Title: EFFECTS OF ISOFLURANE ON FUNCTIONALLY SKINNED MYOCARDIAL FIBERS FROM RABBITS

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Introduction. Isoflurane(I)[1] like halothane (H) and enflurane(E),[2] at clinical concentrations depresses myocardial contractility in isolated intact cat papillary muscle. The mechanisms of the action of H[3,4] and E[5] have been shown mainly due to decreasing Ca^{2+} uptake by the sarcoplasmic reticulum(SR) in functionally skinned myocardial fibers from rabbits. The isomeric structure of I and E led us to hypothesize that I would have similar mechanisms of action as E.[5] The present study was designed to test the hypothesis by studying the effects of I on functionally skinned myocardial fibers.

Methods. Right ventricular papillary muscles from rabbits were isolated. Pieces of the muscle were homogenized in relaxing solution($-\log[Ca^{2+}]$ = pCa > 9) to disrupt the sarcolemma. A fiber bundle was dissected from the homogenate and mounted between forceps, and attached to a photodiode tension transducer. Study on the Contractile Proteins: The fibers were activated with one of the submaximal $[Ca^{2+}]$(pCa 5.6-5.0) and the maximal $[Ca^{2+}]$(pCa 3.8) and were relaxed with a relaxing solution(pCa > 9) in between contractions. The steady-state tension development was measured. The submaximal Ca^{2+}-activated tension development was expressed as percentage of the maximal Ca^{2+}-activated tension as 100%. Study on the SR: The fibers were immersed sequentially in five different solutions to load Ca^{2+} into the SR and to release Ca^{2+} from the SR with caffeine producing a tension transient. The area of the tension transient was measured as an estimate of the amount of Ca^{2+} released. Three types of tests were performed: (i) uptake phase- the fibers immersed in loading solutions saturated with I, (ii) release phase- the fibers immersed in the releasing solution saturated with I, and (iii) uptake-and-release phase- the fibers immersed in (i) and (ii) solutions. Isoflurane was delivered through a Verni-Trol® vaporizing system. The partial pressure of I in the solutions was assayed by gas chromatograph. Each preparation was immersed in control solutions (saturated with pure N_2), followed by test solutions (saturated with I and N_2 mixture) and finally again the control solutions. The test results were compared with the mean of the two bracketting controls by paired t-test. The mean and the standard error of the mean were calculated from at least 6 preparations of at least 3 rabbits.

Results. Isoflurane (2,3,4%) slightly decreased(7-9%) the maximal Ca^{2+}-activated tension. The submaximal Ca^{2+}-activated tension was decreased by I(2-4%) so that higher$[Ca^{2+}]$ was required to generate the same amount of tension (Fig.1, left). Isoflurane(3,4%) decreased 16% and 30% respectively the caffeine-induced tension transient at the uptake phase, and did not change the tension transient at the release phase(Fig.1, right). Isoflurane(4%) decreased 21% the tension transient at the uptake-and-release phase. However, I(4%) increased the submaximal caffeine (2 mM)-induced tension transient at the release phase(Fig.1, right).

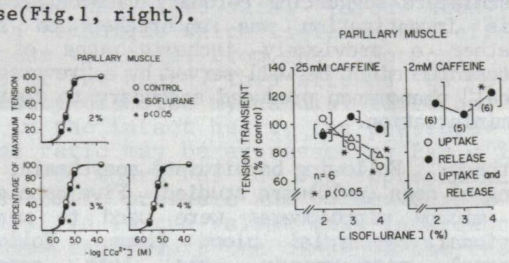

Fig. 1. Effects of I(2,3,4%) on(left)$[Ca^{2+}]$-tension relationship and on(right) the caffeine-induced tension transient at three experimental conditions(Mean ± SE(n)). * $p < 0.05$ compared with the control.

Discussion. The results prove that our hypothesis is correct: the decreased Ca^{2+} activation of the contractile proteins and decreased Ca^{2+} uptake by the SR by I are similar to that of H[3,4] and E.[5] At clinical concentrations of I(1-3%), the slight decrease in the Ca^{2+}-activated tension development of the contractile proteins and Ca^{2+} uptake by the SR could only partly be responsible for the marked myocardial depression observed in isolated intact cat papillary muscle.[1] We conclude that I-induced myocardial depression is partly achieved by decreasing Ca^{2+} activation of the contractile proteins. Isoflurane has a much less depressive effect on the SR than H or E.

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