Title : DIFFERENTIAL EFFECTS OF HALOTHANE, ENFLURANE AND ISOFLURANE ON Ca^{++} TRANSIENTS AND PAPILLARY MUSCLE TENSION IN THE GUINEA PIG

Authors : ZJ Bosnjak, Ph.D., Aggarwal A, M.D., Turner LA, M.D. and JP Kampine, M.D., Ph.D.

Affiliation: Department of Anesthesiology, The Medical College of Wisconsin, and VA Medical Center, Milwaukee, Wisconsin 53295

INTRODUCTION. Isoflurane (I)-induced depression of ventricular function in the intact animal models[1] and isolated myocardial preparations[2,3] 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,[2] while others attribute the difference to a greater effect on the SR.[3] 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, E and I in the papillary muscle of the guinea pig.

METHODS. Right ventricular papillary muscles (mean OD = 0.7 mm) were removed from 13 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.[4] 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: 0.31 & 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 concentration 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[2] or depression of sarcoplasmic reticulum.[3] 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.[5] 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

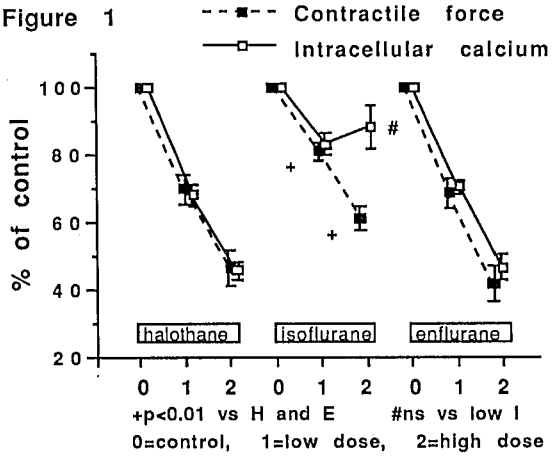

Figure 2