Comparative actions of propofol and thiopentone on cell membranes of isolated guineapig ventricular myocytes

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Summary
We have examined the effects of propofol and thiopentone on membrane potentials and currents of isolated guineapig ventricular myocytes using the whole-cell patch-clamp technique. After current clamping, propofol at concentrations greater than 0.5 μmol litre−1 shortened the plateau and action potential duration (APD) (P<0.05). Thiopentone 10 μmol litre−1 prolonged APD (P<0.05), whereas concentrations of 50 μmol litre−1 or higher decreased plateau height (P<0.05) and resting membrane potential (RMP) (P<0.05) with abbreviation of the prolonged APD. With voltage clamping, propofol 1 μmol litre−1 decreased the L-type Ca2+ current (I calcium,L) to 88.4% of control (P<0.01) without affecting the delayed rectifier K+ current (IK) and propofol 10 μmol litre−1 decreased I calcium,L and IK to 75.0% (P<0.01) and 78.4% (P<0.01), respectively, with no effect on the inward rectifier K+ current (IK1). Thiopentone 10 μmol litre−1 decreased I calcium,L to 88.5% (P<0.01) and IK to 78.3% (P<0.05), while thiopentone 100 μmol litre−1 depressed I calcium,L to 82.8% (P<0.01), IK to 27.0% (P<0.01) and IK1 to 67.3% (P<0.05). These results indicated that propofol, at concentrations greater than those that are clinically relevant, shortened APD mainly by suppression of IK1 and to suppress delayed rectifier K+ currents at therapeutic concentrations should aid understanding of their inotropic and chronotropic effects. Therefore, we assessed the comparative actions of propofol and thiopentone on membrane currents forming the repolarization phase of action potentials of isolated guineapig ventricular myocytes.

Materials and methods
The experimental procedure was approved by the Animal Care and Use Committee of Tokyo Medical and Dental University. Single ventricular myocytes were isolated from guineapig hearts by enzymatic dissociation, as described previously. Briefly, animals weighing 300–400 g were anaesthetized with sodium pentobarbitone 40–50 mg kg−1 i.p. after heparinization (300 u. kg−1 i.v.). The chest was opened during artificial ventilation and the aorta was cannulated in situ and then perfused with Tyrode’s solution before the heart was dissected out. Using a Langendorff apparatus, the heart was perfused retrogradely at 37°C with low-Ca2+ (30 μmol litre−1) Tyrode’s solution, followed by perfusion with 0.04% collagenase (type 1, Sigma Chemical Co., St Louis, MO, USA) dissolved in low-Ca2+ Tyrode’s solution.

It remains controversial as to which is the more potent negative inotropic and pro- or antiarrhythmic drug, because previous studies in vitro have focused mainly on trans-sarcolemmal Ca2+ influx and sarcoplasmic reticulum function. In single ventricular myocytes, propofol at relatively high concentrations has been shown to shorten action potential duration (APD) and suppress delayed rectifier K+ currents (IK) without affecting the inward rectifier K+ current (IK1). In contrast, thiopentone has been shown to induce prolongation of APD in multicellular preparations, and to suppress ICaL, IK and IK1 in single myocytes, suggesting that propofol and thiopentone have different actions on membrane currents.

Because IK1 and IK together with ICaL regulate APD by determining repolarization of action potentials, modification of any one of these currents could alter contractile function and refractory period. Knowledge of the precise actions of propofol and thiopentone on repolarizing currents at therapeutic concentrations should aid understanding of their inotropic and chronotropic effects. Therefore, we assessed the comparative actions of propofol and thiopentone on membrane currents forming the repolarization phase of action potentials of isolated guineapig ventricular myocytes.

Key words
for about 20 min. Single cells were obtained by gentle agitation of small pieces of ventricular tissue in a beaker containing the high-K⁺, low-Cl solution (KB medium\(^{19}\)) and stored at 4 °C. The preparations were transferred to a recording chamber filled with bath solution (normal Tyrode), which was placed on the stage of an inverted phase-contrast microscope (Diaphot TMD, Nikon, Tokyo, Japan). A single isolated cell with a smooth surface and clear striations was selected for electrical measurements. Electrophysiological experiments were performed within 12 h of cell isolation.

Test solutions of propofol (2,6-diisopropylphenol; Zeneca, Macclesfield, UK) were obtained by adding appropriate amounts of an aqueous emulsion (1% (w/v) propofol in 10% (w/v) soya bean oil, 1.2% (w/v) egg phosphate and 2.25% (w/v) glycerol) to normal Tyrode’s solution. Thiopentone (5-ethyl-5-(1-methyl butyl)2-thiobarbiturate; Tanabe Pharmaceut Co., Osaka, Japan) was prepared freshly before every experiment. This agent was also diluted in normal Tyrode’s solution to obtain the final concentrations indicated in the text. All anaesthetic concentrations in this study, therefore, are expressed as free concentrations in aqueous solution.

The composition of normal Tyrode’s solution used in cell dissociation and the bath solution was (mmol litre\(^{-1}\)): NaCl 144, NaH\(_2\)PO\(_4\) 0.33, KCl 4.0, CaCl\(_2\) 1.8, MgCl\(_2\) 0.53, glucose 5.5 and HEPES 5.0, and the pH was adjusted to 7.3–7.4 by adding NaOH. The high-K⁺, low-Cl solution had the following composition (mmol litre\(^{-1}\)): K-glutamate 70, taurine 15, KCl 30, KH\(_2\)PO\(_4\) 10, MgCl\(_2\) 0.5, glucose 11, EGTA 0.5 and HEPES 10, and the pH was adjusted to 7.4 by adding KOH. The composition of the pipette solution used in recording action potentials and membrane currents was (mmol litre\(^{-1}\)): KCl 130, K\(_2\)ATP 5.0, creatine phosphate 5.0, EGTA 0.2 and HEPES 5.0, and the pH was adjusted to 7.2 with KOH. For isolation of \(I_{\text{Ca,L}}\) the pipette solution replacing internal K⁺ with Cs⁺ and a TEA-rich external solution for Na⁺ were used. The TEA-rich solution contained (mmol litre\(^{-1}\)): TEA-Cl 154.0, CaCl\(_2\) 2.0, MgCl\(_2\) 2.0, glucose 10.0 and HEPES 10.0, and the pH was adjusted to 7.4 with TEA-OH. The pipette solution contained (mmol litre\(^{-1}\)): CsCl 110.0, TEA-Cl 20.0, CaCl\(_2\) 0.068, MgCl\(_2\) 4.0, BAPTA 5.0, HEPES 10.0, K\(_2\)ATP 5.0 and cAMP 3.0, and the pH was adjusted to 7.2 with CsOH.

The whole-cell variation of the patch-clamp technique was used to record action potentials and membrane currents using an amplifier (Axopatch 1C, Axon Instruments, Foster City, CA, USA) and low-pass filtered at 10 kHz. Action potentials and membrane currents were recorded under whole-cell current-clamp and voltage-clamp modes, respectively. Acquisition and analysis of the data, and generation of the stimulus procedure, were performed with the pCLAMP software package (version 5.5.1; Axon Instruments). The temperature of the perfusion chamber was maintained at 35–36 °C. At the beginning and end of each experiment, the junction potentials between the pipette and bath solutions were checked and if differences in the two values were more than 2 mV, membrane potential was corrected accordingly. The resistance of the pipette filled with standard pipette solution was 2–4 MΩ. Test solution was applied to the bath solution at concentrations indicated in the text for 5–10 min of the observation. The washout data were observed 15 min after removal of the drug from the bath solution. Some depression of membrane currents after administration of drug may result from “rundown”, and therefore data were excluded if washing with control solution did not yield recovery to at least 80% of control.

To examine the kinetics of \(I_{\text{Ca,L}}\) produced by the drug, the time course of development was assessed by a curve-fitting procedure using a simple non-linear least-squares algorithm on a personal computer (IBM-AT). The formula for the curve fitting used in this study is: \[ I_{\text{Ca,L}} = A_1 \exp(-bC_1) + A_2 \exp(-bC_2) + A_3 \exp(-bC_3) + A \] where \( b \) = pulse number or time, and \( C_1, C_2 \) and \( C_3 \) = onset rates. Applicability of either one, two or three exponential functions was always examined using the \( F \) test.

All values are expressed as mean (SEM). Statistical significance of a drug treatment was determined by paired or unpaired Student’s \( t \) test; \( P < 0.05 \) was considered significant, except in the \( F \) test where \( P < 0.01 \) was significant.

**Results**

**EFFECTS OF PROPOFOL AND THIOPENTONE ON ACTION POTENTIALS**

Propofol 0.1 \( \mu \)mol litre\(^{-1}\) had no effect on action potential variables (\( n = 4 \), fig.1A). Propofol shortened APD at 90% repolarization (APD\(_{90}\)) at concentrations of 0.5 \( \mu \)mol litre\(^{-1}\) or greater (\( P < 0.05 \)). At concentrations of 1 \( \mu \)mol litre\(^{-1}\) or higher, propofol shortened APD at 20% repolarization (APD\(_{20}\)) (\( P < 0.05 \)). Propofol changed neither action potential amplitude (APA) nor resting membrane potential (RMP) (fig.1A, table 1). Administration of the vehicle alone (0.002% Intralipid; Otsuka Pharmaceutical Co., Tokyo, Japan), in an amount equal to that contained in propofol 10 \( \mu \)mol litre\(^{-1}\), did not significantly affect action potential variables (\( n = 5 \), data not shown).

Administration of thiopentone 1 \( \mu \)mol litre\(^{-1}\) had little effect on APD\(_{20}\) or APD\(_{90}\). Thiopentone 10 \( \mu \)mol litre\(^{-1}\) induced prolongation of APD\(_{90}\) (\( n = 5 \), \( P < 0.05 \)) without change in APD\(_{20}\) (table 1). At 50 and 100 \( \mu \)mol litre\(^{-1}\), thiopentone caused a decrease in RMP (\( P < 0.05 \)) and shortened APD\(_{20}\) (\( P < 0.05 \)). The prolonged APD\(_{90}\) was abbreviated by thiopentone 50 and 100 \( \mu \)mol litre\(^{-1}\); values were almost the same as those of the control (fig.1B, table 1).

**EFFECTS OF PROPOFOL AND THIOPENTONE ON MEMBRANE CURRENTS**

Figure 2 shows the changes in current-voltage relationships (\( a \)) and current traces (\( b \)) induced by the two agents. At concentrations of 1 \( \mu \)mol litre\(^{-1}\) or higher, propofol had almost no observable effects on the late current at potentials negative to −30 mV, which reversed its polarity at about −90 mV. Propofol decreased the late current at voltages positive to −30 mV. These results suggest that propofol reduced \( I_{\text{Ca,L}} \) but had no detectable effect on \( I_{\text{K,Ca,L}} \). In addition, propofol depressed the initial peak inward current on depolarization from −30 mV without change in its reversal potential.
At concentrations of 10 μmol litre⁻¹ or higher, thiopentone suppressed the late current at all voltages tested, suggesting that thiopentone depresses both I_K1 and I_K. Thiopentone decreased the late current at test pulses to −110 mV to 89.2 (1.9)% (10 μmol litre⁻¹; ns vs control as 100%), 82.7 (5.5)% (50 μmol
EFFECTS OF PROPOFOL AND THIOPENTONE ON \textit{I}_{\text{Ca.L}}

Propofol and thiopentone decreased the initial peak inward current on depolarization (fig. 2), suggesting suppression of \textit{I}_{\text{Ca.L}}. Therefore, we examined the effects of these agents on isolated \textit{I}_{\text{Ca.L}} (fig. 3). The amplitude of \textit{I}_{\text{Ca.L}} was decreased to 88.4 (1.8) % by propofol 1 \text{µmol litre}^{-1} (n=5; P<0.01 \text{vs control as } 100\%) and 75.0 (5.3) % at propofol 10 \text{µmol litre}^{-1} (n=5; P<0.01) at a frequency of 0.2 Hz. The currents recovered to 87.8 (2.8) % (P<0.05 \text{vs } 10 \text{µmol litre}^{-1}) after washout of propofol 10 \text{µmol litre}^{-1}. Administration of thiopentone 10 and 100 \text{µmol litre}^{-1} decreased \textit{I}_{\text{Ca.L}} to 88.5 (1.2) % (n=5; P<0.01 \text{vs control as } 100\%) and 82.8 (1.6) % (n=5; P<0.01), respectively. After washout of thiopentone 100 \text{µmol litre}^{-1}, the current recovered to 89.7 (2.4) % of control (P<0.01 \text{vs } 100 \text{µmol litre}^{-1}) (fig.3A).

Use-dependent block of \textit{I}_{\text{Ca.L}} by propofol and thiopentone was examined by applying 11 depolarizing pulses at 0.2 Hz or 50 pulses at 1 Hz (fig.3B). In the absence of drug (control), the currents at the 11th (0.2 Hz) or 50th (1 Hz) pulse were decreased by 6% or less of the first pulse of \textit{I}_{\text{Ca.L}}. Thus steady-state \textit{I}_{\text{Ca.L}} was 94% or the higher of the current as the first pulse. In the presence of propofol 1 \text{µmol litre}^{-1}, \textit{I}_{\text{Ca.L}} at the 11th pulse at 0.2 Hz was decreased to 91.8 (1.0) % of the current at the first pulse (P<0.01; n=4). The current at the 50th pulse at 1 Hz was decreased to 60.0 (4.9) % (P<0.05; n=4). In the presence of thiopentone 10 \text{µmol litre}^{-1}, \textit{I}_{\text{Ca.L}} at the 11th pulse at 0.2 Hz was decreased to 90.0 (2.0) % of the first pulse (P<0.05; n=4) and the current at the 50th at 1 Hz was 68.0 (5.3) % of the first pulse (P<0.05; n=4). Therefore, both drugs produced use-dependent block of \textit{I}_{\text{Ca.L}}.

EFFECTS OF PROPOFOL AND THIOPENTONE ON THE KINETICS OF \textit{I}_{\text{Ca.L}}

The inactivation time course of \textit{I}_{\text{Ca.L}} was analysed using the current evoked by depolarization to +10 mV at 0.2 Hz with the voltage procedure similar to figure 3B. The time course of the current was well fit-
to the sum of two exponentials with the fast \( (\tau_{\text{fast}}; 9.0 (1.8) \text{ ms}) \) and slow \( (\tau_{\text{slow}}; 64.0 (4.8) \text{ ms}) \) time constants in the control \( (n=7) \). Administration of propofol 1 and \( 10 \mu\text{mol litre}^{-1} \) increased \( \tau_{\text{fast}} \) to \( 10.1 (1.8) \text{ ms} \) \((P<0.05)\) and \( 12.6 (2.0) \text{ ms} \) \((P<0.01)\), respectively, with no change in \( \tau_{\text{slow}} \). In contrast, thiopentone 10 and \( 100 \mu\text{mol litre}^{-1} \) decreased \( \tau_{\text{slow}} \) from \( 66.4 (3.6) \text{ ms} \) in the control \( (n=12) \) to \( 57.1 (3.4) \text{ ms} \) \((P<0.01)\) and \( 49.0 (3.6) \text{ ms} \) \((P<0.01)\), respectively, without affecting \( \tau_{\text{fast}} \). Washout of thiopentone reversed \( \tau_{\text{slow}} \) to \( 60.6 (5.1) \text{ ms} \) \((P<0.01 vs \text{thiopentone } 100 \mu\text{mol litre}^{-1})\).

Effects of the drugs on steady-state inactivation and activation processes of \( I_{\text{Ca,L}} \) were evaluated. Steady-state inactivation curves \( (f_{\text{i}}) \) were drawn by least-square fitting to the empirical Boltzmann equation to the mean values from each group of data:

\[
f_{\text{i}} = 1/(1+\exp((V_{\text{m}}-V_{\text{h}})/s))
\]

where \( V_{\text{m}} = \) pre-pulse potential, \( V_{\text{h}} = \) membrane voltage at which \( I_{\text{Ca,L}} \) is half maximal, and \( s = \) slope factor. Under control conditions, \( V_{\text{h}} \) and \( s \) were \( -19.4 (0.2) \text{ mV} \) and \( 5.7 (0.2) \text{ mV} \), respectively \((n=5)\). These values did not change significantly during administrations of drugs (fig. 4A).

Steady-state activation curves \( (d_{\text{a}}) \) were drawn by fitting the Boltzmann equation to data points of the mean values:

\[
d_{\text{a}} = 1-1/(1+\exp((V_{\text{m}}-V_{\text{h}})/s))
\]

where \( V_{\text{m}} = \) membrane voltage, \( V_{\text{h}} = \) voltage, where the current amplitude is half maximal, and \( s = \) slope factor. Control values of \( V_{\text{h}} \) and \( s \) were \( -8.2 (0.4) \text{ mV} \) and \( 8.9 (0.4) \text{ mV} \), respectively \((n=5)\). Neither anaesthetic had any effect on these variables (fig. 4B).

We investigated the effects of propofol and thiopentone on recovery from inactivation of \( I_{\text{Ca,L}} \) using a double pulse design. Under control conditions the recovery process was well fitted to a single exponential with a time constant of \( 84.6 (16.4) \text{ ms} \). In the presence of propofol \( 1 \mu\text{mol litre}^{-1} \), the time constant increased to \( 142.4 (22.9) \text{ ms} \) \((P<0.05; n=7)\). Similarly, thiopentone \( 10 \mu\text{mol litre}^{-1} \) increased it from a control value of \( 77.4 (22.6) \text{ ms} \) to \( 106.1 (24.3) \text{ ms} \) \((P<0.05; n=5)\) (fig. 4C).

**Effects of Propofol and Thiopentone on the Delayed Rectifier K⁺ Current**

The drug effects on \( I_{\text{K}} \) were estimated by measuring
the tail current of $I_K$ ($I_{K,tail}$) on repolarization to $-30$ mV. Steady-state activation of $I_{Ca,L}$ and the drug effects are shown in figure 5 (inset). During administration of propofol 1 μmol litre$^{-1}$, $I_{K,tail}$ did not change from control, but propofol 10 μmol litre$^{-1}$ significantly suppressed the current. $I_{K,tail}$ at test pulses to $+80$ mV was decreased to 78.4 (4.0)% of control ($P<0.01; n=6$) in the presence of propofol 10 μmol litre$^{-1}$. Administration of thiopentone 10 and 100 μmol litre$^{-1}$ significantly decreased $I_{K,tail}$ at test pulses to $+80$ mV to 78.3 (6.9)% ($P<0.05$ vs control as 100 %; $n=4$) and 27.0 (4.2)% ($P<0.01; n=4$), respectively. After drug washout, $I_{K,tail}$ recovered to 91.7 (3.2)% ($P<0.05$ vs propofol 50 μmol litre$^{-1}$; $n=6$) and 84.6 (4.4)% ($P<0.05$ vs thiopentone 100 μmol litre$^{-1}$; $n=4$), respectively. The normalized activation curves of $I_{Ca,L}$ were fitted to the Boltzmann equation (fig. 5). $V_h$ was 20.3 (0.2) mV and $s$ was 15.6 (0.2) mV in the control ($n=11$). These values remained almost unchanged during administration of drug ($n=11$ for propofol and $n=5$ for thiopentone), except for a slight negative shift by thiopentone 100 μmol litre$^{-1}$.

**Discussion**

We have demonstrated that at concentrations of 0.5 μmol litre$^{-1}$ or higher, propofol shortened APD without affecting RMP, and thiopentone had a biphasic effect on APD. Thiopentone 10 μmol litre$^{-1}$ pro-
longed APD while concentrations higher than 50 μmol litre⁻¹ decreased RMP and abbreviated the prolonged APD to the control level. Propofol at concentration greater than 1 μmol litre⁻¹ suppressed mainly \( I_{Ca,L} \) with minimal changes in \( I_K \) without affecting \( I_{K1} \). In contrast, thiopentone 10 μmol litre⁻¹ predominantly suppressed \( I_K \) with mild suppression of \( I_{Ca,L} \) and minimal effects on \( I_{K1} \). At concentrations of 50 μmol litre⁻¹ or higher, thiopentone profoundly depressed \( I_{Ca,L} \), \( I_K \), and \( I_{K1} \). These results at high concentrations are generally in agreement with previous reports [10, 12].

Because the main currents underlying the plateau and repolarization phases of action potentials in guineapig ventricular myocytes are \( I_{Ca,L} \), \( I_K \), and \( I_{K1} \), changes in action potentials can be ascribed mainly to the different potencies of the drugs against these membrane currents. Although at high concentrations propofol suppressed both \( I_{Ca,L} \) and \( I_K \) [12], the main target channel of the drug at lower concentrations has not been clarified. Anesthetic EC₅₀ concentrations of propofol and thiopentone required for lack of response to a painful stimulus are 0.4 μmol litre⁻¹ and 25 μmol litre⁻¹ in free aqueous phases, respectively [6]. The low concentrations used in the our experiments (propofol 1 μmol litre⁻¹ and thiopentone 10 μmol litre⁻¹) correspond approximately to the therapeutic concentrations of the two agents. Our data clearly demonstrated that propofol, at clinically relevant concentrations, predominantly suppressed \( I_{Ca,L} \) with minimal or no action on \( I_{K} \) while thiopentone, at clinically relevant concentrations, was found to exert a preferential action on \( I_K \) rather than \( I_{Ca,L} \) and \( I_{K1} \).

Barbiturates such as pentobarbitone and thiopentone most likely affect similar parts of the GABAₐ receptor, therefore, a confounding effect of a previous pentobarbitone anaesthetic may affect the in vitro results of subsequent thiopentone exposure. To the best of our knowledge, however, there has been no report describing the existence of GABAₐ receptors in heart tissue. In addition, the effects of pentobarbitone on the cell membrane are not expected to affect the outcome of this study in view of the extensive washing and equilibration periods, including the cell isolation procedures, before the experiments were performed.

The most distinct difference in the membrane actions of the two i.v. anaesthetics was suppression of \( K^+ \) currents. Propofol exerted minimal suppression of \( I_K \) at low concentrations (1 μmol litre⁻¹) when \( I_{Ca,L} \) was depressed, but had no effect on \( I_{K1} \) even at high concentrations (50 μmol litre⁻¹). In contrast, thiopentone significantly suppressed \( I_K \) at low concentrations (10 μmol litre⁻¹) with a mild effect on \( I_{Ca,L} \) and at high concentrations exhibited strong suppression on \( I_K \) with moderate effects on \( I_{K1} \). Concentration-dependent depression of \( I_{K1} \) by thiopentone at concentrations greater than 10 μmol litre⁻¹ was also reported in frog atrial and guineapig ventricular myocytes [16]. These may contribute to the different effects of propofol and thiopentone on APD.

Recent studies have highlighted the existence of at least two components of \( I_K \); fast activating \( I_K \) (\( I_{Kf} \)) and slow activating \( I_K \) (\( I_{Ks} \)). Although we did not examine selective inhibition of the two components of \( I_K \), it is conceivable that propofol and thiopentone have a predominant blocking action on \( I_{K1} \) because of the pulse design (1000 ms depolarization) used and dominant \( I_{Ca,L} \) in guineapig ventricular myocytes [23]. Suppression of \( I_{K1} \) induces depolarization of RMP and prolongation of APD. While the latter action may exert prevention of re-entrant arrhythmias because of the long refractory period, similar to class III antiarrhythmic agents, the former induces serious effects on arrhythmogenesis. A decrease in RMP inactivates the fast sodium current (\( I_{Na,fast} \)) to cause slowing of cardiac impulses. This may facilitate development of re-entry and produce abnormal automaticity. Additionally, depolarization of RMP may account for the negative inotropic effect because...
it promotes inactivation of \( I_{\text{Ca,L}} \) under certain conditions. Therefore, thiopentone may be more responsible for the proarrhythmic and negative inotropic actions in ischaemic heart\(^2\).

Three i.v. anaesthetics, ketamine 100 µmol litre\(^{-1}\), methohexitone 100 µmol litre\(^{-1}\) and propofol 28 µmol litre\(^{-1}\), have been shown to have different actions on \( I_{K1} \) and \( I_{K2} \). Ketamine, thiopentone, etomidate, propofol and midazolam at relatively high concentrations were shown to depress the transient outward \( K^+ \) current (\( I_{K1} \)) in canine ventricular myocytes\(^3,5,22\). Our study demonstrated that propofol and thiopentone had different selectivity of effects on two voltage-dependent \( K^+ \) currents. This evidence suggest that i.v. anaesthetics have specific site(s) of actions on the cardiac cell membrane, such as individual ion channels\(^24\) or the lipid environment of the channel, or both, to exert their effects\(^3\), rather than a generalized membrane effect.

Both anaesthetics not only suppressed \( I_{\text{Ca,L}} \) but also affected current kinetics in a slightly different manner. Although the values of \( I_{\text{Ca,L}} \) measured included components of “rundown”, propofol and thiopentone at clinically relevant concentrations suppressed the peak amplitudes of \( I_{\text{Ca,L}} \). These results indicate that propofol and thiopentone at anaesthetizing concentrations depress cardiac contractility, at least partly as a result of abbreviation of \( \text{Ca}^{2+} \) influx through the sarclemma. Compared with an equipotent dose of propofol, the decrease in the amount of \( \text{Ca}^{2+} \) influx produced by thiopentone may be smaller than that produced by propofol in each action potential because of prolonged APD in the former. This observation is compatible with reports that the cardiodepressant effects of propofol are more pronounced and more prolonged than those of equipotent doses of thiopentone when given as a single bolus\(^25\). This explanation, however, conflicts with most of the previous studies that showed that propofol had little or no effect on cardiac contractility\(^26,27\), or was less potent than thiopentone\(^4,6\).

There may be additional factors involved in the modification of \( \text{Ca}^{2+} \) influx and cardiac contractility by these drugs. During excitation–contraction coupling, \( \text{Ca}^{2+} \) release from the sarcoplasmic reticulum and trans-sarcosomal \( \text{Ca}^{2+} \) entry are two main sources for the \( \text{Ca}^{2+} \) supply, but the contribution of each component may differ in various species (higher dependence on sarcoplasmic reticulum \( \text{Ca}^{2+} \)-release in the order of rat > dog, cat > human > guinea pig, rabbit > frog ventricle)\(^8,26\). Thiopentone\(^11\) but not propofol\(^15\) has been reported to impair sarcoplasmic reticulum function. In addition, propofol was shown to reduce the second inward current during action potential plateau or depolarizing pulses at positive voltages which was carried presumably by the \( \text{Na}^+–\text{Ca}^{2+} \) exchange mechanism\(^8\). Reduction of this inward current could also be partly attributed to the negative inotropic effect of propofol.

In summary, we found that propofol suppressed mainly \( I_{\text{Ca,L}} \), with minimal depression of \( I_K \) and little or no change in \( I_{K2} \) while thiopentone, at clinically relevant concentrations, demonstrated predominant block of \( I_K \) rather than \( I_{\text{Ca,L}} \) and \( I_{K2} \). The distinct suppressive effects on cardiac function of propofol and thiopentone may result, at least in part, from the different actions on membrane currents forming the repolarization phase of action potentials.

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References


