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Differential Effects of Inhalation Anesthetics on Myocardial Potentiated-state Contractions In Vitro

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The effects of enflurane, halothane, and isoflurane on myocardial potentiated-state contractions were examined in a study in which each of the anesthetics was presented, in random order, to each of eight isolated rabbit papillary muscles. Post-rest potentiated-state contractions were elicited by imposing a stimulus at precisely timed intervals following a 2-Hz steady-state stimulus train. The strength of these contractions is known to be highly dependent on sarcoplasmic reticulum (SR) Ca^{2+} release. The *increment* in tension developed in potentiated state, as compared to the steady state, is directly attributed to the potentiation process, and is defined here as *potentiated-state strength* (PSS). Effects of enflurane, halothane, and isoflurane on the time course of development of the potentiated state were characterized, as were the effects of incremental doses of these anesthetics on PSS.

Anesthetic gas phase concentrations that produced 50% depression of contractile tension at 0.05 Hz steady-state stimulation were 0.6% halothane, 1.4% isoflurane, and 1.6% enflurane. Muscles exhibited maximal PSS of 0.91 ± 0.01 g/mm² in the absence of anesthetics. Halothane (0.6%) and enflurane (1.6%) caused significant depression of PSS to 0.45 ± 0.06 and 0.61 ± 0.06 g/mm², respectively, while isoflurane (1.4%) preserved PSS at 0.95 ± 0.09 g/mm². Concentration profiles showed that the depression of PSS by halothane and enflurane was dose dependent. Isoflurane, up to 2.3%, failed to depress PSS. The time interval for development of optimum PSS, 1.5 to 2.0 s, was unaffected by any of the anesthetics. Isoflurane is unique among the volatile anesthetics in that it does not inhibit PSS and, therefore, is unlikely to inhibit net SR Ca^{2+} release involved in the potentiated-state contraction. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane; mechanisms of action. Heart: myocardial contractility; negative inotropy; potentiated-state contractions; sarcoplasmic reticulum.)

THE VOLATILE ANESTHETICS inhibit myocardial contractility at clinically relevant doses both *in vivo*[1] and *in vitro*.[2] In intact animal models,[3] as well as in humans,[4] the depression of cardiac output by isoflurane is less than that of halothane or enflurane. A previous *in vitro* study reported that equivalent doses of isoflurane and halothane inhibited contractility to the same degree,[5] suggesting that isoflurane preserves cardiac performance by a peripheral circulatory effect. More recently, however, two laboratories have described conditions under which *in vitro* contractile inhibition by isoflurane is minimized,[6,7] suggesting that preservation of cardiac performance also may occur directly at the level of the myocardium.

The mechanisms through which anesthetics alter contractility are not fully understood. Cellular energy supplies are well maintained during anesthesia,[8,9] although, at very high anesthetic concentrations, measurable inhibition of actomyosin adenosine triphosphatase (ATPase)[10,11] may limit transduction of this energy. At clinically used concentrations, anesthetic-induced alterations in the availability of contractile-activator calcium have been suggested by functional[3,7,12-17] and electrophysiologic[18-20] studies, as well as by studies involving Ca^{2+} analysis.[21,22] The excitation-contraction coupling mechanism induces a transient rise in free intracellular calcium which is derived from functionally distinguishable pools:[23,24] free extracellular calcium, calcium bound to superficial sarcolemmal sites (a polyvalent inorganic-ion displaceable pool), and sarcoplasmic reticular (SR) calcium. Calcium from both extracellular pools enters through the slow calcium channel and, possibly, through the Na/Ca exchange system during the action potential. The relative contribution from each of the pools may change under the varying influences of contraction frequency, hormonal regulation (*e.g.*, beta-receptor), and drugs (*e.g.*, inotropic agents and anesthetics).

Lynch[6] has demonstrated that the degree of contractile inhibition caused by isoflurane is diminished as stimulation frequency increases. We have previously confirmed this observation and further demonstrated that, with high stimulation rates in the presence of isoproterenol, isoflurane's depressant action may be reversed completely. Such is not the case for contractile inhibition by halothane. These reports indicate that the two anesthetics modulate the sources of contractile-activator calcium differently, and imply distinctly different subcellular mechanisms of action. Controversy exists,

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however, in identifying the major site of isoflurane's contractile inhibition: SR *versus* sarcolemmal. Lynch[6] observed that the late-peaking tension of low-frequency contractions was inhibited by isoflurane to a much greater extent than the rate of upstroke (measure of Ca^{2+}-mediated slow inward current) of the associated slow action potentials. Espousing a proposal by Reiter *et al.*,[25] that late-peaking tension is activated by Ca^{2+} that enters the cell during the action potential but that is then sequestered and released by the SR before reaching the myofibrils, Lynch suggested that decreased Ca^{2+} entry contributed little to isoflurane-induced depression of contractility, and that an inhibition of SR Ca^{2+} uptake or release would explain the marked depression of late-peaking tension caused by this anesthetic. In contrast, we have shown that potentiated-state contractions (known to be highly dependent upon Ca^{2+} released internally from the SR for their activation[23,26–28]) are relatively insensitive to the inhibitory action of isoflurane, and have suggested that isoflurane causes only minimal inhibition of SR function. Our previous studies are lacking in complete evaluation of anesthetic concentration profiles, and in none has each muscle been exposed to all three anesthetics for comparison of effects.

The present study thus was undertaken to evaluate and compare, in each of a group of rabbit papillary muscles, the effects of several concentrations of three volatile anesthetic agents on potentiated-state strength (PSS) and the time course of the potentiation process *in vitro*. The potentiated state, achieved by restimulation following a high-frequency train, is, as noted above, highly dependent upon SR Ca^{2+} stores. Thus, effects on PSS infer direct interaction with the SR and may provide further details in a biochemically unaltered preparation regarding anesthetic interactions with this important subcellular organelle.

Materials and Methods

Rabbits weighing 2.1 ± 0.3 kg (mean ± SD) were anesthetized by intravenous injection of pentobarbital (approximately 45 mg/kg). The heart was excised rapidly and bathed in oxygenated buffer. Right-ventricular papillary muscles (0.95 ± 0.14 mm diameter by 4.8 ± 0.7 mm length) were dissected free and mounted in a 50-ml tissue superfusion chamber maintained at 30° C. The base of each muscle was tied with 5-0 silk to a stationary support, and the tendinous end tied likewise to a connecting rod from a Gould-Statham® UTC-2 force transducer. At the temperature studied, preparations were stable (defined by reproducibility of controls) for more than 8 h. The buffer used was a modified Krebs-Henseleit bicarbonate containing the following: 115 mM NaCl; 5.9 nM KCl; 2.5 mM $CaCl_2$; 1.2 mM $MgCl_2$; 1.2 mM NaH_2PO_4; 1.2 mM Na_2SO_4; 25 mM $NaHCO_3$; 5.6 mM glucose; and 50 μM ethylenediaminetetraacetate (added to chelate trace metals). It was equilibrated to *p*H 7.4 by constant bubbling with a 95% O_2 + 5% CO_2 gas mixture.

Muscles were stimulated with field electrodes at 1.5 times threshold voltage with a Grass® S48 laboratory stimulator, and the force of contraction was recorded on a Gilson® polygraph. All timing functions of the stimulator were calibrated against a Norland® 2001 programmable digital oscilloscope. Each muscle's diameter was obtained under 1.0-g load by measurement with an optical micrometer assuming a cylindrical shape, then resting tension was readjusted to 1.0 g/mm^2 area, determined in previous studies to be near the peak in the length-tension relation for muscles stimulated at 2 Hz.[29] To insure adequate core oxygenation (defined as lack of fatigue during 2-Hz 10-s stimulation), experiments were performed at 30° C, and muscles larger than 1.15 mm in greatest diameter were not studied. Muscles were stimulated continuously at 0.1 Hz during a 3-h stabilization period before each experiment, and during 30-min equilibration periods following each drug change. Anesthetics were added to the superfusion gas using calibrated Dräger® vaporizers, and achieved steady-state liquid phase concentrations within 15 min as assayed by extraction and gas chromatography.[30] All reported anesthetic concentrations represent volume per cent composition of anesthetic in the superfusion gas.

The time course for development of the potentiated state was evaluated in a series of experiments using ten papillary muscles. After initial stabilization (or post-drug equilibration), muscles were allowed to develop steady-state contractile tension with stimulation at 0.05 Hz, defined as "slow" stimulation. Following this, stimuli were delivered in 8-s trains at 2 Hz with interposed rest periods of at least 20 s. This allowed a steady-state "fast" stimulation contractile tension to be achieved after approximately ten trains that did not fatigue on further repetition.

Potentiated-state contractions were obtained by delivering a stimulus that was delayed 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, or 5.0 s after the last stimulus in the train. These delays were interposed in random order. The corresponding PSS was defined as the increment in tension obtained with the extra stimulus as compared with the last stimulus in the preceding train (figure 1). Each

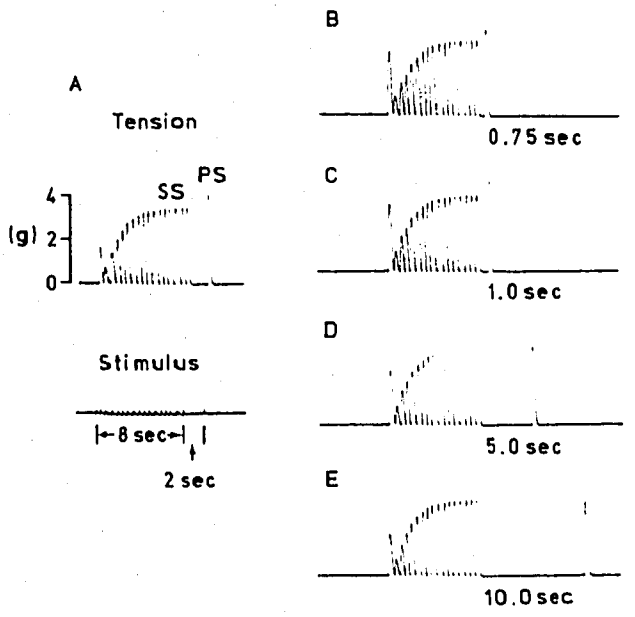

FIG. 1. *A.* Stimulus artifact (*lower trace*) and developed tension (*upper trace*) for papillary muscle stimulated at 2 Hz for 8 s, followed by a stimulus which elicits a potentiated-state contraction delivered 2.0 s after the last stimulus in the train. Developed tension is in grams (g), muscle area was 0.71 mm^2. Potentiated-state strength is 0.85 g/mm^2, calculated as the difference between the tension developed in the potentiated-state (PS) contraction and that of the last (SS) steady-state contraction. *B,C,D,E.* Exemplary traces showing tension development for potentiation stimuli delayed 0.75, 1.0, 5.0, and 10.0 s from the last train stimulus. Potentiated-state strengths were 0.70, 0.92, 0.15, and −0.07 g/mm^2, respectively.

experiment consisted of determination of steady-state tension with "slow" stimulation, steady-state tension with "fast" stimulation, and a full set of timed potentiated-state contractions; this sequence was completed for the control (no anesthetic), followed by each volatile agent (in random sequence), and a repeat control.

Anesthetic concentrations were selected as those that produced 50% contractile inhibition at the "slow" stimulus rate, and those representative of several multiples of human MAC equivalents (*vide infra*). Anesthetic-induced contractile inhibition (expressed as per cent of control tension) at "slow" *versus* "fast" stimulus rates was analyzed with an ANOVA and Scheffe's *F* test for multiple comparisons. The effect of anesthetics on the time course of PSS was analyzed with an analysis of variance (ANOVA) at each time point, comparing each anesthetic to control (no anesthetic) using Dunnett's *t* test for multiple comparisons to a common control. All statistical analyses were considered significant at the 95% level of confidence.

The influence of anesthetic concentration on maximal PSS was evaluated in a series of experiments using eight papillary muscles. Following initial stabilization, muscles were exposed to increasing concentrations of anesthetics representing 0.0, 0.5, 1.0, 1.5, and 2.0 human MAC equivalents (1.0 MAC equals 1.68% enflurane, 1.15% isoflurane, or 0.75% halothane). Note that MAC equivalents for the rabbit are available and would produce similar results, since it has been shown that there is internal consistency (constancy of "MAC for anesthesia" potency ratios) across many species, including human and rabbit.[31]

Anesthetics were introduced in random order with 30-min equilibration periods after changing agents, and 15-min equilibration periods after changing the concentration of each agent. At each concentration of each agent, the steady-state contractile tension was determined at "slow" (0.05 Hz) and "fast" (2 Hz) stimulus rates, as previously described. Differences in contractile inhibitory effect among the anesthetics were analyzed with an ANOVA and Scheffe's *F* test. Following this, potentiated-state contractions were elicited using an extra stimulus interposed 1.75 s after the last stimulus in a 2-Hz train. PSS (as previously defined) at each anesthetic concentration was compared with the corresponding control (no anesthetic) using an ANOVA and Dunnett's method, as above.

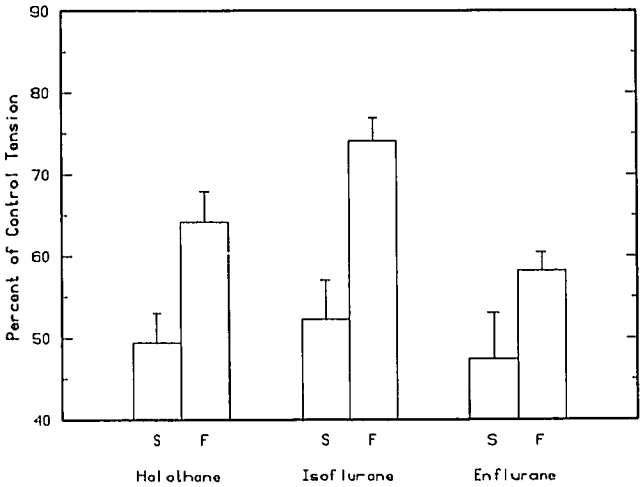

FIG. 2. Histogram comparing the degree of papillary muscle contractile inhibition produced by halothane, isoflurane, and enflurane at slow 0.05-Hz stimulation (S) *versus* fast 2-Hz stimulation (F). Data are expressed as per cent of control (no anesthetic) tension at the same stimulation frequency. Error bars represent SEM (N = 10). Anesthetic doses (0.6% halothane, 1.4% isoflurane, and 1.6% enflurane) were chosen to give similar (50%) contractile inhibition at 0.05 Hz. Contractile inhibition at 2 Hz was significantly less for isoflurane than for the other two anesthetics.

Results

Contractile Inhibition with Slow *Versus* Fast Steady-State Stimuli

Only after selecting equally myocardial-depressant doses of anesthetic under a defined condition may comparisons be made of the effect of varying stimulation frequency. For this reason, the doses used in this series were chosen as those that provided equal 50% contractile depression at the slowest stimulus rate examined. These muscles developed 1.76 ± 0.20 (mean ± SEM) g/mm^2 tension with 0.05-Hz stimulation in the absence of anesthetics (control). As shown in figure 2, 0.6% (gas phase) halothane caused inhibition of contractile tension to 49.4 ± 3.6% of control, 1.4% isoflurane caused inhibition to 52.3 ± 4.7%, and 1.6% enflurane caused inhibition to 47.4 ± 5.6%. These values were not statistically different.

At the faster stimulation rate (2 Hz), partial reversal of the inhibitory effect of all three anesthetics was observed. Control steady-state developed tension at this stimulus rate was 5.14 ± 0.36 g/mm^2. Halothane 0.6% inhibited to 64.2 ± 3.7% of control, 1.4% isoflurane to 74.1 ± 2.8%, and 1.6% enflurane to 58.2 ± 2.3%. The rate-related reversal of isoflurane's contractile inhibition was significantly greater than that seen with the other two anesthetics.

Anesthetic Effects on the Time Course of Development of the Potentiated State

An increment in tension directly attributable to SR (here defined as potentiated-state strength) was obtained for each measurement by taking the tension developed with the extra stimulus and subtracting the corresponding 2-Hz steady-state tension from it. These data are shown in figure 3. Maximal potentiation occurred at 1.5 to 2.0 s for control and for each anesthetic, similar to results obtained for halothane in a separate earlier study.[14] Within the resolution of the experiment, no differences among the anesthetics in time to peak potentiation could be detected. However, comparison of the three anesthetics, at the concentrations noted above to be equally depressant at the steady-state frequency of 0.05 Hz, revealed significant differences in their effects on PSS. The peak control potentiated-state strength was 0.91 ± 0.07 g/mm^2. Peak potentiated-state strengths for 1.6% enflurane and 0.6%

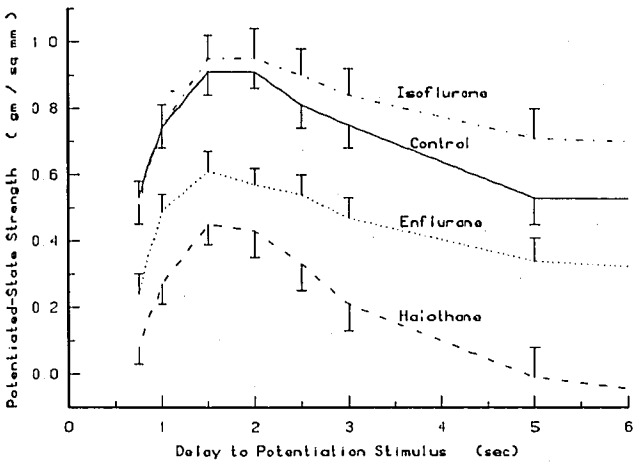

FIG. 3. Time course of potentiated-state strength (first 6 s) for control (*solid line*), 1.6% enflurane (*dotted line*), 1.4% isoflurane (*alternating dot with dash*), and 0.6% halothane (*dashed line*). Error bars represent SEM (N = 10).

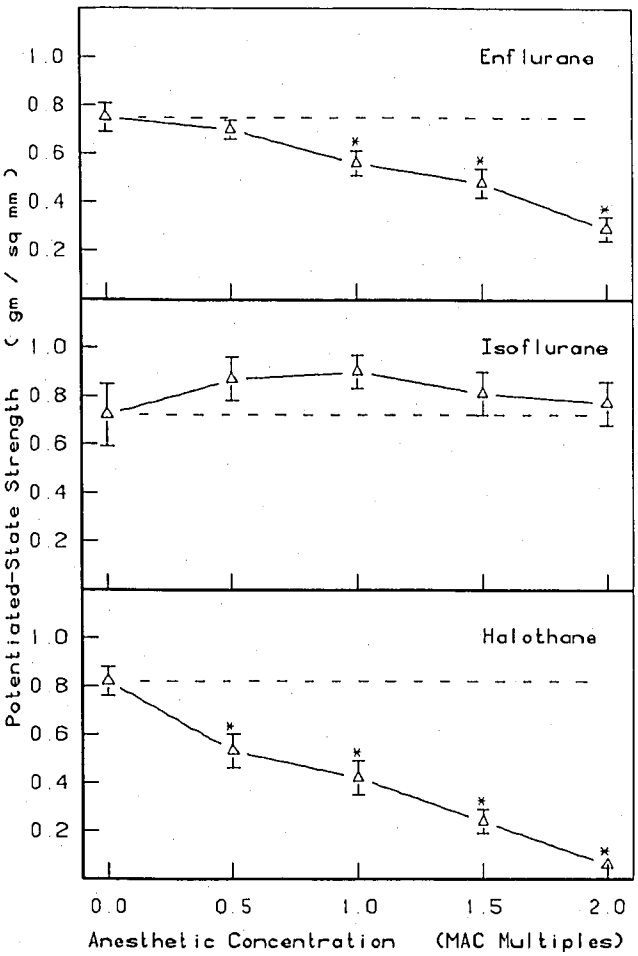

FIG. 4. Concentration dependence of potentiated-state strength for enflurane (*upper frame*), isoflurane (*middle frame*), and halothane (*lower frame*). Broken line is an extension of the 0.0 MAC control strength for each series. Asterisks denote values significantly depressed from control. Error bars represent SEM (N = 8).

halothane were 0.61 ± 0.06 and 0.45 ± 0.06 g/mm^2, respectively. At all time points, potentiated-state strength with enflurane and halothane was significantly less than that of control. PSS with 1.4% isoflurane peaked at 0.95 ± 0.09 g/mm^2 and was not distinguishable from control. Thus, for isoflurane, PSS was maintained at control levels, despite the fact that the 2-Hz steady-state tension was depressed to 74.1% of control.

Anesthetic Concentration Effect on Potentiated-State Strength

Potentiated-state strength *versus* anesthetic concentration is plotted in figure 4. Anesthetic concentrations have been normalized to 0 to 2 MAC equivalents (*i.e.*, 0 to 3.36% enflurane, 0 to 1.5% halothane, and 0 to 2.3% isoflurane). With enflurane (upper frame, fig. 4), PSS was preserved at 0.5 MAC, but fell significantly below control at greater concentrations. With halothane (lower frame, fig. 4), PSS was depressed significantly at all concentrations in a dose-dependent fashion. In striking contrast, PSS was preserved for all concentrations of isoflurane (middle frame, fig. 4).

Discussion

Potentiated-state contractions may be elicited in myocardial tissues either by paired-pulse stimulation (post-extrasystolic potentiation)[32] or by stimulation after a brief rest following high-frequency stimulation (post-rest potentiation),[26] as in the present study. The incremental strength of potentiated-state contractions as compared with steady-state strength is felt to result from an increase in myofibrillar-activating Ca^{2+} supplied from the SR and can be abolished by specific SR inhibitors such as ryanodine.[23] The interval between the uptake of Ca^{2+} by the SR and its availability for maximal release defines an optimum time for maximal potentiation. This time may depend upon transit of Ca^{2+} from uptake to release sites,[26] or may represent a time-dependent recovery from inactivation of SR Ca^{2+} release channels,[33] these alternatives being kinetically indistinguishable. Beyond the optimum time, potentiated-state contractions decay, ultimately to the level of weak rested-state contractions.

The present work compared effects of halothane, enflurane, and isoflurane on PSS in isolated, intact rabbit papillary muscles, where each of these anesthetics (at several concentrations) was administered in random order to each of the muscles studied. The maximal PSS in the presence of isoflurane was indistinguishable from control at all concentrations used. In the presence of enflurane, PSS was attenuated above 0.5 MAC. Halothane attenuated PSS at all concentrations studied. These results indicate that inhibition of SR function very likely contributes to the negative inotropic effect of enflurane and halothane.

Isoflurane is unique among the anesthetics studied in that it appears not to inhibit SR Ca^{2+}, release as indicated by its lack of effect on PSS. No anesthetic appreciably affected the optimum time for maximal potentiation in the present series of experiments, suggesting that these anesthetics have little effect on the rate-limiting step of the SR Ca^{2+} uptake to release transition (although effects occurring between 0.0 and 0.5 s may have been missed at this experimental sampling interval). A small effect of halothane to shorten the optimum time was noted in an earlier separate study.[14]

In a previous study, we have compared the inhibitory effects of Ni^{2+} (an inhibitor of trans-sarcolemmal Ca^{2+} influx), ryanodine (an inhibitor of SR function), and isoflurane on steady-state and potentiated contractions.[7] Isoflurane, like Ni^{2+}, predominantly inhibited steady-state contractions, whereas halothane inhibited the potentiated-state contraction more strongly than the steady-state contraction.[14] We postulated, at that time, that isoflurane's major inhibitory action thus was at the sarcolemma, while halothane was inhibitory to the sarcolemma and to SR function as well.

The present study refines this postulate by 1) suggesting a net negative effect of both halothane and enflurane at the SR (presumably by decreasing the Ca^{2+} store), and 2) suggesting *no* net effect of isoflurane on the availability of Ca^{2+} stored in and released from the SR. Furthermore, preservation of net SR Ca^{2+} release may partly explain the rate-related reversal of isoflurane's inhibitory effect, as total internal Ca^{2+} stores are larger at higher stimulation rates. The proven inhibitory effects of all three anesthetics on the slow AP[6,19,20] may be an indicator of decreased slow-channel Ca^{2+} influx *during* the action potential, and this is likely to contribute to the negative inotropic effects of all three anesthetics. Independent effects on sarcolemmal Ca^{2+} transport (*e.g.*, through Na/Ca exchange[34] or through Na/K-ATPase[35]) also may occur.

Su and colleagues[15–17] have studied the effects of halothane, isoflurane, and enflurane on SR Ca^{2+} uptake and caffeine-induced Ca^{2+} release in rabbit myocardial fibers rendered functionally devoid of their sarcolemma. Their studies suggest that all three anesthetics depress SR Ca^{2+} uptake, but that isoflurane does so to a much lesser extent than either halothane or enflurane. Luk *et al.*[36] have observed, in dog ventricular tissue, that potentiated-state contractions are inhibited to a much lesser extent by isoflurane than by halothane.

Our present data are consistent with these findings. Taken together, we would offer the interpretation that for halothane and enflurane, a major action underlying negative inotropy is one of decreased SR Ca^{2+} uptake (or storage), with a net effect of less SR Ca^{2+} release. In contrast, the present data suggest that isoflurane has little or no net effect on SR Ca^{2+} reuptake/storage/release, and corroborates our previous suggestion[7] that isoflurane decreases SR function to a lesser extent than halothane. Note that the experimental method we have used cannot distinguish independent effects on uptake, storage, or release at the level of the SR.

Halothane depresses the rate of upstroke of the slow AP (an indirect measure of sarcolemmal Ca^{2+} influx) less than it depresses late peak tension.[19] For isoflurane, this discrepancy is even greater.[6] In interpreting this finding (using the hypothesis of Reiter *et al.*[25] that all of the Ca^{2+} that enters the cell must transit the SR), Lynch[6] concludes that both agents inhibit the SR, and that isoflurane does so more than halothane. The handling of the Ca^{2+} responsible for activating the late peaking tension that accompanies contractions of low stimulation frequency is poorly understood and may be different from the handling of the Ca^{2+} responsible for activating potentiated-state contractions.

Indeed, the SR component suggested by Reiter *et al.*[25] to be involved in "delaying" the access of transsarcolemmally derived Ca^{2+} to the myofibril (*i.e.*, the postulated SR component through which the Ca^{2+} entering the cell must pass, *during the same beat*, before activating late peaking tension) may be anatomically different from the SR component involved in the release of the Ca^{2+} *stored during previous beats* and released immediately upon stimulation to activate a potentiated-state contraction. Assuming that two such SR components actually do exist, and that Lynch[6] examines phenomena associated with the former, while Komai and Rusy's[7] experiments deal with the latter, then the controversy over the interpretation of the separate (different) phenomena observed by these authors may only be apparent.

In summary, this study confirms *in a common experimental preparation* that the negative inotropic potencies of the volatile anesthetics are different *in vitro* as they are *in vivo*. Halothane and enflurane inhibit net SR Ca^{2+} release as measured by potentiated-state strength, but isoflurane does not. Additional quantitative studies of cellular and subcellular Ca^{2+} fluxes (*e.g.*, Ca^{2+} fluxes governed by Na/Ca exchange, by sarcolemmal Ca^{2+} ATPase, and by the separate mechanisms of SR uptake, storage, and release) are needed to better define the mechanisms of anesthetic negative inotropy.

References

1. Prys-Roberts C: Ventricular performance, The Circulation in Anaesthesia. Edited by Prys-Roberts C. Oxford, Blackwell, 1980, pp 115–146
2. Brown BR Jr, Crout JR: A comparative study of five general anesthetics on myocardial contractility. ANESTHESIOLOGY 34:236–245, 1971
3. Merin RG: Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? ANESTHESIOLOGY 55:398–408, 1981
4. Stevens WC, Cromwell TH, Halsey MJ, Eger EI II, Shakespeare TF, Bahlman SH: Cardiovascular effects of a new inhalational anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. ANESTHESIOLOGY 35:8–16, 1971
5. Kemmotsu O, Hashimoto Y, Shimosato S: Inotropic effects of isoflurane on mechanics of contraction in isolated cat papillary muscles from normal and failing hearts. ANESTHESIOLOGY 39:470–477, 1973
6. Lynch C III: Differential depression of myocardial contractility by halothane and isoflurane *in vitro*. ANESTHESIOLOGY 64:620–631, 1986
7. Komai H, Rusy BF: Negative inotropic effects of isoflurane and halothane in rabbit papillary muscles. Anesth Analg 66:29–33, 1987
8. Merin RG, Verdouw PD, deJong JW: Dose-dependent depression of cardiac function and metabolism by halothane in swine (Sus scrofa). ANESTHESIOLOGY 46:417–423, 1977
9. Kissin I, Aultman DF, Smith LR: Effects of volatile anesthetics on myocardial oxidation-reduction status assessed by NADH fluorometry. ANESTHESIOLOGY 59:447–452, 1983
10. Merin RG, Kumazawa T, Honig CR: Reversible interaction between halothane and Ca^{++} on cardiac actomyosin adenosine triphosphatase: Mechanism and significance. J Pharmacol Exp Ther 190:1–14, 1974
11. Pask HT, England PJ, Prys-Roberts C: Effects of volatile anesthetic agents on isolated bovine cardiac myofibrillar ATP-ase. J Mol Cell Cardiol 13:293–301, 1981
12. Rusy BF: Effect of general anesthetics on the activation process in cardiac muscle: A study of the mechanism of anesthetic-induced myocardial depression, Molecular Mechanisms of Anesthesia. Progress in Anesthesiology, Vol. 1. Edited by Fink BR. New York, Raven Press, 1975, pp 625–636
13. Komai H, Rusy BF: Effect of halothane on rested-state and potentiated-state contractions in rabbit papillary muscle: Relationship to negative inotropic action. Anesth Analg 61:403–409, 1982
14. Komai H, Rusy BF: Differences in the myocardial depressant action of thiopental and halothane. Anesth Analg 63:313–318, 1984
15. Su JY, Kerrick WGL: Effects of halothane on caffeine-induced tension transients in functionally skinned myocardial fibers. Pflügers Arch 380:29–34, 1979
16. Su JY, Kerrick WGL: Effects of enflurane on functionally skinned myocardial fibers from rabbits. ANESTHESIOLOGY 52:385–389, 1980
17. Su JY, Bell J: Intracellular mechanism of action of isoflurane and halothane on striated muscle of the rabbit. Anesth Analg 65:457–462, 1986
18. Ikemoto Y, Yatani H, Arimura H, Yoshitake J: Reduction of the slow inward current of isolated rat ventricular cells by thiamylal and halothane. Acta Anaesthesiol Scand 29:583–586, 1985

19. Lynch C III, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. ANESTHESIOLOGY 55:360–368, 1981
20. Lynch C III, Vogel S, Pratila MG, Sperelakis N: Enflurane depression of myocardial slow action potentials. J Pharmacol Exp Ther 222:405–409, 1982
21. Porsius AJ, VanZwieten PA: Influence of halothane on calcium movements in isolated heart muscles and in isolated plasma membranes. Arch Int Pharmacodyn Ther 218:29–39, 1975
22. Bosnjak ZJ, Kampine JP: Effects of halothane on transmembrane potentials, Ca^{2+} transients, and papillary muscle tension in the cat. Am J Physiol 251:H374–H381, 1986
23. Bers D: Calcium influx and sarcoplasmic reticular Ca release in cardiac muscle. Am J Physiol 248:H366–H381, 1985
24. Langer G, Frank J: Lanthanum in heart cell culture: Effects on calcium exchange correlated with its localization. J Cell Biol 54:441–455, 1972
25. Reiter M, Vierling W, Seibel K: Excitation-contraction coupling in rested-state contractions of guinea-pig ventricular myocardium. Naunyn Schmiedebergs Arch Pharmacol 325:159–169, 1984
26. Edman KAP, Johannsson M: The contractile state of rabbit papillary muscle in relation to stimulation frequency. J Physiol (Lond) 254:565–581, 1976
27. Lukas A, Bose R: Mechanisms of frequency-induced potentiation of contractions in isolated rat atria. Naunyn Schmiedebergs Arch Pharmacol 334:480–487, 1986
28. Sutko JL, Willerson JT, Templeton GH, Jones JR, Besch HR: Ryanodine: Its alteration of cat papillary muscle contractile state and responsiveness to inotropic interventions. J Pharmacol Exp Ther 209:37–47, 1979
29. Komai H, Rusy BF: Calcium and thiopental-induced spontaneous activity in rabbit papillary muscle. J Mol Cell Cardiol 18:73–79, 1986
30. Cowles AL, Borgstedt HH, Gillies AJ: Solubilities of ethylene, cyclopropane, halothane and diethyl ether in human and dog blood at low concentrations. ANESTHESIOLOGY 35:203–211, 1971
31. Drummond JC: MAC for halothane, enflurane, and isoflurane in the New Zealand white rabbit and a test for the validity of MAC determinations. ANESTHESIOLOGY 62:336–338, 1985
32. Bass O: The decay of the potentiated state in sheep and calf ventricular myocardial fibers. Influence of agents acting on transmembrane Ca^{2+} flux. Circ Res 39:396–399, 1976
33. Wier W, Yue D: Intracellular calcium transients underlying the short-term force-interval relationship in ferret ventricular myocardium. J Physiol (Lond) 376:507–530, 1986
34. Adams RJ, Pruett JK: Inhibition of cardiac sarcolemmal Na^+/Ca^{++} exchange by the volatile anesthetic enflurane. Fed Proc 46:398, 1987
35. Pratila M, Vogel S, Sperelakik N: Inhibition by enflurane and methoxyflurane of hyperpolarization in canine Purkinje fibers. J Pharmacol Exp Ther 229:603–607, 1984
36. Luk H-N, Lin C-I, Chang C-L, Lee A-R: Differential inotropic effects of halothane and isoflurane in dog ventricular tissues. Eur J Pharmacol 136:409–413, 1987