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Direct Effect of Halothane and Isoflurane on the Function of the Sarcoplasmic Reticulum in Intact Rabbit Atria

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The negative inotropic effect of halothane and isoflurane on potentiated-state contractions of isolated rabbit atria in a normal Ca^{2+} (2.5 mM) medium was compared with the force depression in low Ca^{2+} media without an anesthetic. When this comparison was made in the presence of 1 μM ryanodine so that the force of contraction was dependent only upon transsarcolemmal Ca^{2+} influx with no Ca^{2+} contribution from the sarcoplasmic reticulum (SR), the force of contraction was depressed equally by 0.6% halothane in a normal Ca^{2+} medium and by a 1.5 mM Ca^{2+} medium without the anesthetic. Similarly, 1.0% halothane or 1.5% isoflurane and a 1.0 mM Ca^{2+} medium were equally depressant as were 2.4% isoflurane and a 0.5 mM Ca^{2+} medium. In the absence of ryanodine, where the atrial contractile activity is largely dependent on Ca^{2+} released from the SR, 0.6% halothane in the normal Ca^{2+} medium depressed contractile force by 32%, whereas the force was depressed by only 16% in the 1.5 mM Ca^{2+} medium without the anesthetic. Similar results were obtained when the effects of 1.0% halothane and of 1.0 mM Ca^{2+} were compared. In contrast, the force of contraction measured in the absence of ryanodine was not at all inhibited by 1.5% isoflurane and minimally (11%) inhibited by 2.4% isoflurane. Consequently, the force depression by isoflurane was less than that found in the low Ca^{2+} media. These results suggest that 1) halothane causes a direct inhibitory effect on SR function in addition to causing a reduction in the availability of SR Ca^{2+} secondary to a reduction in transsarcolemmal Ca^{2+} influx, and 2) isoflurane does not have a direct inhibitory effect on SR function. (Key words: Anesthetics, volatile; halothane; isoflurane. Heart, atria: contractility. Sarcoplasmic reticulum.)

HALOTHANE[1,2] and isoflurane[2] inhibit the function of isolated cardiac sarcoplasmic reticulum (SR) and SR in skinned cardiac muscles.[3,4] However, it is not known to what extent these anesthetics directly inhibit the function of the SR in intact myocardium. To evaluate the direct effect of an anesthetic on the function of the SR in intact myocardium, it is necessary to subtract the force reduction due to a decrease in the availability of SR Ca^{2+} secondary to the anesthetic-induced reduction[5–8] in the transsarcolemmal Ca^{2+} influx. This is because even in a contraction predominantly activated by Ca^{2+} released from the SR, the availability of SR Ca^{2+} is influenced by the transsarcolemmal Ca^{2+} influx.[9] In the present study we have compared the effects of halothane and isoflurane in a normal Ca^{2+} (2.5 mM) medium to that in a low Ca^{2+} medium (no anesthetic) on the force of contraction of isolated rabbit atria. As the force of contraction in the presence of ryanodine is considered to be activated solely by transsarcolemmal Ca^{2+} influx,[10] we used depression of developed force by an anesthetic or by low extracellular Ca^{2+} measured in the presence of ryanodine as an index of the reduction in transsarcolemmal Ca^{2+} influx. Note that ryanodine has been previously used by Marban and Wier[11] as a tool to determine the contributions of transsarcolemmal Ca^{2+} influx and Ca^{2+} release from the SR to the Ca^{2+} transient and contraction of Purkinje fibers. These authors[11] have shown that the addition of 10 μM nitrendipine completely suppresses the aequorin luminescence and tension in fibers exposed to 1 μM ryanodine, indicating that the contraction in the presence of ryanodine is activated by extracellularly derived Ca^{2+}. Similarly, Marban *et al.*[12] have shown that tetanic contractions elicited by high-frequency stimulation of ryanodine-treated ferret papillary muscles are abolished by nitrendipine. Horackova[13] also used ryanodine to distinguish the source of activator Ca^{2+} in contractions of ventricular myocytes from the rat, dog, and rabbit in the absence and in the presence of various inotropic agents, attributing the ryanodine-resistant contractions to activation by Ca^{2+} influx across the sarcolemma. We determined, in the presence of ryanodine, the concentrations of anesthetic and of extracellular Ca^{2+} (decreased), which caused equal depression of force and, thus, equal depression of transsarcolemmal Ca^{2+} influx. If, in the absence of ryanodine, where SR function is intact, the depressant effects of these same concentrations of anesthetic and the decreased concentration of extracellular Ca^{2+} are again equal, it is likely that the anesthetic effect on the transsarcolemmal Ca^{2+} influx and the secondary reduction in the Ca^{2+} content of the SR account for the negative inotropic effect of the anesthetic. If, however, the depressant effect of an anesthetic in the absence of ryanodine exceeds that of low Ca^{2+}, it follows that the anesthetic has a direct depressant effect on the SR in addition to its effect to reduce transsarcolemmal Ca^{2+} influx. To ensure high sensitivity for

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the detection of anesthetic effects on the function of the SR, we have used rabbit atria, the contractile activity of which is known to be highly dependent on the Ca^{2+} released from the SR.[10,14] Furthermore, we employed (postrest) potentiated-state contractions, which depend largely on Ca^{2+} released from the SR.[15,16]

Materials and Methods

Following approval from the Animal Care and Use Committee of the University of Wisconsin, Madison, rabbits weighing about 2 kg were anesthetized by iv injection of pentobarbital (45 mg/kg). The hearts were excised and a strip of left atrial muscle was cut along the strands of trabeculae. The size (mean ± SD, n = 27) of the muscle strips was as follows: length, 9 ± 2 mm (at a resting tension of 10 milliNewtons (mN)), width, 2 ± 0.4, and wet weight, 14 ± 5 mg. The muscles were mounted vertically in a tissue bath (45 ml) maintained at 30° C, and the force of isometric contraction was measured with a Statham UC-2 force transducer and recorded on a Gilson polygraph. The force was expressed as milliNewtons or as percent of control. The control medium used was a Krebs-Henseleit bicarbonate (*p*H 7.4) of the following composition: NaCl, 115 mM; KCl, 5.9 mM; $CaCl_2$, 2.5 mM; $MgCl_2$, 1.2 mM; NaH_2PO_4, 1.2 mM; Na_2SO_4, 1.2 mM; $NaHCO_3$, 25 mM; glucose, 5.6 mM; and EDTA, 0.05 mM (to chelate contaminating heavy metal ions). The media were equilibrated with a gas mixture of 95% O_2 and 5% CO_2. Halothane or isoflurane was added to the gas mixture using Dräger vaporizers. Anesthetic concentrations in the gas phase as well as those dissolved in the medium were measured by gas chromatography.[17] The muscles were stimulated by a pair of silver–silver chloride field electrodes using an American Electronics Laboratory stimulator Model 104A. Stimuli of 4 ms duration and a voltage slightly above threshold were used. The resting tension was maintained at 10 mN, which stretched the muscles to L_{max}. Following isolation the muscles were stimulated at 0.1 Hz for a period of about 3 h for stabilization. Effects of an anesthetic and low Ca^{2+} on (postrest) potentiated-state contractions elicited 2 s after discontinuation of 3 Hz stimulation were measured. In practice, the muscles were stimulated by repeated trains at 2 Hz with each train duration of 10 s interrupted by 2 s of rest until a stable force of contraction was reached (after about 3 min). This was followed by stimulation at 3 Hz with each train duration of 5 s interrupted by 2 s of rest. Only the results obtained for the postrest contraction elicited after 3 Hz stimulation are reported because preliminary studies using stimulation frequencies of 2–4 Hz have shown that maximal potentiation was obtained after 3 Hz stimulation (results obtained using 4 Hz stimulation were similar to those obtained using 3 Hz stimulation). The repeated trains of relatively short duration were used to prevent muscle fatigue caused by prolonged stimulation at the high frequency. The first contraction after the rest period following a steady-state train was a (postrest) potentiated-state contraction. To study the effect of low Ca^{2+}, the force of contraction was first measured in the absence of ryanodine in media containing 0.5–2.5 mM Ca^{2+} in 0.5 mM increments, and then the measurements were repeated in the presence of 1 μM ryanodine. This concentration of ryanodine was chosen as preliminary experiments (n = 5) in which the muscles were exposed to 0.01–2 μM ryanodine showed that the force of contraction did not significantly decrease further when the ryanodine concentration was increased from 1 μM to 2 μM (Dunnett's *t* test, $P > 0.05$). Note that Meissner[18] has shown that 1 μM ryanodine maximally stimulates Ca^{2+} efflux from the SR but is not a high enough concentration to inhibit the efflux. To study the effects of halothane or isoflurane, the force was first measured in the absence of ryanodine with no anesthetic, then with increasing concentrations of an anesthetic. This sequence was then repeated (after first removing the anesthetic) in the presence of 1 μM ryanodine. After washout of the anesthetics, the force of contraction recovered to 96 ± 2% (mean ± SEM, n = 9) of the initial control value in the halothane series and 105 ± 3% (mean ± SEM, n = 8) in the isoflurane series. There was no statistically significant difference between the force after washout of either anesthetic and the corresponding initial control value (paired *t* test, $P > 0.05$). Anesthetic effects were studied in media containing 2.5 mM Ca^{2+}. It should be noted that in "Results," data obtained in the presence of ryanodine are described before those obtained in the absence of ryanodine, notwithstanding the order of experiments. A stabilization period of 10–30 min was allowed following each change in the composition of the medium before the measurements of force of contraction were made. The duration of the stabilization period varied as, for example, 10 min was sufficient for the force of contraction to reach a stable value after a change in Ca^{2+} concentration, whereas 30 min was required for washout of an anesthetic. The "control" medium in all experiments contained 2.5 mM Ca^{2+} and no anesthetic. Preliminary experiments showed that the force of contraction increased during the first 1–2 h and remained stable thereafter for 3–4 h. Experiments were carried out during the latter period. Data were statistically evaluated by repeated-measure analysis of variance (ANOVA) followed by Dunnett's *t* test for comparison of the mean force of contraction obtained in low Ca^{2+} or anesthetic containing media against corresponding control values (Ca^{2+} 2.5 mM, no anesthetic) and unpaired *t* test for comparisons of two mean values of force expressed as percent of control obtained from different series of experiments. $P < 0.05$ was considered significant.

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Results

Figure 1 shows the effect of ryanodine on the force of postrest contractions elicited after 2 s of rest following a train of stimulation at 3 Hz in a control medium containing 2.5 mM Ca^{2+} and no anesthetic. The force of contraction (mean ± SEM, n = 27, of all the muscles used in this study) in the control medium was 17.02 ± 0.82 mN in the absence of ryanodine and 1.88 ± 0.14 mN in the presence of 1 μM ryanodine. Thus, such contractions can be considered to be predominantly activated by Ca^{2+} released from the SR with a minor (about 11%) contribution of activation by the (ryanodine-resistant) transsarcolemmal Ca^{2+} influx.[10]

Figure 2 shows the negative inotropic effect of halothane or isoflurane in normal Ca^{2+} (2.5 mM) medium and the effect of low Ca^{2+} medium in the absence of the anesthetic, each determined in the presence of 1 μM ryanodine so that the force of contraction was activated by the transsarcolemmal Ca^{2+} influx. Developed force in the presence of halothane (0.6% and 1.0%), isoflurane (1.5% and 2.4%), or that in media containing 1.5 mM or lower concentrations of Ca^{2+} were significantly lower than the control value. There was no statistically significant difference (unpaired t test, $P > 0.05$) between the negative inotropic effect of 0.6% halothane in normal Ca^{2+} (2.5 mM) medium and the negative inotropic effect of low (1.5 mM) Ca^{2+} medium without the anesthetic. Similarly, there was no statistically significant difference between the negative inotropic effect of 1.0% halothane or 1.5% isoflurane

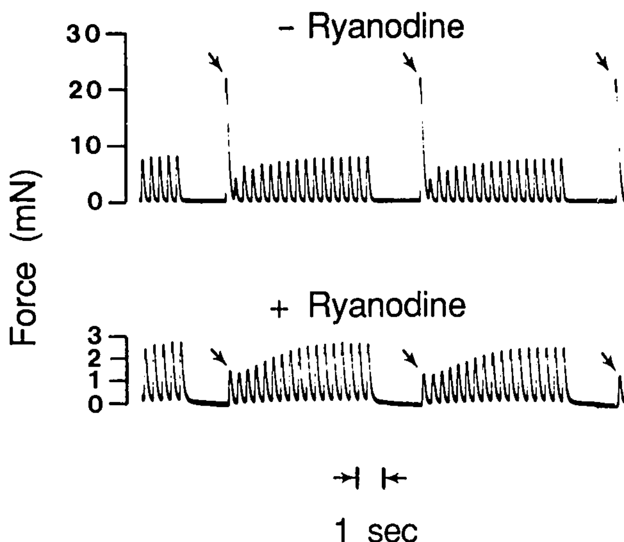

FIG. 1. Effect of ryanodine on postrest contraction. Arrows indicate postrest contractions elicited after 2 s of rest following 3 Hz stimulation. Such contractions are potentiated-state contractions in the absence of ryanodine. Note different scales for the force in the absence and in the presence of ryanodine.

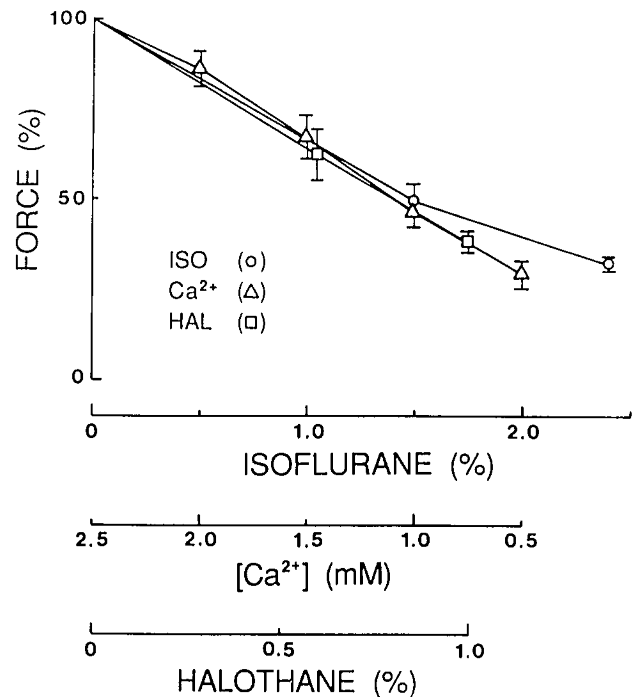

FIG. 2. Negative inotropic effect of an anesthetic and force depression in low Ca^{2+} medium measured in the presence of ryanodine. ISO (O), effect of isoflurane (1.5% and 2.4%) in normal Ca^{2+} (2.5 mM) medium. Mean ± SEM (n = 8) of the force expressed as percent of control (no anesthetic) is shown. Control force was 1.72 ± 0.25 mN (mean ± SEM, n = 8). Ca^{2+} (△), effect of Ca^{2+} concentration in the absence of an anesthetic. Mean ± SEM (n = 10) of the force expressed as percent of control (Ca^{2+} 2.5 mM) are shown. Control force was 2.23 ± 0.24 mN (mean ± SEM, n = 10). HAL (□), effect of halothane (0.6% and 1.0%) in normal Ca^{2+} (2.5 mM) medium. Mean ± SEM (n = 9) of the force expressed as percent of control (no anesthetic) are shown. Control force was 1.65 ± 0.22 mN (mean ± SEM, n = 9). The scales of abscissas were chosen so that the three curves approximately overlap.

and the force depression in 1.0 mM Ca^{2+} as well as between 2.4% isoflurane and 0.5 mM Ca^{2+}.

In the absence of ryanodine (*i.e.*, when the contractile activity was dependent largely on the SR Ca^{2+}), halothane (0.6% and 1.0%) significantly inhibited the force of contraction as did 1.5 mM or lower concentration of Ca^{2+} in the absence of halothane, whereas the effect of isoflurane was significant at 2.4% but not at 1.5% (fig. 3). Unlike the effects measured in the presence of ryanodine, the negative inotropic effect of 0.6% halothane measured in normal Ca^{2+} medium in the absence of ryanodine was significantly ($P < 0.01$) greater than the force depression in 1.5 mM Ca^{2+} medium without the anesthetic, and the effect of 1.0% halothane was significantly ($P < 0.01$) greater than the force depression in 1.0 mM Ca^{2+} medium (fig. 3). In contrast to the effect of halothane, the negative inotropic effect of isoflurane was significantly ($P < 0.01$) less than that found in the low Ca^{2+} medium (fig. 3).

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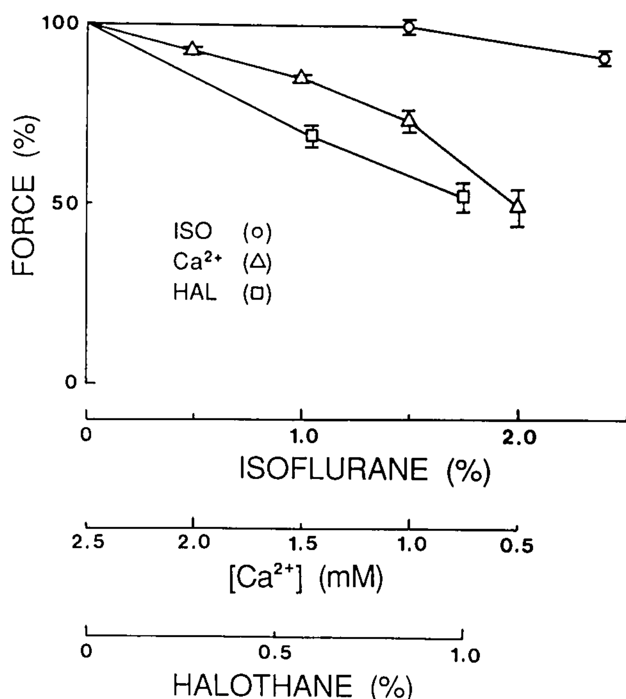

FIG. 3. Negative inotropic effect of an anesthetic and force depression in low Ca^{2+} medium measured in the absence of ryanodine. ISO (O), effect of isoflurane (1.5% and 2.4%) in normal Ca^{2+} (2.5 mM) medium. Mean ± SEM (n = 8) of the force expressed as percent of control (no anesthetic) are shown. Control force was 17.25 ± 1.38 mN (mean ± SEM, n = 8). Ca^{2+} (Δ), effect of Ca^{2+} concentration in the absence of an anesthetic. Mean ± SEM (n = 10) of force expressed as percent of control (Ca^{2+} 2.5 mM) are shown. Control force was 17.56 ± 1.56 mN (mean ± SEM, n = 10). HAL (□), effect of halothane (0.6% and 1.0%) in normal Ca^{2+} (2.5 mM) medium. Mean ± SEM (n = 9) of force expressed as percent of control (no anesthetic) are shown. Control force was 16.19 ± 1.39 mN (mean ± SEM, n = 9). The scales of abscissas are same as in figure 2.

Discussion

The force of contraction measured in the presence of ryanodine can be considered to be activated by the transsarcolemmal influx of Ca^{2+} with no contribution from Ca^{2+} released from the SR.[10] Thus, from the equal inhibition of force measured in the presence of ryanodine, 0.6% and 1.0% halothane in normal Ca^{2+} medium can be considered to have reduced Ca^{2+} influx to the same extent as found in a medium containing, respectively, 1.5 mM and 1.0 mM Ca^{2+}, but no anesthetic. When the comparison was made in the absence of ryanodine, the negative inotropic effects of 0.6% and 1.0% halothane were about twice as great as the force depression in the lower Ca^{2+} media, suggesting that halothane directly inhibited the function of the SR in addition to its indirect effect of reducing SR Ca^{2+} availability secondary to a reduction in transsarcolemmal Ca^{2+} influx. Of the total negative inotropic effect of halothane, about one-half can be accounted for if halothane's effect is like that of lowering extracellular Ca^{2+} concentration. The remaining one-half, however, is most likely due to the direct effect of halothane on SR function. A caveat to this interpretation is that anesthetics such as halothane may reduce the Ca^{2+} affinity of troponin C or the myofibrillar response to the same troponin C occupancy by Ca^{2+}. The magnitude of such effects in intact muscle is not known. Much higher concentrations of anesthetics than those used in the present study are required to inhibit the Ca^{2+}-activated ATPase activity of isolated myofibrils prepared without using a detergent[19] as well as the Ca^{2+}-induced force development in mechanically skinned cardiac muscles.[4,20] More recently, Murat *et al.*[21] have shown a depression of Ca^{2+} induced force development in myocardium treated with Triton X-100 to the extent of 20% by 1% halothane or 1.5% isoflurane at half-maximal activation and to the extent of 8% by the same concentrations of the anesthetics at maximal activation. In the present study, we assumed that equal depression of the force measured in the presence of ryanodine meant equal depression of transsarcolemmal Ca^{2+} influx, ignoring the possible contribution of an anesthetic effect on the Ca^{2+} affinity of troponin C. Supposing, however, that halothane does reduce Ca^{2+} affinity of troponin C, then the force depression caused by this anesthetic would be due in part to a direct myofibrillar effect and in part to a depression of transsarcolemmal Ca^{2+} influx. It follows, then, that inhibition of the Ca^{2+} influx, for example, by 0.6% halothane would be less than that found in 1.5 mM Ca^{2+} medium for the same degree of force depression, or a higher concentration of halothane would be required to match the extent of inhibition of the Ca^{2+} influx. The potential error introduced by ignoring the effect (if it is significant) of halothane on the Ca^{2+} affinity of troponin C will be to underestimate the direct effect of the anesthetic on SR function. If halothane does have a direct myofibrillar effect, such an effect is expected to be greater for the weaker force in the presence of ryanodine than for the stronger force in the absence of ryanodine because Murat *et al.*[21] have shown that the myofibrillar depressant effect of anesthetics is more pronounced when the activation is half-maximal than when it is maximal.

The observed negative inotropic effect of isoflurane measured in the presence of ryanodine is consistent with an inhibition of the transsarcolemmal Ca^{2+} influx.[7,8] Unlike halothane, however, isoflurane had minimal depressant effect on the force of potentiated-state contraction measured in the absence of ryanodine. This is consistent with the small effect of isoflurane on SR function in skinned cardiac muscles.[4] The depressant effect of isoflurane was less than that found in the low Ca^{2+} media. The results suggest that isoflurane does not have a direct inhibitory effect on the SR function. The observation that

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the depressant effect of isoflurane was even less than that found in the low Ca^{2+} media may be explained if isoflurane significantly lowers the Ca^{2+} affinity of troponin C. Such an effect, which is less pronounced in strong contractions than in weak contractions,[21] is expected to be smaller for the contraction measured in the absence of ryanodine than in weak contractions measured in the presence of ryanodine. It is also possible that more SR Ca^{2+} is available for the activation of potentiated-state contractions in the presence of isoflurane than in its absence. This could occur if isoflurane inhibited spontaneous Ca^{2+} release (or leak) from the SR. Spontaneous Ca^{2+} release from skeletal muscle SR has been shown by Palade *et al.*[22] and by Volpe *et al.*[23] to involve a mechanism distinct from other forms of Ca^{2+} release. A similar Ca^{2+} release mechanism may be involved in a type of contractile activity (the late peak of a biphasic contraction), which has been shown to be inhibited by isoflurane.[7]

In summary, the results of the present study suggest that in intact rabbit atria, halothane but not isoflurane has a direct inhibitory effect on SR function. To maximize the sensitivity to detect such a direct effect, we used potentiated-state contractions of atrial muscles. Furthermore, the preparations were superfused at 30° C instead of 37° C. Thus, further studies are necessary to assess the extent the conclusion drawn from the results of the present study is applicable to ventricular myocardium contracting at 37° C at a physiologic heart rate.

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