Clinical Presentation, Treatment, and Complications of Malignant Hyperthermia in North America from 1987 to 2006

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BACKGROUND: We analyzed cases of malignant hyperthermia (MH) reported to the North American MH Registry for clinical characteristics, treatment, and complications.
METHODS: Our inclusion criteria were as follows: *AMRA* (***a***dverse ***m***etabolic/***m***usculoskeletal ***r***eaction to ***a***nesthesia) reports between January 1, 1987 and December 31, 2006; "very likely" or "almost certain" MH as ranked by the clinical grading scale; United States or Canadian location; and more than one anesthetic drug given. An exclusion criterion was pathology other than MH; for complication analysis, patients with unknown status or minor complications attributable to dantrolene were excluded. Wilcoxon rank sum and Pearson exact χ^2 tests were applied. A multivariable model of the risk of complications from MH was created through stepwise selection with fit judged by the Hosmer-Lemeshow statistic.
RESULTS: Young males (74.8%) dominated in 286 episodes. A total of 6.5% had an MH family history; 77 of 152 patients with MH reported ≥2 prior unremarkable general anesthetics. In 10 cases, skin liquid crystal temperature did not trend. Frequent initial MH signs were hypercarbia, sinus tachycardia, or masseter spasm. In 63.5%, temperature abnormality (median maximum, 39.1°C) was the first to third sign. Whereas 78.6% presented with both muscular abnormalities and respiratory acidosis, only 26.0% had metabolic acidosis. The median total dantrolene dose was 5.9 mg/kg (first quartile, 3.0 mg/kg; third quartile, 10.0 mg/kg), although 22 patients received no dantrolene and survived. A total of 53.9% received bicarbonate therapy. Complications not including recrudescence, cardiac arrest, or death occurred in 63 of 181 patients (34.8%) with MH. Twenty-one experienced hematologic and/or neurologic complications with a temperature <41.6°C (human critical thermal maximum). The likelihood of any complication increased 2.9 times per 2°C increase in maximum temperature and 1.6 times per 30-minute delay in dantrolene use.
CONCLUSION: Elevated temperature may be an early MH sign. Although increased temperature occurs frequently, metabolic acidosis occurs one-third as often. Accurate temperature monitoring during general anesthetics and early dantrolene administration may decrease the 35% MH morbidity rate.
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Malignant hyperthermia (MH) is an inherited muscle disorder characterized by hypermetabolism and is usually triggered after susceptible individuals are given volatile anesthetics and/or depolarizing muscle relaxants.[1]

We recently demonstrated that muscular build and disseminated intravascular coagulation were associated with an increased risk of cardiac arrest and death during MH episodes.[2] However, there has been no systematic evaluation of MH clinical characteristics, treatment, and other complications since the 1970

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study by Britt and Kalow[3] that analyzed 94 case reports before use of dantrolene, with a reported mortality rate of 61%.

We analyzed epidemiologic characteristics of episodes reported to the North American Registry* database over a 19-year period with a focus on presentation, treatment including dantrolene, and factors associated with significant complications attributed to MH.

METHODS

With exempt status by the Penn State College of Medicine IRB (Hershey, PA), we examined AMRA reports received by the Registry from January 1, 1987 through December 31, 2006. The *AMRA* is a standardized report form concerning relevant medical and anesthetic history that clinicians complete and submit to the MH Registry after a patient's ***a***dverse ***m***etabolic and/or ***m***usculoskeletal ***r***eaction to ***a***nesthesia.† Inclusion criteria were as follows: event occurred on January 1, 1987 or later and the AMRA report was received at the Registry by December 31, 2006; episode occurred in the United States or Canada; at least one anesthetic drug was given; and episode ranked by the MH clinical grading scale (CGS) as "very likely" or "almost certain" MH event.[4]

The CGS estimates the qualitative likelihood of MH in a given patient without the use of specialized diagnostic testing and is based on points assigned for specific abnormal signs and laboratory findings (rigidity, muscle breakdown, respiratory and metabolic acidosis, temperature increase, and cardiac involvement) observed during an acute anesthetic reaction. Seventy percent of the points are assigned based on critical cutoff values (e.g., inappropriately increased temperature >38.8°C in the perioperative period adds 10 points to the total score). Points are assigned when they are judged by the anesthesiologist to be inappropriate for the patient's underlying medical condition, anesthetic technique, and surgical procedure (e.g., 0 points instead of 15 points when hypercarbia is judged secondary to an inadequate airway or when a rapid increase in temperature is judged to be secondary to sepsis).‡[4]

Exclusion criteria were a pathologic condition other than MH (e.g., Duchenne muscular dystrophy, hypothalamic injury, and sepsis), and the surgical procedure being the likely cause as independently judged by the authors with MH expertise (MGL, GAG, GCA, and BWB).

For the complication analysis only, cases were excluded if complication status was unknown or was judged by the authors to be secondary to minor complications of dantrolene (e.g., thrombophlebitis). Cardiac arrest or death cases were included if additional complications were reported as part of their event.

We analyzed each episode for the order of appearance of each clinical sign (numbered by the clinician from 1 through 9). Clinicians were instructed to assign the same number to signs that occurred simultaneously (e.g., if masseter spasm and tachycardia were observed simultaneously as the first sign, then masseter spasm and tachycardia both received the number 1). The order of the clinical sign appearance did not influence CGS rank (e.g., no additional points were added if a sign was observed first).

The patterns of clinical presentation were defined as follows: a muscular presentation was defined as masseter spasm, generalized muscular rigidity, cola-colored urine, peak creatine kinase >10,000 U/L, or peak potassium >6.0 mEq/L. A respiratory acidosis presentation was defined as inappropriate hypercarbia, inappropriate tachypnea, maximum end-tidal carbon dioxide >55 mm Hg, or arterial Pco_2 >60 mm Hg. A metabolic acidosis presentation was defined as an arterial base excess more negative than −8 mEq/L. Numeric thresholds matched those of the CGS.[4]

Complications were defined as a change in consciousness level and/or coma; disseminated intravascular coagulation; pulmonary edema; cardiac, renal, or hepatic dysfunction; or "other" complication as specified by the reporting clinician. Independent variables for complication analysis included demographics, body build, procedure type and urgency, type of temperature monitor, nature of anesthetic (volatile anesthetic, succinylcholine, tracheal intubation, maximum end-tidal Pco_2, and maximum temperature), initial and total dantrolene dose, adjunctive treatment (active cooling, anesthesia circuit change, bicarbonate administration, hyperventilation, and IV fluid loading), time interval between first clinical sign and first dantrolene dose, and time intervals between induction to: first clinical sign, maximum end-tidal Pco_2, maximum temperature, and first dantrolene dose.

Descriptive statistics (median, first and third quartiles, and range) of the population experiencing MH are presented. For continuous variables such as time or dosage in which 2 groups of variables were compared, a Wilcoxon rank sum test compared their medians with first and third quartiles as surrogates for confidence intervals (CIs). For continuous variables in which >2 groups of variables were compared, a Kruskal-Wallis test compared their medians with first and third quartiles as surrogates for CIs. For categorical variables such as gender and absence of a temperature probe, a Pearson exact χ^2 tested the difference in proportion between categories. Exact odds ratios with exact 95% CIs quantified magnitude and direction of

†Samples of one of the earliest (1.2) and one of the latest (9.0) versions used to report adverse anesthetic events for this study may be found in the supplementary material posted on the *Anesthesia & Analgesia* Web site (see Supplementary Digital Content 1, http://links.lww.com/AA/A43, Supplementary Digital Content 2, http://links.lww.com/AA/A44. To report a new case, clinicians may obtain a current AMRA report form (version 9.3) from The North American Malignant Hyperthermia Registry Web site at www.mhreg.org (downloads).

‡The MH clinical grading scale may be found in the supplementary material posted on the *Anesthesia & Analgesia* Web site (Supplementary Digital Content 3, http://links.lww.com/AA/A45).

the difference between proportions. A Bonferroni correction adjusted for multiple comparisons within groups of clinically related variables to maintain an overall error rate of 0.05.

Univariate analysis was used to identify independent variables associated with complications, adjusting for multiple comparisons by the Hochberg method.[5] A multivariable model was built with stepwise selection of significant variables with fit judged by the Hosmer-Lemeshow statistic.[6] A P value ≥ 0.05 for this statistic demonstrates adequate fit. Statistical analysis was performed using SAS version 9.1.3 Service Pack 4 (SAS Institute, Cary, NC).

RESULTS

Two hundred eighty-six cases (47.9% of all submitted AMRA reports) met entry criteria, but not all data were reported for all of the cases. Thus, some categories include <286 values. One hundred twelve cases (39.2%) were graded by the CGS as "very likely" MH, and 174 cases (60.8%) were "almost certain" MH.

Clinical Characteristics Before MH Triggering

Demographics

A total of 1.8% were from Canada, 74.8% were males, 69.4% were Caucasian, and 29% of all patients had a muscular body build. Of the 269 with age data, the median age was 22.0 years (10.0, 41.0 years), range 116 days to 78.0 years, and 45% were 19 years and younger. Gender distribution did not change with age.

Family History

Sixteen of 248 patients (6.5%) had an MH family history (although in many cases it was not known preoperatively§); one patient had received a non-MH triggering anesthetic. There was a family history of heat stroke in 3.6% of cases ($n = 9$), and 6 of these patients received one or more unremarkable general anesthetic before MH.

Medical History

In 7.0% of patients, there was a personal history of increased muscle tone. Muscle weakness (2.1%), muscle cramps (3.9%), exercise intolerance (0.7%), cola-colored urine (1.1%), heatstroke (1.1%), and heat intolerance (0.4%) were also reported. Nine patients (3.3%) reported an unusual metabolic response during previous anesthetics, whereas 77 patients (50.7%) had ≥2 prior unremarkable general anesthetics. The number of unremarkable general anesthetics before 152 MH events was 2 (1, 2, range 0–30). Whether these included MH triggers is unknown, but the median year of the last uneventful anesthetic was 1991 (1984, 1996, range 1940–2006), when volatile anesthetics were frequently administered during general anesthesia.

§Comments include: "family didn't think it was relevant to bring it up (second cousin's death from MH thought to be inherited through the nonrelated side of the family)," "reported after surgery (first cousin's similar anesthetic event in Japan)," "discovered only after the event," "not known preop" (MH history in a daughter, MH history in a nephew). In one case, the family MH history was "questionable, thought unlikely at time of preop."

Table 1. Anesthetic Drug Triggers for 284 Malignant Hyperthermia Events

Anesthetic drug	Frequency	%
+Succinylcholine, −Volatile	2	0.7
+Succinylcholine, +Volatile	153	53.9
−Succinylcholine, +Volatile	128	45.1
−Succinylcholine, −Volatile[a]	1	0.4

Type of anesthetic administered before 284 malignant hyperthermia events. All but one administration of succinylcholine was IV. Volatile anesthetics included: halothane (15.6%), enflurane (2.8%), isoflurane (57.8%), desflurane (12.1%), and sevoflurane (20.6%). In 2 patients with missing data, we know that a volatile anesthetic was discontinued but whether succinylcholine was also used was not documented.

[a] This was a 2-year-old patient with a suspected family history of malignant hyperthermia susceptibility undergoing a dental procedure.

Procedure Urgency/Type

The procedure was an emergency in 24.1% of 282 cases. Succinylcholine was given 3.8 times more often in emergency cases (95% CI, 2.0–7.0; $P < 0.0001$). Volatile anesthetics were used as frequently in emergency as in nonemergency cases. MH occurred most frequently during orthopedic (25.5%); ear, nose, and throat (ENT) (15.7%); and general surgical (14.0%) procedures. Succinylcholine was given 1.9 times more often during these 3 procedure types when analyzed together compared with all other procedure types (95% CI, 1.2–3.0; $P = 0.009$).

Prediagnosis Monitoring

Pulse oximetry was used in 99.3%, capnography in 96.2%, and temperature monitoring in 90.9% ($n = 259$) of cases. A skin liquid crystal temperature indicator was used as the sole temperature probe in 39 cases (13.8%). In 10 patients, skin liquid crystal temperature probes did not accurately trend with core temperature probes. (Appendix A, cases 1 and 2 contain events that did not trend during simultaneous esophageal and skin liquid crystal temperature monitoring.) Although the simultaneous liquid crystal temperature readings are unknown, the maximum temperature was 40.0°C (range, 36.5°C–41.2°C) at tympanic, esophageal, and nasopharyngeal sites. When patients with ($n = 259$) and without ($n = 26$) temperature probe monitoring were compared, no significant difference was observed in the interval between anesthetic induction and first MH sign. However, in 5 of 26 patients with no temperature monitoring when the first MH sign was recognized, there was a rapidly increasing temperature or increased temperature with a median maximum temperature of 39.1°C (range, 37.5°C–42.4°C).

Prediagnosis Anesthetic

The median year for the anesthetic was 1996 (1993, 2000, range 1987–2006). A total of 218 patients (76.2%) received tracheal intubation. Laryngeal mask airway use is unknown. Table 1 depicts the frequency with which volatile anesthetics and/or succinylcholine were administered. Patients aged 19 years and

Table 2. Order of Appearance of Clinical Signs[a] During 255[b] Malignant Hyperthermia Events

Clinical sign	Median, first, third quartile appearance number[c]	Range of appearance number[c]	Percentage of patients with sign	Number of patients with sign
Masseter spasm	1.00 (1.00, 1.00)	1.00–4.00	26.7	68
Hypercarbia	2.00 (1.00, 2.00)	1.00–8.00	92.2	235
Sinus tachycardia	2.00 (1.00, 2.00)	1.00–7.00	72.9	186
Generalized muscular rigidity	2.00 (1.00, 3.50)	1.00–6.00	40.8	104
Tachypnea	2.00 (1.00, 3.00)	1.00–6.00	27.1	69
Other	2.00 (1.00, 4.00)	1.00–7.00	16.9	43
Cyanosis	2.00 (2.00, 4.00)	1.00–7.00	9.4	24
Skin mottling	2.00 (1.00, 3.50)	1.00–7.00	6.3	16
Rapidly increasing temperature	3.00 (3.00, 4.00)	1.00–7.00	64.7	165
Elevated temperature[d]	3.00 (2.00, 4.00)	1.00–8.00	52.2	133
Sweating	4.00 (3.00, 5.00)	1.00–8.00	17.6	45
Ventricular tachycardia[d]	4.00 (2.00, 5.00)	1.00–7.00	3.5	9
Cola-colored urine	5.00 (3.00, 5.00)	2.00–9.00	13.7	35
Ventricular fibrillation[d]	5.50 (4.00, 8.00)	1.00–8.00	2.4	6
Excessive bleeding	6.00 (5.00, 6.00)	4.00–8.00	2.7	7

Lists the abnormal clinical sign appearance order during malignant hyperthermia (MH) events. Clinical signs are listed in order of occurrence with the earliest signs listed first and the latest signs listed last.

[a] Abnormal signs judged to be inappropriate by the attending anesthesiologist or other physician. (No points on the clinical grading score are accumulated for the presence of the following adverse signs: cyanosis, skin mottling, sweating, excessive bleeding, and other.)

[b] For 31 cases, clinical sign appearance order was not known. (Appearance order is not required to calculate clinical grading scale score and no additional points accrue for an early appearance.)

[c] Appearance number = numerical order in which a clinical sign appeared e.g. the first clinical sign that appeared during an MH event would be assigned the appearance number of 1, the second clinical sign that appeared during an MH event would be assigned the appearance number of 2, and so on.

[d] An early version of the AMRA (*a*dverse *m*etabolic/*m*usculoskeletal *r*eaction to *a*nesthesia) report form, did not request these signs in 1 fatal case in which the maximum temperature was 41°C but these findings were noted elsewhere in the AMRA report and have been counted in this table.

younger were 11.6 times more likely to receive a volatile anesthetic without IV induction drug (95% CI, 5.8–23.2; $P < 0.0001$) and had a shorter time from induction to volatile anesthetic discontinuation (45 minutes [19.0–90.0 minutes] vs 112 minutes [60.0–180 minutes]; $P < 0.0001$) than those older than 19 years. There was no difference in exposure to succinylcholine with age or gender.

Abnormal Signs and Presentation Pattern

Abnormal Signs

For 255 cases in which the order of clinical sign appearance (Table 2) was known, a median of 4 signs was noted (3, 5, range 1–9). The first or only MH clinical sign noted was hypercarbia (38.0%), sinus tachycardia (31.0%), or masseter spasm (20.8%). Induction of anesthesia to first sign interval was shorter in patients aged 19 years and younger (30 minutes [9.5, 70 minutes] vs 94 minutes [32.5, 168 minutes]; $P < 0.0001$) and for females (34 minutes [8.0, 105.0 minutes] vs 70 minutes [21.5, 143.5 minutes]; $P = 0.0026$).

The time between induction and first sign was <30 minutes for 89 of 268 events for which data were available including 0 minutes for 6 cases (i.e., immediately on induction). For 5 of these zero interval cases, masseter spasm followed succinylcholine administration. In one, generalized muscular rigidity with sinus tachycardia followed sevoflurane induction.

For the 255 patients in which the order of appearance of the signs was known, inappropriately elevated (>38.8°C) or rapidly increasing temperature was one of the first signs in 8.2% and the only initial sign in 3.9% of patients. Temperature abnormalities were the first to third signs in 63.5% of patients with a median temperature maximum of 39.1°C (38.4°C, 40.0°C). Although the median time interval from induction to maximum temperature was 105 minutes (50.0, 197.5 minutes), the range was large (0–880.0 minutes).‖ Because of the wording of the AMRA report, we do not know the interval from induction to rapidly increasing temperature unless it was the first sign noted. However, there was no significant difference in the interval from induction to first sign between the group that had rapidly increasing temperature as the first sign and the group that did not.

Presentation Pattern

The dataset includes 196 cases in which relevant clinical signs (hypercarbia, tachypnea, generalized muscular rigidity, and cola-colored urine) were observed, and/or maximum expired CO_2, creatine kinase, potassium, and arterial blood gas measurements were made. Ninety-nine percent developed respiratory acidosis, but only 26% developed a metabolic acidosis with all but one of those cases also having respiratory acidosis. A total of 79.6% had a muscular presentation.

Table 3 lists the frequency with which combinations of each presentation type occurred. The most frequent presentation was a combined respiratory acidosis and

‖In 3 lean, nonorthopedic pediatric or adolescent patients without infection, a maximum temperature >38.8°C (39.2°C, 39.7°C, and 41.1°C) was observed 12, 10, and 25 minutes, respectively, after anesthetic induction. In 2 nonobese patients, inappropriately elevated or rapidly increasing temperature was the first sign <30 minutes after induction.

Table 3. Clinical Presentation Pattern for 196 Malignant Hyperthermia Events

Presentation pattern	Frequency	%
+Respiratory, +Metabolic, +Muscular	40	20.4
+Respiratory, +Metabolic, −Muscular	10	5.1
+Respiratory, −Metabolic, +Muscular	114	58.2
−Respiratory, +Metabolic, +Muscular	1	0.5
+Respiratory, −Metabolic, −Muscular	30	15.3
−Respiratory, −Metabolic, +Muscular	1	0.5

Lists the distribution of the 196 malignant hyperthermia events with data permitting evaluation for the presence (+) or absence (−) of respiratory acidosis, metabolic acidosis, and/or muscular presentations.

Respiratory = a respiratory acidotic presentation and was defined as: inappropriate hypercarbia, inappropriate tachypnea, maximum end-tidal carbon dioxide >55 torr, arterial pCO2 >60 torr, or arterial pH <7.25.

Metabolic = a metabolic acidotic presentation and was defined as an arterial base excess more negative than −8 mEq/L.

Muscular = a muscular presentation and was defined as masseter spasm, generalized muscular rigidity, cola-colored urine, peak creatine kinase >10,000 U/L, or peak potassium >6.0 mEq/L.

All numeric thresholds matched those of the malignant hyperthermia clinical grading scale.[4]

Table 4. Dantrolene Dosage for 229 Malignant Hyperthermia Events

Dantrolene dose	Median	First quartile	Third quartile	Range
Initial (mg/kg)[a]	2.4	1.9	2.8	0.01–15.00
Total (mg/kg)	5.9	3.0	10.0	0.02–100.00
Absolute Total (mg)[b]	340	140	720	2–6,860

Contains data on dantrolene doses used during 229 malignant hyperthermia events.

[a] Initial doses are reported for 228 events because there was 1 unreported initial dose.

[b] Dantrolene is supplied in 20 mg/vial of lyophilized crystals that are mixed with sterile water prior to use. Total vials required were 17 (first quartile 7, third quartile 36, range 1–343).

muscular presentation (58.2%). Twenty percent of patients had signs or abnormal laboratory findings that were representative of all possible (respiratory acidosis, metabolic acidosis, and muscular) presentation types. Presentation type was not significantly associated with varying combinations of volatile anesthetic and succinylcholine exposure.

Evaluation and Treatment

Evaluation

Although 232 of 286 patients (81.1%) had maximum expired CO_2, creatine kinase, potassium, and arterial blood gas measurements, only 91 patients (31.8%) also had maximum temperature, platelet count, and prothrombin or partial thromboplastin time determinations. Seven percent of patients had no documented arterial blood gas analysis.

Dantrolene

The time between the first sign and the first dantrolene dose used to treat MH events was 30 minutes (15, 60 minutes). Table 4 lists the dantrolene doses used to treat MH events. There was no significant difference in total dantrolene dose administered to those experiencing a "very likely" versus an "almost certain" MH event. There was also no significant difference in total dantrolene dose according to presentation pattern.

Table 5. Frequency of Adjunctive Treatment Use in 284[a] Malignant Hyperthermia Events

Variable	Number	%
Hyperventilation with F_{IO_2} = 1	247	87.0
IV fluid loading	218	76.8
Active cooling[b]	200	70.4
Bicarbonate	153	53.9
Anesthesia circuit change	137	48.2
Mannitol[c]	97	34.2
Furosemide	92	32.4
Glucose and insulin	39	13.7
Cardiopulmonary resuscitation	7	2.5
Calcium	6	2.1
Lidocaine	6	2.1
Procainamide	6	2.1
Epinephrine	5	1.8
Vasopressors	5	1.8
Dopamine	4	1.4
Defibrillation	3	1.1
Norepinephrine	3	1.1
Atropine	2	0.7
Bretylium	2	0.7
Hemodialysis	2	0.7
Phenylephrine	2	0.7

Lists the adjunctive treatments reported for 284 malignant hyperthermia events if the treatment was reported for more than 1 event. (8 of the 284 events included cardiac arrests.[2])

F_{IO_2} = fraction of inspired oxygen.

[a] Data from 2 malignant hyperthermia events were not reported.

[b] Type of active cooling used was not requested on the AMRA (*a*dverse *m*etabolic/*m*usculoskeletal *r*eaction to *a*nesthesia) report form and is unknown.

[c] Mannitol given separately from that contained within the dantrolene solution.

Twenty-two patients received no dantrolene and survived their event without cardiac arrest. Eleven of these cases had information regarding MH complications. There were 2: hepatic dysfunction and bilateral lower extremity soreness in association with a peak creatine kinase of 365,970 U/L (Appendix A, cases 3 and 4). Those treated with dantrolene were 2.97 times more likely to have an "almost certain" episode than those not treated with dantrolene (95% CI, 1.19–7.14; $P = 0.019$).[4] There was inadequate power to detect differences between the group receiving dantrolene and the one not receiving dantrolene regarding age, sex, muscular body build, MH triggers, time between induction and first MH sign, time between induction and maximum end-tidal P_{CO_2}, time between induction and finish time, length of volatile anesthetic exposure, and MH complications.

Trigger Anesthetic Discontinuation

The time between the first sign and volatile discontinuation was 10 minutes (2, 30 minutes). However, 2 young ENT patients had volatile anesthetics continued and they survived (Appendix A, cases 5 and 6). A 30-year-old cesarean delivery patient given a second dose of succinylcholine after masseter spasm also survived (Appendix A, case 7).

Adjunctive Treatment

Table 5 lists the adjunctive treatments reported for 284 MH events. Treatment frequency correlated with the severity of abnormal findings (Appendix B).

Table 6. Complication Frequency in 181 Malignant Hyperthermia Events

Complication	Number	%
Any complication[a]	63	34.8
Consciousness level change/coma[b]	17	9.4
Cardiac dysfunction[c]	17	9.4
Pulmonary edema	15	8.4
Renal dysfunction	13	7.3
Disseminated intravascular coagulation[d]	13	7.2
Hepatic dysfunction[b]	10	5.6
Other[e]	23	12.7

Contains data on the frequency of reported complications in 181 malignant hyperthermia events. With the exception of "other" complications, the complications are listed in order of decreasing frequency. Nineteen percent of patients experiencing a complication, also recrudesced by developing a new clinical sign of malignant hyperthermia >120 min after initial presentation.

[a] Does not include patients experiencing recrudescence, cardiac arrest, or death unless additional complications were also reported.

[b] Presence of this complication noted in the comments section of 1 report but complete data on all complications not queried on this early version of the AMRA (*a*dverse *m*etabolic/*m*usculoskeletal *r*eaction to *a*nesthesia) report form.

[c] Eight of 17 patients with cardiac dysfunction arrested. Four of 17 patients with cardiac dysfunction died.

[d] Presence of this complication noted on the comments section of 2 reports but complete data on all complications not queried on these early versions of the AMRA report form.

[e] Other complications included, in part: compartment syndrome ($n = 2$) leading to an above-knee amputation in 1 survivor and fasciotomies in another before death, a fully resolved stroke ($n = 1$) after cardiac arrest, optic nerve ischemia ($n = 1$) affecting visual fields, bilateral brachial plexopathy ($n = 1$), generalized muscle weakness ($n = 2$), significant muscle loss ($n = 1$), and prolonged intubation ($n = 2$). For 10, the sole complication was designated "other."

Complication Outcomes

Complication data covered 181 patients. Of these, 34.8% ($n = 63$) reported 1 or more complications other than recrudescence, cardiac arrest, or death. The median complication number observed in 63 cases was 1 (1, 2, range 1–5). Table 6 lists the frequency of neurologic, cardiac, pulmonary, renal, hematologic, hepatic, and/or "other" complications.

There was no significant difference between the group experiencing complications and the group not experiencing complications regarding rapidly increasing temperature or temperature exceeding the CGS threshold value of >38.8°C. For the 13 patients experiencing disseminated intravascular coagulation, the median maximum temperature of 40.3°C was higher than the median (39.0°C) in the 162 patients without this complication ($P = 0.0067$). Twenty-one patients experienced hematologic and/or neurologic complications with maximum temperatures <41.6°C. Six of these experienced neurologic complications without cardiovascular instability during a nonneurologic and noncardiac procedure. For those with maximum temperatures <41.6°C, there was no significant difference in the frequency of bicarbonate administration between those experiencing and those not experiencing hematologic and/or neurologic complications.

Univariate analysis identified maximum temperature as a significant independent variable for the experience of an MH complication ($P = 0.024$). One hundred twenty-one subjects had data for all variables analyzed in the multivariable model; 38 subjects experienced a complication, 6 of whom also had a cardiac arrest. According to the multivariable model, the likelihood of a complication increased 1.61 times (95% CI, 1.16–2.25) for every 30-minute increase in time between the first sign and the first dantrolene dose and 2.85 times (95% CI, 1.60–5.08) for every 2°C increase in maximum temperature. The Hosmer-Lemeshow goodness of fit test for this model is $P = 0.140$. When the 6 patients experiencing cardiac arrest were eliminated from the multivariable dataset, the multivariable model still identified these 2 variables as increasing the likelihood of an MH complication with a Hosmer-Lemeshow goodness of fit test ($P = 0.135$).

DISCUSSION

We used the AMRA report database with well-documented clinical experiences and the MH clinical grading scale to determine clinical MH likelihood and selected only patients at the highest MH likelihoods. The CGS has served as a clinical case definition for the MH syndrome for multiple research studies including those validating the North American caffeine halothane contracture test[7] and the in vitro contracture test (European MH Group).[8,9,10,2,11] In addition, the 4 authors with MH expertise excluded cases involving a pathologic condition other than MH or a likely causative surgical procedure. Although the North American MH Registry database also has biopsy reports from caffeine halothane contracture tests on probands and their relatives and, in some cases, molecular genetic analyses, proband clinical experiences are variably documented and less well suited to a study of MH clinical presentation.

Our study may be limited by incomplete patient data, underreporting, or biased reporting, but a disorder as rare as MH precludes a multicenter prospective study.[12] Similarly, we could not perform a case-control study of MH complications because the AMRA report portion of the Registry database lacks appropriate control cases. In addition, our study of factors associated with MH complications may be biased because the CGS independent classification of MH and our dependent variable temperature may be correlated because of the importance of temperature as 1 of 6 possible categories contributing to the CGS score. However, complication analysis bias seems to be minimal because there were no significant differences between the group with and without complications regarding the frequency with which temperature exceeded the critical cutoff value of 38.8°C or the frequency with which inappropriately rapid increase in temperature was noted.

Although MH susceptibility is inherited as an autosomal dominant, we confirmed in our study that its expression is primarily in males.[3,13] Males with MH also had a longer period of anesthesia before first sign recognition.

Our results confirm those of others who reported that predominantly younger patients develop MH.[14,15,13]

We also demonstrated that MH occurred sooner in patients aged 19 years and younger who solely received volatile anesthetics for induction. The minimum alveolar concentration (MAC) that prevents incisional movement in 50% of patients exposed to a surgical incision decreases with age[16–18]; therefore, compared with older patients, younger patients were more likely to receive an increased dose of the inhaled anesthetics. It may be reasonable to extrapolate that the young experienced a higher initial dose of volatile anesthetics, although the total dose of volatile anesthetic may have been equivalent to that given to those who were older, because of their shorter exposure time.

A total of 6.5% of our patients had a family history of MH that was frequently not known at the time of the perioperative evaluation, illustrating the difficulty anesthesiologists may have in obtaining an accurate family history.¶

Our data regarding prior unremarkable general anesthetics (2, range 0–30) confirm the observation made by Halsall et al.[19] in 20 patients that lack of MH during prior anesthetic triggers does not indicate insusceptibility to MH. However, our dataset also included 9 patients who had experienced an unusual metabolic response during a prior anesthetic. We do not know when the anesthesiologist learned this. We recommend that MH trigger-free anesthetics be administered to anyone with this history unless a thorough review of past anesthetic and hospital records reveals a cause other than MH.

Skin liquid crystal temperature indicators were inaccurate in 10 MH cases, human findings that confirm prior porcine observations.[20] We recommend that skin liquid crystal temperature monitors not be used for detection of MH.

It is likely that more frequent administration of succinylcholine underlies the prevalence of emergency and orthopedic, ENT, and general surgical procedures in this dataset. Because 45% of MH cases involved the administration of volatile anesthetics without concomitant succinylcholine, we believe that MH cases will continue to occur even without succinylcholine use.

The most frequent initial MH sign was hypercarbia, sinus tachycardia, or masseter spasm with temperature abnormalities as a further relatively early sign. This finding was unbiased by our use of the CGS for case selection because the order of appearance of MH signs does not influence the CGS score. Although no single pattern of clinical signs consistently occurs during the onset of MH, the majority of patients had both muscular and respiratory acidotic presentations although some presented with acidosis without evidence of rigidity or muscle destruction. Early clinical investigations documented metabolic acidosis during MH events.[3,13] Our low incidence of metabolic acidosis may have been attributable to dantrolene treatment (given to none of the patients in the study by Britt et al.[14] and only to 15% of the patients in the study by Mauritz et al.[13]) or failure to obtain arterial blood gases during the most acute phase of the MH reaction.

Before dantrolene's introduction, Britt and Kalow[3] documented a 36% survival rate with symptomatic treatment only. Our study documents 9 patients (3.3%) who did not receive dantrolene and survived MH without cardiac arrest or significant complication. There was inadequate power to determine whether a shorter exposure to volatile anesthetics explains this outcome. We also document survival albeit with significant rhabdomyolysis of 3 patients who received additional MH triggers after the diagnosis of MH. Nevertheless, we do not recommend withholding dantrolene or continuing MH triggers when MH is suspected.

Our study of 229 MH episodes with documented dantrolene doses found a wide range with an initial median dantrolene dose of 2.4 mg/kg and a total median dantrolene dose of 5.9 mg/kg. These doses approximate those recommended by the Malignant Hyperthermia Association of the United States (MHAUS). Our findings for initial dantrolene dose are similar to those of Kolb et al.[21] in their first multicenter study of dantrolene use in humans from 1977 to 1979, in which 11 MH patients received a dose of 2.5 ± 0.5 mg/kg. The median total vials of dantrolene required were 17 (first quartile 7, third quartile 36). Our data support current MHAUS recommendations for initial dantrolene treatment doses. MHAUS recommendations for the availability of at least 36 dantrolene vials in anesthetizing locations# were predicated on an average patient body weight of 70 kg. However, because 25% of our cases required >36 vials of dantrolene and considering the current obesity epidemic, local demographics may suggest that >36 vials be stocked where feasible and reasonable.

Unfortunately, the AMRA report form did not request data on the techniques used to achieve active cooling or the expired or arterial carbon dioxide levels achieved after initiation of hyperventilation. Although MHAUS does not currently recommend the use of mannitol for MH events, 34% of our patients were treated with mannitol. We suggest that mannitol be stocked on MH carts and that its possible administration be added to the current MHAUS treatment protocol.** We were also able to show a correlation between the severity of abnormal findings and the use of other adjunctive treatments. This lends support to the remainder of the MHAUS treatment protocol,

¶MHAUS has sample letters that may be used by individuals to notify their family members of their possible MH susceptibility. See www.mhaus.org. When consent has been given, a summary of a registered patient's anesthetic history may be obtained by contacting the MH Registry by phone at 888-274-7899 or by e-mail to Dr. Brandom (BrandomBW@anes.upmc.edu).

#Available at: www.mhaus.org (medical professionals; general FAQs). Accessed December 12, 2008.

**Available at: www.mhaus.org (medical professionals; MH crisis management; MH Protocol Poster). Accessed April 21, 2009.

although we were unable to demonstrate that any of these adjunctive treatments decreased the MH complication rate.

Twenty-one patients with MH experienced disseminated intravascular coagulation or neurologic dysfunction at a temperature <41.6°C. Our data suggest that MH may decrease this potentially lethal human critical thermal maximum.[22,23]

Our earlier study found that disseminated intravascular coagulation was associated with a 50-fold increased likelihood of cardiac arrest ($n = 8$) and an 89-fold likelihood of death ($n = 4$).[2] We now report higher maximum temperatures in 13 patients experiencing disseminated intravascular coagulation. Furthermore, we identify higher maximum temperatures as significantly increasing the likelihood of all complications. Because core temperature perturbations during the first 30 minutes are difficult to interpret, Sessler[24] recommends temperature monitoring during general anesthetics that exceed 30 minutes in duration. We agree and suggest revision of current American Society of Anesthesiologists Standards†† and Canadian Anesthesiologists' Society Guidelines.‡‡ Although the actual dantrolene dose administered was not significant, a longer interval from first sign of MH to first dantrolene dose also increased the likelihood of MH complications. Accurate temperature monitoring can facilitate an early diagnosis of MH, and with prompt dantrolene administration may prevent complications and death.

APPENDIX A: CASE HISTORIES FOR SELECTED MH EVENTS

Case 1: Liquid Crystal Temperature Trend Failure

This 25-year-old man with a muscular body build was anesthetized with isoflurane but no succinylcholine for an emergent plastic surgical/dental repair after a gun shot wound. He had a familial history positive for MH. He had never previously been anesthetized. Before his adverse reaction, he was monitored with both skin liquid crystal and esophageal temperature probes. While intubated and on controlled ventilation, he developed sinus tachycardia, tachypnea, hypercarbia (maximum expired CO_2, 80.9 mm Hg), and inappropriately increased temperature. The anesthesia providers reported that the skin liquid crystal temperature probe did not accurately trend with the core temperature probe. A maximum temperature of 40.0°C was reported 105 minutes after induction. The order of appearance of the adverse signs was not reported, but the first sign occurred 20 minutes after induction. Results of an arterial blood gas drawn 100 minutes after induction while the patient was being hyperventilated with a fraction of inspired oxygen of 1.0 were a pH of 7.14, a Pco_2 of 69 mm Hg, a Po_2 of 256 mm Hg, a base excess of −8.1 mEq/L, and a bicarbonate level of 21.7 mEq/L. Peak potassium was 6.7 mEq/L, and peak creatine kinase was 16,570 U/L. He was treated with volatile anesthetic discontinuation 100 minutes after induction, dantrolene (0.9 mg/kg initial dose 130 minutes after induction and total dose of 8.9 mg/kg), active cooling, fluid loading, and bicarbonate. He experienced no MH-related complications.

Case 2: Liquid Crystal Temperature Trend Failure

This 34-year-old man with a muscular body build was anesthetized for an elective ENT procedure. He had never previously been anesthetized. He had a positive family history of MH of which he was unaware at the time of his anesthetic. His anesthetic included sevoflurane and succinylcholine. Before his adverse reaction, he was monitored with both a skin liquid crystal and an esophageal temperature probe. One hundred fifty-five minutes after anesthetic induction, when surgery had already been completed but the patient was still in the operating room, he developed generalized muscular rigidity and tachypnea, sinus tachycardia, sweating, hypercarbia (maximum expired CO_2, 76 mm Hg), and rapidly increasing temperature. His maximum temperature was 39.1°C at 160 minutes after anesthetic induction. The anesthesiologists reported that the liquid crystal temperature probe did not accurately trend with his esophageal temperature probe. Results of an arterial blood gas drawn 171 minutes after induction while the patient was being hyperventilated with a fraction of inspired oxygen of 1.0 were a pH of 7.06, a Pco_2 of 95.9 mm Hg, a Po_2 of 269 mm Hg, a base excess of −6.7 mEq/L, and a bicarbonate level of 27.1 mEq/L. Peak potassium was 5.5 mEq/L, and peak creatine kinase was 52,700 U/L. He was treated with volatile anesthetic discontinuation, dantrolene (2.5 mg/kg initial dose 170 minutes after induction and total dose of 10.1 mg/kg), active cooling, fluid loading, furosemide, mannitol, glucose and insulin, and bicarbonate. He experienced no MH-related complications.

Case 3: No Dantrolene, Complication Reported

This 13-year-old boy was anesthetized with desflurane and succinylcholine for an elective ENT operation. He developed masseter spasm, dark-colored urine, generalized muscular rigidity, inappropriate sinus tachycardia, inappropriately increased temperature, tachypnea, and sweating. His peak creatine kinase was recorded as 37,911 U/L. He was not treated with dantrolene. Although hepatic dysfunction was reported as an MH complication, no further details on its severity or nature were noted.

Case 4: No Dantrolene, Complication Reported

This 35-year-old woman was anesthetized with propofol, sevoflurane, and succinylcholine for an elective plastic surgical procedure. She developed masseter

††Available at: www.asahq.org/publicationsAndServices/standards/02.pdf. Accessed December 12, 2008.

‡‡Available at: www.cas.ca/members/sign_in/guidelines/practice_of_anesthesia/default.asp?load=patient_monitoring. Accessed December 12, 2008.

spasm, sinus tachycardia, rapidly increasing temperature, and hypercarbia. Her peak creatine kinase was 365,970 U/L. Her sevoflurane was discontinued within 1 minute of its initiation, but she received no dantrolene. Her MH complication was reported as other: bilateral lower extremity muscle soreness. No renal dysfunction was reported.

Case 5: Continued Volatile Anesthetic, Survivor with Rhabdomyolosis

This MH survivor was a 6-year-old boy undergoing an elective ENT procedure who had a 65-minute anesthetic that included halothane and succinylcholine. He developed masseter spasm, inappropriate hypercarbia (maximum expired CO_2, 51 mm Hg), and inappropriate sinus tachycardia. Volatile anesthetics were continued. Five hours and 10 minutes after the anesthetic was finished, inappropriate rapidly increasing temperature with a peak temperature of 40°C developed and dantrolene was administered. His peak creatine kinase was 33,000 U/L. He was noted to have significant muscle weakness after his event.

Case 6: Continued Volatile Anesthetic, No Dantrolene, Survivor with Rhabdomyolysis

This MH survivor was a 9-year-old boy undergoing an elective ENT procedure who had a 50-minute anesthetic that began with halothane and succinylcholine. Five minutes after anesthetic induction, he developed masseter spasm. The halothane was discontinued, and isoflurane was begun. It is not clear when he developed inappropriate tachypnea, dark-colored urine, and a peak creatine kinase of 45,300 U/L. The isoflurane was continued, and he was not treated with dantrolene. No information exists as to whether this child had any MH-related complications such as acute renal failure.

Case 7: Second Dose of Succinylcholine, Survivor with Severe Myalgia

A 30-year-old woman for an emergency Caesarean delivery was given a second dose of succinylcholine after developing masseter muscle rigidity. She then developed inappropriate tachypnea, inappropriate hypercarbia, generalized muscular rigidity, and dark-colored urine with a peak creatine kinase of 3,860 U/L. She was given 2 mg/kg dantrolene and survived, but she complained of severe myalgia. Fetal outcome was not reported.

APPENDIX B: CORRELATION BETWEEN TREATMENT FREQUENCY AND SEVERITY OF ABNORMAL FINDINGS DURING MH EVENTS

Hyperventilation was used when end-tidal Pco_2 was higher (median 68.5, first quartile 59.0, third quartile 80.0 mm Hg with hyperventilation vs median 54.5, first quartile 45.0, third quartile 66.0 mm Hg without hyperventilation) ($P < 0.0001$).

Active cooling was associated with a higher maximum temperature of 39.2°C (first quartile 38.5°C, third quartile 40.2°C) vs 37.7°C without cooling (first quartile 36.7°C, third quartile 38.9°C) ($P < 0.0001$).

Furosemide, mannitol, and/or glucose and insulin adminstration were associated with higher maximum potassium (median 5.4, first quartile 4.6, third quartile 6.2 mEq/L with drug vs median 4.7, first quartile 4.3, third quartile 5.2 mEq/L without drug treatment) ($P < 0.0001$).

Bicarbonate use was associated with lower arterial pH (median 7.19, first quartile 7.07, third quartile 7.25 with bicarbonate vs 7.25, first quartile 7.20, third quartile 7.33 without bicarbonate therapy) ($P < 0.0001$) and a more negative base excess (median −6.9, first quartile −2.5, third quartile −9.0 with bicarbonate vs −3.5, first quartile −1.4, third quartile −6.0 without bicarbonate) ($P < 0.0001$). Four patients received bicarbonate and no dantrolene. The median year for bicarbonate administration was 1997 (first quartile 1994 and third quartile 2000 with a range of 1988–2006) and was later than the median year of 1996 for those not receiving bicarbonate (first quartile 1992 and third quartile 2000 with a range of 1987–2006) ($P = 0.020$).

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