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standard polyvinyl chloride endotracheal tubes has been estimated to occur 2% of the time during emergent tracheal intubation in an emergency department. Presumably this number is far less in the controlled setting of the operating room, but no data are available. Perforation by nasal airway, with or without inflation of the endotracheal space, is likewise a rare occurrence but must be considered in the appropriate setting as a cause of acute airway obstruction.

References


Intraoperative Hyperkalemia as a Triggering Mechanism or Presenting Sign of Malignant Hyperthermia in Two Patients with Chronic Renal Failure

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AN unexplained increase in end-tidal carbon dioxide is the earliest and most sensitive presenting sign of malignant hyperthermia (MH), whereas hyperkalemia and hyperpyrexia are late symptoms. The presumed mechanism underlying MH is an abnormal handling of myoplasmic calcium released from the sarcoplasmic reticulum of skeletal muscles. Increased cellular metabolism leads to an increase in carbon dioxide and H⁺ production. The increased myoplasmic calcium may result in an abnormal myofibrillar contraction. The metabolic and respiratory acidosis may further affect the redistribution of intracellular potassium to the extracellular space. In addition, increased permeability of the muscle cell membranes will increase serum levels of potassium, ionized calcium, creatine phosphokinase (CPK), lactate dehydrogenase, and myoglobin. Renal excretion and cellular reuptake of potassium both protect against hyperkalemia. However, in patients with end-stage renal disease (ESRD) and diabetes, both of these mechanisms are adversely affected; thus such patient may manifest acute hyperkalemia. Hyperkalemia triggers MH in MH-susceptible swine, but this mechanism has never been reported in humans. We believe that, in diseases with impaired potassium handling (ESRD, diabetes mellitus), acute hyperkalemia may either trigger an MH episode or be its presenting sign. We present two cases of MH with this atypical presentation. The first occurred recently at our institution and the second, which occurred in 1982, was obtained from our archives.

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Case 1

A 55-year-old man with a history of hypertension, juvenile-onset diabetes mellitus, and ESRD was scheduled for cadaveric renal transplant. He also reported general fatigue and frequent muscle cramps in the lower extremities, which were treated with quinine. The patient's medications included 22 units of NPH insulin in the morning and afternoon, 0.2 mg clonidine daily, 2 mg doxazosin twice daily, 60 mg nifedipine twice daily, 0.25 mg calcitriol daily, and 260 mg magnesium twice daily. The patient had had three previous surgeries, all of which were uneventful in regard to anesthesia. One was performed to place a peritoneal dialysis catheter (general anesthesia: sodium thiopental, isoflurane/nitrous oxide, fentanyl, and vecuronium); the catheter was later removed under monitored anesthesia care with midazolam and fentanyl sedation. The third surgery was performed with regional anesthesia (brachial plexus block) to create an arteriovenous fistula. His family history revealed that his sister has "occasional increases in body temperature even after minor procedures, such as dental work" (this information was obtained after the event).

This patient received hemodialysis three times per week and underwent hemodialysis before surgery. Postdialysis electrolyte concentrations were sodium 141 mEq/l, potassium 4.7 mEq/l, chloride 96 mEq/l, bicarbonate 22 mEq/l, calcium 9.5 mg/dl, phosphate 5.3 mg/dl, blood urea nitrogen 81 mg/dl, creatinine 13.1 mg/dl, and glucose 80 mg/dl. The electrocardiogram results were normal. Preoperatively, he received his regular oral medications as above, including nifedipine and 12 U of NPH insulin. Standard noninvasive monitors and a central venous catheter were placed. Before anesthesia induction, blood pressure was 175/90 mmHg and heart rate was 72 beats/min. Anesthesia was induced with 325 mg sodium thiopental, 150 μg fentanyl, and 40 mg atracurium and maintained with 1.0%–1.5% isoflurane in a mixture of oxygen and nitrogen, 50%,70% Postinduction blood pressure and heart rate were 110/65 mmHg and 70 beats/min, respectively. The lungs were mechanically ventilated with a tidal volume of 650 ml at a respiratory rate of 10 breaths/min. The end-tidal carbon dioxide was 26 mmHg. Esophageal temperature was 35.2°C. To prevent intraoperative hyperthermia, a forced-air patient warming system (Bair-Hugger, Augustine Medical, Eden Prairie, MN) was used.

About 30 min after anesthesia induction, electrolyte concentrations were sodium 137 mEq/l, potassium 7.2 mEq/l, and glucose 83 mg/dl. To exclude hemolysis as a possible cause of the unexpected hyperkalemia, a second blood sample was analyzed. The repeat potassium concentration was 7.1 mEq/l (fig. 1). At the same time, end-tidal carbon dioxide was 27 mmHg, and the body temperature was 35.4°C. To reduce hyperkalemia, we initiated hyperventilation (respiratory rate was increased to 15 breaths/min) followed by a continuous infusion of glucose and insulin. After 30 min the increased respiratory rate had not affected end-tidal carbon dioxide, and the tidal volume was increased to 800 ml. Venous blood gas measurements were pH 7.34, PaCO2 45 mmHg and bicarbonate 24 mEq/l; potassium was 6.4 mEq/l and glucose 241 mg/dl. Despite increased ventilation, end-tidal carbon dioxide increased to 32 mmHg. The slightly increased body temperature (37.2°C) was attributed to effective heat preservation, and the warming system was turned off. Four hours after anesthesia induction, a surgen injected 5 mg verapamil into the renal artery. Fifteen minutes later, ventilation difficulties occurred. Peak inspiratory pressure increased from 32 to 48 cmH2O, but there was no audible wheezing. The ventilator was checked to ensure it was functioning properly, and 20 mg atropine was administered. Despite hyperventilation, the end-tidal carbon dioxide increased to more than 60 mmHg, and the waveform indicated a rebreathing pattern with abrupt change in slope of the ascending limb; the soda lime also turned purple. Over 45 min, the patient's temperature increased from 37.2°C to 38.6°C. Blood pressure was 140/60 mmHg and heart rate 95 beats/min.

At this point, MH was considered. Hyperventilation was continued with a high oxygen flow, isoflurane was discontinued, and a propofol infusion was started, cold intravenous solutions were administered. Arterial blood gas measurements revealed a pH of 7.1, PaCO2 97 mmHg, PaO2 77 mmHg, bicarbonate 24 mEq/l, and potassium 7.5 mEq/l. Dantrolene, 2.5 mg/kg, was given. Over the next 15 min, the body temperature reached 39°C, and at that time, arterial blood gases and electrolyte concentrations were pH 6.88, PaCO2 146 mmHg, PaO2 98 mmHg, bicarbonate 21 mEq/l; potassium was 8.6 mEq/l, ionized calcium 1.34 mmol/l, and lactate 11.1 mmol/l. The same dose of dantrolene was administered again, and although the temperature immediately decreased to 37.6°C, serum potassium increased to 8.8 mEq/l despite continuous infusion of glucose and insulin (fig. 1). The electrocardiogram demonstrated wide QRS complexes with peaked T waves that soon converted to asystole. A 30-min course of cardiopulmonary resuscitation was characterized by episodes of severe bradycardia, asystole, ventricular fibrillation, and ventricular tachycardia. The hyperkalemia was treated with continuous hyperventilation, calcium, insulin, and 50% glucose. Resuscitation was successful, and a third dose of dantrolene (2.5 mg/kg) was given. The arterial blood gases after resuscitation were pH 7.33, PaCO2 32 mmHg, PaO2 218 mmHg, bicarbonate 17 mEq/l; potassium was 8.3 mmol/l and glucose was 435 mg/dl. After resuscitation, the kidney appeared ischemic, and the transplant attempt was aborted.

The patient was transferred to the intensive care unit, where he underwent hemodialysis twice over the next 12 h that decreased his

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Case 2

A 25-year-old man was admitted in December 1982 for surgical incision, required because of neurovascular glaucoma. He had a history of chronic renal failure induced by congenital obstructive uropathy and was undergoing hemodialysis three times a week. His preoperative medications included 40 mg furosemide and 80 mg propranolol three times per day, which was administered before surgery. His preoperative blood pressure was 130/70 mmHg, and his pulse was 85 beats/min. The electrocardiogram results were normal. Previously, he had undergone several uneventful anesthesias for cystoscopy with thiopental and a mixture of oxygen and nitrous oxide as well as an uneventful anesthesia with cyclopropane and succinylcholine for tonsillectomy at age 9. Postdialysis electrolyte concentrations (3 h before surgery) were sodium 140 mmol/L, potassium 4.7 mmol/L, chloride 101 mmol/L, blood urea nitrogen 115 mg/dL, and creatinine 17 mg/dL.

Anesthesia was induced with 375 mg sodium thiopental and 120 mg succinylcholine and maintained with a mixture of oxygen and nitrous oxide, 66%/34%, and 0.5-1% halothane. Postinduction blood pressure was 140/100 mmHg; heart rate 100 beats/min, and rectal temperature 36.8°C. Approximately 80 min after anesthesia induction, supraventricular and ventricular ectopy were noted. Serum potassium was 6.3 mmol/L. Treatment for hyperkalemia was initiated with insulin, 50% dextrose, and hyperventilation, but the arrhythmias did not resolve. Despite treatment, the serum potassium concentration 30 min later was 7.1 mmol/L, and arterial blood gas measurements (FiO2 1.0) were pH 6.92, PaCO2 61 mmHg, PaO2 77 mmHg, and bicarbonate 12 mmol/L. Glucose was 351 mg/dL. The patient’s temperature increased to 37.4°C, and MH was considered. Hyperventilation with high oxygen flow was continued, halothane was discontinued, and dantrolene was administered. Over the next 15 min, the body temperature increased to 38.8°C, and serum potassium increased to 9.4 mmol/L, resulting in a wide-complex bradycardia followed by asystole. The patient died despite cardiopulmonary resuscitation, repeated dantrolene administrations, and cooling. The hyperkalemia was aggressively but unsuccessfully treated during the 60-min resuscitation effort with 50% glucose, 3.2 L of regular insulin, bicarbonates, and hyperventilation. The patient’s serum potassium concentration was 8.8 mmol/L, and the CPK was 2,200 IU/L.

Discussion

The course of intraoperative events in our patients with ESRD was unusual for MH. The most prominent sign was acute hyperkalemia followed much later by hypercarbia and hyperpyrexia. The onset of hyperkalemia was surprising, and initial, poor potassium homeostasis caused by ESRD was thought to be the problem in both cases. Although patient 1 declined muscle biopsy, the entire clinical picture suggests a diagnosis of MH. Massive increases in carbon dioxide production, an acute increase in temperature from 35.8°C to 39°C, and a prompt decrease in temperature (signifying a decrease in metabolism) after dantrolene administration strongly support our diagnosis. A valuable nonspecific diagnostic sign of MH, such as an unexplained increase in the serum CPK level, was present in patient 1, but not in patient 2. Both cases were consistent with discrepancies in the diagnosis of MH. However, in patient 1, increased serum CPK level was not consistent with MH diagnosis. In patient 2, tachycardia and increased serum CPK level were consistent with MH diagnosis. Therefore, the diagnosis of MH was confirmed during the operation. The patient died due to respiratory failure and hypothermia.

Table 1. Patient 1 Score on a Malignant Hyperthermia Grading Scale for Clinical Indicators

<table>
<thead>
<tr>
<th>Process</th>
<th>Indicator</th>
<th>Patient 1 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Rigidity</td>
<td>Generalized muscle rigidity (difficult to ventilate)</td>
<td>15</td>
</tr>
<tr>
<td>II: Muscle breakdown</td>
<td>Elevated CPK &gt;10,000 IU/L after anesthetic without succinylcholine; myoglobin in serum &gt;170 ng/mL</td>
<td>15</td>
</tr>
<tr>
<td>III: Respiratory acidosis</td>
<td>End-tidal CO2 &gt;55 mm Hg; PaCO2 &gt;60 mm Hg with appropriately controlled ventilation; inappropriate hypercarbia</td>
<td>15</td>
</tr>
<tr>
<td>IV: Temperature increase</td>
<td>Inappropriate rapid temperature rise; inappropriately increased temperature &gt;38.8°C in the perioperative period</td>
<td>15</td>
</tr>
<tr>
<td>V: Cardiac involvement</td>
<td>Ventricular tachycardia or ventricular fibrillation</td>
<td>3</td>
</tr>
<tr>
<td>Other indicators that are not part of the single process</td>
<td>Arterial pH &lt;7.25; rapid reversal of MH signs of metabolic and/or respiratory acidosis with intravenous dantrolene</td>
<td>10</td>
</tr>
<tr>
<td>Total score</td>
<td>78*</td>
<td></td>
</tr>
</tbody>
</table>

CPK = creatine phosphokinase; MH = malignant hyperthermia.

* A total score of at least 50 represents the highest possible MH rank and describes the MH likelihood as “almost certain,” according to the MH grading scale developed by Larach et al.6


increase in the serum CPK level, was present in patient 1, but not in patient 2. Both cases were consistent with discrepancies in the diagnosis of MH. However, in patient 1, increased serum CPK level was not consistent with MH diagnosis. In patient 2, tachycardia and increased serum CPK level were consistent with MH diagnosis. Therefore, the diagnosis of MH was confirmed during the operation. The patient died due to respiratory failure and hypothermia.
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Increase in heart rate, was absent in both patients. In patient 1, marked tachycardia was absent, possibly because of diabetic autonomic neuropathy, premedication with clonidine and nifedipine, or both. In patient 2, tachycardia was absent, possibly because of premedication with propranolol. In the absence of diagnosis confirmed by muscle biopsy, an MH clinical grading scale may be used to define the probability that an event is MH. According to this scale, the probability that MH occurred in patient 1 was "almost certain" (table 1). Both patients had previous uneventful exposures to general anesthesia with a triggering agent, but such uneventful exposure does not discredit our diagnoses, because approximately 21% of all human MH episodes have been preceded by one or more uneventful anesthetics. Also, the late manifestation of MH during anesthesia is not atypical, especially after the use of depressant drugs such as barbiturates, benzodiazepines, and nondepolarizing muscle relaxants; thiopental has been found to decrease sarcoplasmic reticulum Ca2+ release, but this mechanism was not studied in relation to MH.

The initial acute increase in serum potassium from 4.7 to 7.2 mmol/l in patient 1 occurred in the absence of acidosis. We postulate that this hyperkalemia may be the result of one of the following two mechanisms. First, the acute hyperkalemia might have been caused by MH, with a large shift of extracellular potassium from skeletal muscles into extracellular space early during the course of anesthesia. The following findings support this mechanism: end-tidal carbon dioxide moderately increased (from 26 to 32 mmHg) despite a 75% increase in minute ventilation; and body temperature slowly increased immediately after induction of anesthesia, although this finding also can be attributed to active warming (fig. 1). Thus, it is possible that the MH episode started with an unusual presentation—with hyperkalemia as a primary event—progressed slowly and was recognized late; after sudden increases in end-tidal carbon dioxide and temperature during the 4th hour of anesthesia.

Alternatively, acute hyperkalemia as a primary event triggered MH episodes in MH-susceptible ESRD patients at the beginning of anesthesia, but the MH did not fully develop until 3 h later. Although it is not clear which mechanism caused acute hyperkalemia in patient 1 because hyperglycemia and acidosis were absent, it has been shown that acute hyperkalemia can develop during anesthesia in patients with diabetes who have ESRD. Most often the hyperkalemia that occurs in diabatic patients is related to hyperglycemia, but the concomitant ESRD would substantially increase the tendency toward hyperkalemia. The role of potassium in increasing muscle metabolism is less well defined. Van der Knoop showed that, in normal muscle, potassium increases oxygen consumption (metabolism), but only at concentrations above 20 mmol/l. Moulds and Denborough showed in vitro that increased potassium stimulates skeletal muscle metabolism and produces the contracture at lower concentrations in MH-susceptible muscle than in normal human muscle. Therefore, it is unlikely that hyperkalemia in our patients triggered an increase in metabolism that caused an MH-like syndrome in non-MH-susceptible individuals. Gronert et al. found that hyperkalemia greater than 6.0 mmol/l precipitates MH in MH-susceptible swine, and he postulated that the pathogenetic mechanism may be a "hyperkalemic muscle cell depolarization." Acute and severe hyperkalemia after anesthetic induction occurred in our patients in the absence of other obvious signs of hypermetabolism (Paco2 rise, acidosis, or hyperpyrexia), and this clinical picture supports the hypothesis that acute hyperkalemia developed in patients with ESRD who were MH-susceptible as a primary event and then triggered an MH episode.

The acute increase in serum potassium in the patient with diabetes (patient 1) was initially reversed with treatment (from 7.2 to 6.4 mmol/l). The second potassium increase in this patient may be attributed to acute development of respiratory acidosis because a Pco2 increase of 10 mmHg can increase serum potassium by up to 0.3 mmol/l. In our patient, Pco2 increased from 45 to 146 mmHg, and serum potassium concentration from 6.4 to 8.6 mmol/l. After dantrolene administration, the respiratory acidosis was easily corrected with hyperventilation, suggesting that hypermetabolism was halted; the hyperkalemia, however, resisted all therapeutic interventions.

The acidosis and hyperkalemia also resulted in cardiac arrest, but an interaction between dantrolene and verapamil must be considered as a contributing factor. Concomitant administration of verapamil and dantrolene has been shown to induce hyperkalemia and cardiovascular collapse in animals and humans. Salzman postulated that verapamil alters the normal homeostatic mechanism for potassium regulation. Simultaneous increase in serum potassium caused by dantrolene can augment negative dromotropic and inotropic effects of verapamil on the heart. Hall et al.
found that, 15 min after dantrolene administration, potassium production increased fourfold in the leg muscle of an MH-susceptible swine, which suggests an increased potassium release from the skeletal muscle. The mechanism of dantrolene-induced hyperkalemia has never been elucidated, but because mannitol is added to dantrolene (5 g mannitol per 20 mg dantrolene), it is possible that dantrolene-induced hyperkalemia is a result of mannitol-induced hyperosmolarity; plasma potassium concentration may rise by as much as 0.4–0.8 mmol/l for every 10 mOsm/kg elevation in effective plasma osmolality.

In our second case, we cannot precisely document the temporal sequence of the early MH signs, such as an increase in end-tidal carbon dioxide, because technology for monitoring such signs was unavailable at the time. Nonetheless, with such severe hypercarbia, we would have expected to see spontaneous breathing efforts in an anesthetized patient who was not paralyzed; however, we did not. The first obvious symptom was dysrhythmia caused by hyperkalemia; hyperpyrexia followed. In both patients, the hyperkalemia was resistant to treatment (including postoperative hemodiagnosis in patient 1), which might be attributable to ESRD. hyperosmolar states induced by mannitol, glucose administration, and patient 2, also to propranolol.

We believe that these cases suggest an atypical presentation or triggering of MH by hyperkalemia. They also suggest that MH-susceptible patients may be at increased risk for an MH episode if they have a coexisting disease that alters potassium homeostasis. Finally, the cases point out a potential therapeutic dilemma: In the patient with ESRD who develops MH, hyperkalemic cardiovascular complications may be more prominent and difficult to treat because dantrolene can potentiate primary hyperkalemic hyperthermia.

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