Title: EFFECTS OF ISOFLURANE AND HALOTHANE ON FREQUENCY-TENSION AND LENGTH-TENSION RELATIONSHIPS OF THE RAT MYOCARDIUM

Authors: S. Saeki, M.D., S. Shimosato, M.D., Ph.D., J.H.Tinker, M.D. and F. Kosaka, M.D., Ph.D.*

Affiliation: Anesthesia Research Laboratory, University of Iowa College of Medicine, Iowa City, Ia 52242. Department of Anesthesia & Resuscitology, Okayama University Medical School, Okayama 700, Japan*

Introduction. Developed tension during contraction of cardiac muscle is augmented by two intrinsic factors; namely frequency of stimulation (Bowditch effect) and fiber length prior to contraction (Frank-Starling mechanism). Both isoflurane and halothane evoke a negative inotropy in isolated heart muscles.[1] Thus, we tested the hypothesis that those two factors may counteract the negative inotropic effects of anesthetics.

Methods: Two groups of trabeculae carneae from left ventricles of male Wistar rats were used (3 mos old). Both length and tension of the muscle were controlled by servo-system. Muscles were allowed to contract isotonically at Lmax (0.4 Hz, $[Ca^{2+}]e$=2.0mM, 30°C). Passive tension (PT), maximal developed tension (Tm), maximal rate of tension development (dT/dt) and time to maximal tension (TTTm) were measured on a superimposed isometric contraction during isotonic contraction. Measurements were repeated at 98%, 96% and 94% of Lmax. Stimulation rate was then changed (0.1, 0.2, 0.4, 0.6, 0.8 and 1.6 Hz) at Lmax. Following these measurements, 6 muscles were exposed to 2.0% isoflurane and other 6 were exposed to 1.0% halothane, and measurements were repeated. Back controls were measured following anesthetic washing out. Controls and back controls were normalized by the values at Lmax from length tension relationship. Anesthetic effects were expressed as percent changes from the controls. Data were expressed as mean ± SEM. Analysis of variance was used for statistical analysis. Differences with $p<0.01$ were considered significant. In addition, comparisons of the individual group were made using the Newman-Keuls multiple range test (α=0.05).

Results. Without anesthetics, mean values of PT, Tm, dT/dt and TTTm at Lmax at 0.4 Hz were not different in both groups. Neither length-tension relationship nor frequency-tension relationship was different in 2 groups. Each increase of stimulation rate from 0.1 to 0.8 Hz caused significant decreases of mean percent values of both Tm and dT/dt (Fig.1). Further increase of stimulation rate to 1.6 Hz did not cause any changes in Tm, but increased dT/dt. Both anesthetics decreased Tm significantly at 0.4 Hz ($p<0.001$). Preload alteration did not change the negative inotropic effects of isoflurane ($p=0.167$) and halothane ($p=0.269$). Changes in dT/dt with preload alteration were similar to those in Tm. Increase of stimulation rate at Lmax resulted in decrease of Tm by isoflurane ($p<0.001$), but not by halothane ($p=0.052$) (Fig.2). Changes in dT/dt were similar to those of Tm. Back controls were not different from the controls.

Discussion. Length related increase of Tm is due to increase of the number of crossbridges which produce tension and increase their affinity to calcium.[2] Changes of the stimulation rate increase Tm through augmentation of calcium transient.[3] Our data indicate that the negative inotropic effects of isoflurane could be counteracted by Bowditch effect which increases calcium transient. In rat heart, increased stimulation rate does not allow enough time for sarcoplasmic reticulum (SR) to uptake calcium, and results in decrease of twitch tension,[4] though fraction of activator calcium from extracellular source is increased.[5] Therefore decrease of negative inotropic effects of isoflurane at low stimulation rate may be related to increased dependence of activator calcium from SR. In contrast, halothane seems insensitive to these mechanisms. Our finding suggests that the manner by which isoflurane and halothane alter the inotropic responses to changes in the frequency of contraction and those of the length of fiber prior to contraction may be due to different mechanisms.

References.

1. Kemmotsu O et al. Anesthesiology 39:470, 1973
2. Blinks JR et al. Circulation 73 (Suppl 3): 85, 1986
3. Allen DG et al. Eur Heart J 1 (Suppl 1):5, 1980
4. Capogrossi MO et al. J Gen Physiol 91:133, 1988
5. Stemmer P et al. Am J Physiol 251:H1106, 1986

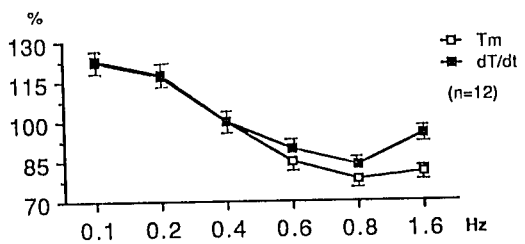
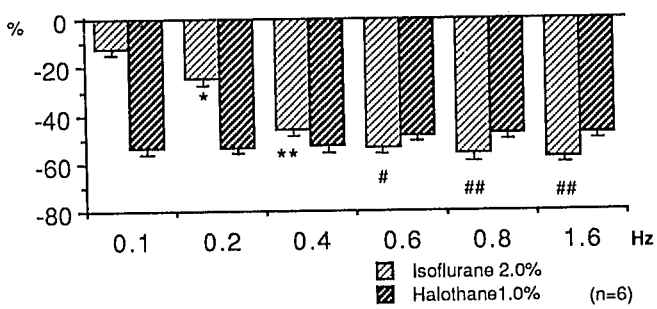


Fig. 1. Frequency-tension relationship and frequency -dT/dT relationship.



Value of $p<0.05$ in all cases :

* vs 0.1; ** vs 0.1 & 0.2; #vs 0.1-0.4; and ##vs 0.1-0.6 Hz

Fig 2. Comparison of percent depression of Tm: Isoflurane vs Halothane at different frequency of contraction.