Association of post-anaesthetic hyperthermia with abnormal muscle characteristics: A CASE REPORT

Benjamin J. Kripke MD,
Thomas J.J. Blanck MD PH D,
David A. Sizemore MD PH D,
Francis L. Comunale MD, Judy Christiansen MSC
Raphael Gruener PH D

A previously healthy 18-year-old male, following appendectomy developed post-anaesthetic hyperthermia (42.1° C) with an elevation of serum creatine kinase and activated partial thromboplastin time. Repeated arterial blood gases were normal. Cooling and anti-pyretic medication did not control the fever. In contrast, sodium dantrolene appeared effective in lowering the patient's temperature and normalizing the vital signs, both acutely and over the following three days. Subsequent muscle biopsy revealed a normal contracture response to caffeine alone or in the presence of halothane. However, the muscle had a larger than normal potentiation of evoked twitch tension in the presence of caffeine and halothane. Electrophoresis of the muscle revealed a marked increase of an unidentified low molecular weight protein. The patient's clinical course, and the results of the muscle studies, sugest that an abnormality of skeletal muscle, other than that seen in the classic malignant hyperthermia syndrome may result in anaesthesia-related hyperthermia.

Key words
HYPERTHERMIA: following anaesthesia, dantrolene; MUSCLE, SKELETAL: electrophoresis.

Anaesthetics and depolarizing muscle relaxants can cause abnormal responses in certain patients. These reactions include masseter muscle spasm, rhabdomyolysis and malignant hyperthermia (MH).[1]

We report a case in which postoperative hyperthermia occurred. Muscle biopsy, performed several months after the episode, revealed normal contracture responses to challenges with caffeine and halothane, but a larger-than-normal potentiation of twitch tension under the same conditions and an abnormal muscle electrophoresis. The relevance of these findings to a possible diagnosis of MH is discussed.

Case Report

A previously healthy 18-year-old 63.5 kg, 118 cm Mexican-American male was admitted with a diagnosis of acute appendicitis and underwent an appendectomy. The pathologist confirmed the diagnosis. The medical history was non-contributory, including a negative family history of abnormal responses to anaesthesia. Vital signs on admission included: temperature 37.5° C, blood pressure 15/11 kPa (112/78 mmHg), heart rate 104 beats (b)/min, and respirations 20 breaths/min. Admitting laboratory data were within normal limits except for

From the Department of Anesthesiology, San Bernardino County Medical Center, San Bernardino, California and the Departments of Physiology and Anesthesiology, University of Arizona Health Sciences Center, Tucson, Arizona.

Address correspondence to: Dr. Benjamin J. Kripke, Department of Anesthesiology, San Bernardino County Medical Center, 780 E. Gilbert Street, San Bernardino, CA 92404.

The study was funded in part by the Benjamin J. Kripke, M.D. Inc. Research Fund, The Muscular Dystrophy Association, the National Institute of Health and the National Institute for General Medical Services.

a white cell count of 16×10^9 cells/litre (16,000 cells/mm^3).

Both anaesthesia and surgery were uneventful. Sodium thiopental, 350 mg IV, succinylcholine, 100 mg IV, nitrous oxide and oxygen (2:1 L/min), enflurane, fentanyl, 0.01 mg IV, and pancuronium 2.5 mg IV were used during the procedure. Glycopyrrolate 0.6 mg IV and pyridostigmine 20 mg IV antagonized the neuromuscular block at the completion of surgery. No intraoperative rigidity or arrhythmias were noted. Temperature was monitored throughout surgery with an oesophageal probe. The temperature initially was 38.7° C, fell to 37.8° C during surgery, and was 38.3° C at the conclusion of surgery. The blood pressure ranged from 15/8 kPa (110/60 mmHg) to 12/7 kPa (90/50 mmHg) during surgery and was 14/9 kPa (102/70 mmHg) after extubation. The heart rate varied from 110–120 b/min. The patient was apnoeic during the surgery secondary to the use of muscle relaxants, fentanyl, and controlled respiration. No respiratory effort was noted prior to the administration of pyridostigmine. Extubation was performed after the patient responded to commands. He was transferred to the recovery room at 0745 where he received oxygen by mask (4 L/min) and was monitored by ECG.

At 0830 the patient's skin felt hot. The oral temperature was 42.1° C. Blood pressure was 16/5 pKa (120/40 mmHg), with a thready pulse of 140 b/min, and respirations of 30 breaths/min. The ECG revealed sinus tachycardia. Immediately, an acetominophen suppository, 600 mg, was given and ice water soaks were applied to the body with ice packs to the groin, back of neck and axilla. Cold saline was administered intravenously. The temperature decreased slightly to 41.7° C. Arterial blood gases at 0835 were: PO_2 22 kPa (165 mmHg), PCO_2 4 kPa (31 mmHg), H+ activity 34 nmol/litre, (pH 7.48), base excess +1 nmol/litre. Over the next 30 minutes, the temperature diminished slowly to 40.0° C. At 0910 a normal chest *x*-ray was obtained and blood, drawn for culture, subsequently showed no growth. At this time, arterial blood gases were again found to be normal. Cooling continued but the temperature rose to 41.1° C at 0935. Since the fever was not controlled by aggressive cooling and antipyretic medication, malignant hyperthermia was considered and sodium dantrolene, 60 mg, was injected IV. Following dantrolene, the body temperature did not change for 15 minutes and then declined over 10 minutes to 38.0° C. Blood pressure was 13/11 kPa (160/80 mmHg), pulse 115 b/min, and respirations of 30 breaths/min. The patient was alert and comfortable. Arterial blood gases remained normal. The urinary output was 300 ml during the recovery room period and was straw-coloured.

At 1140 the patient was transferrred to the ICU. Temperature, on admission, was 37.0° C, blood pressure 13/10 kPa (100/72 mmHg), pulse 89 b/min and respirations of 20 breaths/min. At 2000 hrs, the temperature rose to 38.1° C and continued to rise, despite the use of a cooling blanket, to 39.6° C. The pulse increased to 111 b/min. Dantrolene (30 mg) was again administered IV, and the temperature fell to 37.9° C while the pulse declined to 76 b/min. Sodium dantrolene was administered thereafter three times daily (tid) at 0.5 $mg \cdot kg^{-1}$ for three additional days. During this period the temperature continued to fluctuate and on one occasion was 40.0° C. Antibiotics were not given postoperatively and no signs of intercurrent infection were evident. The ECG remained normal. The creatine kinase (CK) peaked at 1355 IU on the day of surgery (laboratory normal 0–75 IU), and the activated partial thromboplastin time (APTT) increased to 40.8 sec from 31.9 sec. The patient's course was uneventful after discontinuance of dantrolene and he was discharged on the eighth postoperative day. No complaints of muscle pain or stiffness were noted throughout the course.

A muscle biopsy was performed eleven weeks after the episode for evaluation of malignant hyperthermia susceptibility. Laboratory values ten days prior to biopsy showed a CK value of 36 IU and an APTT of 26.7 sec (35.1 sec for control).

Biopsy

The muscle biopsy was obtained utilizing local anaesthesia as previously described.[2] A muscle specimen 1 cm in diameter and 3 cm long was taken from the vastus lateralis. (This procedure was undertaken with the patient's consent and with the approval of the Human Subjects Committee.)

A Physiologic Measurements

The muscle strips were superfused with modified Krebs solution (KSS) bubbled with 95 per cent O_2, 5 per cent CO_2 at pH 7.4. The KSS composition was

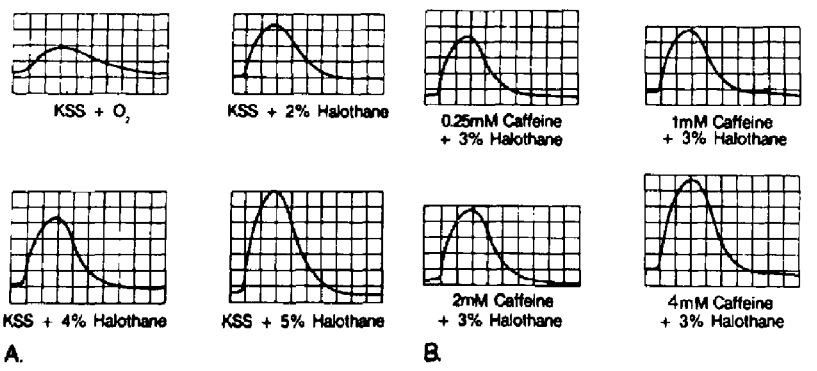

FIGURE 1 Oscilloscopic traces of the effect of halothane and caffeine on twitch tension of a muscle strip from reported patient. (A) Twitch tension responses during exposure to increasing concentrations of halothane. (B) Twitch tension responses during exposure to increasing concentrations of caffeine in the presence of 3 per cent halothane. Each horizontal box is 50 msec. Each vertical box is 70 mg tension in panel A and 140 mg in panel B.

(in mM): NaCl 135, $NaHCO_2$ 15, KCl 5, $MgCL_2$ 1, $CaCl_2$ 2, Tris-Cl 5, Na_2HPO_4 5, glucose 11. Contracture and twitch tension were monitored. Contracture tension is that tension produced by the muscle strips in response to exposure to caffeine or halothane without electrical stimulation.[3] Twitch tension is the force generated in response to electrical stimulation. Electrical stimulation was accomplished with platinum field electrodes at a frequency of 0.2 Hz, with a pulse duration of 1 msec and supramaximal amplitude of 50–80 V (Grass Instrument Stimulator – Model S4). Tension was monitored continuously during the 5 min exposure periods of the strips to incrementing concentrations of halothane, caffeine, and caffeine with 3 per cent halothane. Twitch tension results are expressed as per cent change from control values.

B Electrophoresis

150 mg of muscle was homogenized and an aliquot of homogenate dissolved in 2 per cent sodium dodecylsulfate (SDS), 2 per cent mercapoethanol and 8 M urea at 90° C for three minutes.[4] Approximately 50 μg of protein was electrophoresed on 7.5 per cent polyacrylamide gel containing SDS (0.1 per cent). After electrophoresis, the gel was stained with a protein dye, Coomasie Blue.

Results

Cumulative contracture tension of the muscle strips of our patient did not differ from the response of muscle of normal patients to incremental concentrations of caffeine. Contracture tension produced in response to caffeine and 3 per cent halothane were not different from normal muscle.

The effects of halothane and caffeine on twitch tension are shown in Fig. 1. Twitch tension increased during exposure of the muscle strip to incremental concentrations of halothane (panel A), and it was further potentiated when caffeine was added to a constant concentration of halothane (panel B). Twitch tension responses of our patient were compared to laboratory normal values. The response to 2 mM caffeine in 3 per cent halothane was significantly greater than tensions obtained from normal muscle ($t = 2.6$; $p < 0.02$).[5] A mean increase of 640 per cent over initial tension was demonstrated.

Electrophoresis of muscle homogenate from our patient demonstrated a marked increase in a low molecular weight protein that has been observed only in trace amounts in normal human muscle (Fig. 2). The protein is approximately 12,500 molecular weight based on coelectrophoresis of protein standards.

Discussion

This case report is of interest because it presents a patient who developed fever after anaesthesia, responded to dantrolene, and had evidence of

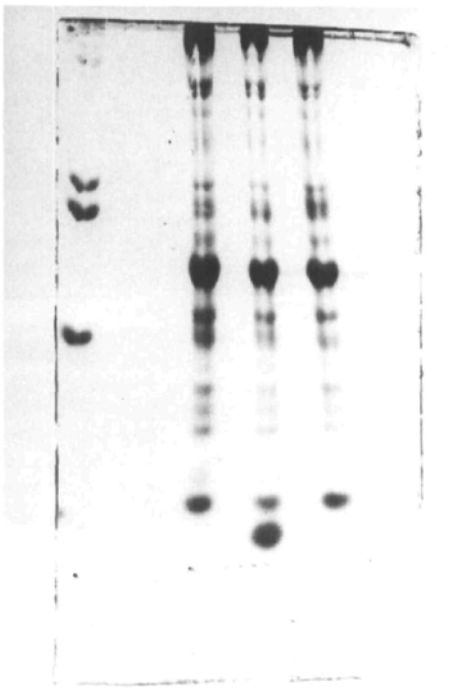

FIGURE 2 Sodium dodecylsulfate-polyacrylamide electrophoresis of human muscle. Bands on far left represent standard proteins of 68,000, 57,000, and 37,000 molecular weight respectively from top to bottom. Muscle from patient described is electrophoresed between the muscles from two normal age matched patients. Our patient's leading band (lowest stained protein in figure) represents a 12,500 molecular weight protein not seen in either control muscle.

abnormal skeletal muscle from twitch measurements and electrophoresis. Britt's description of non-rigid MH is similar to that observed in our patient: the development of hyperthermia, lack of visually detectable or palpable muscle rigidity preceding, during, or after the episode, lack of respiratory or metabolic acidosis, and the absence of striking tachycardia, dysrythmia, tachypnoea, and cyanosis.[6] In common with many rigid MH patients and the non-rigid patient reported by Britt, a test of blood coagulation (APTT) was prolonged. Also, in common with Britt, we report here the relatively normal arterial blood gas values which may be an expression of the lung's ability to temporarily compensate for the increased metabolism.[6,7] In contrast to the patient reported by Britt, our patient's CK level was elevated following the episode suggesting the presence of skeletal muscle damage.[6]

Laboratory studies measuring the *in vitro* contracture response to caffeine and halothane have been utilized to distinguish MH muscle from normal muscle. There is agreement that muscle from rigid MH patients does produce contractures at a lower caffeine concentration than muscle from normal individuals.[3,8] In common with non-rigid MH muscle responses, our patient's muscle did not show the classical MH response.

The high temperature and the rapid defervescence following use of dantrolene further suggest that this case was MH. The maximum temperature of our patient was 42.1° C. Rarely do body temperatures in clinical fever exceed 41° C.[9] In contrast, higher temperatures (as in this patient) may occur in the syndromes of MH and heat stroke which have been reported to share other features.[10,11] To date only the syndromes of MH, heat stroke, anaesthetic-induced rhabdomyolysis in patients with Duchenne muscle dystrophy[12] and the "toxic-shock syndrome" with severe rhabdomyolysis (personal communication: Norwich-Eaton Pharmaceutical Co.) have responded well to dantrolene IV. This muscle relaxant has proven its effectiveness both as a prophylactic and as a therapeutic agent in MH-susceptible pigs.[13] Dantrolene has been advocated for a similar role in man. Effective doses in man remain uncertain. However, a recent study found that a mean initial dantrolene dose of 2.5 $mg \cdot kg^{-1}$ was usually successful.[14] We used 1 $mg \cdot kg^{-1}$ IV during the acute episode and 0.5 $mg \cdot kg^{-1}$ tid for three days as a follow-up regimen. Perhaps a higher dose may have prevented the relapsing temperature course.

We reported previously that tetanic tension was markedly potentiated in MH muscle in the presence of caffeine and halothane.[2] Subsequently, we have found that the caffeine sensitivity of the twitch response of MH patients' muscle is also greater than normal (Gruener and Blanck: unpublished observations). In the present paper, we demonstrate the marked potentiation of vastus lateralis muscle twitch tension by caffeine and halothane and the presence of large amount of a low molecular weight protein in the muscle of this patient that is observed only in trace amounts in normal muscle.

The presence of an elevated CK and the apparent effectiveness of sodium dantrolene therapy in reducing body temperature suggest skeletal muscle

involvement in this patient's post-anaesthetic development of fever. The fact that the patient had an elevated CK after anaesthesia, that muscle twitch tension responses were markedly potentiated by caffeine and halothane, and that there was a marked increase in a low molecular weight protein in this patient's muscle indicates that his muscle is abnormal. In view of the normal contracture response to caffeine, alone and with halothane, the abnormality observed in our patient's skeletal muscle might be different from that present in "rigid MH." One possible conclusion is that there exists more than one abnormality of skeletal muscle that can result in anaesthesia-related hyperthermia.

Acknowledgements

The authors gratefully acknowledge the statistical analysis by Lynda Rose of the Boston University Department of Bio-Statistics, Enid Cosman, Department Secretary, for typing, and Robert Ross Ph.D., Professor, School of Communications, Boston University, for editing.

References

1 *Lewandowski KB*. Rhabdomyolysis, myoglobinuria and hyperpyrexia caused by suxamethonium in a child with increased serum creatine kinase concentrations. Br J Anaesth 1981; 53: 981–4.

2 *Gruener R, Blanck TJJ*. Volatile anesthetics and skeletal muscle: evidence for sarcolemmal involvement in malignant hyperthermia. *In*: Fink BR, ed. Progress in Anesthesiology, 2. New York: Raven Press, 1980; 423–7.

3 *Kalow W, Britt BA, Richter A*. The caffeine test of isolated human muscle in relation to malignant hyperthermia. Can Anaesth Soc J 1977; 24: 678–94.

4 *Zahler WL*. Analytical polyacrylamide gel electrophoresis and molecular weight determination. *In* Fleischer S, ed. Methods in Enzymology, 32. New York: Academic Press 1974; 70–81.

5 *Snedecor CW, Cochran WG*. Statistical Methods. 6th ed. Ames, Iowa, The Iowa University State Press, 1967; 128.

6 *Britt BA, Kalow W*. Malignant hyperthermia: a statistical review. Can. Anaesth Soc J 1970; 17: 293–315.

7 *Gatz EE, Kerr DD, Wingard DW*. Earlier diagnosis of malignant hyperthermia. *In*: Aldrete, JA, Britt BA eds. Malignant Hyperthermia. New York: Grune and Stratton, 1978; 147–57.

8 *Gronert CA*. Malignant hyperthermia. Anesthesiology. 1980; 53: 395–423.

9 *DuBois EF*. Why are fever temperatures over 106° F rare? Am J Med Sci 1949; 217: 361–8.

10 *Bernheim HA, Block LH, Atkins E*. Fever: pathogenesis, pathophysiology and purpose. Annals of Internal Medicine 1979; 91: 261–7.

11 *Lydiatt JS, Hill GE*. Treatment of heat stroke with dantrolene. JAMA 1981; 246: 41.

12 *Marchildon MB*. Malignant hyperthermia. Arch Surg 1982; 117: 349–51.

13 *Flewellen EH, Nelson TE*. Dantrolene dose response in malignant hyperthermia susceptible swine. Anesthesiology 1980; 52: 303–7.

14 *Kolb ME, Horene ML, Martz R*. Dantrolene in human malignant hyperthermia: A multi-center study. Anesthesiology 1982; 56: 254–62.

Résumé

Un jeune patient de dix-huit ans, auparavant en bonne santé, développa, après l'intervention chirurgicale de l'appendicite, une hyperthermie (42.1° C), ainsi qu'une hausse de sérum de créatine-kinase et un temps de céphaline-kaolin. Les résultats de l'analyse des gaz sanguins furent normaux à maintes reprises. Les médicaments anti-pyrétiques et le refroidissement de surface n'ont pas réussi à contrôler la fièvre. Par contre, le sodium dantrolène semble efficace pour diminuer la température du patient et pour normaliser les signes vitaux durant la période immédiate et pendant les trois jours suivants. Après une biopsie subséquente du muscle, on observa une réponse normale de contracture avec la caféine seulement ou avec la caféine en présence d'halotane. Cependant, on observa une augmentation plus grande que la normale de la secousse musculaire en présence de caféine et d'halotane. L'électrophorèse du muscle révèla une augmentation marquée d'une protéine non identifiée de faible poids moléculaire. L'évolution du patient en clinique et les résultats des observations sur l'étude des muscles suggèrent qu'une abnormalité des muscles squelettiques, autre que celle observée dans les cas d'hyperthermie maligne peut mener à l'hyperthermie associée à l'anesthésie.