of the above drugs were dissolved in normal saline and infused to achieve the desired perfusate concentration. In agreement with previous studies, Intralipid at a concentration that corresponds with 50 μM propofol had no significant effect on atrioventricular nodal function and atrial wavelength. The atrioventricular nodal conduction times (stimulus-to-His bundle [S-H] interval) in the absence and presence of Intralipid were 47.0 ± 0.8 ms (n = 3) and 47.0 ± 0.4 ms (n = 3), respectively (P = 0.94). Likewise, Intralipid had no effect on atrial CV (1.70 ± 0.11 vs 1.68 ± 0.13 m/s) and ERP (56.0 ± 2.0 vs 57.0 ± 1.7 ms).

Isolated Perfused Hearts

Before the study began, all protocols were reviewed and approved by the Animal Use Committee of the University of Florida Health Sciences Center. Guinea pigs of either sex weighing 250–300 g were anesthetized with halothane and killed by cervical dislocation. Hearts were quickly removed and rinsed in ice-cold Krebs-Henseleit solution. The aorta was cannulated for perfusion of the coronary arteries at a constant flow rate of 8 ml/min with modified Krebs-Henseleit solution gassed with 95% oxygen and 5% CO₂. This solution contained, in mM: 117.9 NaCl; 4.8 KCl; 2.5 CaCl₂;
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1.18 MgSO₄; 1.2 KH₂PO₄; 0.5 Na₂EDTA; 25.0 NaHCO₃; 0.14 ascorbic acid; 2.0 pyruvate; and 5.5 glucose. The \( pO₂ \), temperature, and pH of the Krebs-Henseleit solution were maintained at 500–600 mmHg, 35 ± 0.5°C, and 7.3–7.4, respectively.

Atrial Recordings

Left atrial tissue obtained from the guinea pig isolated-perfused hearts were pinned to the bottom of a custom-designed tissue bath (Radnoti Glass Technology, Monrovia, CA) and superfused with modified Krebs-Henseleit solution. A stimulating and two recording electrodes were placed on a single atrial trabecula. Computer-assisted point stimulation at a cycle length of 300 ms (3.33 Hz) was achieved via a bipolar electrode at one end of the trabecula. Stimuli were square-wave pulses of 2-ms duration that were delivered at 1.5 times the threshold intensity via a stimulus isolation unit (Model A360, WPI, Sarasota, FL). Atrial electrocardiograms were recorded using a hanging microelectrode technique,12 that used a 3 M KCl-filled glass capillary micropipette with a tip resistance of approximately 30 MΩ. Signals were amplified (WPI amplifier Model S7050A, WPI) and recorded using an automated online data acquisition program (AXOTAPE, Axon Instruments, Foster City, CA) with a sampling resolution of 6 µs. Interelectrode distance (d) was measured with the aid of a stereo dissecting microscope (Model 13301, WPI) fitted with calibrated ocular lenses accurate to 0.01 mm. Interelectrode distance (mean ± SEM) for the propofol (5.0 ± 0.4 mm), thiopental (4.0 ± 0.1 mm), and ketamine (4.0 ± 0.1 mm) groups were not significantly different (\( P = 0.16 \)). The time (t) required for a propagated impulse to traverse d was measured using AXOTAPE. Conduction velocity was calculated as t/d.

Atrioventricular Nodal Recordings

To facilitate pacing of the heart and recording of the His bundle electrogram (HBE), the sinoatrial nodal region was excised. Unless otherwise indicated, hearts were paced electrically at a cycle length of 300 ms via a bipolar electrode placed on the low atrioseptal area. An interval generator (Model A310, WPI) delivered the stimuli through a stimulus isolation unit (Model A360, WPI) as square wave pulses of 3 ms in duration and at least twice the threshold intensity. A unipolar extracellular electrode constructed of polytetrafluoroethylene-coated stainless steel was placed in the atrioventricular nodal area to record the His bundle electrogram.13 The S-H interval was used as an index of atrioventricular nodal conduction.14 It is unlikely that atrial effects of the anesthetics significantly contributed to the drug-induced prolongation of atrioventricular nodal conduction time. This is based on the fact that the site of atrial stimulation was at the low atrioseptal junction, which effectively minimizes atrial path length and the contribution of atrial conduction to atrioventricular nodal conduction time.

After completion of the dissection and instrumentation, the hearts were allowed to equilibrate for 45 min before the experiments were begun. Experimental interventions were always preceded and followed by measurements of S-H intervals. Whenever the pre- and postintervention values differed by more than 15%, the intervening data were discarded. In the event an intervention caused second-degree atrioventricular block, the longest stable S-H interval before the onset of atrioventricular block was considered the maximum dromotropic effect, and that value was used for data analysis.

Protocols

Effects of Intravenous Anesthetic on Atrial Torsade. In this series of experiments, concentration–response relations for atrial CV and ERP were obtained for propofol, thiopental, and ketamine. After the control CV and ERP were measured, the anesthetics were administered at successively higher concentrations (10–50 µM) and the measurements repeated. Atrial ERP was measured in an isolated atrial trabecula stimulated at a fixed basic cycle length (\( S₁ \), interval of 300 ms, using the following premature stimulus protocol. After a train-of-15 stimuli (\( S₁ \)), a single premature (test) stimulus (\( S₂ \)) was introduced. The coupling interval (\( S₁S₂ \)) between the last \( S₁ \), and the test stimulus (\( S₂ \)) was progressively shortened in 3-ms steps after every train of stimuli. The longest \( S₁S₂ \) interval for a stimulus that failed to produce an atrial response was defined as the atrial ERP. Atrial wavelength (\( \lambda \)) was calculated as CV × ERP.

Dromotropic Effects of Intravenous Anesthetics. In this series of experiments, concentration–response relations were obtained for the negative dromotropic effect of propofol, thiopental, and ketamine in hearts paced at an atrial cycle length of 300 ms. After a control His bundle electrogram was recorded, the anesthetics were administered at successively higher concentrations, ranging from 5–100 µM. The effect of a given

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concentration of anesthetic was measured when the response had reached a steady state.

In addition, the following three programmed stimulation protocols were used to study the frequency-dependent effects of intravenous anesthetics on atrioventricular nodal conduction: 1) **Wenckebach cycle length** (WCL). The WCL was determined by decreasing the atrial pacing cycle length in 3-ms steps every 10 stimuli until second-degree atrioventricular block occurred. The longest S1S1 interval for a stimulus that failed to conduct through the atrioventricular node and produce a His bundle response was defined as the WCL. 2) **Effective refractory period**. The atrioventricular nodal ERP was measured using the premature stimulus protocol described above for atrial ERP. 3) **Simulated atrial tachycardia protocol**: This stimulation protocol consisted of an abrupt transient decrease (single step) in atrial pacing cycle length. After 30 s of pacing at a fixed atrial cycle length of 300 ms (slow rate), the heart was paced at an atrial cycle length 10% above the WCL (fast rate) for 90 s, followed by a return to the original pacing cycle length. A pacing duration of 60 s has been shown to be sufficient for atrioventricular nodal conduction time to achieve steady state, regardless of the baseline atrial cycle length. During the experiments, the S-H interval was continuously recorded, using a custom-made data acquisition system and the steady or the longest S-H interval before atrioventricular block was measured. In this series of experiments, each heart underwent the protocol twice (**i.e., in the absence and in the presence of a drug concentration that prolonged the S-H interval approximately 5 ms. The ratio between S-H interval prolongations at fast and slow pacing rates in the presence and absence (control) of drug defines the frequency dependence ratio, calculated as (S煌drug - S煌control) / (S煌drug - S煌control)slow**.

**Data Analysis**

All measurements are reported as the mean ± SEM. The concentrations of drug that caused a 10% and 20% increase in effective refractory period (ERP10; ERP20), Wenckebach cycle length (WCL10; WCL20), and S-H interval (SH10; SH20) were determined by fitting the concentration–response data to a parabolic equation (equation 1) using a nonlinear (Marquardt-Levenberg) regression algorithm (Table Curve 2.0 program, Jandel Scientific, San Rafael, CA).

Equation 1: y = a + bx^2

where y, x, a, and b denote either ERP, WCL, or S-H interval, the concentration of drug, and two curve fitting parameters, respectively.

Statistical tests were performed using SigmaStat 2.0 (Jandel Scientific, San Rafael, CA). Differences among means were tested by analysis of variance followed by Student-Newman-Keuls testing. *P < 0.05* was considered statistically significant.

**Results**

**Effects of Intravenous Anesthetics on Atrial Wavelength**

Ketamine caused a concentration-dependent decrease in atrial CV throughout a concentration range of 0–50 μM, whereas propofol and thiopental had no significant effect (fig. 1A). As shown in figure 1B, thiopental exhibited a significant concentration-dependent increase in atrial ERP, but propofol and ketamine caused no significant effect on atrial ERP. Therefore, propofol had no significant effect on λ, whereas thiopental increased and ketamine decreased λ in a concentration-dependent manner (fig. 2). Neither the control CV values, 1.44 ± 0.16 m/s, 1.93 ± 0.35 m/s, and 1.74 ± 0.26 m/s (*P = 0.45*), nor the control ERP values, 55 ± 3 ms, 56 ± 5 ms, and 60 ± 5 ms (*P = 0.60*) for propofol, thiopental, and ketamine, respectively, were significantly different.

**Dromotropic Effects of Intravenous Anesthetics**

The effects of propofol, thiopental, and ketamine on atrioventricular nodal conduction were examined throughout the concentration range of 0–100 μM. All three anesthetics exhibited concentration-dependent prolongation of atrioventricular nodal conduction time (fig. 3). The drug concentrations that caused a 10% and 20% increase in the S-H interval (SH10 and SH20, respectively) are indicated in table 1. The SH10 and SH20 values of propofol were significantly lower than those of thiopental and ketamine, which, in turn, were not statistically different from each other. Fifty micromolar propofol caused second-degree atrioventricular block in 3 of 5 paced hearts at an atrial cycle length of 300 ms, whereas thiopental and ketamine did not induce second-degree atrioventricular block in any heart, even at a concentration of 100 μM. The control S-H intervals for the propofol (40 ± 2 ms), thiopental (45 ± 5 ms) and ketamine (43 ± 2 ms) groups were not statistically different (*P = 0.41*).
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Fig. 1. Effects of intravenous anesthetics on atrial conduction velocity (CV) and atrial effective refractory period (ERP). Shown are concentration–response curves demonstrating the effects of anesthetics on (A) atrial conduction velocity (CV) and (B) atrial effective refractory period (ERP) in isolated atrial trabeculae. Each point represents a mean ± SEM of 5 experiments for the propofol and thiopental groups and of 4 experiments for the ketamine group. *P < 0.05 indicates a significant difference from control.

Frequency-dependent Effects of Intravenous Anesthetics on Atrioventricular Nodal Conduction

Atrioventricular nodal ERP concentration–response curves for propofol, thiopental, and ketamine are shown in figure 4A. All anesthetics caused a concentration-dependent increase in the ERP (P < 0.001). As shown in figure 4A and table 1, the rank order of potency was propofol > thiopental > ketamine. The control values of atrioventricular nodal ERP were 135 ±

Fig. 2. Effects of intravenous anesthetics on atrial wavelength. Shown is a concentration–response curve for the effects of propofol, thiopental, and ketamine on atrial wavelength (λ), the product of atrial conduction velocity (CV) and effective refractory period (ERP) in isolated atrial trabeculae. Each point represents a mean ± SEM of 5 experiments for the propofol and thiopental groups and of 4 experiments for the ketamine group. *P < 0.05 indicates a significant difference from control.

Fig. 3. Dromotropic effects of intravenous anesthetics on atrioventricular nodal conduction. Shown are the concentration–response relations for the effects of propofol, thiopental, and ketamine on stimulus-to-His bundle (S-H) interval in guinea pig isolated-perfused hearts. Each point represents a mean ± SEM of data from five experiments. The line represents the curve fit to Equation 1 (see Data Analysis).
Table 1. Comparison of the Effects of Intravenous Anesthetics on Atrioventricular Nodal Conduction Time (S-H Interval), Effective Refractory Period, and Wenckebach Cycle Length

<table>
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<th>SH₁₀</th>
<th>SH₃₀</th>
<th>ERP₁₀</th>
<th>ERP₃₀</th>
<th>WCL₁₀</th>
<th>WCL₃₀</th>
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<tr>
<td>Propofol (µM)</td>
<td>9 ± 2</td>
<td>16 ± 2†</td>
<td>7 ± 1†</td>
<td>14 ± 2†</td>
<td>9 ± 1†</td>
<td>17 ± 2†</td>
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<tr>
<td>Thiopental (µM)</td>
<td>45 ± 7*</td>
<td>83 ± 12*</td>
<td>11 ± 2*</td>
<td>26 ± 3†</td>
<td>23 ± 1*†</td>
<td>50 ± 1*†</td>
</tr>
<tr>
<td>Ketamine (µM)</td>
<td>50 ± 7*</td>
<td>97 ± 10*</td>
<td>26 ± 7*</td>
<td>62 ± 11*</td>
<td>75 ± 33*</td>
<td>123 ± 19*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM (n = 5-7).
The concentration of drug that caused a 10% and 20% increase in the atrioventricular nodal conduction time (SH₁₀ and SH₃₀), effective refractory period (ERP₁₀ and ERP₃₀), and Wenckebach cycle length (WCL₁₀ and WCL₃₀) were determined by fitting the concentration-response data to a parabolic equation as described in Materials and Methods.

Comparisons between drugs: * P < 0.05 versus propofol; † P < 0.05 versus ketamine.

8 ms, 125 ± 6 ms, and 131 ± 7 ms for the propofol, thiopental, and ketamine groups, respectively. These values were not statistically different (P = 0.57).

The Wenckebach cycle length, the atrial pacing cycle length at which second-degree atrioventricular block occurs, was significantly increased by the anesthetics in a concentration-dependent manner (Fig 4B). The same rank order of potency was found for this parameter as for atrioventricular nodal ERP (Fig 4, Table 1). In the absence of anesthetic, the WCL for the propofol (168 ± 8 ms), thiopental (180 ± 6 ms) and ketamine (184 ± 4 ms) groups were not significantly different (P = 0.15).

The frequency-dependent negative dromotropic effects of the intravenous anesthetics were investigated further by comparing the effect of an abrupt and transient increase in atrial rate after an equivalent increase (i.e., approximately 5 ms) in the baseline S-H interval caused by propofol, thiopental, and ketamine. Although all anesthetics caused greater prolongation of the S-H interval during rapid atrial pacing than at slow atrial pacing (i.e., frequency dependence ratio > 1), the frequency dependence ratio of ketamine was significantly lower than that of propofol and thiopental (Fig 5). In fact, during the 90-s pacing at an atrial cycle length 10% greater than the WCL, 4 of 5 hearts in the propofol group, 5 of 6 hearts in the thiopental group, and 0 of 3 hearts in the ketamine group exhibited second-degree atrioventricular block.

Discussion

This report is the first to describe the effects of intravenous anesthetics on both atrial wavelength and atrioventricular nodal conduction. In guinea pig heart, intravenous anesthetics had markedly different actions on atrial and atrioventricular nodal conduction and refractoriness (Table 2). Propofol caused the greatest negative dromotropic and frequency-dependent atrioventricular nodal effects, but had the least effect on atrial wavelength, because it did not significantly change atrial CV or ERP. Thiopental markedly increased atrial wavelength by prolonging atrial ERP, while having moderate negative dromotropic effect. Ketamine markedly decreased atrial wavelength by slowing CV, but caused minimal depression of atrioventricular nodal conduction.

Atrial Wavelength and Dysrhythmogenesis

Using a chronic conscious dog model in which λ, the product of ERP and CV, can be correlated directly with the induction of dysrhythmias, Rensma et al. found that λ correctly predicted the induction of atrial tachydysrhythmia in 75% of the cases (750 responses in 19 dogs). In contrast, the overall predictive value of ERP or CV alone was only 48% and 38%, respectively. Wavelength was also the most sensitive (88–100%) and most specific (80–96%) predictor of the inducibility of atrial dysrhythmias. In addition, the value of λ, unlike that of ERP and CV, was highly predictive of the type of SVT. Taken together, although ERP and CV are widely recognized to be important parameters in predicting the vulnerability of the heart to tachydysrhythmias, λ is a much better index for predicting atrial dysrhythmogenesis than either CV or ERP alone. In addition, because the effects of a drug on one variable (either ERP or CV) may be counteracted by an opposite effect on the other variable, conclusions based on measurements of ERP or CV alone may be misleading. For example, if atrial ERP alone had been measured in this study, we would not have recognized that ketamine shortens λ by decreasing CV. Likewise, by measuring only CV, the potentially antidysshythmic effect of thio-

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Fig. 4. Frequency-dependent effects of intravenous anesthetics on atrioventricular nodal conduction. Shown are the concentration–response relations for propofol (n = 7), thiopental (n = 6), and ketamine (n = 5) in guinea pig isolated-perfused hearts on (A) atrioventricular nodal effective refractory period (ERP) and (B) Wenckebach cycle length (WCL). All anesthetics significantly increased ERP and WCL in a concentration-dependent manner. Each point represents a mean ± SEM. The line represents the curve fit to Equation 1 (see Data Analysis).

Fig. 5. Frequency-dependent prolongation of the S-H interval caused by anesthetics. Frequency-dependence ratios (\(\frac{S_{\text{drug}} - S_{\text{control}}}{S_{\text{drug}} - S_{\text{control}}_{\text{max}}}\)) for propofol (n = 5), thiopental (n = 6), and ketamine (n = 3) (A) at drug concentrations that produced statistically-equivalent prolongations in the S-H interval at an atrial cycle length (ACL) of 300 ms (B). A ratio greater than one indicates a greater effect of an agent at a faster pacing rate than at a slower pacing rate. As per the simulated tachycardia experiments, ACL was abruptly shortened from 300 ms to an interval 10% above WCL for 90 s and then returned to 300 ms. Bars represent means ± SEM. *P < 0.05 versus thiopental and propofol.

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previous work has systematically studied the direct effects of these agents on atrial CV or ERP, the results of numerous earlier studies support our findings. For example, because lengthening of repolarization is associated with an increase in the ERP of cardiac tissues, the fact that barbiturates prolong ventricular action potential duration (APD) in rabbit and guinea pig heart is consistent with our results showing that thiopental increases by prolonging atrial ERP. Likewise, depression of myocardial conduction by ketamine is supported by a study demonstrating that ketamine (30–300 μM) causes a dose-dependent decrease in the maximum rate of ventricular depolarization (\(V_{\text{max}}\)) and CV in guinea pig papillary muscle. In addition, other investigators have shown that ketamine increases APD in atrial and ventricular tissue of guinea pig and rat, but only at high drug concentrations (100–500 μM). This is consistent with our finding that ket-
Table 2. Summary of the Supraventricular Electrophysiologic Effects of Intravenous Anesthetics

<table>
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<th>Atria</th>
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<th>Atrioventricular Node</th>
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<tr>
<td></td>
<td>CV</td>
<td>ERP</td>
<td>λ</td>
</tr>
<tr>
<td>Propofol</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Thiopental</td>
<td>++</td>
<td>↑↑</td>
<td>++</td>
</tr>
<tr>
<td>Ketamine</td>
<td>↓↓↓</td>
<td>++</td>
<td>↓↓↓</td>
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CV = conduction velocity; ERP = effective refractory period; WCL = Wenckebach cycle length; λ = wavelength; S-H = stimulus-to-His bundle; ++ = no change; ↑ = increase, ↓ = decrease. The number of arrows indicate the relative magnitude of the change.

Amine (10–50 μM) decreases λ by causing a significant concentration-dependent decrease in atrial CV while having no significant effect on atrial ERP. In lieu of the fact that activation of M₂-muscarinic cholinergic receptors shortens atrial action potential, and that a significant component of propofol’s effects on atrioventricular nodal conduction is mediated by M₂-receptors, it was interesting that propofol had no significant effect on atrial refractoriness and λ. However, numerous previous studies showed that, despite the strong correlation between myocardial repolarization and refractoriness under baseline (drug-free) conditions, a drug-induced decrease (or increase) in APD is not necessarily reflected in an equal decrease (or increase) in ERP. In other words, electrophysiologically complex drugs may modulate myocardial refractoriness by both voltage- and time-dependent mechanisms. The voltage-dependent changes in refractoriness correlate well with changes in APD, whereas the time-dependent postrepolarization refractoriness increases the ERP/APD ratio. For example, amidodarone is known to prolong ventricular ERP more than APD, and LeGrand et al. showed that nivorcanol shortens APD significantly more than ERP. In addition, recent studies in our laboratory (unpublished) show that propofol (10–50 μM) causes a concentration-dependent shortening of atrial monophasic action potential at 50% repolarization without significantly changing ERP. Taken together, our findings do not exclude the possibility that propofol shortens atrial APD by activating M₂-receptors, but rather indicate that it causes complex electrophysiologic effects that involve time-dependent action(s) on atrial refractoriness.

Negative Dromotropic and Frequency-dependent Effects of Intravenous Anesthetics
Among the anesthetics examined, propofol on an equimolar basis caused the greatest negative dromotropic effect. This finding confirms and expands on earlier studies of this and other laboratories. Our rank order of potency (i.e., propofol > thiopental > ketamine) for the negative dromotropic effects is in agreement with the findings of Stowe et al., with propofol being the most potent and ketamine the least potent in prolonging atrioventricular nodal conduction in guinea pig isolated heart. The recent study by Graf et al., which demonstrated that ketamine (25–200 μM) causes prolongation of atrioventricular nodal conduction in the isolated guinea pig heart, further supports our conclusion that clinically relevant concentrations of anesthetics can exert significant negative dromotropic effects.

In the current study, we showed that propofol, thiopental, and ketamine augment the modulatory effect of atrial rate on atrioventricular nodal conduction. Consistent with their depressant effects on atrioventricular nodal conduction (i.e., prolongation of the S-H interval), propofol, thiopental, and ketamine caused concentration-dependent prolongation of atrioventricular nodal ERP and WCL. The ERP of the atrioventricular nodal and WCL are two distinct but complementary indices of the frequency-dependent effects of drugs on atrioventricular nodal conduction. Effective refractory period is a measure of the ability of the atrioventricular node to filter a single premature supraventricular stimulus. Wenckebach cycle length takes into consideration the effect of atrioventricular nodal accommodation, and therefore is a more accurate measure of the filtering capacity of the atrioventricular node to sustain supraventricular stimuli. Therefore, although the drug-induced increase in atrioventricular nodal ERP and especially in WCL suggests that all the anesthetics would enhance the filtering capacity of the atrioventricular node, their rank order of potency indicates that propofol on an equimolar basis would most effectively reduce the transmission of atrial impulses to the ventricles.

The magnitude of the concentration-dependent effects on atrioventricular nodal conduction time (S-H...
interval) and frequency-dependent negative dromotropic indices (WCL, ERP) were similar for propofol and ketamine. Interestingly, however, we found that thiopental had a greater concentration-dependent effect on atrioventricular nodal ERP and WCL than on S-H interval (see table 1 and figures 3 and 4). The precise reason why this relation for thiopental is different than that of propofol or ketamine remains to be determined.

The increase in the ratio between S-H prolongation at fast and slow pacing rates (i.e., frequency dependence ratio > 1) suggests that the negative dromotropic effects of the intravenous anesthetics and their ability to block atrioventricular nodal conduction will be greater as atrial rate is increased. The ideal drug for the treatment of atrioventricular nodal reentrant tachycardias should have little or no effect on atrioventricular nodal conduction during normal heart rates, but markedly depress conduction during tachycardias. Therefore, an anesthetic with a larger frequency dependent ratio (e.g., propofol or thiopental compared with ketamine; fig. 5) would be expected to be safer and more effective in protecting the ventricle from rapid atrial impulses in patients with SVTs.

**Clinical Implications**

Similar to antidysrhythmic agents, 8,9,30,31 anesthetics that depress atrioventricular nodal conduction in a frequency-dependent manner may effectively filter rapid suprnumerary atrial impulses and protect the heart from excessive ventricular rates during the perioperative period. Therefore, although we are not advocating the use of anesthetics to treat SVTs, the rank order of potency for the negative dromotropic and frequency-dependent atrioventricular nodal effects of the anesthetics tested suggest that propofol is an appropriate anesthetic in patients with history of SVTs involving the atrioventricular node. In addition, the lack of propofol’s effect on λ indicates that this phenol derivative will neither facilitate nor prevent atrial reentrant tachydysrhythms. However, among the anesthetics studied, thiopental, by prolonging the atrial λ, will most likely prevent initiation of atrial reentrant tachydysrhythms, whereas ketamine, by shortening λ, may be prodsyrhythmic.

Data concerning plasma concentrations of intravenous anesthetics are limited and controversial. Regardless of the possible inaccuracies in determining free anesthetic concentration in vivo, the concentrations used in our experiments are within the range of estimated unbound concentrations of propofol (20–60 μM), 11,32 thiopental (7–60 μM) 11,17,33 and ketamine (5–90 μM). 34,35 Therefore, it is likely that intravenous anesthetics will also cause significant electrophysiologic effects in humans, particularly during induction of anesthesia. Although two recent clinical reports failed to demonstrate any significant effect of propofol on atrioventricular nodal conduction and refractoriness, 36,37 numerous case reports 38–45 support our interpretation that propofol may cause significant negative dromotropic effect in the perioperative setting. However, as a consequence of its frequency-dependent effect on atrioventricular nodal conduction, low concentrations (≤5–10 μM) of propofol are likely to cause only minimal negative dromotropic effects during normal sinus rhythm or slow SVT (e.g., atrioventricular nodal reciprocating tachycardia), but cause much greater atrioventricular nodal depression during atrial fibrillation or flutter.

The results of our study should provide an impetus for the development of an anesthetic classification based on a drug’s effect(s) on ionic currents and underlying dysrhythogenic mechanisms. Such a framework, analogous to that developed for antidysrhythmic drugs (i.e., Sicilian Gambit), 44 would provide a rational basis for the selection of the most appropriate anesthetic(s) in the patient with a history of or a susceptibility to experience SVTs.

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