Title: DIFFERENTIAL EFFECTS OF HALOTHANE, ENFLURANE AND ISOFLURANE ON Lumen TRANSIENTS AND PAPILLARY MUSCLE TENSION IN THE GUINEA PIG

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INTRODUCTION. Isoflurane (I)-induced depression of ventricular function in the intact animal models and isolated myocardial preparations appears to be less than that of halothane (H) and enflurane (E). The mechanism responsible for this difference is controversial. Some investigators have concluded that the major effect of I is via inhibition of Ca++ influx, while others attribute the effect to a greater effect on the SR. In order to directly examine the availability of intracellular Ca++ we have performed a comparative study of intracellular Ca++ transients and contractile force in the presence of H and I in the papillary muscle of the guinea pig.

METHODS. Right ventricular papillary muscles (mean OD = 0.7 mm) were removed from I guinea pigs and superfused with oxygenated Krebs solution (30°C) containing 5 mM Ca++. The muscles were field stimulated and the isometric force of contraction measured at 0.5-1 Hz pacing rate. The Ca++ sensitive bioluminescent protein aequorin was pressure injected into multiple superficial cells of each papillary muscle. Digital signal averaging of 100 successive light signals was performed to obtain a good signal-to-noise ratio. The intracellular aequorin light signals provide a good indication of the overall magnitude and time course of the intracellular myoplasmic Ca++ concentrations. Peak Ca++ transients and peak isometric tension were determined before and after introduction of H, E and I in random order. The effects of all three anesthetic agents were tested in each preparation under identical conditions at following concentrations in the tissue bath: H: 3.01 & 0.55 mM, E: 0.48 & 1.06 mM and I: 0.37 & 0.78 mM as measured using a gas chromatograph. Statistical differences were determined using a 2-way ANOVA and LSD test.

RESULTS. The effects of H, E and I on the calcium transients and isometric force are summarized in Figure 1 (values are mean ± SEM as a % of control). As seen, the negative inotropic effects of H and E were dose-dependent and closely related to a decrease in intracellular Ca++. I also reduced contractile force in a dose-dependent manner but the decrease was significantly less as compared to H or E. A most striking feature observed with I was a dissociation between intracellular Ca++ availability and contractile force. Although the magnitude of the Ca++ transients did not change when the concentration of I was increased from 0.37 to 0.78 mM, the contractile force decreased. The effects of inhalational anesthetic agents at higher concentrations on Ca++ transients and contractile force in a typical preparation are seen in Figure 2.

DISCUSSION. The comparative influence of inhalational anesthetic agents was examined on contractile force and intracellular Ca++ transients in isolated cardiac muscle. The results of our experiments indicate that: (1) the negative inotropic effect of I is less than that of either H or E at equipotent doses; (2) this effect is associated with smaller depression of the intracellular Ca++ concentration during I; and (3) at higher concentrations of I, myocardial depression may involve other factors such as: decreased affinity of troponin C for Ca++ and/or reduced myofibrillar responsiveness to Ca++, rather than inhibition of Ca++ influx or depression of sarcoplasmic reticulum. At the lower concentrations of I, H and E a decrease in intracellular Ca++ is at least in part due to a reduced calcium inward current, as directly measured using the whole-cell voltage clamp method in isolated cardiac cells. In conclusion, I produces less myocardial depression than that produced by H or E in part due to a smaller depression of intracellular Ca++.

REFERENCES.
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Figure 1

Figure 2