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Effect of Thiopental on Ca^{2+} Release from Sarcoplasmic Reticulum in Intact Myocardium

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Background: **While thiopental is known to inhibit the myocardial transsarcolemmal influx of Ca^{2+}, the effect of thiopental on sarcoplasmic reticular Ca^{2+} release has not been characterized.**

Methods: **Isolated papillary muscles of rabbits were used. We measured postrest contractions to assess the Ca^{2+} release by sarcoplasmic reticulum in response to electrical stimulation. Contractures induced by rapid cooling were used as an index of Ca^{2+} content of sarcoplasmic reticulum. The effect of thiopental on the availability of extracellularly derived Ca^{2+} was evaluated from measurements of contractions at 0.1 Hz in the presence of 1 μM ryanodine.**

Results: **Thiopental sodium (10, 20, and 30 mg/l; 38, 76, and 113 μM) inhibited the postrest contraction but not the contracture induced by rapid cooling. In the presence ryanodine, thiopental inhibited the postrest contraction elicited after 10 s of rest after 2-Hz stimulation much less than the steady-state contraction at 0.1 Hz (beat interval 10 s). Thiopental inhibited the postrest contraction (no ryanodine present) more strongly than did Ni^{2+} (an inhibitor of the transsarcolemmal Ca^{2+} influx) when the contraction at 0.1 Hz in the presence of ryanodine was inhibited to the same extent.**

Conclusions: **These results suggest that thiopental decreases sarcoplasmic reticulum Ca^{2+} release induced by electrical stimulation and inhibits the ryanodine-induced efflux of sarcoplasmic reticulum Ca^{2+}. (Key words: Anesthetics, intravenous: thiopental. Heart, contractility: calcium release; muscle length; postrest contraction; rabbit papillary muscle; rapid cooling-induced contracture; ryanodine; sarcoplasmic reticulum. Ions: calcium; nickel.)**

THIOPENTAL is known to inhibit myocardial transsarcolemmal Ca^{2+} influx.[1–3] Whether this effect alone can account for the negative inotropic effect of this anesthetic is not known. Other possible actions of the anesthetic include the inhibition of Ca^{2+} release from the sarcoplasmic reticulum (SR).

In the current study, we evaluated the effect of thiopental on the releasability and the content of SR Ca^{2+} in intact myocardium. We measured postrest contractions and the contractures induced by rapid cooling (RCC) to assess the effects of thiopental on the releasability and the content of the SR Ca^{2+}. The postrest contraction is largely activated by Ca^{2+} released from the SR in response to electrical stimulation.[4] Thus, the postrest contraction reflects SR Ca^{2+} release triggered by the transsarcolemmal Ca^{2+} influx. The RCC is activated by Ca^{2+} released from the SR by a mechanism that does not involve membrane depolarization in the myocardium of guinea pig[5] and rabbit.[6] The force of RCC reflects SR Ca^{2+} content,[7] which may be different from the amount of SR Ca^{2+} released in response to electrical stimulation. We used the force of contraction at 0.1 Hz in the presence of 1 μM ryanodine (which inhibits SR function) as an indicator of the availability of extracellularly derived Ca^{2+}.

The current study demonstrates that thiopental most likely inhibits SR Ca^{2+} release triggered by the transsarcolemmal Ca^{2+} influx and that it inhibits the ryanodine-induced efflux of SR Ca^{2+}.

Materials and Methods

The procedure was approved by the Animal Care and Use Committee of the University of Wisconsin, Madison. Right ventricular papillary muscles of rabbits were used. The heart was excised from rabbits (about 2 kg) anesthetized by the intravenous injection of pentobarbital (about 50 mg/kg). One end of the muscle was fixed at the base of the tissue bath and the other end was connected to a force transducer (Gould Statham UC-2, Gould, Oxnard, CA) mounted on a micrometer. Isometric force of contraction was recorded on a Gilson polygraph (Gilson Medical Electronics, Middleton,

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WI). A tissue bath (45 ml) maintained at 30°C was used except when the RCC was measured. For the measurements of the RCC, a flow-though chamber (1.5 ml) was used, and the medium (100 ml) maintained at 30°C was recirculated through the chamber at a rate of 50 ml/min. To induce the RCC, the medium was switched to the medium cooled to 3°C. The temperature was monitored with a Tele-thermometer (Yellow Springs Instrument, Yellow Springs, OH). The rate of cooling had a half-time ($t_{½}$) of about 2 s. The control medium used was a Krebs-Henseleit bicarbonate (*p*H 7.4) of the following millimolar composition: NaCl 115, KCl 5.9, $MgCl_2$ 1.2, NaH_2PO_4 1.2, Na_2SO_4 1.2, $NaHCO_3$ 25, glucose 5.6, $CaCl_2$ 2.5, and ethylenediaminetetraacetic acid 0.05. The medium was equilibrated with a gas mixture of 95% O_2 and 5% CO_2.

The muscle was stimulated with a pair of field electrodes (S48, Grass Instruments, Quincy, MA). Stimulation voltages 1.5 × threshold were used. After a stabilization period of 2–3 h, the minimal muscle length at which the developed force is maximal (L_{max}) was determined at a stimulation frequency of 1 Hz; except when the effects of muscle length were studied, force measurements were carried out at L_{max}. The diameter and the length of the muscles were determined with an ocular micrometer in a microscope. The muscles (n = 29) used in this study were 0.9 ± 0.2 mm (mean ± SD) in diameter and 4.8 ± 1.0 mm in length. The force of contraction was expressed as millinewtons per square millimeter of the cross-sectional area, calculated by assuming cylindrical shape of the muscle. The muscles were stable for a subsequent 2–3 h, during which time force measurements were carried out.

For the measurements of the postrest contraction and the RCC, the muscles were stimulated by repeated trains (train duration about 10 s) of stimuli at 2 Hz with 2 s of rest between the trains. Unless noted otherwise, the postrest contraction was the first beat of the train after 2 s of rest after steady-state contraction at 2 Hz. The RCC was elicited by rapidly cooling the muscle from 30°C to 3°C after the end of the steady-state train of stimulation at 2 Hz. The effect of thiopental (n = 6) on the steady-state contraction at 2 Hz, the postrest contraction elicited after 2 s of rest, and on the RCC were measured. Force measurements were carried out 20 min after the addition of thiopental. Muscle length is known to alter the Ca^{2+} sensitivity of the myofibril and the developed force.[8,9] We altered muscle length to determine whether this affects the force of the RCC (n = 9). The effects of shortening the muscle length to 95% and 90% of L_{max} were measured within about 5 min after changing the muscle length.

To measure the force of contraction in the presence of ryanodine, 1 μM of ryanodine (Progressive Agri-Systems, Wind Gap, PA) was added while the muscle was stimulated at 0.1 Hz. Twenty minutes after the addition of ryanodine, the muscle was stimulated by repeated trains of stimuli at 2 Hz (train duration about 10 s, rest interval 2 s) to ensure the maximal inhibition of the postrest contraction. The effects of thiopental (n = 6) on the postrest contraction elicited after 2, 5, 10 s of rest and those on the steady-state contraction at 0.1 Hz were measured in the presence of ryanodine. Because of the marked difference in the effects of thiopental on the postrest contraction and those on the steady-state contraction at 0.1 Hz in the presence of ryanodine (see Results), we report the corresponding data obtained with Ni^{2+} for comparison (n = 8).

Thiopental sodium (Abbott Laboratories, North Chicago, IL) concentrations of 10, 20, and 30 mg/l (38, 76, and 113 μM) were used. All the data are expressed as mean ± SEM. Data were statistically analyzed by paired or unpaired *t* test as appropriate for comparison of two mean values and by repeated-measures analysis of variance and Dunnett's *t* test for comparison of more than two mean values; $P < 0.05$ was considered significant.

Results

Figure 1 shows that thiopental inhibited the steady-state contraction at 2 Hz and the postrest contraction but not the RCC. The results obtained with different concentrations of thiopental are shown in figure 2. In contrast to the selective effect of thiopental on these contractile activities, shortening the muscle length decreased the force of the RCC as well as the force of the steady-state contraction and the postrest contraction (fig. 3).

In a previous study, we found that Ni^{2+} (an inhibitor of the transsarcolemmal influx of Ca^{2+}) strongly inhibited the postrest contraction in the presence of ryanodine.[10] Thus, in the presence of ryanodine even the postrest contraction appeared to be activated by the extracellularly derived Ca^{2+}. We found that thiopental also inhibited the force of the postrest contraction in the presence of ryanodine. However, thiopental inhibited the subsequent contractions at

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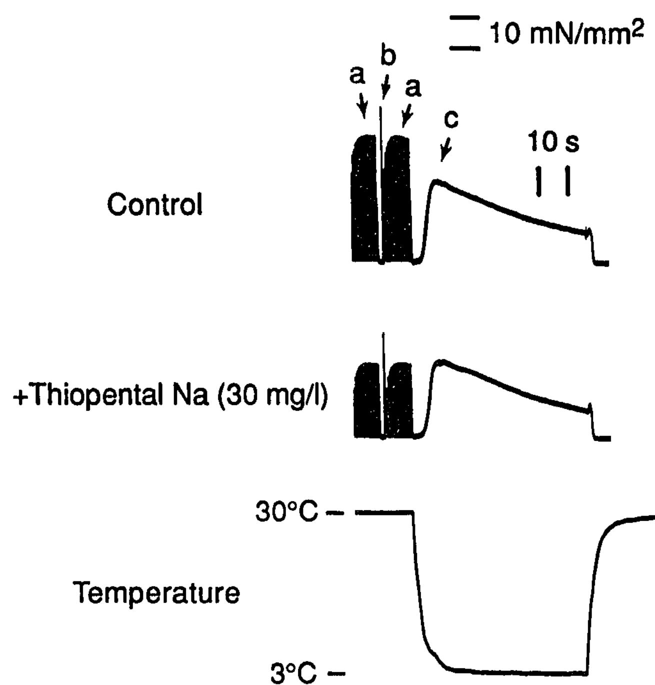

Fig. 1. Effect of thiopental on the force of steady-state contraction at 2 Hz, the postrest contraction, and the contracture induced by rapid cooling (RCC). (*a*) Steady-state contraction at 2 Hz. (*b*) Contraction elicited after 2 s of rest. (*c*) RCC.

2 Hz more strongly, resulting in a pattern of contractions similar to that found under the control condition (fig. 4). Thiopental also reversed the ryanodine-induced elevation in the resting tension (fig. 4). With six muscles, the extent of elevation in diastolic tension (expressed as percentage of peak force) was 6% ± 2% in the absence of ryanodine and 25% ± 4% in the presence of ryanodine but no thiopental. The effect of ryanodine was statistically significant ($P < 0.01$). The extent of elevation in diastolic tension in the presence of ryanodine decreased in the presence of 10, 20, and 30 mg/l thiopental sodium to 24% ± 6%, 14% ± 4%, and 11% ± 4% respectively. The values at 20 and 30 mg/l thiopental sodium were not significantly different from that obtained in the absence of ryanodine.

The interpretation of the results obtained with the steady-state contraction at 2 Hz and the postrest contraction is complicated by the difference in the beat interval of the two types of contraction. For this reason, we compared the effects of thiopental on the postrest contraction elicited after 10 s of rest after 2-Hz stimulation and the steady-state contraction at 0.1 Hz (beat interval 10 s), both measured in the presence of 1 μM ryanodine. Figure 5 shows that thiopental inhibited the postrest contraction much less than the steady-state contraction at 0.1 Hz. Similar results were obtained when the postrest contraction elicited after 2 or 5 s was compared with the contraction at 0.1 Hz (Data not shown). In the absence of ryanodine, inhibitors of the transsarcolemmal Ca^{2+} influx, such as Ni^{2+} and Co^{2+}, are known to have much less effect on the postrest contraction than on the steady-state contraction.[11] In the presence of ryanodine, however, the difference in the effects of Ni^{2+} on the two types of contraction was much smaller compared with that found with thiopental (compare figs. 5 and 6). The effect of Ni^{2+} on the force of the postrest contraction elicited after 2 s of rest in the presence of ryanodine had been reported previously.[10]

Thiopental decreased the force of the postrest contraction (measured in the absence of ryanodine) more strongly than did Ni^{2+} when the force of contraction at 0.1 Hz in the presence of ryanodine was decreased to the same extent (fig. 7). The results with Ni^{2+} were similar to those of the previous study[10] in which the postrest contraction in the presence of ryanodine rather than the contraction at 0.1 Hz in the presence of ryanodine was used.

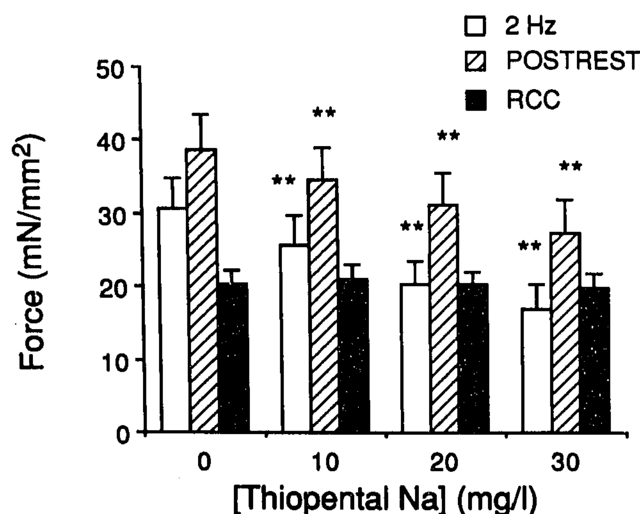

Fig. 2. Effect of different concentrations of thiopental on the force of steady-state contraction at 2 Hz, postrest contraction, and RCC. **$P < 0.01$ compared with control.

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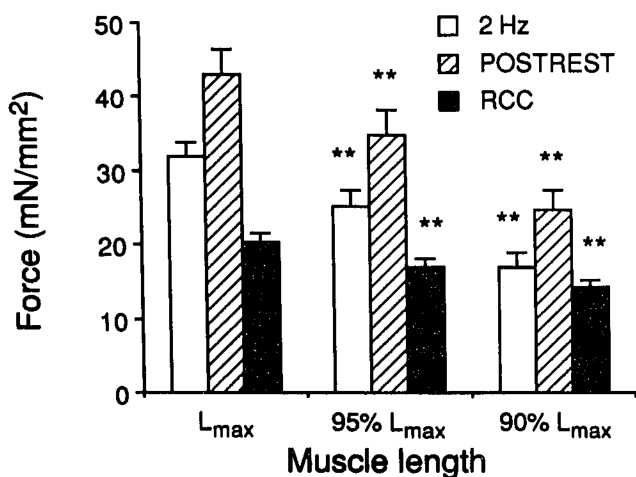

Fig. 3. Effect of muscle length on the force of steady-state contraction at 2 Hz, postrest contraction, and RCC. $^{**}P < 0.01$ compared with the corresponding value at L_{max}.

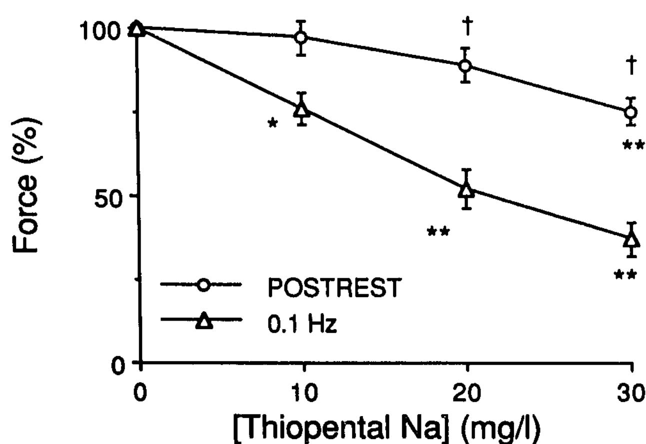

Fig. 5. Effect of thiopental on the force of postrest contraction and steady-state contraction at 0.1 Hz in the presence of ryanodine. Force expressed as a percentage of the corresponding value in the absence of thiopental is shown (n = 6). Force of contraction in the absence of thiopental was 11.4 ± 1.7 mN/mm² for postrest contraction and 9.4 ± 1.5 mN/mm² for contraction at 0.1 Hz. $^{*}P < 0.05$ and $^{**}P < 0.01$, compared with corresponding value in the absence of thiopental; $^{\dagger}P < 0.01$ compared with corresponding value for steady state at 0.1 Hz.

Discussion

Thiopental inhibition of the steady-state contraction at 2 Hz and the postrest contraction with no effect on the RCC suggests that the anesthetic inhibits SR Ca^{2+} release without decreasing SR Ca^{2+} content. Blanck and Stevenson[12] have shown that thiopental does not alter Ca^{2+} uptake in isolated SR vesicles.

The decrease in the force of the RCC observed upon shortening of the muscle length indicated that both the RCC and the contractions elicited by electrical stimulation at 30°C responded similarly to this maneuver

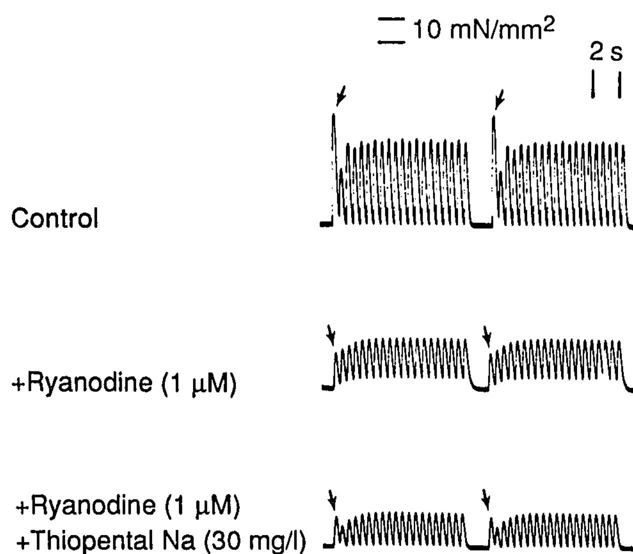

Fig. 4. Thiopental modification of the selective effect of ryanodine on the postrest contraction relative to the steady-state contraction at 2 Hz. Arrows = contraction elicited after 2 s of rest.

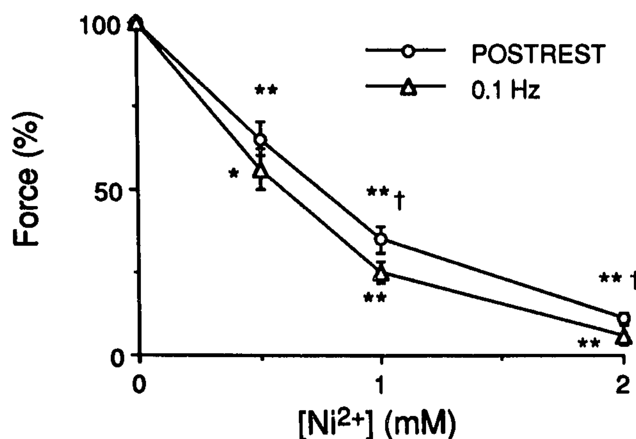

Fig. 6. Effects of Ni^{2+} on the force of the postrest contraction and the steady-state contraction at 0.1 Hz in the presence of ryanodine. Force expressed as a percentage of the corresponding value in the absence of Ni^{2+} is shown (n = 8). Force of contraction in the absence of Ni^{2+} was 6.0 ± 1.1 mN/mm² for postrest contraction and 4.9 ± 1.1 mN/mm² for contraction at 0.1 Hz. $^{*}P < 0.05$ and $^{**}P < 0.01$ compared with corresponding value in the absence of Ni^{2+}; $^{\dagger}P < 0.01$ compared with corresponding value for steady state at 0.1 Hz.

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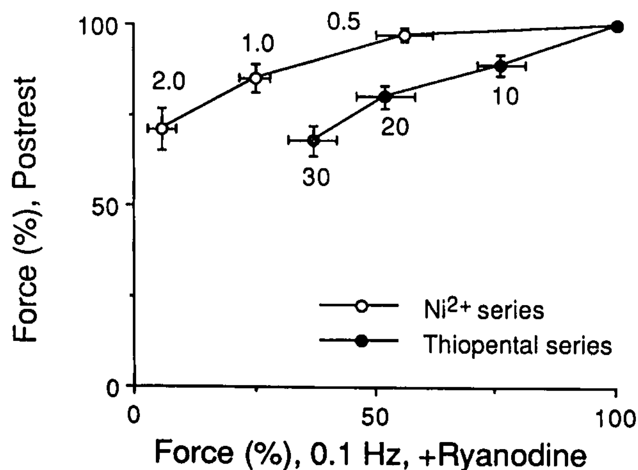

Fig. 7. Comparison of the effect of thiopental and Ni^{2+} on the relation between the force of the contraction elicited after 2 s of rest after 2-Hz stimulation (measured in the absence of ryanodine) and the force of contraction at 0.1 Hz measured in the presence of ryanodine. Force expressed as a percentage of the corresponding value obtained in the absence of Ni^{2+} (Ni^{2+} series) or in the absence of thiopental (thiopental series) is shown. In the Ni^{2+} series, data for the postrest contraction in the absence of ryanodine were obtained from the same eight muscles used to obtain data for contraction at 0.1 Hz in the presence of ryanodine (fig. 6). Numbers indicate the millimolar concentrations of Ni^{2+}. In the thiopental series, data for the postrest contraction in the absence of ryanodine were obtained from those in figure 2 (n = 6), and data for the contraction at 0.1 Hz in the presence of ryanodine were those of figure 5 (n = 6). The two groups of muscles did not differ significantly with respect to the force of steady-state contraction at 0.1 Hz and contraction elicited after 2 s of rest under control conditions (no ryanodine and no thiopental). Numbers indicate the concentration (milligrams per liter) of thiopental sodium. For contraction at 0.1 Hz in the presence of ryanodine, there was no statistically significant difference between the extent of inhibition by 20 mg/l thiopental sodium and that by 0.5 mM Ni^{2+}. The postrest contraction (in the absence of ryanodine) was significantly decreased in the presence of 20 mg/l thiopental sodium but not in the presence of 0.5 mM Ni^{2+}.

which is known to decrease the Ca^{2+} sensitivity of the myofibril. Although we did not measure the effect of thiopental on the Ca^{2+} sensitivity of the myofibril, we would expect a decrease in the force of the RCC if thiopental markedly decreased the Ca^{2+} sensitivity of the myofibril. In this regard, Kudsioglu *et al.*[13] recently reported that thiopental may *increase* the Ca^{2+} sensitivity of the myofibril in intact ferret papillary muscles.

The observed difference between the effect of thiopental on the postrest contraction and that on the contraction at 0.1 Hz, both in the presence of ryanodine, suggests that this anesthetic inhibits the ryanodine-induced efflux of SR Ca^{2+} that has been accumulated in the SR during high frequency stimulation. This effect of thiopental does not seem to be a secondary consequence of the inhibition of the transsarcolemmal Ca^{2+} influx, as Ni^{2+} did not have a markedly different effect on these two types of contraction. We measured the postrest contraction elicited after 10 s of rest, because of the possibility that the ryanodine-induced depletion of SR Ca^{2+} is incomplete after 2 s but is essentially complete after 10 s of rest.[14] Furthermore, the preceding interval (10 s) is same for both types of contraction. The only difference between the postrest contraction elicited after 10 s of rest and the steady state contraction at 0.1 Hz is that the muscle was stimulated at 2 Hz (a condition for SR Ca^{2+} accumulation) before the rest in the former but not in the latter. With the contraction at 0.1 Hz in the presence of ryanodine, there should be very little if any SR Ca^{2+} accumulation, as the Ca^{2+} influx per unit time is expected to be low and the diastolic interval is long enough for effective depletion of SR Ca^{2+}. Comparison of the contractions with the same interval (10 s) from the preceding beat ensures that the extent of the time-dependent change in the availability of SR Ca^{2+} and the use-dependent block (if any) of SR Ca^{2+} release channel are likely to be similar.

When the muscle is stimulated in the presence of ryanodine, the SR still accumulates Ca^{2+} but the accumulated Ca^{2+} is rapidly lost,[7] as ryanodine binds to the open state of the SR Ca^{2+} release channel and locks it in a low conductance open state.[15] In the presence of ryanodine, stimulation of the muscle after a short interval as occurs in paired pulse stimulation results in incomplete relaxation of the first contraction and enhanced (summationlike) force of the second contraction.[16] In the extreme situation, the muscle does not relax as long as the muscle is stimulated at a high frequency.[17] In the current study a similar situation occurred after resumption of 2 Hz stimulation after 2 s of rest (fig. 4). Uptake of Ca^{2+} by the SR followed by rapid efflux in the presence of ryanodine may be involved in these phenomena (at ryanodine concentrations lower than that which *inhibits*[18] SR Ca^{2+} release). If so, the thiopental reversal of the ryanodine-induced elevation in the diastolic tension may also reflect thiopental reversal of the effect of ryanodine to enhance SR Ca^{2+} efflux.

The results of figure 7 suggest that, compared with Ni^{2+}, thiopental more strongly inhibited the contraction that is activated by SR Ca^{2+} when the availability of the extracellularly derived Ca^{2+} was decreased to the same extent. In view of the possible inhibitory effect of thio-

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pental on the ryanodine-induced Ca^{2+} efflux (See above), we speculate that thiopental may directly inhibit SR Ca^{2+} release triggered by the transsarcolemmal Ca^{2+} influx as occurs in the physiologic contraction. Further studies, such as simultaneous measurements of the intracellular Ca^{2+} transients and the Ca^{2+} current under the condition of voltage clamp, are required to test the validity of this speculation.

Although the contraction at 0.1 Hz in the presence of ryanodine is most likely activated by the extracellularly derived Ca^{2+} and not by the release of Ca^{2+} *previously stored* in the SR, the possibility that the extracellularly derived Ca^{2+} *transiently goes through* the SR cannot be excluded. Thus, inhibition of SR Ca^{2+} release by thiopental may contribute to the negative inotropic effect of thiopental on such a contraction. Park and Lynch[3] reported that thiopental strongly inhibits the late peak of biphasic contraction elicited in K^+-depolarized guinea pig papillary muscles in the presence of isoproterenol while having relatively small effect on the transsarcolemmal Ca^{2+} influx. Lynch[19] suggested that the late peak, which is not inhibited by ryanodine, may be activated by Ca^{2+} transiently sequestered by the SR. Because, as Wendt-Gallitelli[20] has shown, there is no SR Ca^{2+} accumulation 80 ms after stimulation of the muscle (just before the beginning of the late peak), the late peak is not likely to be activated by Ca^{2+} previously stored in and released from the SR.

Previously, we compared the effects of halothane with those of low extracellular Ca^{2+} on the postrest contraction in the absence and presence of ryanodine using rabbit atrial muscles, and concluded that halothane has a direct effect on the SR function.[21] Terrar and Victory[22] showed that the negative inotropic effect of halothane is much larger than that of verapamil when the Ca^{2+} current is inhibited to the same extent. Unlike thiopental, halothane decreases the force of the RCC.[23] Halothane also decreases the caffeine-induced force transient[24] and the caffeine-induced intracellular Ca^{2+} transient.[25–27] Halothane enhances rather than inhibits SR Ca^{2+} release,[28,29] consistent with the notion[25,26] that this anesthetic decreases the SR Ca^{2+} content. In addition, halothane most likely decreases the Ca^{2+} sensitivity of the myofibril in intact myocardium, as the anesthetic decreases the time to half-relaxation of isometric contraction.[30]

Because the transsarcolemmal Ca^{2+} influx triggers SR Ca^{2+} release,[31] any agent that inhibits the Ca^{2+} influx is expected to decrease SR Ca^{2+} release even if SR Ca^{2+} content and the sensitivity of SR Ca^{2+} release to the transsarcolemmal Ca^{2+} influx are unchanged. The results of the current study suggest that thiopental inhibits the ryanodine-induced efflux of SR Ca^{2+}. Further studies are required to test our proposal that thiopental directly inhibits SR Ca^{2+} release in physiologic contraction.

The current study was carried out using isolated rabbit papillary muscles in a Krebs-Henseleit medium at 30°C. Because about 85% of injected thiopental becomes protein-bound, only the lowest concentration (thiopental sodium 10 mg/l) used in this study is comparable to the free thiopental concentration attained immediately after bolus intravenous injection of 6 mg/kg of thiopental in humans.[32] Thus, additional studies are necessary to evaluate the applicability of the conclusions of the current study to the mechanism of action of thiopental in human myocardium during clinical anesthesia.

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