

Bruno Riou, M.D., Ph.D., Editor

Case Scenario: Increased End-tidal Carbon Dioxide

A Diagnostic Dilemma

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MONITORING of end-tidal carbon dioxide is one of the most important means of determining the physiologic well-being of anesthetized patients. Exhaled carbon dioxide, both in terms of its quantity and pattern, provides detailed information on the cardiopulmonary system. Many things must occur for the exhaled carbon dioxide tracing to appear normal (fig. 1). This hypothetical case acts as a spring board to a discussion of the differential diagnosis of a rapidly rising exhaled carbon dioxide concentration, with special emphasis on malignant hyperthermia (MH).

Case Report

A 55-yr-old man was scheduled to have incision and drainage of a large thigh abscess during general anesthesia. He admitted to extensive substance abuse, including alcohol, tobacco, methamphetamines, and cocaine. He inhaled an unknown quantity of methamphetamines 12 h before his arrival in the operating room. He denied family or personal problems with anesthesia. He did not take any medications. He did not have any history of cardiac or pulmonary disease. He weighed 77 kg and was 189-cm tall. His preoperative blood pressure was 145/85 mmHg, and his resting heart rate was 85 beats/min. His tympanic membrane temperature was 37.8°C. Two hundred milligrams of propofol was administered intravenously followed by 50 mg of rocuronium. The trachea was intubated with an 8.0-mm endotracheal tube. Chest auscultation revealed equal bilateral breath sounds. Mechanical ventilation was initiated with tidal volume = 600 ml and 12

breaths/min. Sevoflurane was started at 2.5% on the vaporizer. Thirty minutes after induction of anesthesia, and 10 min after the surgery had begun, the end-tidal carbon dioxide was 35 mmHg; end-tidal sevoflurane was 2.2%. Over the next 30 min, the end-tidal carbon dioxide increased from 35 to 45 mmHg, accompanied by a slight increase in heart rate from 95 to 105 beats/min. Nasopharyngeal temperature was 38.9°C. The increasing end-tidal carbon dioxide, heart rate, and temperature suggested a physiologic perturbation that required immediate attention and investigation.

A thorough check of the anesthesia machine and circuit revealed no leaks. Inspiratory pressures were 15 cm H₂O, and chest auscultation demonstrated equal breath sounds with no wheezing; chest excursion with each breath seemed adequate and appropriate for the tidal volume. The ventilation rate was increased to 15 breaths/min. Despite the change in ventilation, the end-tidal carbon dioxide continued to increase to 60 mmHg over 5 min. Heart rate was 110 beats/min.

Antibiotics (1 g of cephazolin and 100 mg of gentamicin) were administered in response to surgical manipulation of the abscess and possible bacterial seeding into the bloodstream, but end-tidal carbon dioxide continued to increase and was 65 mmHg despite a further increase in minute ventilation (tidal volume, 900 ml; rate, 20 breaths/min). The electrocardiogram showed sinus tachycardia with normal T waves. There did not seem to be any muscle rigidity, but after placing a urinary catheter to follow urine output, the urine was observed to be dark. A urine dipstick test was positive for hemoglobin or myoglobin. A muscle twitch monitor (electrodes placed over the ulnar nerve) demonstrated only one twitch in a train-of-four stimulation. An arterial blood gas analysis showed pH = 7.13, PaCO₂ = 73 mmHg, PaO₂ = 225 mmHg, O₂ saturation = 99%, HCO₃⁻ = 19 mEq/l, and K⁺ = 5.0 mEq/l. The end-tidal carbon dioxide was 67 mmHg at the time of the blood gas sampling. The creatine kinase was 1200 IU/l, and the partial thromboplastin time was normal.

Diagnosis of Increasing End-tidal Carbon Dioxide

Carbon dioxide is produced in cells, and after diffusing into the blood, it is transported to the lung for excretion. The

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Received from Department of Anesthesiology, University of California, Davis, Davis, California. Submitted for publication July 29, 2009. Accepted for publication November 10, 2009. Support was provided solely from institutional and/or departmental funds.

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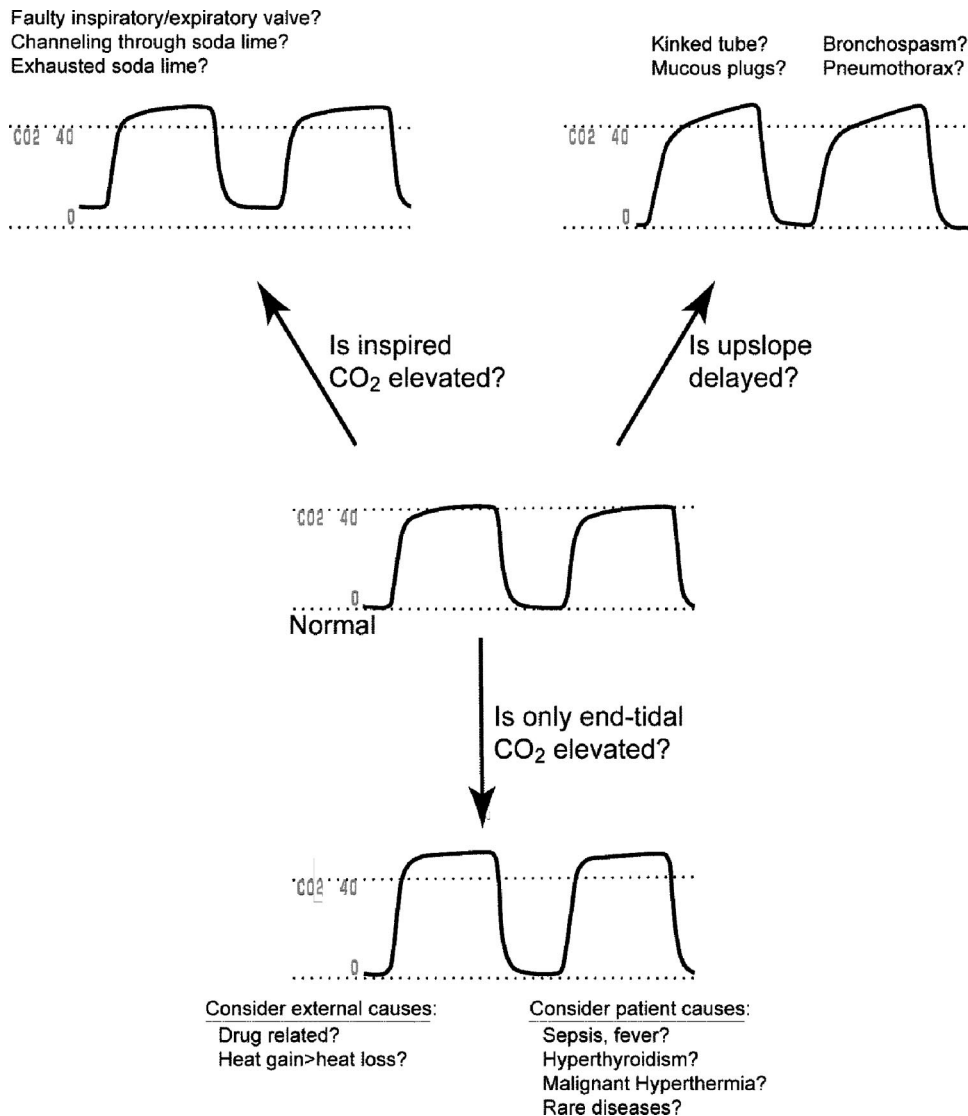


Fig. 1. End-tidal carbon dioxide (CO₂) tracings. A normal tracing is shown in the center, whereas examples of increased end-tidal carbon dioxide are shown around it. There are several causes for increased expired carbon dioxide, but these can be separated based on whether the inspired carbon dioxide level is increased or whether there is a delayed upstroke (indicating high resistance), as would be seen with mucous plugging or bronchospasm. When only the end-tidal carbon dioxide is increased (no inspired carbon dioxide and no delayed upstroke) then external and patient causes must be explored. However, a low inspired carbon dioxide tracing does not exclude the possibility of rebreathing. The clinician must also consider the possibility of artifact, for example, problems with the sampling or the gas analyzer, such as calibration error.

differential diagnosis of increased end-tidal carbon dioxide is long but can be separated into two categories: decreased excretion or increased production. The causes of decreased excretion can be further divided into increased inspired carbon dioxide, decreased ventilation, and increased dead space. Increased production can have many causes, as shown in table 1, and is discussed later. Furthermore, there are iatrogenic causes, such as carbon dioxide insufflation during laparoscopy, tourniquet release, and treatment of acidosis with bicarbonate. In addition, the clinician must always consider the possibility of a monitor malfunction, a calibration error, or a gas supply switch.² Whenever there is an unexplained increase in end-tidal carbon dioxide (>10–20% above baseline) and it does not respond to appropriate measures (*e.g.*, increased ventilation and additional anesthesia), the clinician

should consider obtaining an arterial blood gas and electrolyte analysis.

Problems with the anesthesia machine can cause increased expired carbon dioxide by increasing inspired carbon dioxide. Exhausted soda lime, channeling through the soda lime, or a faulty inspiratory or expiratory valve might increase the end-tidal carbon dioxide level. Under normal patient conditions, carbon dioxide absorbents will last several hours, but there is substantial variation. Although dye indicators can help determine remaining capacity, these can be inaccurate. Channeling is difficult to detect but could be treated in the same way as in the case of exhausted soda lime, that is, by replacement. A faulty valve in the circle system can be observed and replaced if needed. All these causes would result in increased inspired carbon dioxide, although careful inspec-

Table 1. Conditions That Can Increase End-tidal Carbon Dioxide

External causes
Alcohol therapy for limb arteriovenous malformation
Contrast dye
Drug toxicity or abuse
Environmental heat gain more than loss
Exercise hyperthermia
Heat stroke
Ventilation problems (kinked or blocked endotracheal tube)
Equipment malfunction (faulty expiratory valve)
Treatment of acidosis
Tourniquet release
Neuroleptic malignant syndrome
Carbon dioxide insufflation
Disease related
Cystinosis
Hypokalemic periodic paralysis
Intracranial free blood
Muscular dystrophies (Duchenne, Becker)
Central core disease
Myotonias
Diabetic coma
Freeman-Sheldon syndrome
Hyperthyroidism
Osteogenesis imperfecta
Pheochromocytoma
Prader-Willi syndrome
Rhabdomyolysis
Sepsis
King Denborough disease
Wolf-Hirschhorn syndrome
Idiopathic hyperCKemia
Malignant hyperthermia

Each of the nonmalignant hyperthermia conditions can potentially increase end-tidal carbon dioxide and, depending on the specific condition, produce other signs and symptoms (such as muscle breakdown, hyperkalemia, metabolic acidosis, and hyperthermia) that will mimic malignant hyperthermia. The conditions are separated according to whether the primary cause is an external factor (such as drug ingestion or administration) or whether it is related to a specific patient disease. In some cases, this distinction is not clear. Adapted from Gronert et al.¹ with permission.

tion of the waveform is needed. Increased inspired carbon dioxide was not observed on the capnograph of this patient. It is possible that the nadir of the inspired carbon dioxide concentration could be zero, but that some of the inspired gas has carbon dioxide in it, although this would not likely lead to a markedly increased end-tidal carbon dioxide.

Inadequate ventilation would also lead to increased carbon dioxide partial pressure. Indeed, high carbon dioxide levels will result whenever metabolic production exceeds excretion. Thus, despite the fact that no changes were made to the ventilator parameters, it is possible that something was amiss with ventilation. There could be a leak in the circle system, such that part of the “tidal volume” is leaking out (e.g., a nasogastric tube placed inadvertently into the trachea). This leak would be large enough to decrease minute ventilation but small enough to not trigger the low-pressure alarm. Bronchospasm will impede ventilation and is usually

associated with wheezing; bronchodilators are often (but not always) effective. Partial tube blockage, either with mucous plugging or a kink, could prevent normal ventilation, and this would lead to increased inspiratory pressures; tube blockage is particularly problematic during pediatric cases where small endotracheal tubes are used. Suctioning the endotracheal tube will remove secretions, but replacement might be needed in extreme cases. Increased dead space would also decrease minute ventilation; causes include adult respiratory distress syndrome.

Because there seemed to be no problem with ventilation in this patient, consideration must be given to increased carbon dioxide production as the cause of the hypercapnia. There are numerous causes, and common things occur frequently. Ventilatory problems have already been ruled out. Awakening from anesthesia can increase metabolic production of carbon dioxide; however, the delivery of sevoflurane seemed adequate, and the end-tidal sevoflurane was inconsistent with the scenario of inadequate anesthesia. Furthermore, the patient received rocuronium that would minimize the risk of light anesthesia causing muscle shivering.

Sepsis is a common cause of increased metabolism, as is fever from any cause. This patient had pathology (*i.e.*, an abscess) that could lead to bacteremia, entry of pyrogens into the blood stream, and fever, resulting in increased metabolism and carbon dioxide production. His recent history of substance abuse increases the possibility of toxic drug reaction. For example, methamphetamines or cocaine could cause hypermetabolism (*i.e.*, metabolic rate above normal) and possibly rhabdomyolysis. Blood toxicology would address this possibility, although results would not be available quickly enough to permit a fast diagnosis.

Other possible causes of increased metabolism include surgical stress, seizures, hyperthyroidism, and burns. Although this patient was anesthetized, physiologic responses to surgery (*i.e.*, surgical stress) will result in increased metabolism. Seizures, especially if there is marked muscle tonic-clonic activity, will markedly increase carbon dioxide production. This patient did not have tonic-clonic seizures. The presence of hyperthyroidism could be investigated with blood tests for thyroid hormone, although this might take considerable time. The diagnosis of burns is self-evident. More rarely, a pheochromocytoma or transfusion reaction might cause an increased metabolic rate.

Most of the diseases and situations described in the preceding paragraphs would cause a nonprogressive increased carbon dioxide. MH is looking more likely as the cause of this patient’s clinical presentation, in part, because there was a progressive increase in carbon dioxide. Although its occurrence is rare, and there are numerous conditions that mimic it (table 1), the clinician must think of MH, because its treatment is lifesaving and dependent on time of initiation. A clinical grading scale has been developed, which assigns qualitative likelihood to a clinical episode of suspected MH (table 2).^{3,4} In this case, points would be assigned for respiratory and muscle processes, as well as temperature increase and

Table 2. Criteria Used in the Clinical Grading Scale for Malignant Hyperthermia

Process	Clinical Criteria	Points
Muscle rigidity	Generalized rigidity	15
Muscle breakdown	Masseter muscle rigidity	15
	Creatine kinase > 10,000 units/l	15
	Cola-colored urine	5
Respiratory acidosis	Excess myoglobin in urine or serum	3
	K ⁺ > 6 mEq/l	15
	End-tidal CO ₂ > 55 mmHg; Paco ₂ > 60 mmHg	10
Temperature increase	Inappropriate tachypnea	15
	Rapidly increasing temperature	10
Cardiac involvement	Inappropriate temperature > 38.8°C	3
	Unexplained sinus tachycardia, ventricular tachycardia or ventricular fibrillation	15
Family history	MH history in first-degree relative	5
	MH history in family, not first-degree relative	

Only the highest score in any one process should be used when more than one event or sign occurs in a process. The more criteria that a patient fulfills, the more likely that an MH episode has occurred. If only one criterion is fulfilled then malignant hyperthermia is not likely, whereas malignant hyperthermia is almost certain if all criteria are fulfilled. Other criteria to consider include base excess > -8 mEq/L (10 points), pH < 7.25 (10 points), and rapid reversal of malignant hyperthermia signs with dantrolene therapy (5 points). The likelihood according to point score: 0, almost never; 3-9, unlikely; 10-19, somewhat less than likely; 20-34, somewhat greater than likely; 35-49, very likely; ≥50, almost certain. Adapted from Larach et al.³ with permission.

CO₂ = carbon dioxide; MH = malignant hyperthermia; Paco₂ = arterial carbon dioxide tension.

possible cardiac involvement (unexplained tachycardia). The dark urine indicates possible muscle breakdown and is another sign of MH. If rhabdomyolysis is suspected, aggressive therapy is warranted to prevent kidney damage and hyperkalemia. Although increased temperature is part of the syndrome, it usually occurs late and the clinician must not wait for this sign before making the diagnosis and initiating therapy (dantrolene). Delaying diagnosis and treatment will increase mortality.

Intraoperative Management

The sevoflurane was discontinued, and anesthesia was maintained with remifentanyl and propofol. Dantrolene (2.5 mg/kg) was administered over more than 15 min (the slow rate of mixing and solvation prevents faster administration). Cooling measures were initiated, including placing iced wet towels on the torso. Intravenous fluids were administered at a

rapid rate, both to help cool the patient and to prevent renal damage from rhabdomyolysis. There was a rapid resolution of the hypercarbia, and end-tidal carbon dioxide was 25 mmHg; ventilation was decreased (tidal volume, 700 ml; rate, 8 breaths/min). Nasopharyngeal temperature was 37.4°C. After the surgery was completed, the patient was awakened and extubated. Serial blood samples showed no hyperkalemia but creatine kinase peaked at 25,000 IU/L 24 h postoperatively.

Postoperative Management

There are several issues that must be addressed when taking care of a patient who has had a suspected episode of MH. First, the patient must be watched closely for recrudescence. Risk factors for recrudescence include muscular build, a temperature increase, a high score (>35) on the clinical grading scale, and a delayed period between exposure to triggers and the initial reaction.⁵ Frequent monitoring of vital signs, urine, electrolytes, and arterial blood gases should help guide management. Any increases in potassium, worsening acidosis, or resumption of hypermetabolism should prompt repeated doses of dantrolene (1 mg/kg every 6-12 h). Because coagulation can be impaired as a result of the shock state, baseline clotting values (prothrombin time, partial thromboplastin time, and D-dimer) should be obtained. Second, because of muscle breakdown, there is a risk of kidney damage.⁶ This patient should receive alkalization of his urine and diuretics (furosemide and mannitol) to help clear myoglobin that might have been deposited in the renal tubules. Third, creatine kinase in blood must be determined every 6-8 h until values begin to fall. If markedly increased, the clinician must be more aggressive about administering diuretic therapy to increase renal clearance of myoglobin. In many cases of suspected MH, creatine kinase does not increase or does so only mildly.⁷ Fourth, serum electrolytes need to be monitored, especially potassium, because rhabdomyolysis can lead to hyperkalemia. Failure to diagnose and treat hyperkalemia can lead to cardiac arrhythmias and death. The risk of death for patients with an acute MH episode ranges between 1 and 17%.^{8,9} In unusual cases, MH can present in the immediate postoperative period.¹⁰

This patient must be advised regarding the presumptive diagnosis of MH and that, because it is almost always an inherited disorder, family members must be told about their risk of having this subclinical disease. Currently, the accepted standard for diagnosis is the *in vitro* contracture test. Patients with a high likelihood of MH given the clinical events should be actively encouraged to pursue testing as the positive predictive value is increased for them. Genetic testing is also available, but this has limited sensitivity because it does not detect all genetic abnormalities that are likely to be associated with MH.

A patient who is suspected of having had a MH episode can be referred to a biopsy center, of which there are 6 in North America (2 in Canada and 4 in the United States), 24

in Europe, and 4 in Australia and New Zealand (updated lists are available).[§] In general, most biopsy centers will need to review the medical records in addition to speaking with the patient and the anesthesiologist or anesthetist. Once this information is reviewed, a decision is made regarding the advisability of performing the biopsy procedure. Clinical information, along with the biopsy results, can be entered into the MH registries to facilitate future data analysis.

The caffeine-halothane contracture test requires fresh muscle sample that must be obtained immediately before testing and therefore in close proximity to the biopsy center. The muscle sample cannot be mailed or sent by express delivery service. The test requires a small muscle sample (2 cm × 2 cm × 2 cm) obtained from the vastus lateralis. A video of the procedure is available for viewing.||

Like all biologic tests, contracture testing has limits on its sensitivity and specificity (the former is the ability to detect the disorder and the latter relates to whether the test will be positive when the disorder is not present). Usually, there is a tradeoff between the two, such that increased sensitivity comes at the expense of decreased specificity. The diagnostic thresholds were established to minimize the possibility of false-negative results. The North American protocol has a sensitivity and a specificity of 97–98% and 78–80%, respectively (although specific values will vary from laboratory to laboratory).¹¹ Thus, there is a 2% chance that contracture testing will incorrectly mislabel a MH-susceptible individual as normal, whereas there is a 20% chance that a person without the disease will be labeled as susceptible.

Some clinicians question the value of the contracture test other than for research purposes. They argue that, given the less than 100% sensitivity of contracture test, a patient who tests negative still should not receive triggering agents. Thus, if testing will not change anesthetic practice, then why perform invasive and expensive biopsy procedures? Generally, it is quite practical to give anesthesia using nontriggering anesthetics. However, for certain patients (pediatrics, severe asthmatics, and those with difficult airways) and procedures (myringotomy tubes), potent inhaled anesthetics are useful. Further, the implications for family members of patients labeled MH susceptible can become burdensome. If a single patient is incorrectly presumed susceptible without biopsy, what about their children and grandchildren? Biopsy center directors routinely evaluate patients whose elective procedures were cancelled by anesthesiologists who were uncomfortable anesthetizing them before their MH status had been established by biopsy. Nevertheless, we cannot fault a clinician who wishes to give a nontriggering anesthetic to a person who has had contracture testing and who is not susceptible to MH. The consensus among experts, however, is that such patients can safely receive triggering anesthetics.

§ www.mhaus.org and www.emhg.org. Accessed September 24, 2009.

|| <http://medical.mhaus.org/index.cfm/fuseaction/video.display/videoId/1.cfm>. Accessed September 24, 2009.

Pathophysiologic Basis of MH

MH, a pharmacogenetic disturbance of skeletal muscle, occurs in susceptible individuals on exposure to potent halogenated anesthetic vapors (sevoflurane, desflurane, isoflurane, and halothane) or the depolarizing muscle relaxant succinylcholine.¹² The reaction is characterized by skeletal muscle hypermetabolism after exposure to these triggering drugs. Patients susceptible to MH exhibit uncontrolled intracellular calcium release in muscle, triggering large increases in aerobic and anaerobic metabolism as the muscle cells attempt to sequester unbound ionized calcium and restore homeostasis. Muscular rigidity occurs when the unbound intracellular calcium concentration reaches myofibrillar contractile thresholds. Heat production and lactic acid levels increase, initiating respiratory and metabolic acidosis, whereas adenosine triphosphate stores are depleted, which leads to increased cell permeability. When left unchecked, rhabdomyolysis will occur, which can lead to acute renal failure. Similarly, other organs can fail and result in death.

Therapy should be aimed at stopping the uncontrolled calcium release by discontinuing triggering agents and administering dantrolene. Dantrolene is a skeletal muscle relaxant that slows the release of calcium from the sarcoplasmic reticulum, permitting the cell time to reestablish homeostasis; it does not act at the neuromuscular junction. Once the diagnosis of MH is entertained every effort should be exerted to obtain, mix, and administer dantrolene. Hyperventilation, external cooling, correction of acidosis with bicarbonate and intravenous fluids are important but should be instituted in parallel with dantrolene therapy not in place of it.

Epidemiology of MH

MH in humans is a syndrome often inherited as an autosomally dominant trait with variable expressivity and incomplete penetrance. Some individuals might have an episode on the first exposure to triggering agents whereas another individual might not trigger on repeated exposures. There is recent evidence linking ryanodine receptor variants and quantitative differences in phenotype, including onset time after exposure to triggering agents.¹³ Because the presence of other anesthetic drugs and exposures to low concentrations of triggering agents can affect the onset of a MH episode,¹⁴ it is unclear to what extent true phenotypic variation impacts the variable clinical picture.

A primary genetic defect is in the genes that code for the ryanodine receptor. The ryanodine receptor is located in skeletal muscle sarcoplasmic reticulum where it functions as a calcium channel to modulate contraction and release. Genetic testing for MH in humans focuses on the ryanodine receptor. There are more than 300 known mutations in the ryanodine receptor.¹⁵ So far, 29 causative mutations have been identified in humans on chromosome 19 in the loci coding for the ryanodine receptor; however, only approximately 50% of susceptible individuals have one of the known defects.¹⁶ Unfortunately, because of genetic complexity, the

absence of mutations does not establish MH negative status. Discordance between contracture testing and genetic mutations occurs among families. In such cases, patients might have second mutations in unscreened portions of the ryanodine receptor or a defect in another focus entirely. There may be polymorphisms or variants that have unclear significance. There are only two certified laboratories in North America that perform genetic analysis for MH.[#] The problems noted earlier have diminished the clinical diagnostic value of genetic testing for MH susceptibility, although continued research should improve its usefulness.

Although research has focused on the ryanodine receptor, other defects have been described. For example, the *CACNLIA3* gene that encodes the α -1 subunit of the skeletal muscle dihydropyridine receptor has been implicated to play a causative role.¹⁷ In addition, calsequestrin-1 is a calcium-binding protein in skeletal muscle that, when absent, leads to MH-like episodes in mice.¹⁸ Whether this defect is present in humans remains to be determined, but such a defect could explain susceptibility to MH in patients who do not have abnormal ryanodine receptors.

In our opinion, genetic testing should be done for patients with MH diagnosed through contracture testing to screen for a causative mutation. If found, first-degree relatives may undergo screening and establish MH susceptibility if the causative mutation is found, thus avoiding contracture testing. If no mutations are found, relatives must still undergo muscle biopsy testing to establish their status.

Plasma concentrations of creatine kinase can be increased in patients susceptible to MH, although by itself such an elevation is not diagnostic for this disorder (*e.g.*, it lacks specificity). On the other hand, if creatine kinase is increased in an individual who has a first-degree relative who has proven MH susceptibility, then that individual may also be considered to be susceptible.

Contrasts of Evaluation of MH in North America and Europe

One of the major goals of MH research has always been the development of a reliable diagnostic screening test. After publication of the increased sensitivity of skeletal muscle of MH-susceptible individuals to caffeine or halothane or both, *in vitro* muscle contracture testing was introduced as a diagnostic tool using various protocols, drugs, and drug combinations.^{19,20} This development led to the formation of two different groups worldwide, the North American MH Group and the European MH Group. Both groups created their own protocols using caffeine and halothane in a slightly different way. However, comparisons of both protocols showed more or less similar test results.²¹ These findings and the aim of the individual laboratories to use their own exper-

ience for the investigation of new patients made it difficult to establish one single protocol for MH screening in the world.

Although *in vitro* muscle contracture testing has been used much more frequently in several European countries over the past decades, it is obvious that the basis for further MH research, particularly genetics, is larger in Europe compared with North America. Pooled clinical data, *in vitro* muscle contracture testing, and genetic data of several MH investigation units led to the publication of guidelines using both contracture testing and genetic screening according to the individual patient.²² The reason for this approach is patient safety, because it is crucial that a MH negative diagnosis is correct. The application of trigger agents may be harmful in such persons and relatives in case of a false-negative diagnosis.

Knowledge GAP

Because there are numerous causes of increased end-tidal carbon dioxide, and each can have a variable course, it is difficult to use the capnograph as a diagnostic tool by itself. Thus, the current diagnostic specificity of capnography is not likely to be improved. It is possible, however, that further research into each cause of increased end-tidal carbon dioxide will reveal patterns of accompanying measures (such as heart rate, blood pressure, respiratory flow, and inspired/expired volumes) that, when combined with the capnograph, will improve diagnostic accuracy. Such a grading scale would be similar to that used for the diagnosis of a MH episode.

One of the most important goals of research of MH is to minimize morbidity and mortality. This could be achieved in several ways, including having a test for MH susceptibility that is inexpensive and could be applied to all patients undergoing general anesthesia. Although this might not seem practicable by the standards of today, the advances in pharmacogenetics make it likely that one day patients will be tested for a wide variety of diseases and drug sensitivities, and that this could be done cheaply.

In the short term, however, our understanding of all genetic mutations that are associated with and cause MH susceptibility is incomplete. Once all (or nearly all) mutations are known, a sensitive and specific genetic test can be used for diagnosing MH. Nonetheless, spontaneous mutations will occur and the list of genetic defects will lengthen over time. Thus, genetic testing will require continual updating. In addition, advances are being made in developing a less invasive test than muscle biopsy. One of these techniques uses *in vivo* microdialysis of skeletal muscle.²³ In brief, a small microdialysis probe is placed into the muscle, and halothane and caffeine are passed through the probe. Lactic acid is measured in the dialysate. Patients with MH susceptibility have increased lactic acid compared with normal patients. While still experimental and under development, microdialysis holds some promise in replacing the more invasive muscle biopsy procedure. There is also an interest in testing blood lymphocytes for a diagnosis of MH susceptibility.²⁴

[#] Center for Medical Genetics, <http://path.upmc.edu/divisions/mdx/diagnostics.html>. Accessed July 9, 2009; Prevention Genetics, LLC, <http://www.preventiongenetics.com/>. Accessed July 9, 2009.

We also do not have a thorough understanding of how the defect in the ryanodine receptor leads to the clinical syndrome, nor do we know all the specific details regarding the mode of action of dantrolene. Although dantrolene has been lifesaving, it is not a perfect drug. Drawbacks include phlebitis, respiratory muscle weakness with difficulty weaning from a ventilator, difficulty with solvation, and others. Finding a replacement for dantrolene would be an advance. Finally, we still do not completely understand the relationship between MH and other diseases.²⁵⁻²⁷

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