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Delayed Onset of Malignant Hyperthermia Induced by Isoflurane and Desflurane Compared with Halothane in Susceptible Swine

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Background: **Desflurane (difluoromethyl 1-fluoro 2,2,2-trifluoroethyl ether) is a new inhalational anesthetic currently under investigation for use in humans. Recently, the authors showed that desflurane is a trigger of malignant hyperthermia (MH) in susceptible swine. To date, there has been no *in vivo* comparison of the relative ability of inhalational anesthetics to trigger MH. The effects of desflurane, isoflurane, and halothane on six MH-susceptible purebred and six MH-susceptible mixed-bred Pietrain swine were examined.**

Methods: **The animals were exposed to 1 MAC and 2 MAC (if MH was not triggered after 1 MAC hour) doses of each of the three volatile anesthetics in random sequence at 7–10-day intervals and changes in end-tidal CO_2, arterial blood gases, serum lactate, core and muscle temperature, blood pressure, and heart rate were measured.**

Results: **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 (20 ± 5 min), compared with isoflurane (48 ± 24 min) and desflurane (65 ± 28 min), both of which required significantly longer exposures. There was no statistical difference between the MH purebred and mixed-bred swine in the time required to trigger MH (defined as a Pa_{CO_2} of 70 mmHg) with a given agent, and time to triggering was also independent of the order of exposure to the three anesthetics. Malignant hyperthermia susceptibility was confirmed in ten surviving animals, by both *in vivo* succinylcholine challenge and *in vitro* contracture testing.**

Conclusions: **Although all three volatile anesthetics triggered MH, exposure to halothane resulted in significantly shorter times to MH triggering when compared with desflurane and isoflurane. (Key words: Anesthetics, volatile: desflurane; halothane; isoflurane. Animal: swine, Pietrain. Malignant hyperthermia. Neuromuscular relaxants: succinylcholine.)**

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RECENTLY, we reported that desflurane is a trigger of MH in susceptible swine.[1] It is interesting that, in that study, two of six purebred MH-susceptible Pietrain swine did not develop MH episodes during a 60-min exposure to 2 MAC desflurane. We hypothesized that desflurane was not as strong an MH trigger as other commonly used volatile anesthetics. The relative ability of volatile anesthetics to augment caffeine contractures has been shown *in vitro*.[2,3] The ability of individual volatile anesthetics to produce MH episodes in swine has been shown *in vivo*.[4] However, there has been no *in vivo* comparison of the relative effects of inhalational anesthetics in triggering MH.

This study was performed to determine whether there was a difference between desflurane, isoflurane, and halothane in inducing MH in both purebred and mixed-bred Pietrain swine susceptible to MH. We proposed that such differences, if they existed, would be helpful in explaining the clinical variability of MH onset seen in humans. We administered each of these three volatile anesthetics in random sequence to each animal until either MH was triggered (defined as a Pa_{CO_2} of 70 mmHg) or the total exposure time to the anesthetic reached 120 min. Malignant hyperthermia susceptibility of each animal was subsequently confirmed by both an *in vivo* exposure to succinylcholine and *in vitro* contracture testing.

Materials and Methods

Animals

This protocol was approved by the Mayo Institutional Animal Care and Use Committee. Two groups of animals were used: 1) six Pietrain swine from a special breeding program (University of Minnesota) that were homo-

zygous for susceptibility to MH based on genetic records and subsequent linkage analysis of animals from the same breeding program; and 2) six mixed-bred swine genotypically homozygous for susceptibility to MH from the same breeder. The mixed-bred group of swine resulted from a cross-breeding of purebred Pietrain sows and "near"-Pietrain heterozygous boars. The "near"-Pietrain strain was the result of back-crossing purebred animals to heterozygous animals over five to seven generations, resulting in both MH allele heterozygous (MH-negative) and homozygous (MH-susceptible) animals that are approximately 90–95% genetically similar to the purebred Pietrain swine from the same breeding program. All animals in this study had positive barnyard halothane challenges,[5] and were approximately the same age and weight (23.9 ± 4.4 kg; X ± SD). An intravenous catheter was inserted percutaneously into an ear vein. Intravenous atropine 0.4 mg was followed by thiopental (19.4 ± 3.8 mg/kg) to induce anesthesia. After tracheal intubation, the lungs were mechanically ventilated with a mixture of oxygen and nitrogen to maintain a Pa_{O_2} of 90–100 mmHg and normocarbia (Pa_{CO_2} 40 ± 5 mmHg). Minute ventilation was held constant throughout the experimental period.

Monitoring

Anesthesia was maintained with additional doses of intravenous thiopental as needed (8.8 ± 4.0 mg/kg), while a small incision was made in the medial aspect of the thigh and a catheter inserted into a superficial branch of the femoral artery for monitoring and blood sampling. Bupivacaine, 0.25% (2.5 ml), was injected in the thigh incision after cannulation and again after closure of the wound at the end of the experimental protocol. Esophageal temperature, muscle temperature, blood pressure (BP), and heart rate (HR) were monitored as previously reported.[1] Blood Pa_{O_2}, Pa_{CO_2}, and pH were monitored by analyzing fresh arterial blood samples (1 ml with heparin added) using a 1304 blood gas analyzer, 482 cooximeter (Instrumentation Laboratories, Inc., Lexington, MA). Blood lactate was measured using membrane bound enzymatic analyzers (Yellow Springs Instruments, Yellow Springs, OH).

In Vivo *Measurements*

After satisfactory placement of the monitors and arterial catheter, a stabilization period of 20 min was begun, during which normocarbia and adequate oxygenation, as previously defined, were maintained. During this period, the animals were not stimulated, and no further thiopental was given. Following control measurements, the experimental protocol was initiated; 1 MAC of one of the three randomly assigned volatile anesthetics was administered. Halothane and isoflurane were delivered through an Ohio vaporizer and end-tidal concentrations monitored *via* a raman scattering multiple gas analyzer (Rascal, Albion Instruments, Salt Lake City, UT). Desflurane was administered *via* a modified DM 5000 vaporizer (Datex Instruments, Helsinki, Finland), and end-tidal anesthetic concentrations were monitored continuously using a modified and calibrated Datex analyzer. One MAC end-tidal concentration was then administered until either MH was triggered (*i.e.*, Pa_{CO_2} of 70 mmHg) or 60 min of exposure had taken place. The MAC of desflurane in swine is 10.0 ± 0.9%.[6] If hypercarbia was not observed following 1 MAC exposure for 60 min, 2 MAC end-tidal concentration of the same anesthetic was administered, again either until a Pa_{CO_2} of 70 mmHg was reached or 60 min of exposure had taken place. Throughout the study period, HR, BP, temperature, and end-tidal gas concentrations were continuously monitored, and values for these parameters were recorded every 15 min. Mean arterial blood pressure was maintained between 90 and 105 mmHg with an intravenously administered phenylephrine infusion (345.0 ± 234.3 μg/kg). As end-tidal CO_2 measurements neared 70 mmHg, ABGs were checked more frequently to determine as accurately as possible when a Pa_{CO_2} of 70 mmHg was reached. We chose the Pa_{CO_2} cutoff as our MH triggering indicator to identify a single reliable indicator that would result in a clear onset time. We showed, in a previous study, that other indicators of hypermetabolism in this animal model (pH, lactate levels, temperature, end-tidal CO_2, and buffer base) parallel the change in Pa_{CO_2}.[1] Once a clear episode was initiated, the volatile anesthetic was discontinued, hyperventilation with 100% oxygen was begun, sodium bicarbonate was administered intravenously to normalize pH, and surface cooling was accomplished using ice packs and topical ethanol. During treatment, the blood pressure was maintained with an intravenous phenylephrine infusion, as necessary. If aggressive supportive treatment was inadequate to control the episode as judged by: 1) $Pa_{CO_2} > 100$ mmHg, 2) pH < 7.15, and 3) increasing serum lactate levels, small doses of dantrolene were administered intravenously (0.1–0.4 mg/kg) until the episode was reversed. When the animals, with or without dantrolene treatment, demonstrated reversal of blood gas and met-

abolic abnormalities and were breathing spontaneously, they were transferred to recovery. When the animals were awake and stable, the trachea was extubated. The three animals treated with dantrolene were not exposed to the next anesthetic for 9–10 days to allow for complete clearance of and recovery from the drug. All other animals were exposed to the next anesthetic at 7-day intervals. Two of the 12 animals died during the recovery period after exposure to the third volatile anesthetic (desflurane).

In Vivo *Challenge with Succinylcholine*

The ten animals that survived the three anesthetic exposures were housed and fed for 1–2 weeks. The animals were then anesthetized with intravenous thiopental, the trachea was intubated, and anesthesia was maintained with 70% N_2O and 30% O_2 and intravenous thiopental. Muscle biopsies were obtained from the latissimus dorsi muscle. Subsequently, a bolus of succinylcholine (2 mg/kg) was administered to each animal. We monitored and recorded the parameters described above. The animals were observed for signs of MH as described above. If MH was not initiated within 10 min, a second dose of succinylcholine was given, again followed by a 10-min observation period. If an MH episode was still not initiated, they were exposed to 2 MAC halothane until MH occurred.

In Vitro *Contracture Testing*

Excised muscle specimens were contracture tested according to the guidelines of the North American MH Group for caffeine[7] and the European MH Group for graded responses to halothane.[8] The equipment and techniques used in this laboratory are those previously described by the authors.[9] At least six bundles from a given muscle were studied; three exposed to halothane and three to caffeine. The contracture tests were completed within a 4-h period after the biopsy.

Muscle bundles were exposed to graded halothane concentrations of 0.5, 1.0, 2.0, and 3.0%. Caffeine (anhydrous; Sigma Chemical Co., St. Louis, MO) was added to the bathing solution in graded doses to produce final concentrations of 0.5, 1.0, 2.0, 4.0, 8.0, and 32 mM. Contractures at any concentration of halothane exceeding 500 mg and caffeine thresholds (defined as a contracture of greater than 200 mg) at 2.0 mM or less were considered abnormal. Halothane contractures at the 3.0% concentration are reported as an indication of maximum responses.

Statistics

All results were expressed as mean ± SD. Comparisons of repeated measurements were made by paired *t* tests with Bonferroni corrections. A Bonferroni's corrected *P* value of 0.05/3 = <0.0167 was considered significant when comparing paired data.

Results

There was no difference in mean thiopental dosage for induction or catheter insertion, and no animal received further thiopental during the 20-min stabilization period before any volatile anesthetic exposure.

The time to trigger MH (Pa_{CO_2} of 70 mmHg) was different for each of the anesthetics. Halothane induced MH in the shortest time (20 min ± 5), isoflurane in an intermediate time period (48 min ± 24), and desflurane required the longest time (65 min ± 28). These differences were statistically significant between halothane and isoflurane and between halothane and desflurane, but not between isoflurane and desflurane. Six animals required 2 MAC desflurane to trigger an episode of MH (*i.e.*, MH was not triggered during the 60-min exposure to 1 MAC desflurane). In one of these animals, MH was not triggered even after exposure to desflurane for 120 min (1 MAC for 60 min followed by 2 MAC for 60 min). In contrast, three animals required 2 MAC doses of isoflurane to trigger MH and, in all animals, MH was triggered rapidly during exposure to 1 MAC halothane. There was no statistically significant difference between MH-susceptible purebred and mixed-bred animals in onset of MH, nor did the order of volatile anesthetic exposure affect the time to trigger MH (table 1).

Decreases in pH and increases in lactate levels reflected metabolic changes consistent with the increase in Pa_{CO_2} to 70 mmHg that was chosen as the parameter to define the time to MH triggering in our study (table 2).

The total dose of bicarbonate given for MH treatment did not differ between groups, although the dosage of phenylephrine required to maintain arterial blood pressure of 90–100 mmHg during anesthetic administration was significantly greater for desflurane (445 μg/kg ± SD) and isoflurane (366 μg/kg ± SD) compared with halothane (234 μg/kg ± SD).

Dantrolene was administered intravenously as a life-saving treatment in five different experiments to three different animals (0.30 mg/kg ± 0.07). One animal received dantrolene (0.35 mg/kg) after the adminis-

Table 1. Time to Initiation of an MH Episode for Each Anesthetic Exposure

Animal ID	Anesthetic Agent 1	Time (min)	Anesthetic Agent 2	Time (min)	Anesthetic Agent 3	Time (min)
PP1	Des	27	Iso	60	Hal	27
PP2	Iso	41	Des	>120‡§	Hal	25
PP3	Hal	18	Des	77‡	Iso	95‡
PP4	Hal	12	Iso*	60	Des*	58
PP5	Des	95‡	Hal	20	Iso*	22
PP6†	Iso	23	Hal*	27	Des*	85‡
MP1	Des	40	Hal	21	Iso	71‡
MP2	Des	42	Iso	25	Hal	12
MP3	Iso	21	Des	78‡	Hal	19
MP4	Hal	22	Des	60	Iso*	73‡
MP5	Iso	33	Hal	22	Des	29
MP6†	Hal	20	Iso	56	Des	70‡

PP = purebred (MH-susceptible) pietrain; MP = mixed-bred (MH-susceptible) near-pietrain cross; Hal = halothane; Iso = isoflurane; Des = desflurane.

* Treated with dantrolene.

† Died during third exposure.

‡ 2 MAC volatile agent needed for triggering MH.

§ Pa_{CO_2} of 70 mmHg not reached during 2-h exposure.

tration of halothane (in this case, it was the second agent studied), and also following an episode induced by desflurane on the third exposure (0.20 mg/kg). A second animal received small doses of dantrolene after the second exposure to isoflurane and the third exposure to desflurane. Both animals requiring two treatments of dantrolene were purebred swine. One mixed-bred animal received a single dose of dantrolene following the third anesthetic exposure with isoflurane. Two animals died during the recovery from the third

Table 2. The Effect of Each of the Volatile Anesthetics and Succinylcholine on Various Systemic Variables

	N	Arterial Pa_{O_2} (mmHg)	Arterial Pa_{CO_2} (mmHg)	Arterial *p*H	Blood Lactate (mM/L)	Mean Arterial Pressure (mmHg)	Heart Rate (beats/min)	Esophageal Temperature (° C)
Halothane	12							
Control		103 ± 7	39 ± 1	7.49 ± 0.03	1.5 ± 0.6	112 ± 11	180 ± 27	38.2 ± 0.4
15 min		97 ± 11	45 ± 5	7.38 ± 0.08	3.4 ± 1.4	95 ± 12	148 ± 23	37.9 ± 0.3
Pa_{CO_2} of 70+ mmHg		77 ± 7	70 ± 64	7.15 ± 0.04	7.6 ± 0.8	79 ± 8	163 ± 20	38.2 ± 0.4
Isoflurane	12							
Control		104 ± 5	37 ± 2	7.50 ± 0.02	1.3 ± 1.2	109 ± 8	166 ± 20	38.2 ± 0.2
15 min		104 ± 13	40 ± 6	7.47 ± 0.06	1.8 ± 1.9	96 ± 5	138 ± 11	37.7 ± 0.3
30 min	8	96 ± 8	44 ± 8	7.44 ± 0.08	1.9 ± 1.9	98 ± 90	146 ± 18	37.6 ± 0.3
Pa_{CO_2} of 70+ mmHg		76 ± 7	70 ± 5	7.16 ± 0.04	6.7 ± 2.1	80 ± 12	162 ± 20	38.0 ± 0.5
Desflurane	12							
Control		104 ± 14	38 ± 2	7.50 ± 0.02	1.7 ± 1.1	109 ± 21	178 ± 26	38.2 ± 0.2
15 min		101 ± 16	41 ± 4	7.48 ± 0.04	1.9 ± 1.2	91 ± 11	140 ± 13	37.8 ± 0.4
30 min	10	93 ± 11	43 ± 5	7.46 ± 0.04	1.5 ± 1.2	102 ± 8	137 ± 8	37.7 ± 0.3
45 min	8	99 ± 6	45 ± 5	7.45 ± 0.05	1.3 ± 0.8	98 ± 11	141 ± 11	37.8 ± 0.3
Pa_{CO_2} of 70+ mmHg		73 ± 17	66 ± 10	7.20 ± 0.08	6.6 ± 1.9	81 ± 16	172 ± 21	38.3 ± 0.4
Succinylcholine	10							
Control		110 ± 9	39 ± 3	7.49 ± 0.05	1.3 ± 0.7	108 ± 15	155 ± 24	38.0 ± 0.3
1st dose	8	73 ± 15	74 ± 9	7.17 ± 0.02	8.5 ± 1.8	107 ± 24	166 ± 25	38.1 ± 0.3
Pre 2nd dose	2	100 ± 27	54 ± 4	7.25 ± 0.00	5.5 ± 0.7	129 ± 6	140 ± 14	38.5 ± 0.2
2nd dose	1	63 ± 0	67 ± 0	7.20 ± 0.00	5.7 ± 0.0	139 ± 0	180 ± 0	38.3 ± 0.0

anesthetic exposure (desflurane in both cases). One animal received small doses of dantrolene along with symptomatic treatment. During the recovery, the tracheal tube became displaced and the animal died following reintubation. The second animal responded to symptomatic MH treatment with normalization of blood gases within 25 min of triggering, but died 20 min later after separation from mechanical ventilation.

Malignant hyperthermia susceptibility was confirmed in the ten surviving animals by subsequent *in vitro* contracture testing (table 3) and by an *in vivo* succinylcholine challenge after muscle biopsy.

Succinylcholine administration (2 mg/kg) triggered MH in nine of the ten animals tested (table 2). Eight animals developed MH after a single dose of 2 mg/kg of succinylcholine, whereas one animal required a second dose, and one animal received the additional exposure to 2 MAC halothane in conjunction with the two previous doses of succinylcholine before MH was triggered. Both animals requiring more than a single dose of succinylcholine were mixed-bred.

Discussion

In a previously published paper, we reported that desflurane will trigger episodes of MH in susceptible swine.[1] This result was anticipated; desflurane is a potent volatile anesthetic, and all other known agents in this class of drugs have proven to be MH triggers. However, we observed that desflurane was statistically slower in triggering MH episodes in a group of MH-homozygous purebred Pietrain swine; in fact, in two animals, MH failed to occur after exposure to 2 MAC desflurane for 60 min.

Table 3. Caffeine and Halothane Thresholds Determined by *In Vitro* Contracture Testingman (Latissimus Dorsi Muscle)

Animal ID	Caffeine Threshold (mM)	Fractional Force >7% (mM)	3% Halothane Contracture (g)	Result
PP1	1.0	1.0	2.9	Pos-B
PP2	2.0	3.0	1.5	Pos-B
PP3	2.0	2.0	1.6	Pos-B
PP4	†	†	1.7	Pos-H
PP5	1.0	1.5	4.1	Pos-B
PP6*	—	—	—	—
MP1	1.5	3.0	0.32	Pos-C
MP2	2.0	1.5	3.2	Pos-B
MP3	2.0	8.0	1.9	Pos-B
MP4	2.0	2.0	2.2	Pos-B
MP5	2.0	1.0	1.6	Pos-B
MP6*	—	—	—	—

C = caffeine; H = halothane; B = both; PP = purebred (MH-susceptible) pietrain; MP = mixed-bred (MH-susceptible) near-pietrain cross.

Caffeine threshold was defined as a contracture of >200 mg. Fractional force was defined as the caffeine dose at which a force amplitude of 7% or greater of the maximum induced by 32 mM caffeine was recorded. A normal response for this test component is >2.0 mM. Animals are listed by order of contracture testing.

* Died after third volatile anesthetic exposure.

† No twitch obtained; bundles not tested.

One aim of the current study was to compare, *in vivo,* the responses of MH-susceptible purebred and mixed-bred Pietrain swine to three potent volatile anesthetics (halothane, isoflurane, and desflurane). Our results showed that halothane triggered MH much more rapidly than either isoflurane or desflurane. This finding was true for both the purebred and mixed-bred swine studied. There was a large variation in triggering times for both isoflurane and desflurane. Desflurane was a slow triggering agent in all animals, and, as noted previously, in some animals, it did not induce MH even after 2 h of exposure. However, the two animals that died after the recovery period following the third anesthetic exposure both received desflurane. The severity of their responses to desflurane was not different from that seen with the previous two anesthetics. Death was caused by MH complicated by tracheal tube displacement in one animal and probable respiratory depression in the second. While the finding of two deaths in the group exposed to desflurane during the third anesthetic is interesting, the lack of aggressive treatment and complicating respiratory factors make interpretation difficult.

Multiple factors can affect MH triggering in animals and humans.[10–13] However, we attempted to minimize pharmacologic effects by: 1) maintaining a drug-free period before exposure to the volatile agents; 2) maintaining normal core temperature; and 3) allowing the animals to recover for a minimum of 7 days following exposure. Dantrolene treatment was avoided unless aggressive and timely treatment of the hypermetabolic state with hyperventilation with oxygen, cooling, and bicarbonate for the acidosis was unsuccessful. Minimal doses of dantrolene reversed these symptoms rapidly in all but one case in which it was required. Both MH-susceptible purebred and mixed-bred swine from the same breeder were tested to observe the possible effect of genetic differences; however, both groups of animals were observed to respond similarly. This may be because of similarities in the genetic structure in this closely bred genetic pool.[14] Fujii *et al.* have identified a specific point mutation in the porcine ryanodine re-

ceptor that is associated with MH in all affected breeds.[15] All of our animals were obtained from a special breeding program at the University of Minnesota. Subsequent linkage studies on these continued breeding lines have confirmed the reported substitution of cysteine for arginine 614 in the MH-susceptible animals.

The development of the hypermetabolic state followed a similar pattern for all three anesthetics tested. Halothane had an early, fulminant course with rapid increases in Pa_{CO_2}, decreases in pH, and slower rises in temperature and lactate. Exposure to isoflurane and desflurane resulted in similar metabolic responses; however, there was a significant delay in triggering with both agents. There was no evidence of a gradual early onset of MH triggering during exposures to isoflurane or desflurane; all parameters remained relatively normal until the MH episode was triggered. The similarity in bicarbonate dosages required to reverse episodes induced by all three agents also supports the lack of a smoldering course before MH triggering with the slower onset agents. The differing phenylephrine dosages probably reflect the relative increase in peripheral vasodilatation seen with both isoflurane and desflurane when compared with halothane,[6] as well as the prolonged exposure times.

Variable responses to potent inhalation agents have been previously reported *in vitro* and *in vivo*. Reed and Strobel[2] reported differential augmentation of caffeine-induced muscle contractures by multiple inhalational anesthetics in frog sartorius muscle. Their report showed greater potentiation of these contractures with halothane than either enflurane or isoflurane. Britt *et al.*[3] noted an increase in the magnitude of caffeine-induced contractures in human muscle fascicles from MHS individuals when inhalation anesthetics were added to the contracture baths: halothane > isoflurane > enflurane > methoxyflurane. McGrath *et al.*[4] tested known MHS swine with five inhalational anesthetics delivered *via* face mask for a period of 5 min, a method resembling the halothane challenge test used to determine MH susceptibility in swine. They reported gradations in sensitivity: halothane triggering 12/12 animals (as judged by hind limb skeletal muscle rigidity), isoflurane 11/12, enflurane 7/12, methoxyflurane 1/12, and nitrous oxide 0/12. These differential responses may explain, in part, the known variations in human MH responses, particularly the frequent history of uneventful previous exposure to triggering anesthetic agents in patients diagnosed as MHS.[16]

Although it is not known how each of these agents differentially initiate MH at the cellular level, it has been reported that halothane, enflurane, and isoflurane, to varying degrees, cause dose-dependent increases in (Ca^{2+}) in rat hepatocytes.[17] The differing responses are probably related not only to the site of action of each agent, but also the mechanism by which these agents are metabolized; *e.g.*, the metabolism of halothane results in the formation of intermediate radicals, whereas that of isoflurane does not.[18] It will be of interest to determine how each of these agents alter the function of the sarcoplasmic reticulum Ca^{2+} release channel in MH.

In summary, all three potent volatile agents—halothane, isoflurane, and desflurane—are triggers for malignant hyperthermia in both MH-susceptible purebred and mixed-bred Pietrain swine. However, halothane exposure resulted in a significantly more rapid onset of MH than either of the other two agents. Although known MH-susceptible patients should never be exposed to any potent volatile anesthetic agent, our data may help explain the clinical findings of delayed and variable triggering in the *undiagnosed* MH-susceptible patient.

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