Anesthesia Case of the Month

History

A 9.5-year-old 20.8-kg (45.8-lb) spayed female Border Collie was referred to the Washington State University Veterinary Teaching Hospital for evaluation of excessive and uncontrollable panting. According to the owner, the panting had begun suddenly 2 nights before with no obvious cause. The dog had had a heart murmur for 2 years for which it had been prescribed enalapril (10 mg, PO, q 24 h). The referring veterinarian obtained 2 radiographic views of the thorax to rule out congestive heart failure, but did not notice any radiographic abnormalities, and the dog was subsequently referred to the cardiology service at the Washington State University Veterinary Teaching Hospital for further evaluation of the heart murmur and excessive panting. The owner reported that the dog had been very restless and was unable to sleep or eat properly because of the nonstop panting and was drinking an excessive amount of water. The dog had a littermate that had died suddenly of an unknown cause, but a heart murmur had been identified prior to the dog’s death.

On initial physical examination at the Veterinary Teaching Hospital, the dog was alert and responsive. Body condition score was 5 on a scale from 1 to 9. The dog’s mucous membranes were pink and moist, and the dog’s mucous membranes were pink and moist, and the dog’s respiratory rate (10.8 seconds; reference range, 8.4 to 14.8 seconds) and activated partial thromboplastin time (10.8 seconds; reference range, 8.4 to 14.8 seconds) were within reference ranges. Examination of a urine sample collected via cystocentesis revealed a urine specific gravity > 1.035; dipstick analysis of the urine sample revealed 2+ protein, 3+ blood, and 1+ bilirubin. The urine protein-to-creatinine concentration ratio was 1.4 (reference range, 0.8 to 1.6). Serum total thryoxine concentration was < 0.5 µg/dL (reference range, 1 to 4 µg/dL). An ACTH stimulation test was performed; ACTH concentration prior to cortisol administration was 5.78 µg/dL (reference range, 1 to 6 µg/dL), and ACTH concentration 1 hour after cortisol administration was 13.4 µg/dL (reference range, < 20 µg/dL). An arterial blood sample obtained from the dorsal pedal artery was submitted for arterial blood gas analysis; pH was 7.41, Paco₂ was 23.4 mm Hg, Pao₂ was 97.5 mm Hg (inspired oxygen fraction, 0.21), SaO₂ was 98%, bicarbonate concentration was 15.1 mmol/L, and BE was −7.3 mmol/L. Thoracic radiography revealed normal lung parenchyma and cardiac silhouette. Electrocardiography revealed no abnormalities in heart rate or rhythm. Echocardiography revealed evidence of mild tricuspid and mitral valve endocardiosis.

The next day, MRI of the brain and analysis of a CSF sample were planned to rule out any structural or inflammatory lesions involving the brain. During a preanesthetic evaluation by the anesthesia service, the dog was panting continuously and was assigned an American Society of Anesthesiologists status of II on the basis of the underlying disease processes. A 20-gauge, 3.2-cm catheter had previously been placed in the left cephalic vein. The dog was premedicated with acepromazine (0.01 mg/kg [0.0045 mg/lb], IV) and hydromorphone (0.1 mg/kg [0.045 mg/lb], IV); ECG leads were placed for assessment of heart rhythm, and a size 3 oscillometric cuff was placed on the right forelimb for indirect measurement of blood pressure. The dog was preoxygenated with 100% oxygen delivered through a face mask for 5 minutes, and anesthesia was induced approximately 20 minutes after premedication with propofol administered to effect (2 mg/kg [0.9 mg/lb], IV). An 11-mm cuffed endotracheal tube was placed in the trachea by means of direct observation with a laryngoscope. Anesthesia was maintained with sevoflurane.

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in oxygen (flow rate, 2 L/min) delivered with an out-of-circle precision vaporizer through a circle breathing system. End-tidal concentration of sevoflurane was maintained between 1.6% and 2.2% (vaporizer setting, 2% to 2.5%) throughout the anesthetic period. A pulse oximeter probe was placed on the tongue, and a 20-gauge catheter was aseptically placed in the right dorsal pedal artery for direct blood pressure monitoring in the MRI unit. The dog continued to pant.

The dog was transported to the MRI unit approximately 20 minutes after anesthetic induction and was positioned in sternal recumbency and connected to a multipurpose monitor that recorded the ECG, oxygen saturation (determined by means of pulse oximetry), \( {P_{\text{ET}}}_{\text{CO}_2} \), (determined by use of side-stream capnography), and blood pressure (measured directly through a calibrated disposable transducer). Lactated Ringer’s solution was administered IV at a rate of 10 mL/kg/h (4.5 mL/lb/h). The dog was connected to a long Bain coaxial circuit attached to an anesthetic machine placed outside the MRI unit, and anesthesia was maintained with sevoflurane. The dog was mechanically ventilated with initial ventilator settings consisting of a respiratory rate of 10 breaths/min, tidal volume of 550 mL (25 mL/kg [11.4 mL/lb]), and peak inspiratory pressure of 20 cm H\(_2\)O. At this time, mean arterial blood pressure was 56 mm Hg, so a bolus of LRS (5 mL/kg [2.27 mL/lb], IV) was administered; mean arterial blood pressure subsequently increased to 65 mm Hg. Although \( {P_{\text{ET}}}_{\text{CO}_2} \) was 39 mm Hg, the dog was constantly breathing against the ventilator (bucking). In an attempt to prevent bucking, atracurium (0.15 mg/kg [0.068 mg/lb], IV) was administered. Within 10 minutes after atracurium administration, \( {P_{\text{ET}}}_{\text{CO}_2} \) was 50 mm Hg. At this time, analysis of an arterial blood gas sample indicated that \( p\text{H} = 7.21, {P_{\text{aco}}}_2 = 52.1 \text{ mm Hg, Pa}_{\text{o}}_2 = 342.6 \text{ mm Hg, Sa}_{\text{o}}_2 = 99.9\% \), bicarbonate concentration was 21.2 mmol/L, \( \text{BE} = -6.0 \text{ mmol/L, sodium concentration was 144.3 mmol/L, chloride concentration was 115.4 mmol/L, and potassium concentration was 6.15 mmol/L. The respiratory rate was increased to 12 breaths/min and tidal volume was increased to 600 mL, which caused the peak inspiratory pressure to increase from 20 to 25 cm H\(_2\)O. Despite these changes, \( {P_{\text{ET}}}_{\text{CO}_2} \) increased to 60 mm Hg within 10 minutes. The patient started panting again approximately 30 minutes after atracurium had been administered. After the MRI procedure was completed (approx 1 hour in the MRI unit), the patient was returned to the anesthetic preparation room for collection of a CSF sample. No abnormalities were detected on the MRI images of the brain.

While the patient was being repositioned and prepared for collection of a cisternal CSF sample, the dog’s tongue was observed during placement of a pulse oximeter probe to be very hot to the touch. The patient’s rectal temperature was 42.2°C (108°F). Immediately, administration of sevoflurane was discontinued, IV administration of cool LRS was begun, a fan was turned on to increase convective heat loss, and cold, wet towels were placed around the patient. The dog’s neck had become extremely rigid and difficult to flex, and forelimb extensor rigidity was observed. Analysis of an arterial blood gas sample obtained at this time revealed a \( p\text{H} \) of 7.34, \( {P_{\text{aco}}}_2 \) of 31.2, \( {P_{\text{ao}}}_2 \) of 306.4, \( \text{Sa}_{\text{o}}_2 \) of 99.9%, bicarbonate concentration of 17.1 mmol/L, \( \text{BE} \) of –7.1 mmol/L, sodium concentration of 146.9 mmol/L, chloride concentration of 116.4 mmol/L, magnesium concentration of 0.48 mmol/L, potassium concentration of 7.7 mmol/L, calcium concentration of 1.27 mmol/L, and lactate concentration of 0.6 mmol/L. A few minutes later, multiple ventricular premature contractions were noticed on the ECG and lidocaine (1 mg/kg [0.45 mg/lb], IV) was administered. The rhythm rapidly changed to ventricular tachycardia (> 200 beats/min), and a second bolus of lidocaine (2 mg/kg, IV) was administered. The heart rate decreased to 150 beats/min, with an accelerated idioventricular rhythm. Mean arterial blood pressure was 28 mm Hg at this time. Calcium chloride (1 mg/kg, IV) was administered to antagonize the effects of hyperkalemia on cardiac cell membrane potential. No improvement in the cardiac rhythm was noticed, and the patient went into asystole and respiratory arrest. Chest compressions were started immediately, and epinephrine (0.01 mg/kg, IV) followed by a bolus of LRS (5 ml/kg, IV) was administered. After approximately 2 minutes, atropine (0.04 mg/kg [0.018 mg/lb], IV) and another dose of epinephrine (0.1 mg/kg, IV) were administered. There was no return of spontaneous circulation, and the ECG was isoelectric. The rectal temperature had increased to 43.3°C (110°F). Vasopressin (0.4 U/kg [0.18 U/lb], IV) and epinephrine (0.1 mg/kg, IV) were administered 2 minutes later. Chest compressions were continued throughout this time with momentary pauses to evaluate the ECG rhythm or to allow auscultation for audible heart sounds. Cardiopulmonary cerebral resuscitation was discontinued after 20 minutes.

The patient’s postmortem body temperature continued to increase to a maximum of 44.4°C (112°F). By the time cardiopulmonary cerebral resuscitation was stopped, the skeletal muscles in the neck and extremities were extremely contracted and the dog had developed a sawhorse posture. Intense rigor mortis developed within 10 minutes after resuscitation was discontinued. A necropsy was performed approximately 2 hours later, and no gross abnormalities were identified except trauma to the caudate and middle lung lobes attributed to cardiopulmonary cerebral resuscitation attempts and mild thickening of the cusps of the left and right atrioventricular valves indicative of endocardiosis. Histologic examination revealed mitral valve endocardiosis, a focal area of mild myocardial degeneration in the right ventricle, and a focal cyst in the pars distalis.

**Question**

What was the cause of hyperthermia in this dog?

**Answer**

The most likely cause of hyperthermia in this dog was MH.

**Discussion**

Potential causes of panting in this dog included cardiorespiratory abnormalities, metabolic disorders, pain, and a neurologic problem. Results of thoracic ra-
diography, ECG, and echocardiography ruled out most cardiopulmonary diseases as a cause of the panting. The fact that hemostasis variables, including D-dimer concentration, platelet count, prothrombin time, and activated partial thromboplastin time, were within reference limits suggested that pulmonary and cerebral thromboembolism were less likely causes of the panting, although the mitral valve endocardiosis could have predisposed the dog to thromboembolism. Prior to the MRI, a thorough musculoskeletal examination was performed to rule out any painful neuromuscular problems that might have been causing the panting. Arterial blood gas analysis revealed compensated respiratory alkalosis. The unremarkable serum biochemical analysis and CBC results, normal results of ACTH stimulation testing, and total thyroxine concentration prior to anesthesia helped rule out metabolic and endocrinologic abnormalities. No neurologic deficits were identified during a neurologic examination. The MRI was scheduled to determine whether an intracranial lesion might have been causing the patient to pant excessively, but did not reveal any abnormalities. Finally, no clinically important abnormalities were found during gross or histologic examination at necropsy. However, necropsy findings in dogs with MH have been shown to be inconsistent and nonspecific.1

Hyperthermia can be iatrogenic or a result of heat stroke, pyrexia, infection, sepsis, a drug or transfusion reaction, or a hypermetabolic state. Prior to anesthesia of this patient, the rectal temperature was normal (39.1°C [102.4°F]), and there was no history of heat stroke. Results of physical examination, a CBC, hematostatic testing, and serum biochemical analysis ruled out infection and sepsis. Although the perianesthetic use of hydromorphone is associated with hyperthermia in cats,2,3 similar responses have not been reported in dogs. Because the dog described in the present report had a long, thick coat, warm water blankets were not used during anesthesia.

The dog described in the present report developed hypercapnia, cardiac arrhythmias, hyperthermia, and muscular rigidity, all of which were suggestive of MH. A clinical diagnosis of MH is made on the basis of clinical signs, monitoring data, and results of laboratory tests that can be performed rapidly. Classically, a combination of at least 3 of the following distinct signs is required to diagnose MH: cardiac arrhythmias, acidosis, hypercapnia, hypothermia, and muscle rigidity.4 Because each individual sign alone is nonspecific, the diagnosis often involves ruling out other possible causes. On initial evaluation, the dog described in the present report appeared to be under stress because of its constant panting and inability to sleep and eat properly for the preceding 3 days. The dog constantly paced while in the examination room and appeared apprehensive during the initial examination and subsequent interactions with the hospital staff. This stress coupled with the stress of hospitalization and general anesthesia5 could have potentiated the MH episode. The sudden unexpected death of a littermate raises the suspicion of a genetic predisposition to the condition, although this was not investigated. A diagnosis of MH is most often made by ruling out all other conditions, but clues from the animal’s history and from the history of the animal’s family could support a diagnosis of MH. In other species, physical or emotional stress has been implicated as a trigger of MH even in awake patients.6–9 Genetic testing10 to identify a predisposition to MH in dogs is not commercially available in North America but is offered by some laboratories in Europe. The diagnosis can be confirmed in dogs suspected to have MH by means of in vitro contracture testing. Specific conditions are needed to perform the muscle biopsy, and in vitro contracture testing must be performed immediately after collection of a fresh biopsy specimen.4 In addition, the high cost (> $5,000) and scarcity of laboratories that can perform this test make in vitro contracture testing impractical for routine preoperative screening, especially in veterinary medicine.

Most prominent sign of MH in dogs is increased production of carbon dioxide.4,11 The core body temperature may also increase, but does so slowly, and the increase in core body temperature lags behind the increase in carbon dioxide production.11,12 In the dog described in the present report, rectal temperature was not monitored during the MRI procedure because the monitor that was used did not have the ability to measure temperature. The first abnormality noticed in this dog was an increase in PETCO2, that continued to worsen despite an increase in minute ventilation. Anesthetized patients can become hypercapnic if elimination of exhaled carbon dioxide from the anesthetic circuit is prevented. However, during the MRI procedure in this dog, anesthesia was maintained with a nonrebreathing coaxial Bain circuit and an oxygen flow rate of 190 mL/kg/min (86.4 mL/h/lb/min) and minute ventilation of 262 to 343 mL/kg/min (119.1 to 155.9 mL/h/lb/min), which would have been expected to prevent any rebreathing of exhaled gases.13,14 Thus, increased production of carbon dioxide was the most likely cause of the increase in PETCO2.

Analysis of a blood gas sample obtained during the MRI procedure revealed acidemia (pH, 7.21; reference range, 7.35 to 7.45), high Paco2 (52.1 mm Hg; reference range, 36 to 40 mm Hg), and high potassium concentration (6.15 mmol/L; reference range, 3.7 to 5.3 mmol/L). Ventilation was increased to eliminate the respiratory acidosis and decrease the potassium concentration.

During MH episodes, cardiac arrhythmias can develop secondary to hyperthermia, hypoxia, acidosis, or electrolyte abnormalities.3,15 The arrhythmias initially observed in this dog were likely associated with hyperthermia, although the focal area of myocardial degeneration in the right ventricle found on histologic examination could have contributed. Although use of calcium to treat MH-associated hyperkalemia is controversial, calcium chloride (1 mg/kg, IV) was administered in this dog following detection of hyperkalemia in an attempt to reestablish the gradient between the threshold and resting cardiac membrane potentials.16 High intracellular calcium concentrations are responsible for the hypermetabolic state in dogs with MH, and it is possible that in the dog described in the present report, calcium administration worsened the outcome. No other intervention to decrease the potassium concentration was performed because cardiopulmonary arrest occurred shortly after the high potassium concentration was noticed. Lidocaine was used to treat...
ventricular arrhythmias in this dog. Use of lidocaine to treat tachyarrhythmias associated with MH has been documented to worsen the outcome by raising myoplasmic calcium content, leading to exacerbation of the hypermetabolic state.5,17,18 Procainamide has been recommended for treatment of cardiac dysrhythmias during episodes of MH.4

Unlike MH in pigs, MH in dogs is not typically characterized by an early onset of skeletal muscle rigidity or lactic acidosis,4,11 and lactic acidosis was not observed in the dog described in the present report. In addition, skeletal muscle rigidity was not observed until 70 minutes after administration of sevoflurane was begun, although once skeletal muscle rigidity was first noticed, it progressed to generalized muscular rigidity within 5 to 10 minutes. In vitro, sevoflurane causes abnormal contraction of muscle specimens from humans with MH,19 and use of sevoflurane has been described in previous case reports involving human patients with MH.20-22 In addition, sevoflurane can be used to detect a predisposition to MH in susceptible pigs.23 Rigor mortis has been reported to occur quickly in animals that die as a result of MH.24 Heart rate in the dog described in the present report increased from 80 to 150 beats/min, and ventricular premature complexes and ventricular tachycardia eventually developed. Gadolinium was used as a contrast agent during the MRI procedure in this dog because the incidence of adverse reactions following administration of gadolinium-based contrast agents is much lower than the incidence following administration of iodinated contrast agents.25,26 Tachycardia often is an early response to the onset of MH in humans and pigs. Predominant features of slowly developing hypermetabolic states are tachypnea and tachycardia or other arrhythmias.5

Malignant hyperthermia is a fulminating disorder of skeletal muscle characterized by a hypermetabolic state initiated by uncontrolled release of calcium from the sarcoplasmic reticulum in myocytes. Two main channels for movement of calcium are important for smooth function of the excitation-contraction coupling process. One is the voltage-gated dihydropyridine receptor, which is located in the transverse tubular system membrane, and the other is the calcium release channel or ryanodine receptor, which is located in the sarcoplasmic reticulum membrane. A causal mutation in the ryanodine receptor gene with an autosomal dominant inheritance pattern has been identified in dogs with MH.4,10,27 This mutation is not confined to any specific breed of dogs, and a single mutant allele can cause the clinical syndrome, posing a potential threat to dogs of all breeds. Malignant hyperthermia has been reported in various breeds of dogs, including Greyhounds, Border Collies, Cocker Spaniels, Doberman Pinschers, Pointers, and Saint Bernards.2,3,11,13,26-28 Selective breeding of sighthounds has induced a number of physiologic and anatomic idiosyncrasies in these breeds, and publication of a few case reports4,24,5 of MH in Greyhounds has led some to believe that this breed is predisposed to MH. However, a study39 that used both in vitro and in vivo assays showed no difference in MH susceptibility in Greyhounds, compared with mixed-breed dogs. Like many other sighthound breeds, Greyhounds are predisposed to have a nervous demeanor and are at greater risk of developing stress-induced hyperthermia that might be exacerbated by postanesthetic shivering or pain. Thus, especially in Greyhounds, it is important to differentiate MH from stress-induced or perianesthetic hyperthermia. In contrast to MH, stress-induced hyperthermia responds well to generalized body cooling and administration of analgesics and sedatives.31 The incidence of MH episodes in human patients undergoing anesthesia has been calculated to be between 1 in 5,000 and 1 in 100,000 anesthetic episodes.36

All of the injectable anesthetic agents (acepromazine, hydromorphone, propofol, and atracurium) used during the perianesthetic period in the dog described in the present report are considered safe in patients susceptible to MH. In fact, perianesthetic use of acepromazine17 and thiamylal38 has been shown to delay the onset of MH episodes. Also, use of nondepolarizing muscle relaxants may help prevent obligate depolarization at the neuromuscular junction and subsequent ongoing release of calcium from the sarcoplasmic reticulum.4 It is possible that use of acepromazine and atracurium in this dog delayed the onset of the fulminant MH episode.

All halogenated inhalant anesthetic agents and depolarizing neuromuscular blocking agents can trigger an MH episode, and discontinuing the administration of any triggering agent is the single most important step toward the effective management of an MH episode. Phenothiazines, benzodiazepines, opioids, β-adrenoceptor agonists, propofol, etomidate, barbiturates, dissociative anesthetics, nondepolarizing neuromuscular blocking agents, and nitrous oxide are considered safe in patients suspected to have MH.4 Dantrolene is an intracellular calcium antagonist that decreases the concentration of myoplasmic calcium by preventing the release of calcium from the sarcoplasmic reticulum and is the only specific treatment for the hypermetabolic state associated with MH. Preoperative prophylactic use of dantrolene in dogs has been suggested in a previous case report.3 Although prophylactic use of dantrolene has been recommended for human patients, current opinion emphasizes the use of trigger-free anesthesia without dantrolene prophylaxis.36 When an episode of MH occurs, dantrolene should be administered at a dose of 3 mg/kg (1.4 mg/lb), IV, as soon as the diagnosis of MH is established. Additional doses (up to 10 mg/kg) may be needed.4,35 Dantrolene was not used in the dog described in the present report because it was unavailable at the hospital. It has been suggested to use nondepolarizing neuromuscular blocking agents to interrupt an ongoing MH episode if dantrolene is not available.4

References


c. Transpac IV disposable transducer monitoring kit, Hospira Inc, Lake Forest, Ill.

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