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Cardiac Arrests and Deaths Associated with Malignant Hyperthermia in North America from 1987 to 2006

A Report from The North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States

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Background: **The authors determined associated cardiac arrest and death rates in cases from Canada and the United States as reported to The North American Malignant Hyperthermia (MH) Registry and analyzed factors associated with a higher risk of poor outcomes.**

Methods: **The authors searched the database for AMRA (adverse metabolic/musculoskeletal reaction to anesthesia) reports with inclusion criteria as follows: event date between January 1, 1987, and December 31, 2006; "very likely" or "almost certain" MH as ranked by MH Clinical Grading Scale; location in Canada or the United States; and one or more anesthetic agents given. The exclusion criterion was a pathologic condition other than MH independently judged by the authors. Severe MH outcomes were analyzed as regards clinical history and presentation, using Wilcoxon rank sum tests for continuous variables and Pearson exact chi-square tests for categorical variables. A Bonferroni correction adjusted for multiple comparisons.**

Results: **Of 291 events, 8 (2.7%) resulted in cardiac arrests and 4 (1.4%) resulted in death. The median age in cases of cardiac arrest/death was 20 yr (range, 2–31 yr). Associated factors were muscular build (odds ratio, 18.7; $P = 0.0016$) and disseminated intravascular coagulation (odds ratio, 49.7; $P < 0.0001$). Increased risk of cardiac arrest/death was related to a longer time period between anesthetic induction and maximum end-tidal carbon dioxide (216 *vs.* 87 min; $P = 0.003$). Unrelated factors included patient or family history, anesthetic management, and the MH episode.**

Conclusions: **Modern US anesthetic practice did not prevent MH-associated cardiac arrest and death in predominantly young, healthy patients undergoing low- to intermediate-risk surgical procedures.**

Additional material related to this article can be found on the ANESTHESIOLOGY Web site. Go to http://www.anesthesiology.org, click on Enhancements Index, and then scroll down to find the appropriate article and link. Supplementary material can also be accessed on the Web by clicking on the "ArticlePlus" link either in the Table of Contents or at the top of the Abstract or HTML version of the article.

THE inherited myopathy malignant hyperthermia (MH) (MIM No. 145600)# features sustained skeletal muscle hypermetabolism caused by altered calcium homeostasis. Human MH usually occurs with exposure to volatile anesthetic agents and/or depolarizing muscle relaxants.[1]

Malignant hyperthermia susceptibility, inherited as an autosomal dominant with reduced penetrance, has been associated with mutations in two genes: *RYR1* (ryanodine receptor type 1), encoding the skeletal muscle isoform of the calcium release channel of the sarcoplasmic reticulum; and *CACNA1S*, encoding the α_1 subunit of the L-type calcium channel isoform of the sarcolemma (dihydropyridine receptor).[2] In 2005, Sambuughin *et al.* screened North American MH patients and found 18 different *RYR1* sequence variations in 21 of 30 individuals, 9 of which were known MH mutations. The population was characterized by a high *RYR1* allelic heterogeneity with 9/18 novel *RYR1* variants. No screening was done for *CACNA1S* mutations.[3]

Monnier *et al.* estimated the incidence of MH causative mutations at 1 in 2,000 to 1 in 3,000 in the French population.[4] The incidence of MH episodes in the United States and Canada is unknown because of a lack of universal reporting. Recently, the institution of an International Classification of Diseases, Ninth Revision, code for MH (995.86) permitted Brandom and Muldoon to use a capture–recapture method to estimate the annual number of suspected MH cases in the United States to be 707 (exact 95% confidence interval [CI], 396–1,017) per year (Barbara W. Brandom, M.D., Professor of Anesthesiology, Children's Hospital and the University of Pittsburgh, Pittsburgh, Pennsylvania, written communication, June 12, 2007).

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Online Mendelian Inheritance in Man. Available at: www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM&TabCmd=Limits. Accessed June 27, 2007.

Before US Food and Drug Administration approval of dantrolene in 1980, the mortality rate of MH was 64%.[5] The current US and Canadian mortality rate is unknown.

We analyzed 19 yr of North American MH Registry (Registry) data to determine the cardiac arrest and death rate. We examined the association between severe MH adverse outcomes and personal characteristics, family medical history, previous history of an adverse anesthetic event, anesthetic agents and monitoring devices used before the development of an adverse anesthetic event, MH treatment, and/or MH complications.

Materials and Methods

After the Penn State College of Medicine Institutional Review Board (Hershey, Pennsylvania) determined exempt status, we examined AMRA (adverse metabolic/musculoskeletal reaction to anesthesia) reports received by the Registry from January 1, 1987, through December 31, 2006. Inclusion criteria were as follows: event occurred from January 1, 1987, through December 31, 2006; ranked by MH clinical grading scale as "very likely" MH event or "almost certain" MH event (appendix 1)[6]; event location in the United States of America or Canada; and at least one anesthetic agent given.

The exclusion criterion was a pathologic condition other than MH independently judged by the four senior authors as likely cause (*e.g.*, Duchenne muscular dystrophy, hypothalamic injury, sepsis). For in-depth analysis, reviewers were not blinded to outcome and studied the entire case report complete with comments placed on the form by the reporting healthcare professionals. Cases were excluded from the study only after all four reviewers independently agreed that they were likely attributable to complications of the surgical procedure or an underlying preexisting disorder other than MH.

Variables studied were demographics (United States or Canada, event year, age, sex, race, body build), family history (MH, sudden infant death syndrome, sudden death from unknown cause in a family member at an age > 1.5 to < 45 yr, heat stroke, neurolept malignant syndrome), previous medical history (muscle weakness or muscle cramps or pain interfering with daily activity at least once a week; cola-colored urine; heat stroke or prostration; heat intolerance; exercise intolerance due to pain, weakness, or fever; increased muscle tone; decreased muscle tone; generalized muscular weakness), previous anesthetic history (number of previous anesthetics, number of previous general anesthetics, number of unusual metabolic responses), procedure type and urgency, adverse anesthetic response (agents; ventilation mode; monitor type, including specific temperature monitor used), location (operating room, postanesthesia care area), and MH signs, including the order in which they were observed (masseter spasm, generalized muscular rigidity, cola-colored urine, tachypnea, hypercapnia, skin mottling, cyanosis, sinus tachycardia, ventricular tachycardia, ventricular fibrillation, elevated temperature, rapidly increasing temperature, sweating, excessive bleeding).

Also studied were time intervals from anesthetic induction to development of the first sign of an adverse anesthetic reaction, anesthetic induction to development of maximum end-tidal partial pressure of carbon dioxide (P_{CO_2}), anesthetic induction to the development of maximum temperature, anesthetic induction to discontinuation of volatile anesthetic agents, and anesthetic induction to recrudescence time. Additional evaluations included time between first MH sign and discontinuation of volatile agents, time between first sign and first dantrolene dose, and time between first sign and recrudescence.

Also analyzed were maximum temperature, maximum serum potassium, maximum end-tidal P_{CO_2}, maximum arterial P_{CO_2}, lowest pH, maximum base deficit, lowest arterial bicarbonate, peak lactic acid, peak creatine kinase, prothrombin time, partial thromboplastin time, international normalized ratio, fibrinogen, and platelet count.

Finally evaluated were initial and total dantrolene dose (absolute and mg/kg dose), need for cardiopulmonary resuscitation, MH complication type (cardiac dysfunction, change in consciousness, disseminated intravascular coagulation, hepatic dysfunction, pulmonary edema, renal dysfunction), recrudescence, and survival.

Statistical Analysis

To test the hypotheses that the severe outcomes of either cardiac arrest or death would be associated with a distinctive clinical history and presentation, we took several approaches based on the number of cases available, the type of data, and the distribution of the data. Because there were very few severe outcome cases and many of the data were not distributed normally, nonparametric or exact tests were chosen over parametric or asymptotic tests. The limited number of cases also makes the calculation of CIs for odds ratios more difficult with a much wider range of variability (*i.e.*, wide CIs).

For continuous variables such as time or dosage, a Wilcoxon rank sum test was used to compare the medians for those with cardiac arrest or death to those without cardiac arrest or death, and first and third quartiles were used as a surrogate for a CI. For categorical variables such as muscular build, a Pearson exact chi-square test tested the difference in the proportion of cardiac arrest or death between the categories of each variable. Exact odds ratios with exact 95% CIs were used to quantify the magnitude and direction of the difference between the proportions.

The Bonferroni correction was used to adjust for multiple comparisons to maintain an overall error rate of 0.05. The Bonferroni correction is a very conservative approach that divides the usual level of significance, 0.05, by the number of comparisons being made within a similar set of comparisons. An exact logistic regression including multiple predictor variables and covariates was attempted but, because of the limited number of cardiac arrest and death cases, could not be fit. Statistical analysis was performed using SAS 9.1.3 Service Pack 4 (Chicago, IL).

Results

Five hundred ninety-seven reports were received by the Registry office before December 31, 2006. Two hundred ninety-one cases (48.7%) met entry criteria. (Additional information regarding this is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org.) One hundred sixteen cases (39.9%) were graded as "very likely" MH, and 175 (60.1%) were graded as "almost certain" MH.

Of 291 subjects, 4 (1.4%) survived cardiopulmonary resuscitation during MH, and 4 (1.4%) given cardiopulmonary resuscitation died. Thus, 8 subjects (2.7%) experienced these severe outcomes.

Patients survived cardiac arrest in 1991, 1994, 1997, and 1999. They resided in four different US states and had a median age of 12 yr (range, 2–31 yr, with one missing value). Two procedures were emergencies (open fracture repair and plastic surgery in children), and none had a high surgery-specific cardiac risk.[7]

Deaths occurred in 1990, 2003, 2005, and 2006. The patients resided in four different US states and had a median age of 22 yr (range, 10–24 yr). In these 4 cases, all surgical procedures were elective, and the surgery-specific cardiac risk was low or intermediate. Appendix 2 describes these cases.

No deaths or cardiac arrests were Canadian. Although the Canadian population is 11% of the size of the US population, only 1.8% of MH cases, regardless of outcome, were Canadian. One of the main sources of returned Registry reports is those mailed out by the Malignant Hyperthermia Association of the United States after MH Hotline consultations. In 2006, less than 1% of all calls to the Hotline were from Canadian healthcare providers (Gloria Artist, Malignant Hyperthermia Association of the United States Hotline Coordinator, written communication, June 5, 2007).

Relative to the others, cardiac arrest/death patients were 18.7 times more likely to have a muscular body build. Two of these were elite athletes.

There was a longer interval between anesthetic induction and the time of maximum end-tidal P_{CO_2} in cases with cardiac arrest/death (median, 216 *vs.* 87 min). There was nonsignificant trend toward a longer interval between anesthetic induction and the time of volatile anesthetic discontinuation in cases with cardiac arrest/death (median, 211 *vs.* 75 min); this information was available in 217 cases.

There were differences in the characteristics of MH (table 1) between these two groups. Relative to the cases without cardiac arrest or death, those who arrested or died were 49.7 times more likely to develop disseminated intravascular coagulation (table 2). The median total dose of dantrolene used to treat those with cardiac arrest/death was greater (10.1 *vs.* 5.0 mg/kg).

Cases in which MH was lethal differed from those that survived cardiac arrest. Muscular build was associated with a 13.6-fold greater risk of death during MH. The presentation of the MH event differed in various facets (table 3). Other differences between fatal MH and nonfatal MH cases included cardiopulmonary resuscitation odds ratio of 181.9 and disseminated intravascular coagulation complication odds ratio of 89.4 (table 4).

Table 1. Significant Differences between the Cardiac Arrest/Death Group and the Non–Cardiac Arrest/Nondeath Group Malignant Hyperthermia Events for Continuous Variables

MH Event Variable	Cardiac Arrest and/or Death	No Cardiac Arrest/No Death	*P* Value	Bonferroni-adjusted Level of Significance
Induction to maximum end-tidal P_{CO_2} interval, min	216 (135, 305), n = 8	87 (30, 150), n = 239	0.0025*	0.017
Maximum end-tidal P_{CO_2}, mmHg	80 (75, 100), n = 7	67 (56, 78), n = 253	0.016*	0.025
Maximum temperature, °C	42.5 (40.5, 43.0), n = 8	38.9 (37.9, 39.8), n = 275	0.0001*	0.025
Arterial pH	6.96 (6.89, 7.13), n = 8	7.22 (7.16, 7.28), n = 265	0.002*	0.005
Arterial P_{CO_2}, mmHg	94 (67, 137), n = 8	55 (44, 66), n = 263	0.001*	0.005
Serum potassium, mEq/l	7.75 (7.00, 8.35), n = 8	4.90 (4.40, 5.70), n = 262	0.0001*	0.005
Prothrombin time, s	17 (14.7, 28.0), n = 7	13 (12.0, 14.1), n = 155	0.0004*	0.005
Total dose of dantrolene, mg/kg	10.1 (8.8, 14.9), n = 8	5.0 (2.5, 9.6), n = 248	0.0032*	0.025

Table 1 lists significant differences for continuous variables between cardiac arrest/death malignant hyperthermia (MH) events and non–cardiac arrest/nondeath MH events. Values are expressed as median (first and third quartile). *P* values were determined using a Wilcoxon rank sum test comparing medians.

* To adjust for multiple testing with many variables, we used a Bonferroni correction to determine the adjusted level of significance for each set of variables examined.

n = number of cases for which data were available for each variable; P_{CO_2} = partial pressure of carbon dioxide.

Table 2. Significant Differences between the Cardiac Arrest/Death Group and the Non–Cardiac Arrest/Nondeath Group Malignant Hyperthermia Events for Categorical Variables

Variable	Odds Ratio	Exact 95% CI	*P* Value
Muscular build, n = 8 *vs.* 278	18.7	2.3–857.9	0.0016
Disseminated intravascular coagulation, n = 7 *vs.* 179	49.7	6.9–596.5	0.0000

Table 2 lists significant differences for categorical variables between cardiac arrest/death malignant hyperthermia events and non–cardiac arrest/nondeath malignant hyperthermia events. A Pearson exact chi-square test tested the difference in the proportion of cardiac arrest or death between the categories of each variable. Exact odds ratios with exact 95% confidence intervals (CIs) were used to quantify the magnitude and direction of the difference between the proportions.

n = number of cases for which data were available for each variable.

Table 4. Significant Differences between the Fatal Group and the Nonfatal Group Malignant Hyperthermia Events for Categorical Variables

Variable	Odds Ratio	Exact 95% CI	*P* Value
Muscular build, n = 4 *vs.* 282	13.6	1.7–∞	0.0128
Cardiopulmonary resuscitation, n = 4 *vs.* 287	181.9	12.0–11,160	0.0001
Disseminated intravascular coagulation, n = 4 *vs.* 182	89.4	10.5–∞	0.0000

Table 4 lists the significant differences for categorical variables between the fatal and nonfatal malignant hyperthermia group events. A Pearson exact chi-square test tested the difference in the proportion of cardiac arrest or death between the categories of each variable. Exact odds ratios with exact 95% confidence intervals (CIs) were used to quantify the magnitude and direction of the difference between the proportions.

n = number of cases for which data were available for each variable.

Discussion

We used a two-step process to determine the likelihood that an adverse anesthetic event was MH. First, the MH clinical grading scale, a comprehensive clinical case definition for MH, was applied to the MH Registry cases. This scale ranks the qualitative likelihood that an adverse anesthetic event represents MH with an assigned rank for the lower bound of the likelihood of MH.[6]

Second, the four authors with MH expertise reviewed each case in which cardiopulmonary resuscitation or death occurred to exclude adverse anesthetic events that may have been due to independent medical or surgical complications: hyperkalemia associated with organ transplantation and cardiopulmonary bypass, possible brain stem herniation or hypothalamic injury associated with neurosurgical procedures. Also eliminated were cases in which a diagnosis of Duchenne, Becker, or nonspecific myopathy was established.

We established a presumptive MH diagnosis based on clinical findings at the time of the adverse anesthetic reaction, independent of diagnostic muscle testing (caffeine–halothane contracture test) or mutation evaluation. In most cases, the report form was completed by the anesthesiologists and nurse anesthetists directly caring for the patient at the time of the event. These providers had the best access to clinical and laboratory data and were in the best position to judge the appropriateness of specific clinical signs for the patient's medical condition, anesthetic technique, and surgical procedure (as required by the MH Clinical Grading Scale).

We evaluated events presenting in a classic fashion (*e.g.*, after the administration of at least one anesthetic) to reduce the possibility that non-MH causes contributed to morbidity or mortality. We may have underestimated the true cardiac arrest and death rate for MH cases.

Dantrolene was used in 91.9% of patients, with a mortality rate of 1.4%. Before use of dantrolene, Britt and Kalow[5] reported a mortality rate of 64% in 89 North American cases. Fifty-one Austrian cases of suspected MH, from 1975 to early 1986, demonstrated a 16.4%

Table 3. Significant Differences between the Fatal Group and the Nonfatal Group Malignant Hyperthermia Events for Continuous Variables

Variable	Fatal MH	Nonfatal MH	*P* Value	Bonferroni-adjusted Level of Significance
Maximum temperature, °C	42.0 (40.5, 43.0), n = 4	38.9 (37.9, 39.9), n = 279	0.004*	0.025
Maximum potassium, mEq/l	7.55 (7.00, 8.35), n = 4	4.95 (4.40, 5.80), n = 266	0.002*	0.005
Maximum end-tidal P_{CO_2}, mmHg	100 (75, 110), n = 3	67 (56, 79), n = 257	0.024*	0.025
Maximum arterial P_{CO_2}, mmHg	122 (94, 138), n = 4	55 (44, 67), n = 267	0.003*	0.005
Lowest arterial pH	6.91 (6.84, 6.96), n = 4	7.22 (7.16, 7.28), n = 269	0.001*	0.005
Maximum arterial base deficit	14.0 (15.5, 11.5), n = 4	5.0 (8.1, 2.0), n = 249	0.002*	0.005
Maximum prothrombin time, s	28 (19, 200), n = 3	13 (12, 14), n = 159	0.003*	0.005
Total dantrolene dose, mg/kg	11.1 (10.1, 14.9), n = 4	5.1 (2.5, 9.8), n = 252	0.021*	0.025

Table 3 lists significant differences for continuous variables between fatal and nonfatal malignant hyperthermia (MH) group events. Values are expressed as median (first and third quartile). *P* values were determined using a Wilcoxon rank sum test comparing medians.

* To adjust for multiple testing with many variables, we used a Bonferroni correction to determine the adjusted level of significance for each set of variables examined.

n = number of cases for which data were available for each variable; P_{CO_2} = partial pressure of carbon dioxide.

mortality (9 of 55 cases).** Dantrolene was given to 15% of these patients.[8] The Danish Register analyzed all cases between January 1, 1978, and July 1, 1984, when dantrolene had just been introduced, with 10% mortality in 10 fulminant cases.[9]

Registry studies may be limited by inconsistencies of case ascertainment and incomplete reporting. Underreporting or biased reporting (withholding sensitive cases) could lead to underestimation or overestimation of the severity of MH events. The data we present likely represent an underestimation. We do not know whether cardiac arrests and deaths are proportionately underreported to the Registry as well.

Not all MH deaths were reported to the Registry, because the American Society of Anesthesiologists Closed Claims Project provided at least three additional deaths (not included in this analysis) (Karen L. Posner, Ph.D., Research Professor, Department of Anesthesiology, University of Washington, Seattle, Washington, American Society of Anesthesiologists Closed Claims Project Investigator, written communication, April 2, 2007, April 23, 2007, and May 4, 2007). The MH Hotline service provided two US MH deaths not in the Registry or the Closed Claims databases. A total of nine deaths for the 19-yr period may yet underestimate reality. MH cardiac arrest and deaths continue to occur: The MH Hotline reports a 2007 case of a young woman who died during MH.

There are no known Canadian deaths, but disproportionately few MH cases were reported from Canada. We suspect underreporting rather than a decreased frequency.

Burkman *et al.*[10] described the clinical variables associated with MH recrudescence. Their limitations included ". . . reporting and recall bias, subjectivity of definitions . . . , changes in anesthetic techniques over time, and retrospective data entry into a standardized database that may lack specific details of anesthetic and clinical courses."[10] These limitations apply to us as well because we used the same database.

However, the Registry was established precisely because of the limitations of using original anesthesia and hospital records.[11] Medical records are frequently not available (medical records disappear as a result of floods, fires, planned destruction after a preset interval, and carelessness), are difficult to read (because of the poor quality of the original or copy), and are incomplete. With repeated use over 19 yr, the AMRA form has undergone multiple iterations to increase utility.

Our statistical analyses are limited by the small number of cardiac and death cases. Because of this, the data could not be analyzed with parametric and asymptotic statistical methods. The nonparametric and exact methods used allow us to analyze the data without concern for the distribution of the data or small cell counts invalidating the statistical tests.

Muscular build increased the odds of a life-threatening MH event more than 10-fold. Twenty-five percent of severe MH patients were elite athletes. Whereas muscularity and various musculoskeletal abnormalities may be related to susceptibility[12] and muscular build is associated with MH recrudescence,[10] the association of muscularity with cardiac arrest and death is a new observation.

One possible explanation may be that increased muscle mass may become more energy deficient during an MH event due to limitations of diffusion. Ryanodine receptors with MH mutations may be "leakier" than normal channels.[13] Increased intracellular calcium accentuates muscular force, and perhaps muscular MH individuals have "leakier" channels that predispose them to more severe MH.

There was no difference in outcome in our entire group whether or not temperature was measured. Our small numbers limit conclusions in this regard. However, two of the nine patients (this total is from all sources) who died with MH during this 19-yr period had no temperature monitoring when MH began. They were healthy 10 and 16 yr olds undergoing routine eye and oral surgery. The surgeon and the circulating nurse respectively made the diagnosis of hyperthermia when they touched the patient. With prompting, the anesthesiologists instituted temperature monitoring to discover that their patients' temperatures were 40°C or greater.

There were no reported differences in outcome as regards time to MH diagnosis or treatment. However, our small number of cardiac arrests limits conclusions in this regard.

The time interval between anesthetic induction to maximum end-tidal carbon dioxide was longer in the cases with cardiac arrest/death compared with the others (216 *vs.* 87 min). Britt and Kalow[5] observed in 1970: "The longer the duration of anesthesia the greater was the chance of a cardiac arrest and eventual death." In an Austrian series, Mauritz *et al.* [8] noted increased mortality when surgery or anesthesia exceeded 60 min. Could the time interval between anesthetic induction and maximum end-tidal carbon dioxide be a marker for volatile anesthetic dose?

Disseminated intravascular coagulation develops during severe MH. Britt *et al.*[12] described a total of 43 deaths associated with impaired coagulation in 117 MH events before dantrolene therapy. Using the published data of Britt *et al.*[12], we calculated that impaired coagulation increased the likelihood of death in their series 6.8-fold (exact 95% CI, 2.9–15.7). Defined criteria established our MH diagnoses, but we did not have sufficient laboratory data to formally prove the diagnosis of disseminated intravascular coagulation.[14] Instead, we relied on the healthcare provider's judgment. The development of disseminated intravascular coagulation increased 50-fold

** We omitted from consideration 10 cases of sudden death in infants, unclear postoperative fever, and crisis not related to anesthesia.

the likelihood of a cardiac arrest and/or death and increased 89-fold the likelihood of death. These higher odds ratios may reflect the impact dantrolene has had on reducing other MH complications.

Summary

This North American Malignant Hyperthermia Registry database examination revealed 291 MH episodes with 8 cardiac arrests (2.7%), of whom 4 (1.4%) died, with a median age of 20 yr. Muscular build increased the risk of dying 14-fold and the risk of cardiac arrest 19-fold. A longer period between anesthetic induction to maximum end-tidal carbon dioxide was associated with cardiac arrest and death. The development of disseminated intravascular coagulation during MH made cardiac arrest 50 times more likely and death 89 times more likely.

Some young healthy patients unfortunately continue to die during MH events. To improve our understanding of this potentially lethal condition, we encourage healthcare providers to obtain blood specimens appropriate for molecular genetic analysis on all patients suffering a possible MH-related arrest or death.†† Whenever possible, muscle biopsy contracture studies should be performed on MH-associated cardiac arrest survivors. We urge anesthesiologists, nurse anesthetists, and intensivists to continue to anonymously report adverse anesthetic events to the Registry.

This article is dedicated to the memory of Gregory Alan Larach, son of Drs. David and Marilyn Larach. The authors also honor the many contributions of David R. Larach, M.D., Ph.D. (Chief of Cardiac Anesthesiology [retired] and Chairman of the Institutional Review Board [retired], St. Joseph Medical Center, Towson, Maryland), to The North American Malignant Hyperthermia Registry. The authors thank Michael C. Young, M.S. (Database Manager of The North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States), for his response to our data queries. The authors express their sympathy to the families whose relatives died during malignant hyperthermia events and their gratitude to the many anesthesiologists, intensive care physicians, and nurse anesthetists who submitted adverse metabolic/musculoskeletal reaction to anesthesia **(AMRA)** reports to the Registry.

†† Contact the North American MH Registry (call 1-888-274-7899 or see www.mhreg.org) to obtain appropriate consent forms. Blood preserved in 5-ml anticoagulated (purple top/EDTA-preferred) tubes will be suitable for genetic analysis. If storage is necessary, refrigerate at 4°C. Results from *RYR1* analysis can be linked to clinical event data in the Registry database.

Appendix 1: Malignant Hyperthermia Clinical Grading Score

Scoring Rules‡‡

1. MH indicators
   - Review the list of clinical indicators. If any indicator is present, add the points applicable for each indicator while observing the double-counting rule below, which applies to multiple indicators representing a single process.
   - If no indicator is present, the patient's MH score is zero.
2. Double counting
   - If more than one indicator represents a single process, *count only the indicator with the highest score*. Application of this rule prevents double counting when one clinical process has more than one clinical manifestation.
   - Exception: The score for any relevant indicators in the final category "other indicators" *should* be added to the total score without regard to double counting.
4. Interpreting the raw score: MH rank and qualitative likelihood

Raw Score Range	MH Rank	Description of Likelihood
0	1	Almost never
3–9	2	Unlikely
10–19	3	Somewhat less than likely
20–34	4	Somewhat greater than likely
35–49	5	Very likely
50+	6	Almost certain

Clinical Indicators for Use in Determining the MH Raw Score

Process I: Rigidity

Indicator	Points
Generalized muscular rigidity (in absence of shivering due to hypothermia, or during or immediately after emergence from inhalational general anesthesia)	15
Masseter spasm shortly after succinylcholine administration	15

Process II: Muscle Breakdown

Indicator	Points
Elevated creatine kinase > 20,000 U after anesthetic that included succinylcholine	15
Elevated creatine kinase > 10,000 U after anesthetic without succinylcholine	15
Cola-colored urine in perioperative period	10
Myoglobin in urine > 60 μg/l	5
Myoglobin in serum >170 μg/l	5
Blood/plasma/serum K^+ > 6 mEq/l (in absence of renal failure)	3

Process III: Respiratory Acidosis

Indicator	Points
End-tidal pressure of carbon dioxide (P_{ETCO_2}) > 55 mmHg with appropriately controlled ventilation	15
Arterial carbon dioxide tension (Pa_{CO_2}) > 60 mmHg with appropriately controlled ventilation	15
P_{ETCO_2} > 60 mmHg with spontaneous ventilation	15
Arterial Pa_{CO_2} > 65 mmHg with spontaneous ventilation	15
Inappropriate hypercarbia (in anesthesiologist's judgment)	15
Inappropriate tachypnea	10

Process IV: Temperature Increase

Indicator	Points
Inappropriately rapid increase in temperature (in anesthesiologist's judgment)	15
Inappropriately increased temperature > 38.8°C (101.8°F) in the perioperative period (in anesthesiologist's judgment)	10

Process V: Cardiac Involvement

Indicator	Points
Inappropriate sinus tachycardia	3
Ventricular tachycardia or ventricular fibrillation	3

Other Indicators That Are Not Part of a Single Process§§

Indicator	Points
Arterial base excess more negative than −8 mEq/l	10
Arterial pH <7.25	10
Rapid reversal of MH signs of metabolic and/or respiratory acidosis with intravenous dantrolene	5

‡‡ From Larach *et al.*[6]; modified to delete the MH susceptibility score with permission from the first author. Published with permission from Lippincott Williams & Wilkins. http://lww.com.

§§ These should be added without regard to double counting.

Appendix 2: Individual Case Summaries for Four Fatal Malignant Hyperthermia Events

Case 1

Case 1 was a 23.8-yr-old, 68-kg muscular woman with a personal history of one previous general anesthetic without unusual metabolic responses and a negative family medical history. She had no abnormalities of muscle tone or structure preoperatively and no cardiopulmonary disease. She was an elite athlete. She was anesthetized for a total thyroidectomy and radical neck dissection for thyroid cancer.

Her second general endotracheal anesthetic included isoflurane and succinylcholine. Anesthetic monitoring before the signs of MH included capnometry, pulse oximetry, and an esophageal temperature probe. Four hours 33 min after an anesthetic induction, she developed tachycardia. She subsequently developed (in order of appearance) arrhythmia, rapidly increasing temperature (maximum temperature 41.0°C), generalized muscular rigidity, hypercarbia, and excessive bleeding.

Results of an arterial blood gas drawn 4 h 45 min after anesthetic induction while the patient was being hyperventilated with a fraction of inspired oxygen (F_{IO_2}) of 1 were a pH of 6.78, a partial pressure of carbon dioxide (P_{CO_2}) of 147 mmHg, a partial pressure of oxygen (P_{O_2}) of 250 mmHg, a base excess of −17 mEq/l, and a bicarbonate level of 20 mEq/l. Peak potassium was 6.9 mEq/l, peak creatine kinase was 9,205 U/l, prothrombin time was 28 s (upper limit of normal, 17 s), and partial thromboplastin time was greater than 100 s (upper limit of normal, 40 s).

Unsuccessful treatment included volatile anesthetic discontinuation (4 h 37 min after induction and 4 min after the first adverse sign), hyperventilation with 100% oxygen with a new anesthesia machine and circuit, dantrolene (initial dose of 1.8 mg/kg given 4 h 40 min after anesthetic induction and 7 min after the first adverse sign and then titrated to a total of 10.3 mg/kg), active cooling, fluid loading, furosemide, mannitol, bicarbonate, glucose, insulin, procainamide, dopamine, phenylephrine, epinephrine, norepinephrine, dexamethasone, heparin, extracorporeal membrane oxygenation, and cardiopulmonary resuscitation. No reduction in the patient's rigidity was noted with the dantrolene administration. The patient did not survive this reaction that had begun while the patient was in the operating room.

Information obtained after the patient's death from her family revealed that she had had several childhood febrile episodes of unknown etiology and that she had reported "myalgias" for 4 days after a brief general anesthetic 1 month previously.

Case 2

Case 2 was a 21-yr-old, 95-kg muscular man who had a personal history of hand tremors but no history of unexplained fevers, muscle cramps, dark urine, heat stroke, or heat intolerance. He had no history of cardiopulmonary disease. His family history was remarkable for a great aunt who had died in her sleep as a young adult and a father with one episode of heat exhaustion related to work exposure.

The patient had never had anesthesia before. He was anesthetized with sevoflurane (and no succinylcholine) for an elective orthopedic surgical procedure. His airway was managed with a laryngeal mask with assisted ventilation. Before his event, monitoring included capnometry, pulse oximetry, and an electronic axillary temperature probe.

The first sign of an adverse anesthetic reaction was diaphoresis approximately 20 min after anesthetic induction during the operation. Subsequently, other adverse signs noted were (in order of appearance) tachypnea, sinus tachycardia, hypercarbia (with the maximum P_{ETCO_2} of 110 mmHg noted 4 h 20 min after anesthetic induction), elevated temperature (43°C esophageal while the axillary temperature probe was still reading 35.2°C 4 h 20 min after anesthetic induction), excessive bleeding, and cola-colored urine.

Results of an arterial blood gas obtained 5 h 44 min after anesthetic induction while the patient was being hyperventilated with an F_{IO_2} of 1 were a pH of 6.89, a P_{CO_2} of 128 mmHg, a P_{O_2} of 371 mmHg, a base excess of −9 mEq/l, and a bicarbonate level of 24 mEq/l. Peak potassium was 8.7 mEq/l, peak creatine kinase was 149,750 U/l, prothrombin time was greater than 200 s (upper limit of normal, 12 s), partial thromboplastin time was 80 s (upper limit of normal, 34 s), international normalized ratio was greater than 20, platelet count was 68,000/ml, and fibrinogen was less than 40 mg/dl.

Treatment initiated (once accurate temperature and a high P_{ETCO_2} were noted approximately 4 h after diaphoresis had begun) included volatile anesthetic discontinuation (4 h 20 min after induction and 4 h after the first adverse sign), hyperventilation with an oxygen supply never exposed to volatile anesthetics, dantrolene (initial dose 10 mg/kg 4 h 37 min after anesthetic induction and titrated to a total dose 17.8 mg/kg), active cooling, glucose, insulin, and bicarbonate.

Although the patient survived his initial episode that began in the operating room, he relapsed 38 h after anesthetic induction. During the relapse, he developed rigidity, renal dysfunction, uncontrollable hyperkalemia, and disseminated intravascular coagulation. He died in the intensive care unit approximately 43 h after anesthetic induction.

Case 3

Case 3 was a 23-yr-old, 84-kg muscular man with a negative family medical history and a personal history without unexplained fevers, muscle cramps, dark urine, heat stroke, or heat intolerance. He had no abnormalities of muscle tone or structure preoperatively. He had no history of cardiac disease, and he had mild, well-controlled asthma. He worked at a job that required significant physical effort. This was his second anesthetic, with his first anesthetic administered 3 months previously during a 2-h procedure. The initial unremarkable anesthetic included both desflurane and succinylcholine.

The patient's second anesthetic was administered for a lengthy elective plastic surgical procedure that required intermittent and prolonged tourniquet applications. Anesthetic agents administered included isoflurane and desflurane. No succinylcholine was given. He was tracheally intubated and ventilated in a controlled fashion. Monitors used before the first adverse sign included capnometry, pulse oximetry, and an electronic skin probe placed on the back of the shoulder.

The first adverse sign was sinus tachycardia that developed 6 h 15 min after induction while the surgical procedure was ongoing. This sign was followed by (in order of appearance) hypercarbia (with maximum $P_{ETCO_2} > 100$ mmHg 7 h 40 min after induction), elevated and rapidly increasing temperature (maximum esophageal temperature of 43°C reached 7 h 35 min after induction), generalized muscular rigidity, hypotension, excessive bleeding, and ventricular fibrillation.

Results of an arterial blood gas drawn approximately 8 h 20 min after anesthetic induction while the patient was being hyperventilated with a F_{IO_2} of 1 were a pH of 6.92, a P_{CO_2} of 115 mmHg, a P_{O_2} of 273 mmHg, a base excess of −14 mEq/l, and a bicarbonate level of 20 mEq/l. The peak creatine kinase obtained 8 h after induction was 3,487 U/l. An early prothrombin time was 19 s (upper limit of normal, 15 s), and partial thromboplastin time was 40 s (upper limit of normal, 35 s). Peak potassium was 7.1 mEq/l.

Unsuccessful treatment included discontinuation of volatile anesthetics (7 h 15 min after induction and 1 h after the first adverse sign), hyperventilation with 100% oxygen through a new anesthesia circuit, dantrolene (initial 2.4-mg/kg dose given approximately 1 h 30 min after the first adverse sign and then titrated to a total of 11.9 mg/kg), active cooling, fluid loading, furosemide, glucose, insulin, bicarbonate, phenylephrine, epinephrine, norepinephrine, calcium, atropine, cardiopulmonary resuscitation, and defibrillation. Because the patient's blood vessels were too constricted to be cannulated, an attempt to place the patient on cardiopulmonary bypass failed.

Before his death in the operating room, the observed MH complications included cardiac dysfunction, pulmonary edema (confirmed on autopsy), renal dysfunction, and disseminated intravascular coagulation.

Case 4

Case 4 was a 10-yr-old, 44-kg muscular boy with a family medical history remarkable for ptosis and a personal history without unexplained fevers, muscle cramps, dark urine, heat stroke, or heat intolerance. Although he had a history of toe walking as a toddler, he had no abnormalities of muscle tone or structure preoperatively other than ptosis. He had no cardiopulmonary disease. This was his first anesthetic, and he was anesthetized for an elective eye procedure.

Anesthetic agents included sevoflurane; no succinylcholine or other muscle relaxant was given. He was tracheally intubated and then allowed to breathe spontaneously. Monitors used before the adverse event included pulse oximetry and capnometry. No temperature monitoring was used before the anesthetic event.

Initial adverse signs, noted beginning 20 min after anesthetic induction, included (in order of appearance) sinus tachycardia, premature ventricular contractions (as the surgeon was noting that the patient felt warm), tachypnea and hypercarbia (maximum P_{ETCO_2} of 75 mmHg 1 h 45 min after anesthetic induction), generalized muscular rigidity noted while a rectal temperature probe was being placed, elevated temperature (maximum temperature of 40°C noted 1 h 30 min after induction), cola-colored urine, and asystole.

Results of an arterial blood gas obtained 2 h 13 min after induction and during resuscitation while the patient was being hyperventilated with a F_{IO_2} of 1 were a pH of 7.00, a P_{CO_2} of 73 mmHg, a P_{O_2} of 77 mmHg, a base excess of −14 mEq/l, and a bicarbonate level of 18 mEq/l. Peak potassium was 8.0 mEq/l, and peak creatine kinase was 50,000 U/l.

Unsuccessful treatment included discontinuation of the volatile anesthetics (1 h 15 min after anesthetic induction and 55 min after the first adverse sign), dantrolene administration (first unknown dose given 1 h 35 min after induction and 1 h 15 min after first adverse sign with a total of 10 mg/kg), glucose, insulin, lidocaine, bicarbonate, atropine, epinephrine, and cardiopulmonary resuscitation (required at the same time as the first dose of dantrolene was being given).

The patient was transferred to the intensive care unit without a sustained perfusion pressure and with persistent rigidity, acidosis, and a temperature greater than 40°C. He was noted to develop the following MH complications: cardiac dysfunction, coma, pulmonary edema, disseminated intravascular coagulation, and compartment syndrome.

Approximately 24 h after the first adverse anesthetic sign, the patient became bradycardic, hypertensive, and then unresponsive to resuscitation. A novel variant in the *RYR1* gene on exon 40 Val2210Phe was discovered when molecular genetic analysis was performed on a blood sample obtained at the time of death[3] (Sheila M. Muldoon, M.D., Professor of Anesthesiology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, written communication, February 11, 2007).

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