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TITLE: RELATIVE POTENCY OF DESFLURANE, HALOTHANE, AND ISOFLURANE IN TRIGGERING EPISODES OF MALIGNANT HYPERTHERMIA IN SWINE

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Introduction: Desflurane (difluoromethyl 1-fluoro 2,2,2-trifluoroethyl ether) is a new inhalation anesthetic currently under investigation for use in humans. Recently we showed that desflurane is a trigger of malignant hyperthermia (MH) in susceptible swine.[1] To date, there has been no in vivo comparison of the relative potency of inhalational anesthetics in triggering MH.

Methods: We examined the effects of desflurane, isoflurane, and halothane on six purebred and six mixed-bred Pietrain swine considered susceptible to MH. Animals were randomly exposed to 1 MAC and 2 MAC (as needed) doses of three volatile anesthetics at 7-10 day intervals and observed for changes in end-tidal CO_2, arterial blood gases, lactate, core and muscle temperature, blood pressure, heart rate, and intraoral force. Statistical analysis was performed using Bonferroni's adjustment for multiple tests ($p < 0.0167$). Results are expressed as Mean ± SD.

Results: There was no statistical difference between the mixed and purebred swine in the time required to trigger MH (defined as a $PaCO_2$ of 70 mmHg) with a given agent, and time to triggering was also independent of the order of exposure to the three anesthetics. However, there was a statistical difference between anesthetics in the time required to trigger MH: halothane exposure resulted in the fastest onset of an MH episode (range 20±5 min), compared to isoflurane (48±24) and desflurane (65±28) which both required significantly longer exposures. Intraoral force pressures remained stable or decreased during volatile anesthesia but increased significantly following administration of succinylcholine (Sch). MH susceptibility was confirmed in the ten surviving animals by in vivo Sch challenge and in vitro contracture testing.

Discussion: Our results indicate that the agents we tested have variable potencies in triggering MH (halothane > > isoflurane or desflurane). This is consistent with findings in vitro[2] and in vivo[3] showing varying relative effects of volatile anesthetics. These findings may be clinically applicable, particularly when choosing an anesthetic for short surgical procedures.

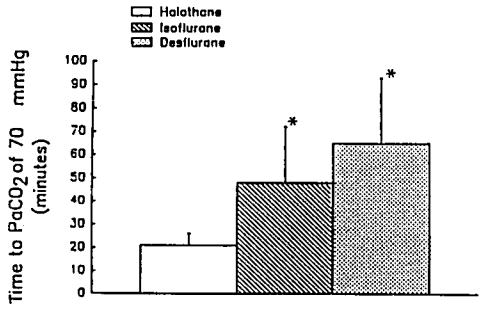

Fig. 1: Time to MH trigger as defined by $PaCO_2$ 70 mmHg. MH susceptible swine receiving halothane triggered statistically earlier than those animals receiving isoflurane or desflurane (* $p < 0.0167$).

References:

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FATTY ACIDS MARKEDLY LOWER THE THRESHOLD FOR HALOTHANE-INDUCED Ca^{2+} RELEASE FROM THE TERMINAL CISTERNAE: IMPLICATIONS FOR MALIGNANT HYPERTHERMIA.

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Unsaturated fatty acids reduce the threshold of Ca^{2+}-induced Ca^{2+} release (TCICR) from the terminal cisternae in preparations from porcine, but not human, skeletal muscle.[1] Since fatty acid production is elevated in porcine[2] and human[3] malignant hyperthermia (MH) muscle, the present study examines whether elevated fatty acid production might cause MH by decreasing the threshold of halothane-induced Ca^{2+} release (THICR) from terminal cisternae. **METHODS.** Institutional approval by the Human Studies Committee was obtained for these studies. Heavy sarcoplasmic reticulum fractions (HSRFs) were isolated and the TCICR determined with arsenazo III and pyrophosphate, as previously described.[1] Aliquots of HSRFs were then preloaded with Ca^{2+} to 30-35% of the TCICR. Halothane (in DMSO) was then added to Teflon-capped cuvettes in concentrations increasing in two-fold increments. The lowest concentration at which halothane induced a sustained Ca^{2+} release was the THICR. The fatty acids were added at a 10 or 20 µM concentrations prior to loading the vesicles with Ca^{2+}. **RESULTS.** The THICR in the absence of fatty acids was identical for MH- and MH+ HSRFs within each species ($P>.05$), but differed by two-fold between human and porcine preparations (Table). Oleic acid, an unsaturated fatty acid, caused a concentration dependent decrease in the THICR in MH- and MH+ HSRFs from human or porcine muscle (Table). Stearic acid (20 µM), a saturated fatty acid, decreased the THICR to a far lesser extent [4.7 ± 1.8 mM (3)] in human MH+ preparations. **DISCUSSION.** The present study demonstrates that the elevated fatty acid production reported to exist in MH+ muscle[2,3] can markedly enhance Ca^{2+} release by halothane in skeletal muscle. Indeed, oleic acid shifted the THICR from high, nonclinical, concentrations of halothane to concentrations used in anesthesia. Since in the absence of fatty acid there was no difference between MH- and MH+ muscle in the THICR, a defect does not appear to reside in the Ca^{2+} release channel in MH. These studies provide further support for altered lipid metabolism as the cause of MH.

Table. Effects of oleic acid on the THICR in HSRFs from swine and humans. All values are mean ± SEM(n).

	THICR	Oleic Acid	
	[Halothane] (mM)	10 µM	20 µM
Swine		THICR - [Halothane] (mM)	
MH-	4.0±0.0(3)	3.3±0.7(3)	0.5±0.0(1)[b]
MH+	4.0±0.0(4)	1.7±0.3(3)[a]	0.5±0.0(3)[a]
Humans			
MH-	8.0±0.0(3)	1.7±0.3(3)[a]	1.0±0.0(3)[a]
MH+	8.0±0.0(6)	1.0±0.0(4)[a]	0.7±0.2(3)[a]

[a]$P<.05$ compared to no oleic acid by t-test.
[b]No statistical analysis possible.
Note: No differences between MH- and MH+ for the THICR within either species.

References.
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