

will not occur with decreases in cardiac output from other forms of cardiac depression where CVP and ET CO₂ may be altered. Thus, alterations in airway pressure may aid in the differentiation of the etiology of incidents where the ET CO₂ and CVP change without other evidence of air embolism. In addition, like CVP and ET CO₂, recovery after the episode allows observation of resolution of the physiologic effect of the embolus.

In summary, this case demonstrates the alteration of airway pressure with venous air embolism. This monitoring technique is a simple, inexpensive, and noninvasive method that offers promise as an adjunct to other techniques for the detection of venous air embolism in sitting neurosurgical operations.

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Unexpected Hyperthermia Manifesting during Outpatient Anesthesia

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Malignant hyperthermia (MH) is a rare and usually unexpected complication of anesthesia. In most cases, the association of tachycardia with cyanosis, metabolic acidosis, hyperthermia, hyperkalemia, or muscle rigidity

alerts the anesthesiologist to the rare but potentially lethal complication MH.¹ We describe a case of unexpected hyperthermia occurring during anesthesia in an outpatient. The development of hyperthermia was not associated with

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tachycardia, muscle rigidity, or acidosis. Nevertheless, the muscle response to *in vitro* caffeine contracture testing fell within the range diagnostic for MH, and the muscle histopathologic and electron microscopic appearance were compatible with MH. Thus, when the patient later required general anesthesia, dantrolene sodium was given prophylactically. Because our patient's primary illness was a protein-losing enteropathy with hypoproteinemia, blood concentrations of dantrolene administered at the time of anesthesia were determined. There was no recurrence of the hyperthermic reaction.

REPORT OF A CASE

A 13-yr-old Caucasian male patient of thin and small stature, weighing 25 kg, had a history of frequent diarrhea complicated by a prolapsed rectum. He also had generalized edema. Fecal excretion of chromium-labeled albumin was markedly elevated. A protein-losing enteropathy was diagnosed. Serum albumin was 25 g/l. Serum immunoglobulins were also low (IgG 26, IgA 34, and IgM 39 IU/ml). Serum cholesterol was 4.8 mm (n < 6 mm). The results of barium meal and follow-through and barium enema studies were normal. A 72-h stool fat collection was normal. The findings from upper gastrointestinal endoscopy and jejunal biopsy were also normal.

To further investigate the diarrhea and protein-losing enteropathy, he was admitted for colonoscopy as an outpatient. Preanesthetic examination revealed an afebrile child of normal intelligence. Arterial blood pressure was 100/85 mmHg, and heart rate was 80 beats/min. The remainder of the physical examination was normal. The patient had undergone anesthesia uneventfully twice previously for dental extractions and for repair of an inguinal hernia. There was no known family history of any anesthetic-related complication. There was no history of allergy, and the patient was receiving no medication.

Premedication consisted of diazepam, 5 mg given orally 100 min before the procedure. Monitoring of the ECG and heart rate was initiated and induction of anesthesia was achieved with thiopental, 100 mg iv, halothane, nitrous oxide, and oxygen. Tracheal intubation was facilitated by the administration of succinylcholine, 25 mg iv. Immediately after uneventful intubation, ventilation was controlled manually with the use of a Bain circuit. Anesthesia was maintained with 1.5% halothane inspired concentration and 50% nitrous oxide in oxygen. Within minutes, the patient's face became flushed and his forehead warm to the touch. An esophageal thermistor probe was inserted immediately; the temperature recorded was 38.2° C. Over the next 5 min the esophageal temperature rose to 40.9° C. Nitrous oxide and halothane were discontinued, and surface cooling was instituted with icepacks in the axillae, groin, and over the abdomen. The patient was fanned, and cooling was noted to be effective immediately. The accuracy of the temperature monitoring was confirmed by a second thermistor probe and recorder.

Dantrolene was immediately available but was not administered, because the response to cooling was rapid and there was no muscle rigidity, tachycardia, or cyanosis. The colonoscopy was completed with three 25-mg bolus doses of thiopental and 25 µg fentanyl iv. Throughout this time, the patient was ventilated manually with a fractional inspired O₂ concentration (F_IO₂) of 1.0. He received 1,000 ml of half-strength Darrow's solution perioperatively. Postoperative recovery was rapid, and the patient was admitted to the postoperative ward for close observation and continuous temperature monitoring for 24 h.

Shortly after the patient reached the ward, his oral temperature was 37° C. Arterial blood gas values were normal. There was no increase in temperature above 37.2° C, and the maximum heart rate recorded was 96 beats/min. Because colonoscopy had revealed no ab-

normality, the patient was discharged the following day and referred for a muscle biopsy 1 month later.

Before the biopsy, the patient was sedated with diazepam. Muscle was removed from the left vastus lateralis after bupivacaine infiltration. The muscle was subjected to tension studies. The caffeine specific concentration^{††} was 1 mM (normal ≥ 2 mM). In the presence of 1% halothane alone, a 0.25 g contracture (normal = 0.0 g) was observed. These values were considered to be strongly positive for MH.

Electron microscopy showed gross loss of muscle fibrils, with grossly distended sarcoplasmic reticulum and swollen mitochondria, compatible with the diagnosis of MH susceptibility (fig. 1). After confirmation of the malignant hyperthermia disorder, arrangements were made for the patient to be given a warning bracelet.

Five months later, the patient was admitted for an exploratory laparotomy because extensive investigation had revealed no cause for his protein-losing enteropathy, and a localized intestinal lymphangiectasia amenable to surgery needed to be excluded.

During the 24 h before anesthesia, the patient received dantrolene in four divided oral doses totaling 4 mg/kg. These were administered in 25-mg capsules, commencing with a 50-mg loading dose 24 h before surgery and 25 mg at 18, 12, and 6 h before surgery. The patient was premedicated with diazepam, 5 mg orally 2 h before surgery. Induction of anesthesia was achieved with iv fentanyl, 75 µg, and thiopental, 75 mg. Intubation of the trachea was facilitated by pancuronium, 3 mg iv. Balanced anesthesia was maintained with additional fractional fentanyl and flunitrazepam administration iv. Total doses were fentanyl 800 µg and flunitrazepam, 2 mg iv. The surgical procedure lasted 90 min. Dantrolene, 30 mg, was administered iv after induction of anesthesia. Postoperatively, the dantrolene was continued iv at doses of 15 mg every 6 h for 24 h because the patient could not take medication orally.

At laparotomy, abnormally dilated lymphatics were visible on the serosal surface of the entire small bowel, particularly the jejunum. Five centimeters of jejunum was resected, and a histologic examination revealed abnormally dilated submucosal lymphatics and prominent lymphoid hyperplasia. The mucosa and villi appeared normal.

Periodically during dantrolene administration, blood specimens for dantrolene assay were drawn. Specimens were assayed by the Bioanalytical/Biopharmaceutics Section of Norwich Eaton Pharmaceuticals, Inc., with a spectrofluorometric procedure specific for dantrolene in the presence of dantrolene-related metabolites.² Plasma dantrolene concentrations after oral and iv drug administration are found in table 1. The dantrolene blood concentration just before anesthesia, after oral drug administration for 24 h, was 1.24 µg/ml, whereas the peak after iv administration of 30 mg dantrolene sodium after induction was 2.78 µg/ml.

DISCUSSION

This case report illustrates several important points. Our patient came to the hospital for a relatively minor outpatient procedure. During careful preoperative inquiry, which included routine specific reference to MH, there was no suggestion that this patient was MH susceptible. He had undergone two previous inhaled anesthetics with no sequelae. There was no history of familial difficulties with anesthesia. Nevertheless, a rapid, sustained rise in temperature soon after induction of anesthesia alerted us to a developing hyperthermic reaction, and we

^{††} Caffeine specific concentration is the dose required to raise the resting tension of a skeletal muscle fascicle by 1 g.

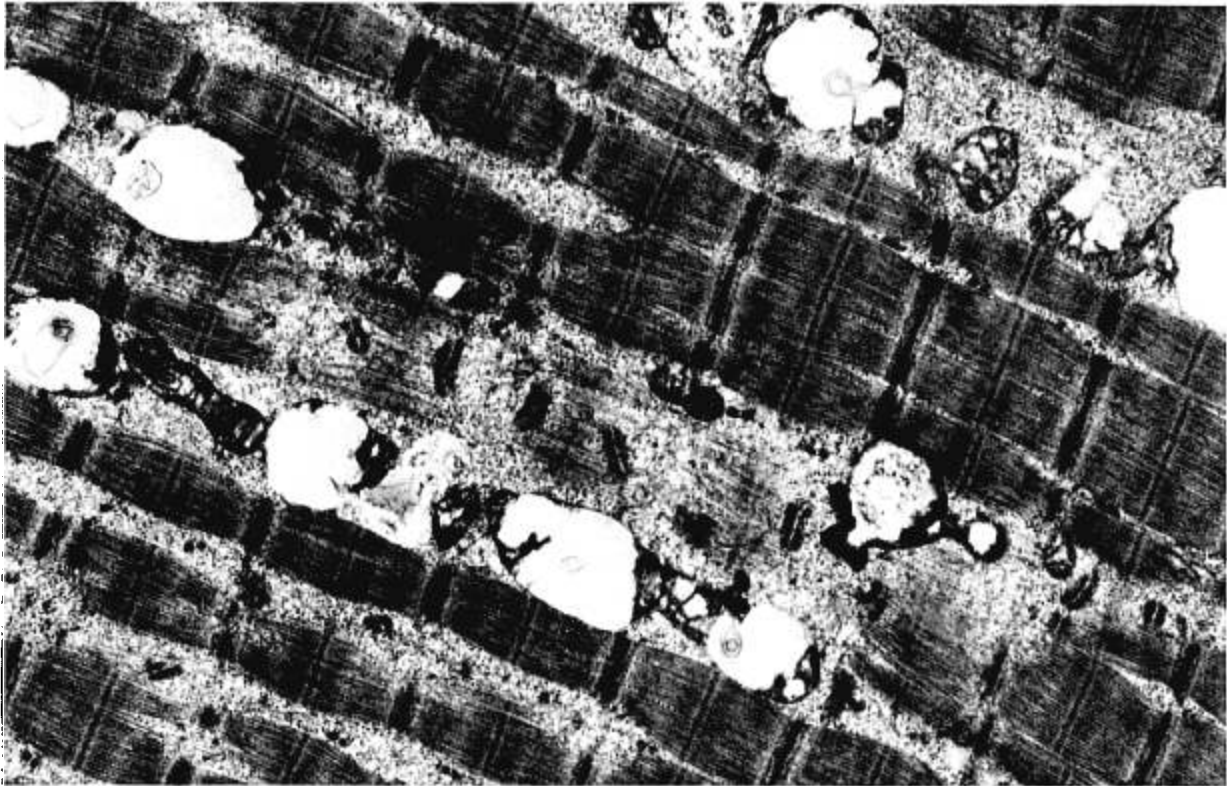


FIG. 1. Electron micrograph of muscle taken at biopsy (×6000). Note distended mitochondria and myofibrillar loss.

immediately took appropriate measures for an MH reaction although other signs of MH were not present.

The absence of tachycardia, cyanosis, and muscle rigidity is unusual in MH. Unfortunately, arterial blood gas determinations, which would have definitively characterized this hyperthermic episode, were not done at the hyperthermic peak. Myoglobin and creatine kinase (CK) levels were also not performed at this time. Repeated CK levels and a 24-h urinary myoglobin estimation were performed when our patient presented for laparotomy, and they were normal. However, because the *in vitro* caffeine contracture test was positive for MH, we believe that the hyperthermic episode was the beginning of an MH crisis that would have produced the classic symptoms if emergency measures had not been initiated immediately. The rapid increase in temperature without concomitant acidosis seen in this case is also unusual in MH. MH is rarely manifest so soon after administration of the triggering agent. The length of exposure to the trigger appears to be critical, because very few cases have been described in patients anesthetized for less than 15 min. Exposure to the trigger in our patient was less than 5 min and may have been the reason that our patient did not proceed to a major MH storm.

Many MH-susceptible patients have had previous uncomplicated anesthesia involving the triggering drugs.³ Halsall *et al.* found that MH occurred on 42% of occasions

when MH-susceptible patients were exposed to halothane and other triggering agents.⁴ Our patient received both succinylcholine and halothane, and patients receiving both triggering drugs may be at greater risk.

This case illustrates that MH should not be considered a syndrome with unvarying characteristics.⁵ The clinical

TABLE 1. Plasma Dantrolene Concentrations after Oral and iv Dantrolene Administration

Dantrolene Administration		Plasma Dantrolene Levels	
Dose/Route	No. of h Before (-) or After (+) Induction	No. of h Before (-) or After (+) Induction	Dantrolene Concentration (µg/ml)*
50 mg po	-24	—	—
—	—	-23	0.73
—	—	-19	0.99
25 mg po	-18	—	—
25 mg po	-12	—	—
25 mg po	-6	—	—
—	—	-0.5	1.24
30 mg iv	induction	—	—
—	—	+0.75	2.78
—	—	+4	1.24
15 mg iv	+6	—	—
15 mg iv	+12	—	—
15 mg iv	+18	—	—
15 mg iv	+24	—	—

* Mean result based on the analysis of duplicate specimens. Method sensitivity is 0.04 µg/ml.

spectrum may have fever as a prominent feature, without the concomitant acidosis, which is a factor of time and rate of progression. Muscle rigidity may not always occur.

We would like to stress the importance of muscle biopsy after any manifestation of MH susceptibility, no matter how minor the symptoms or signs may have been, because subsequent anesthesia may well be fatal. In addition, accumulating evidence suggests that the risk of sudden demise may be greater in the postoperative period than during anesthesia.⁵ Thus, the need for routine temperature monitoring in the perioperative period is also emphasized.

In our patient, of particular interest was the association of MH with protein-losing enteropathy and intestinal lymphangiectasia. For this reason, dantrolene levels were measured and are compared here with levels found during studies reported by others. In a study with normal human volunteers, Flewelling *et al.* administered dantrolene sodium iv to the dose level (\bar{X} = 2.4 mg/kg) that produced a 75% depression of skeletal muscle twitch contraction.⁶ Maximum blood dantrolene concentration (c_{\max}) of 4.2 ± 0.2 $\mu\text{g/ml}$ occurred at 2.9 ± 1.0 h (t_{\max}) after the first dose. In a subsequent pharmacokinetic study, three normal volunteers received doses of 0.6, 1.2, 2.4, 3.6, and 4.8 mg/kg dantrolene sodium iv (unpublished data on file at Norwich Eaton Pharmaceuticals, Inc.). The means of the maximum blood concentrations for each of the above doses were 0.8, 1.9, 4.3, 6.1, and 6.9 $\mu\text{g/ml}$, respectively. (In the first study, the drug was administered as bolus doses of 0.1 mg/kg every 5 min, whereas in the second study, the drug was administered as a constant-volume iv drip over 1 h. This difference in method of administration probably accounts for the t_{\max} of 1 h after the start of the drug infusion in the second study. However, in both studies, the t_{\max} essentially corresponded to the completion time for drug infusion.) Our patient's blood drug level (c_{\max}) of 2.78 $\mu\text{g/ml}$ was higher than that achieved in the pharmacokinetic study after an equivalent dose, possibly because of the oral doses that were administered for the 24 h before surgery.

Flewelling *et al.* predicted that a dose of 2.4 mg/kg (*i.e.*, leading to a blood level of 4.2 ± 0.2 $\mu\text{g/ml}$) should be the effective dose for both therapy and prophylaxis of

MH.⁶ Our patient was given an iv dose of only 1.2 mg/kg of dantrolene as prophylaxis after induction of anesthesia, and a blood drug level of only 2.78 $\mu\text{g/ml}$ was achieved; nevertheless, no signs of MH were observed during or after surgery.

This case represents an unusual manifestation of an MH-like reaction. In this patient, later confirmed by biopsy to be MH susceptible, administration of succinylcholine, halothane, and nitrous oxide triggered a rapid rise in temperature that was not accompanied by muscle rigidity, tachycardia, or cyanosis. The association of hyperthermia with hypoproteinemia and intestinal lymphangiectasia in this patient may be relevant, although there is insufficient evidence for a definitive association at this time.

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