believe it is unlikely that a blood vessel would be entered during epiduroscopy.

We conclude that direct vascular entry of substances during attempted epidural injections can occur without the delivery device (needle, catheter, epiduroscope) in the vessel.

The authors thank Erin Haley, Adam Ross (Student Assistants, Department of Anesthesiology, Texas Tech University School of Medicine, Lubbock, Texas), and Mark Welborn, B.A. (Unit Coordinator, Classroom Support, Texas Tech University Health Sciences Center), for technical assistance in the preparation of the manuscript.

References

1. Williams PL, Warick R, Dyson M, Bannister LH: Gray's Anatomy, 36th edition. London, Churchill Livingstone, 1980, p 755
2. Hogan Q: Distribution of solution in the epidural space: examination by cryomicrotome section. Reg Anesth Pain Med 2002; 27:150–6
3. Jaffe RA, Siegel LC, Schnittger I, Porpst JW, Brock-Utne G: Epidural air injection assessed by transesophageal echocardiography. Reg Anesth 1995; 20:152–5
4. Smuck M, Fuller BJ, Yoder B, Huerta J: Incidence of simultaneous epidural and vascular injection during lumbosacral transforaminal epidural injections. Spine J 2007; 7:79–82
5. Horlocker TT, Wedel DJ, Benzon H, Brown DL, Enneking FK, Heit JA, Mulroy MF, Rosenquist RW, Rowlingson J, Tryba M, Yuan CS: Regional anesthesia in the anticoagulated patient: Defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain Med 2003; 28:172–97

Anesthesiology 2007; 107:350–3

Delayed Onset of Malignant Hyperthermia without Creatine Kinase Elevation in a Geriatric, Ryanodine Receptor Type 1 Gene Compound Heterozygous Patient

Jordan L. Newmark, M.S.-IV, Maria Voelkel, B.A.,† Barbara W. Brandom, M.D.,‡ John Wu, Ph.D.§*

MALIGNANT hyperthermia (MH) is a dominantly inherited pharmacogenetic disorder of skeletal muscle that predisposes individuals to a potentially fatal reaction (a fulminant episode) on exposure to volatile anesthetics and/or succinylcholine.[1] Fulminant MH episodes apparently result from a rapid, sustained increase in myoplasmic calcium (Ca^{2+}). Molecular genetic analysis has identified mutations in the ryanodine receptor type 1 gene (*RYR1*) that codes for the Ca^{2+} release channel in muscle sarcoplasmic reticulum in many MH-susceptible people. Mutations in *RYR1* are the most frequent genetic abnormality that has been associated with MH. However, the MH syndrome is known to be heterogeneous, and the clinical presentation of MH is highly variable. The hallmarks of a life-threatening MH episode are tachycardia, hypercarbia, acidosis, hyperkalemia, muscle rigidity, hyperthermia, and rhabdomyolysis.[2] Muscle membrane damage leads to release of intracellular muscle constituents such as myoglobin, potassium, creatine kinase (CK), and lactate dehydrogenase into the blood. MH is often described in young patients, but we report a slow-onset intraoperative episode in a geriatric patient without an increase in CK. This episode was confirmed as MH by the finding of two *RYR1* mutations known to be causative of this syndrome.

Case Report

A 73-yr-old, 70-kg man with American Society of Anesthesiologists physical status III presented for laparoscopic and open resection of a rectal tumor, colostomy, and lysis of adhesions. His medical history included hypertension, gastroesophageal reflux disease, osteoarthritis, deep vein thrombosis, and pulmonary embolism. The patient reported no serious complications associated with four intravenous general and three spinal anesthetics. He had never received volatile inhalational anesthetic agents. He reported frequent fevers without infection after surgery and annual influenza vaccinations, as well as delayed awakening from general anesthesia and painful muscle spasms after hip replacement.

Medications at time of surgery included diltiazem, lisinopril, metoprolol, famotidine, neomycin, erythromycin, and warfarin stopped 8 days previously and heparin stopped the night before surgery. The patient performed manual farm labor and reported no heat sensitivity, chronic muscle aches, pain, or weakness.

A preoperative family history obtained from the patient did not reveal anesthesia or surgical complications. He had five offspring, all of whom were healthy.

Before induction of anesthesia, standard monitors were applied: electrocardiogram (leads II and V5), noninvasive blood pressure cuff, and pulse oximeter. After induction of general anesthesia, capnography ($ETCO_2$), peripheral nerve stimulation, an esophageal temperature probe (T_e), and a Bispectral Index monitor were used. A BAIR Hugger (Arizant Healthcare, Eden Prairie, MN) delivered air at 43°C to the upper body and lower extremities of the patient.

Induction of anesthesia was achieved with 1 mg midazolam (0.014 mg/kg) and 100 mg propofol (1.4 mg/kg). Rocuronium, 50 mg (0.71 mg/kg), was given to facilitate tracheal intubation, accomplished without complication. Anesthesia continued with isoflurane (end-tidal 0.43–1.0 vol%) and intermittent doses of fentanyl, rocuronium, and hydromorphone. The patient's heart rate was controlled with metoprolol. Ventilation parameters included minute ventilation of 5.2 l/min, with tidal volume of 650 ml, respiratory rate of 8 breaths/min, and peak airway pressure of approximately 30 cm H_2O. Before surgical

* Medical Student, Temple University, Philadelphia, Pennsylvania. † Research Assistant, Department of Anesthesiology, § Assistant Professor, Department of Obstetrics and Gynecology, Uniformed Services University of the Health Sciences, Bethesda, Maryland. ‡ Professor, Department of Anesthesiology, University of Pittsburgh.

Received from the Department of Anesthesiology, University of Pittsburgh, Pittsburgh, Pennsylvania. Submitted for publication January 23, 2007. Accepted for publication April 9, 2007. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Brandom: Children's Hospital of Pittsburgh, 3705 Fifth Avenue at DeSoto Street, Room 7446, Pittsburgh, Pennsylvania 15213. brandombw@anes.upmc.edu.

incision, the patient received ciprofloxacin and metronidazole. Vital signs before incision were as follows: blood pressure, 110/50 mmHg; heart rate, 60 beats/min; transcutaneous oxygen saturation, 98%; T_e, 35.3°C; and $ETco_2$, 23 mmHg.

During abdominal closure approximately 5 h after induction of anesthesia, the surgeon noted muscle rigidity while rocuronium prevented response to 2 Hz for 2 s of stimulation of the facial nerve. Vital signs at this time were as follows: blood pressure, 115/45 mmHg; heart rate, 70 beats/min; oxygen saturation, 96%; T_e, 36.8°C; and $ETco_2$, 40 mmHg during minute ventilation of 8.5 l/min with tidal volume of 850 ml, respiratory rate of 10 breaths/min, and peak airway pressure of 24 cm H_2O. Five milligrams ephedrine (0.07 mg/kg) was given to correct mild hypotension. Within 15 min, $ETco_2$ increased from 40 to 64 mmHg, causing the carbon dioxide absorbent to change color. This was temporally unrelated to carbon dioxide insufflation of the peritoneal space. There was no increase in peak airway pressure. No crepitus was appreciated. T_e increased to 37.1°C, which prompted discontinuation of the 43°C warming blanket. The Foley catheter had drained 400 ml clear urine throughout the case (1.15 ml · kg^{-1} · h^{-1}). The patient was sweating and rigid.

From 5 h 45 min to 6 h 15 min after induction of anesthesia, vital signs increased: T_e from 38.1° to 40.0°C, heart rate from 70 to 118 beats/min, and blood pressure from 115/50 to 140/60 mmHg, and $ETco_2$ reached a maximum of 85 mmHg. After 6 h 15 min of anesthesia, the diagnosis of MH was considered. Isoflurane was discontinued. Active cooling was initiated. Ventilation was increased to provide minute ventilation of 17.1 l/min with tidal volume of 950 ml, respiratory rate of 18 breaths/min, peak airway pressure of 36 cm H_2O, and positive end-expiratory pressure of 5 cm H_2O. This lowered the $ETco_2$ to 68 mmHg. Muscle rigidity made positioning of the arm to place an arterial catheter require two people. Subsequent arterial blood gas with a fraction of inspired oxygen of 1.0 revealed mixed acidosis: pHa, 6.99; arterial carbon dioxide tension ($Paco_2$), 82 mmHg; arterial oxygen tension (Pao_2), 222 mmHg; plasma bicarbonate ion concentration (HCO_3), 19 mEq/ml; base excess, −14 mM; K^+, 4.6 mEq/l; and lactate, 4.4 mM. Hemoglobin was 11.6 g/dl, hematocrit was 36%, Na^+ was 142 mEq/l, Ca^{2+} was 1.21 mM, and glucose was 139 mg/dl. At 6 h 25 min, intravenous boluses of dantrolene were rapidly administered to a total dose of 220 mg (3.14 mg/kg). Then, $ETco_2$ decreased to 60 mmHg, T_e decreased to 39.0°C, and hypertension improved to a blood pressure of 133/60 mmHg with a heart rate of 110 beats/min. Fifteen minutes later, $ETco_2$ decreased to 28 mmHg, and T_e decreased to 38.2°C. A second arterial blood gas, 6 h 45 min after induction of anesthesia, after dantrolene treatment, showed the following: pHa, 7.31; $Paco_2$, 30 mmHg; Pao_2, 370 mmHg; HCO_3, 15 mEq/ml; base excess, −10 mM; K^+, 4.1 mEq/l; lactate, 3.3 mM; hemoglobin, 8.8 g/dl; hematocrit, 27%; Na^+, 142 mEq/l; Ca^{2+}, 1.02 mM; and glucose, 127 mg/dl. At this time, blood tests revealed the following: prothrombin time, 13.8 s; partial thromboplastin time, 24.3 s; international normalized ratio, 1.3; platelet count, 177,000 cells/μl; and CK, 341 U/l. The clinical diagnosis of MH was accepted.

After 7 h of anesthetic management, the patient was transferred to the intensive care unit (ICU), where he received sedation and mechanical ventilation. His $ETco_2$ had decreased to 28 mmHg, and T_e was 37.5°C. Oxygen saturation was 100% while he breathed 100% oxygen. Heart rate was 85–90 beats/min, and blood pressure was 140/60 mmHg. The patient had received 250 μg fentanyl (3.57 μg/kg), 120 mg rocuronium (1.71 mg/kg), 0.4 mg hydromorphone (5.7 μg/kg), 220 mg dantrolene (3.14 mg/kg), 400 mg propofol (5.71 mg/kg), and 4 mg metoprolol (0.06 mg/kg) throughout the entire anesthetic. He received 5.7 l normal saline and produced 510 ml (1.04 ml · kg^{-1} · h^{-1}) clear urine with 200 ml estimated blood loss.

The Clinical Grading Scale[2] was developed to define an MH episode for the purpose of defining the positive diagnostic response of the caffeine–halothane contracture test. The Clinical Grading Scale score for this case is greater than 50 points: 15 for generalized muscle rigidity (process I), 0 for muscle breakdown (process II), 15 for $ETco_2$ greater than 55 mmHg despite appropriate ventilation (process III), 15 for anesthesiologist's judgment of inappropriately rapid increase in T_e (process IV), 3 for sinus tachycardia (process V), and 5 for rapid reversal of MH signs after dantrolene administration. There were also other indicators of MH, base excess more negative than −8 mEq/l and pHa less than 7.25. The Clinical Grading Scale defines this case as almost certain to be an episode of MH.

Table 1. Postoperative Serum CK Levels

Date	Postinduction Time	CK, U/l (Reference Range, 0–200 U/l)
Day of surgery	6 h 45 min	341
Postoperative day 1	24 h	568
Postoperative day 2	48 h	441
Postoperative day 7	168 h	192

CK = creatine kinase.

The patient received dantrolene, 1 mg/kg every 6 h, for 2 days postoperatively and ventilatory support for 7 days in the ICU. His maximum CK was 568 U/l (reference range, 0–200 U/l) 24 h after induction of anesthesia and decreased to 192 U/l on postoperative day 7 (table 1). Serum creatinine was 0.9 mg/dl on postoperative day 12. After experiencing lethargy and muscle weakness for 5 days after tracheal extubation, the patient's strength increased, and he was discharged from the ICU to the hospital floor. He was then discharged home without complication.

During the patient's ICU course, his daughter stated that more than 20 yr ago she had experienced abnormal movement and stiffness after succinylcholine. She was told at that time that the event was a life-threatening MH episode, and had worn a medic-alert bracelet but never underwent further testing of MH susceptibility. The family did not report a family history of MH susceptibility preoperatively.

This patient, his wife, and their daughter chose to donate blood for examination of the *RYR1* gene. Venous blood samples were collected, under an institutional review board approved research protocol, and sent to the Malignant Hyperthermia Diagnostic Laboratory at the Uniformed Services University of the Health Sciences (Bethesda, Maryland). Polymerase chain reaction focused on 17 known mutations causative of MH within *RYR1*.[3] Nucleotide sequencing determined that the patient had two known, previously characterized, causative mutations: Arg614Cys[4,5] in exon 17 and Gly2434Arg[6–8] in exon 45, compound heterozygous status. Only the Arg614Cys mutation was present in his daughter. His wife had no variations within the portions of her *RYR1* gene examined. All of their offspring must be considered MH susceptible because it is likely that each has one of their compound heterozygote father's *RYR1* variants.

Discussion

The most novel aspect of this case is the use of genetic examination of *RYR1* to confirm MH susceptibility in a family after an MH event. This is in contrast to the diagnostic pathways approved by the European and the North American Malignant Hyperthermia Groups, which recommend that muscle contracture testing be performed before genetic screening of *RYR1*.[9,10] This recommendation is based on the fact that a large proportion of patients suspected of having experienced MH will have normal muscle when contracture testing is performed.[11] Until recently, muscle biopsy and contracture testing was the only method available for confirmation of MH-susceptible status, and it remains the only method

available to confirm MH-negative status. The high Clinical Grading Scale score of the anesthetic event in this individual with a positive family history strongly supported the tentative diagnosis of MH. *RYR1* screening[3] in such cases may secure the diagnosis of MH susceptibility without muscle contracture testing for many members of a family. The compound heterozygous *RYR1* status of the proband and the single *RYR1* variant in one offspring implies that the parent has *RYR1* mutations on each chromosome 19. Therefore, it is likely that each of his offspring will have one or the other of these MH-causative mutations.

This is the first report of an individual with a compound heterozygous *RYR1* mutation in North America. However, three *RYR1* compound heterozygous individuals in two unrelated MH-susceptible European families were described previously.[12] In North Americans, these two mutations are the most frequent within the three *RYR1* hot spots.[3] Similarly, Arg614Cys was found in approximately 9% and Gly2434Arg was found in 7% of German MH-susceptible individuals.[8] Gly2434Arg was also found in 18% of British MH-susceptible individuals.[13] This case demonstrates that a medically significant MH event can occur in an individual with these two mutations. This clinical observation is consistent with the laboratory demonstrations that both of these mutations increase the sensitivity of the RYR1 to agonists and thus increase calcium release from the sarcoplasmic reticulum.[4,5,14,15]

The other noteworthy aspects of this case are those illustrating the variable clinical presentations of MH. It may be expected that marked elevation of CK will occur in severe MH episodes. The patient had both respiratory and lactic acidosis and marked muscle rigidity. Rapid increase in core temperature with progressive respiratory and metabolic acidosis have been signs of fatal MH. But his maximum CK postoperatively was less than three times normal. MH without a dramatic increase in CK may be unexpected, but has been observed previously in a patient with delayed onset of MH symptoms and confirmation of the MH diagnosis by the caffeine–halothane contracture test months later.[16] The range of CK after an MH episode in people with caffeine–halothane contracture test results diagnostic of MH overlaps with that of MH-negative patients.[17] Last, he did not develop hyperkalemia, a complication reported during administration of dantrolene in the presence of concomitant metoprolol and diltiazem.[18]

There are several potential explanations why an increase in CK was not observed in this patient. Damage to muscle tissue or changes in muscle membrane permeability are commonly accepted mechanisms for CK release after anesthetic-induced muscle injury or after exercise. Changes in neuromuscular function in the elderly may make them less susceptible to muscle damage during MH. This patient was older than 70 yr. In the elderly, motor units are replaced by adipose tissue. There is denervation of muscle fibers, altered excitation–contraction coupling, and remodeling of motor units. Weisleder *et al.*[19] described aged mouse muscle as having a decreased calcium mobilization which may protect against calcium-induced injury. Aged skeletal muscle has blunted calcium sparking activity after a stress challenge.[19] This is in contrast to the muscle fiber models of Duchenne muscular dystrophy, which have prolonged/irreversible sparking leading to cell death.[20] Furthermore, the sarcoplasmic reticulum of aged muscle contains less calcium, has reduced RYR1 sensitivity to calcium-induced calcium release, and a decreased dihydropyridine receptor–to–ryanodine receptor ratio.[19] Perhaps greater CK elevation did not occur in this patient because the rapid reversal of increased intracellular calcium and muscle metabolism by dantrolene precluded injury to the muscle cells. However, severe muscle rigidity, such as noted in this case, may impair perfusion and delivery of dantrolene to muscle.

It is of interest that this indolent MH episode was not recognized until 6 h after induction of anesthesia. In studies using MH-susceptible swine, the onset of MH was delayed when thiopental or pancuronium was concurrently administered during inhalation anesthesia.[21] Intravenous sedatives and a nondepolarizing neuromuscular blocker had been administered to this man. In humans, MH episodes have occurred after hours of exposure to isoflurane,[16] sevoflurane,[22] or desflurane.[23–25] For example, Karan *et al.*[16] presented a case in which signs of MH did not develop until 6 h after administration of succinylcholine and isoflurane. The modifying factors responsible for delayed presentation of MH are not completely described. But age, for the reasons noted above, may be a factor. In addition, the diagnosis may have also been delayed because the patient was receiving metoprolol. β-Receptor blockade could have masked the patient's sympathetic response to this MH episode.

Malignant hyperthermia is more often described in the young than in the geriatric population. The current case serves as a reminder that it is just as important to obtain a detailed personal and family anesthetic history when interviewing geriatric patients as it is for younger patients before anesthesia. Thermoregulation is impaired in the elderly. There is also decreased expression of heat shock proteins at this age.[26] Therefore, the elderly may have greater risk of serious injury or death during an MH episode than would a young adult. This case is noteworthy for the extended ICU stay of this patient in the absence of rhabdomyolysis, renal failure, or coagulopathy as well as for its delayed onset.

The authors thank Sheila M. Muldoon, M.D. (Professor of Anesthesiology, Uniformed Services University of the Health Sciences, Bethesda, Maryland), for her work in genetic research in malignant hyperthermia at Uniformed Services University of the Health Sciences.

References

1. Gronert GA, Antognini JF, Pessah IN: Malignant hyperthermia, Anesthesia 5th edition. Edited by Miller RD. Philadelphia, Churchill Livingstone, 2000, pp 1033–52
2. Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, Kaplan RF, Muldoon SM, Nelson TE, Ording H, Rosenberg H, Waud BE, Wedel DJ: A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology 1994; 80:771–9
3. Sei Y, Sambuughin NN, Davis EJ, Sachs D, Cuenca PB, Brandom BW, Tautz T, Rosenberg H, Nelson TE, Muldoon SM: Malignant hyperthermia in North America: Genetic screening of the three hot spots in the type 1 ryanodine receptor gene. Anesthesiology 2004; 101:824–30
4. Gillard EF, Otsu K, Fujii J, Khanna VK, De Leon S, Derdemezi J, Britt BA, Duff CL, Worton RG, MacLennan DH: A substitution of cysteine for arginine 614 in the ryanodine receptor is potentially causative of human malignant hyperthermia. Genomics 1991; 11:751–5
5. Otsu K, Nishida K, Kimura Y, Kuzuya T, Hori M, Kamada T, Tada M: The point mutation Arg^{615}à Cys in the Ca^{2+} release channel of skeletal sarcoplasmic reticulum is responsible for hypersensitivity to caffeine and halothane in malignant hyperthermia. J Biol Chem 1994; 269:9413–5
6. Keating KE, Quane KA, Manning BM, Lehane M, Hartung E, Censier K, Urwyler A, Klausnitzer M, Muller CR, Heffron JJA, McCarthy TV: Detection of a novel *RYR1* mutation in four malignant hyperthermia pedigrees. Hum Mol Genet 1994; 3:1855–8
7. Phillips MS, Khanna VK, De Leon S, Frodis W, Britt BA, MacLennan DH: The substitution of Arg for Gly2433 in the human skeletal muscle ryanodine receptor is associated with malignant hyperthermia. Hum Mol Genet 1994; 3:2181–6
8. Brandt A, Schleithoff L, Jurkat-Rott K, Klingler W, Baur C, Lehmann-Horn F: Screening of the ryanodine receptor gene in 105 malignant hyperthermia families: Novel mutations and concordance with the *in vitro* contracture test. Hum Mol Genet 1999; 8:2055–62
9. Urwyler A, Deufel T, McCarthy T, West S, European Malignant Hyperthermia Group: Guidelines for molecular genetic detection of susceptibility to malignant hyperthermia. Br J Anaesth 2001; 86:283–7
10. Nelson TE, Rosenberg H, Muldoon SM: Genetic testing for malignant hyperthermia in North America. Anesthesiology 2004; 100:212–4
11. Girard T, Treves S, Voronkov E, Siegemund M, Urwyler A: Molecular genetic testing for malignant hyperthermia susceptibility. Anesthesiology 2004; 100:1076–80
12. Monnier N, Krivosic-Horber R, Payen JF, Kozak-Ribbens G, Nivoche Y, Adnet P, Reyford H, Lunardi J: Presence of two different genetic traits in malignant hyperthermia families. Anesthesiology 2002; 97:1067–74
13. Robinson RL, Brooks C, Brown SL, Ellis FR, Halsall PJ, Quinnell RJ, Shaw M-A, Hopkins PM: RYR1 mutations causing central core disease are associated with more severe malignant hyperthermia *in vitro* contracture test phenotypes. Hum Mutat 2002; 20:88–97
14. Tong J, Oyamada H, Demaurex N, Grinstein S, McCarthy TV, MacLennan DH: Caffeine and halothane sensitivity of intracellular Ca^{2+} release is altered by 15 calcium release channel (ryanodine receptor) mutations associated with malignant hyperthermia and/or central core disease. J Biol Chem 1997; 272: 26332–9
15. McKinney LC, Butler T, Mullen SP, Klein MG: Characterization of ryanodine receptor–mediated calcium release in human B cells. Anesthesiology 2006; 104:1191–201
16. Karan SM, Crowl F, Muldoon SM: Malignant hyperthermia masked by capnographic monitoring. Anesth Analg 1994; 78:590–2
17. Antognini JF: Creatine kinase alterations after acute malignant hyperthermia episodes and common surgical procedures. Anesth Analg 1995; 81:1039–42
18. Yoganathan T, Casthely PA, Lamprou M: Dantrolene induced hyperkalemia in a patient treated with diltiazem and metoprolol. J Cardiothorac Anesth 1988; 2:363–4
19. Weisleder N, Brotto M, Komazaki S, Pan Z, Zhao X, Nosek T, Parness J, Takeshima H, Ma J: Muscle aging is associated with compromised Ca^{2+} spark signaling and segregated intracellular Ca^{2+} release. J Cell Biol 2006; 174:639–45
20. Melzer W: When sparks get old. J Cell Biol 2006; 174:613–4
21. Gronert GA, Milde JH: Variations in onset of porcine malignant hyperthermia. Anesth Analg 1981; 60:499–503
22. Gillmeister I, Schummer C, Hommann M, Schummer W: Delayed onset of malignant hyperthermia crisis during a living donor liver transplantation caused by sevoflurane [in German]. Anasthesiol Intensivmed Notfallmed Schmerzther 2004; 39:153–6
23. Hoenemann CW: Delayed onset of malignant hyperthermia in desflurane anesthesia. Anesth Analg 2003; 96:165–7
24. Papadimos TJ, Almasri M, Padgett JC, Rush JE: A suspected case of delayed onset malignant hyperthermia with desflurane anesthesia. Anesth Analg 2004; 98:548–9
25. Uskova AA, Matusic BP, Brandom BW: Desflurane, malignant hyperthermia, and release of compartment syndrome. Anesth Analg 2005; 100:1357–60
26. Moseley PL: Heat shock proteins and heat adaptation of the whole organism. J Appl Physiol 1997; 83:1413–17