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Lethal Air Embolism during Cesarean Delivery for Placenta Previa

Mark A. Kostash, M.D., F.R.C.P.C., Fred Mensink, M.D., F.R.C.P.C.†*

CLINICALLY significant venous air embolus (VAE) occurs most often during sitting craniotomies and spinal surgery when venous sinuses are open at a level above the heart. VAE is also a known complication of cesarean delivery. It is more common than would be suspected, with an incidence as high as 97% reported using precordial Doppler monitoring and end-tidal nitrogen sampling as markers for air emboli.[1,2] The majority of emboli are without clinical consequence.[1,2] To our knowledge, this is the first report of a fatal air embolism occurring during cesarean delivery to be published in the anesthesia literature.

Case Report

A 29-yr-old woman, para 5, gravida 1, spontaneous abortion 3, was scheduled for elective cesarean delivery for placenta previa with the fetus in a transverse lie. She was otherwise healthy and did not smoke. At 37 weeks' gestation, 3 days before her scheduled surgical date, she presented to the Maternity Care ward with ruptured membranes and painless vaginal bleeding. On arrival, her blood pressure was 117/72 mmHg, and her heart rate was 80 beats/min. The fetal heart rate was 130 beats/min with decreased variability. A large-bore intravenous cannula was started, volume preload was initiated, a bladder catheter was inserted, and blood work was performed. Consent for surgery and anesthesia were obtained, and the patient was transferred to the operating room for urgent cesarean delivery.

The patient and fetus were stable on arrival in the operating room. Oxygen was administered *via* nasal prongs at 3 l/min. A pulse oximeter, noninvasive blood pressure device, and electrocardiograph were placed, and a spinal anesthetic was performed with the patient in the left lateral decubitus position. A 27-gauge pencil-point spinal needle was placed atraumatically on the first pass, and 10.5 mg hyperbaric bupivacaine, 7.5%, and 300 μg preservative-free morphine were injected without incident. By this time, the patient had received 1.2 l lactated Ringer's solution and 1 g cefazolin. The patient was positioned supine on the operating table with a 10° tilt to the left. A vertical abdominal incision was made, followed by a transverse lower uterine segment incision. The obstetrician noted multiple varicosities across the lower segment, especially laterally. The placenta was dissected through and a breech extraction performed to deliver a healthy male infant. The umbilical cord was double clamped and divided, and the infant was passed to the neonatal team. Oxytocin, 10 U, was administered intravenously, and the uterus was then exteriorized to facilitate repair. Blood loss was approximately 500 ml, and 1,800 ml lactated Ringer's solution had been infused up to this point. The blood pressure was 90/50 mmHg, and the heart rate was 70 beats/min. Ephedrine, 10 mg, was administered intravenously twice.

Approximately 1 min after delivery, the patient became agitated and lifted her head and shoulders off the operating table. She then fell back to the table, underwent a generalized seizure for approximately 5 s, and lost consciousness. The electrocardiogram showed a sinus tachycardia at 130 beats/min, but readings were not measurable on the pulse oximeter and the noninvasive blood pressure device. At that moment, the patient did not have a carotid pulse. A cardiac arrest code was immediately called, the patient's trachea was intubated, 100% oxygen was administered, and cardiopulmonary resuscitation was initiated. The initial end-tidal carbon dioxide on the capnogram was less than 10 mmHg after intubation. The differential diagnosis included amniotic fluid embolism, air embolism, and anaphylaxis. The surgeon closed the uterus as quickly as possible. Advanced cardiac life support protocols were used during resuscitation. With the exception of a short run of ventricular tachycardia and another of ventricular fibrillation, which responded to electrical defibrillation, the patient remained in pulseless electrical activity throughout the resuscitation efforts. Three physicians unsuccessfully attempted to obtain central venous access. End-tidal carbon dioxide was never above 10 mmHg. Resuscitation was unsuccessful, and 49 min after the cardiac arrest, the patient was pronounced deceased.

Postmortem examination was performed within 3 h of the event. The heart was examined under water, and a large amount of air, in excess of 100 ml, escaped from both the right atrium and the right ventricle, consistent with the diagnosis of massive air embolism. There was no evidence of a patent foramen ovale. The rest of the autopsy was unremarkable.

Discussion

Despite the common occurrence of VAE, morbidity and mortality are rare unless large volumes of air are entrained. Extrapolations from canine studies suggest 400–500 ml air is required to cause death in the average human.[3] Recently, a case was described in which there was an injection of 200 ml air into the right ventricle and pulmonary artery during attempted pneumopericardiography.[4] A much lower volume can prove fatal if a right-to-left shunt (cardiac or pulmonary) allows air to bypass the lungs and enter the systemic circulation. A small air embolism entering the cerebral or coronary circulation could then be fatal. In the absence of a right-to-left shunt, death occurs because of obstruction of right ventricular outflow and the pulmonary circulation with global hypoperfusion, resulting in right and left ventricular ischemia and sudden right-sided heart failure. When air embolism is fatal, postmortem examination of the heart must be performed under water to confirm the presence of air in the right ventricle.

* Clinical Assistant Professor, Department of Anesthesiology, Peter Lougheed Centre, University of Calgary. † Associate Professor (Clinical), Department of Anesthesia, University of Iowa Health Care, Iowa City, Iowa.

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Address reprint requests to Dr. Kostash: Department of Anesthesiology, Peter Lougheed Centre, University of Calgary, 3500-26 Avenue Northeast, Calgary, AB, Canada T1Y 6J4. Address electronic mail to: dr.sandman@telusplanet.net. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

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The patient presented herein was at higher risk for VAE because of the presence of placenta previa.[5,6] The large venous sinuses surrounding the lower segment of the uterus and the need to cut through these sinuses and the placenta to extract the fetus predisposes to air entrainment. Exteriorization of the uterus may have contributed by placing the venous sinuses in the uterus above the level of the patient's heart,[7,8] although studies do not consistently support this theory. Placing the operating table 5–10° in head-up tilt may have lessened the risk of air entrainment,[9] but this does not guarantee the heart will be above the level of the incision or that VAE will not occur.[10] The use of a precordial Doppler monitor may have identified air embolism at an earlier stage before the terminal event. Although the signal from the precordial Doppler monitor is not specific for VAE,[1] its use may have provided warning of ongoing air entrainment before cardiac arrest.

After cardiac arrest occurred, therapeutic options were limited because the etiology was uncertain. Differential diagnosis included embolism (air or thrombus or amniotic fluid) or anaphylaxis. The uterus was open and bleeding, making flooding of the surgical field with saline difficult. With the abdomen open, placing the patient in the left lateral decubitus position, as recommended for air embolism, was problematic. Because cardiopulmonary resuscitation was required, the patient had to remain supine during closure. Extreme left tilt and head-down bed position may have helped to trap air in the right ventricle, but this was inadvisable because the surgical field was not covered with saline to prevent further air entrainment. The head-up position may have prevented ongoing air entrainment; however, this was not performed, partly because of ongoing efforts to acquire central venous access. The head-up position is also unfavorable for cerebral perfusion during cardiopulmonary resuscitation.

It is important to identify parturients who may be at high risk for VAE. If cesarean delivery is planned, additional monitoring could include precordial Doppler ultrasonography. Although Doppler signals can come from other sources, such as fetal squames and agitated blood from insertion and removal of intraabdominal packs,[1] its use triggers suspicion of air emboli in high-risk cases. This would help to aid in early diagnosis and lead to formal management plans. In addition to left uterine displacement, the authors recommend that patients be placed 5–10° head up, although the validity of this maneuver is unproven.[10] Exteriorization of the uterus should be avoided if possible. If Doppler monitoring identifies VAE, then flooding the surgical field with saline should stop air entrainment.

Preoperative central venous line placement has been advocated for high-risk obstetric cases.[11] Given that massive VAE is such a rare event, the risk of central venous catheterization would outweigh the benefit. However, when VAE occurs, a central venous catheter should be placed to evacuate as much air as possible.

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High Gastric Output as a Perioperative Sign of Carcinoid Syndrome

Pratik P. Pandharipande, M.D., Peter S. Reichard, M.D.,† Michael F. Vallee, D.O.‡*

CARCINOID syndrome, although rare, may present dramatically secondary to the physiologic effects of the mediators carcinoid tumors secrete. Despite improvement in the tools for detection and treatment, carcinoid syndrome may still pose a diagnostic dilemma for the anesthesiologist.

Case Report

A 47-yr-old man with a history of persistent abdominal pain presented for elective resection of an ileal mass. The patient had no significant medical history and underwent small bowel resection for the ileal mass. At the time of surgery, nodules were noted on the omentum and the liver. His intraoperative course was uneventful. Pathologic examination of the specimens revealed metastatic adenocarcinoma of carcinoid origin with the primary in the ileum.

Postoperatively, the patient had 3–5 l/day of secretions *via* his nasogastric tube, with minimal bowel activity. Abdominal films were consistent with a postoperative ileus or a small bowel obstruction. In view of these findings, the surgeon decided to reexplore the patient's abdomen on the seventh postoperative day.

During abdominal reexploration, a defasciculating dose of d-tubocurare was given before a rapid-sequence induction with succinylcholine. Anesthesia was maintained using 50% oxygen, 50% air, desflurane, and fentanyl. Although no signs of peritonitis or small bowel obstruction were noted, the surgeon revised the small bowel anastomosis. The patient remained hemodynamically stable throughout the procedure. Twenty milligrams morphine was gradually titrated, and the patient underwent extubation while awake and was brought to the recovery room.

In the recovery room, the patient was alert and oriented. During the next 45 min, the patient became agitated and combative, requiring 2 mg lorazepam and 2 mg midazolam intravenously. The complete blood count and electrolytes were within normal limits. Arterial blood gas showed a pH of 7.42, an arterial carbon dioxide tension ($Paco_2$) of 33, and an arterial oxygen tension (Pao_2) of 97 on 4 l oxygen. The patient was sedated through the night using a propofol (25–50 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and lorazepam (1 mg/h) drip.

On the first postoperative day, the patient remained agitated despite having normal complete blood count, arterial blood gas, electrolytes, and computed axial tomography scan of the head. However, his blood glucose concentration was 295 mg/dl. During the course of the day, the patient became hypoxic (Pao_2 = 55 mmHg on 100% oxygen) and underwent reintubation and sedation. A ventilation/perfusion scan was read as low probability for a pulmonary embolus. The chest radiograph revealed bibasilar atelectasis and a right lower lobe infiltrate, and antibiotics were administered. More than 2 l gastric secretions continued to be suctioned from his nasogastric tube every 8 h.

Random urine 5 hydroxyindoleacetic acid (5HIAA), thyroid-stimulating hormone, T3, T4, and cortisol concentrations were taken on postoperative day 2. A presumptive diagnosis of carcinoid syndrome was made, and administration of octreotide, 50 μg subcutaneously every 8 h, was started. During the next several hours, nasogastric tube output decreased to approximately 0.4 l per each 8-h shift. The patient also became more alert and oriented.

The patient continued to show significant improvement and successfully underwent extubation on postoperative day 3. The hyperglycemia had resolved. The random 5HIAA concentration taken the previous day was 9.2 mg/l (normal value 0–6 mg per 24 h). All other hormonal concentrations were normal. The patient was alert and oriented, and nasogastric tube output was minimal. The patient was discharged home on the sixth postoperative day after abdominal reexploration.

Discussion

Carcinoid tumors are tumors of amine precursor cells identified by silver staining of cytoplasmic granules within the cells.[1] These neoplasms tend to be found in a bimodal distribution occurring in patients between the third to fifth decade of life and then again after the age of 60 yr. Carcinoid tumors have an incidence of 1–10 per 100,000, with equal numbers among men and women. More than 75% of tumors originate in the gastrointestinal tract, with the highest incidence in the small bowel, followed by the appendix. The most commonly affected nongastrointestinal organ is the lung.[2]

Carcinoid syndrome is a constellation of signs and symptoms resulting from the direct release of bioactive substances into the circulation. Amines and peptides that have been implicated are serotonin, kinin peptide, gastrin, histamine, substance P, insulin, glucagon, prostaglandins, and bradykinins.[3] Calcitonin gene–related peptide, vasoactive intestinal peptide (VIP), and neurotensin are vasodilatory peptides synthesized by some carcinoid tumors.[3] Symptoms are generally caused by stress, strenuous physical activity, and tumor manipulation, as well histamine-releasing drugs, such as morphine and d-tubocurare. Most of these patients do not present with symptoms of the carcinoid syndrome because the liver metabolizes the active peptides.

Clinical manifestations include flushing (95%), diarrhea, nausea, vomiting, abdominal pain, autonomic instability, hyperglycemia, bronchospasm, and dermatosis. A prolonged time for recovery from anesthesia has also been seen in patients with high serum serotonin concentrations.[1] Mental status changes have infrequently been reported as symptoms seen in carcinoid syndrome.[4]

* Instructor in Anesthesiology, Vanderbilt University, Nashville, Tennessee. † Assistant Attending, ‡ Attending.

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Address reprint requests to Dr. Vallee: Department of Anesthesia, Saint Barnabas Medical Center, 94 Old Short Hills Road, Livingston, New Jersey 07039. Address electronic mail to: mfvdo@netzero.net. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

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The syndrome is diagnosed with a 24-h urinary 5HIAA, which is a metabolic product of serotonin. However, 20% of patients with carcinoid syndrome may have a normal urinary 5HIAA concentration.[1] Diagnosis can be further confirmed by the finding of neuroendocrine cells with argyrophilic properties on pathology.

The gold standard in treating carcinoid syndrome is somatostatin or its synthetic analog, octreotide.[5] Somatostatin receptors, mostly subtype 2, have been found in many carcinoid tumors. This peptide has been shown to be responsible for reducing the production and release of gastropancreatic hormones. VIP release from VIPomas is normalized or significantly improved in 75% of patients.[6]

This case presented a dilemma because no perioperative diagnosis was made for the patient's high gastric output and mental status changes. The patient had definite carcinoid tumor confirmed by pathology. This tumor was found to produce serotonin, gastrin, and VIP. Random urinary 5HIAA concentration was increased compared with the lab reference for a 24-h urine 5HIAA concentration, which suggested the presence of carcinoid syndrome. Unfortunately, only this random urine 5HIAA concentration was obtained, and not a 24-h concentration.

No cases of perioperatively high gastric secretions associated with carcinoid syndrome have been reported in the literature, although diarrhea is a well-documented symptom of carcinoid syndrome. Stimulation of 5-hydroxytryptamine (5-HT) receptors has been shown to increase gastric secretions.[7] Serotonin also interacts with thyrotropin-releasing hormone to augment thyrotropin-releasing hormone–induced stimulation of gastric secretions.[8] The patient's increased glucose is also consistent with glucose intolerance seen with overproduction of VIP or serotonin.[9] The increased gastric secretions could also be due to a direct action of histamine or gastrin, both of which have been reported as substances released by carcinoid tumors.

Alteration in mental status, though infrequent with carcinoid tumors, has been shown to be associated with serotonin syndrome (hyperseratonergic state).[10] This is seen in patients receiving selective 5-HT blockers. An increase in drug-induced intrasynaptic 5-HT results in hyperstimulation of the 5-HT_{1A} receptor in the brain and spinal cord, causing altered mentation. A similar mechanism is possible for the mental status changes seen in this patient. Although we cannot be certain the improvement in mental status in this patient was definitively related to the administration of octreotide, his mental status and gastric output decrease occurred concurrently with the administration of octreotide.

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Subcellular Localization of Trifluoroacetylated Liver Proteins in Association with Hepatitis following Isoflurane

Dolores B. Njoku, M.D., Sanjeeb Shrestha, M.D.,† Roger Soloway, M.D.,‡ Paul R. Duray, M.D.,§ Maria Tsokos, M.D.,‖ Mones S. Abu-Asab, Ph.D.,# Lance R. Pohl, Pharm.D., Ph.D.,** A. Brian West, M.D.††*

IDIOPATHIC, volatile anesthetic–associated hepatitis has been documented with halothane,[1–3] enflurane,[4] isoflurane,[5–7] and desflurane.[8] Among these, halothane-associated hepatitis has been best characterized, and evidence suggests that this type of hepatitis may be caused by an immune reaction induced by liver cell proteins that have been covalently trifluoroacetylated by the trifluoroacetyl chloride metabolite of halothane. It is also believed that hepatitis after the use of enflurane, isoflurane, and desflurane may be caused by a similar mechanism, although the evidence for this idea is not as compelling as that reported for halothane.[9] In this case report, we provide clinical, histochemical, and immunohistochemical evidence supporting a possible role of trifluoroacetyl-modified proteins (TFAMPs) in hepatitis associated with isoflurane.

Case Report

A 66-yr-old man with type II diabetes mellitus, chronic obstructive pulmonary disease, hypertension, and coronary artery disease underwent an uneventful carotid endarterectomy during which anesthesia was conducted with the use of oxygen (30–100%), isoflurane (0.4–1.0%, 135 min), fentanyl, and thiopental. Two months later, he presented with chest pain and underwent three-vessel coronary artery bypass graft. His preoperative medications were morphine sulfate, diazepam, scopolamine, cefazolin, and gentamicin. During this surgery, the patient received fentanyl, pancuronium, ε-aminocaproic acid, mannitol, and heparin in addition to isoflurane and 100% oxygen. The cardiopulmonary bypass time was 110 min, and the cross-clamp time was 89 min. The patient had a postbypass hemoglobin concentration of 8.2 g/dl and received 400 ml pump blood. There were no intraoperative episodes of hypotension, although approximately 15 min after incision, norepinephrine (45 min) and nitroglycerin (60 min) were administered to the patient. Moreover, his cardiac output was 3.7 (on norepinephrine and nitroglycerin) before bypass and 5.0 after bypass without these medications. In addition, his arterial blood gases before, during, and after cardiopulmonary bypass were all within normal range: *p*H 7.39, partial pressure of carbon dioxide (P_{CO_2}) 46, partial pressure of oxygen (P_{O_2}) 157, HCO_3 28 (before); *p*H 7.41, P_{CO_2} 44, P_{O_2} 405, HCO_3 27 (during); *p*H 7.38, P_{CO_2} 45, P_{O_2} 346, HCO_3 26 (after). His immediate postoperative recovery was unremarkable except for a mild fever of 38.1–38.3°C that developed 7 h after the completion of surgery, which was taken as time 0 (fig. 1). He was transferred from intensive care to the surgical floor at 23 h. That night, his temperature fluctuated between 36.8 and 38.0°C, and mild icterus developed. At 45 h, his temperature increased to 38.6°C, and he became more severely icteric. Examination revealed that he had tender hepatomegaly, and he became progressively drowsier until he was able to be aroused only with painful stimuli. His serum aspartate aminotransferase concentration, measured at 38 h, was 3,973 U/l. At 52 h after surgery, liver biochemistry testing revealed alanine aminotransferase of 10,394 U/l; aspartate aminotransferase of 25,515 U/l; total bilirubin of 3.8 mg/dl, and alkaline phosphatase of 55 U/l. The prothrombin time peaked at 20.6 s, and total bilirubin peaked at 10.9 mg/dl. Serologic assays for hepatitis A, B, and C were negative. An ultrasound image showed a normal gallbladder and common bile duct. At 50 h, the patient was transferred back to the intensive care unit, where he had a transient episode of hypotension that was corrected by fluid replacement. From the time of surgery up to that point, his blood pressure had been consistently in the normal range (fig. 1).

On the third day after surgery, a rigid abdomen developed. An exploratory laparotomy, performed to exclude ischemic bowel, revealed a swollen erythematous liver with a firm, rubbery texture. No other pathology was noted in the abdomen. A biopsy of the liver was performed. After the laparotomy, during which fentanyl and cisatracurium besylate were used as anesthetic agents, the transaminases steadily decreased. Four weeks after surgery, the patient was discharged from the hospital with normal liver enzymes and synthetic function.

The patient's medical history was significant for a balloon angioplasty 12 yr earlier and an allergy to intravenous dye and codeine. His only surgery was the recent endarterectomy. His medications at home were gemfibrozil, isosorbide dinitrate, glyburide, aspirin, diltiazem HCl, metoprolol, and oxazepam as needed. The patient was not obese and had no risk factors for hepatitis (history of blood transfusion, sexual promiscuity, alcohol abuse, or intravenous drug use). He had not used alcohol for 15 yr.

Methods and Results

Histopathologic Evaluation

Light Microscopy. A wedge biopsy of the liver was obtained 72 h after surgery and was processed for frozen

* Assistant Professor, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Medical Institutions, and Adjunct Investigator, Molecular and Cellular Toxicology Section, Laboratory of Molecular Immunology, National Heart, Lung and Blood Institute, National Institutes of Health. † Clinical Fellow, ‡ Professor, Department of Internal Medicine (Gastroenterology), University of Texas Medical Branch. § Pathologist, ‖ Chief, Pediatric Tumor Biology/Ultrastructural Pathology Section, # Biologist, Section of Ultrastructural Pathology, Laboratory of Pathology, National Cancer Institute, ** Chief, Molecular and Cellular Toxicology Section, Laboratory of Molecular Immunology, National Heart, Lung and Blood Institute, National Institutes of Health. †† Professor and Director of Anatomic Pathology, Department of Pathology, New York University Medical Center.

Received from the Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland; the Molecular and Cellular Toxicology Section, Laboratory of Molecular Immunology, National Heart, Lung and Blood Institute, the Pediatric Tumor Biology and Ultrastructural Pathology Sections, Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; the Department of Internal Medicine (Gastroenterology), University of Texas Medical Branch, Galveston, Texas; and the Department of Pathology, New York University Medical Center, New York, New York. Submitted for publication March 20, 2001. Accepted for publication October 10, 2001. Supported by a grant from the Foundation of Anesthesia Education and Research, Rochester, Minnesota (to Dr. Njoku).

Address reprint requests to Dr. Njoku: Johns Hopkins Medical Institutions, Department of Anesthesiology and Critical Care Medicine, Blalock 906A, 600 North Wolfe Street, Baltimore, Maryland 21287. Address electronic mail to: dnjoku@jhmi.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

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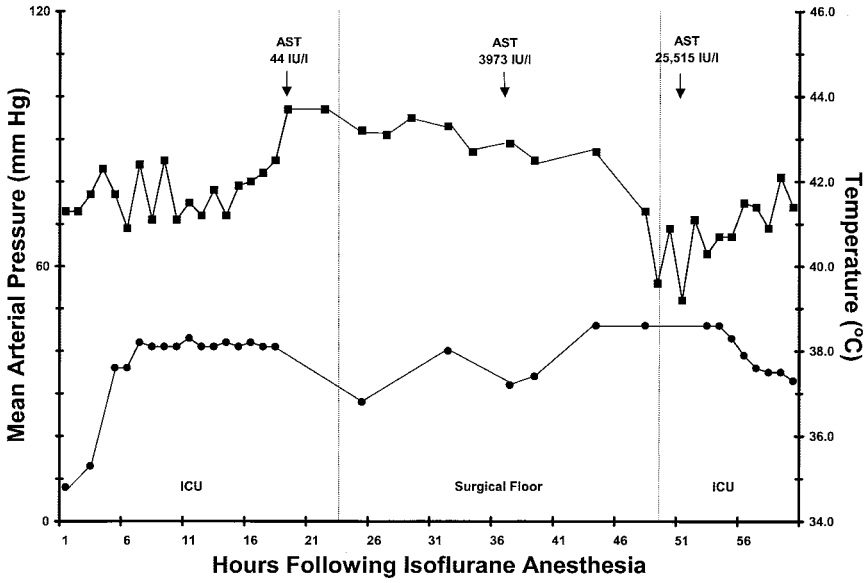

Fig. 1. Time course of the patient's mean arterial pressure (■), temperature (●), and aspartate aminotransferase (AST) in the period after surgery. The vertical lines separate the time spent in the intensive care unit (ICU) and the surgical floor. Fever developed in the patient's early postoperative course. There was a marked increase of AST to 3,973 IU/l before the development of hypotension.

and paraffin sections and for electron microscopy. The liver architecture and the portal tracts were normal, and there was no increase in fibrosis (fig. 2). Hepatocytes in zone 3 exhibited severe macrovesicular steatosis, a finding that is consistent with another case report of isoflurane hepatitis.[7] Coagulative necrosis affected all of zones 3 and 2. These areas were sharply demarcated and separated from the viable-appearing hepatocytes of zone 1 (figs. 2A and B). A few scattered neutrophils were present in some of the necrotic areas. Central veins and most sinusoids were empty of erythrocytes, but there was erythrocyte extravasation into the space of Disse in zone 3 (fig. 2C). In the portal tracts, there were early signs of ductular proliferation. Bilirubinostasis was evident in a few ducts and ductules, and occasionally in hepatocytes and sinusoids in zone 1 (fig. 2D). Glycogen was present in hepatocytes in zone 1 but was absent from zones 2 and 3 (fig. 2E). Indicative of the acute nature of the process, a normal reticulin pattern was retained throughout the lobule (fig. 2F).

Electron Microscopy. Electron microscopic evaluation showed that the less severely affected cells in zone 1 exhibited dilatation and proliferation of smooth endoplasmic reticulum, swelling of mitochondria, microvesicular steatosis, abundant lipolysosomes, and increased peroxisomes. In more severely affected cells, which appeared dark in electron micrographs, there were marked nuclear changes, with irregularity of the nuclear outline, peripheral clumping of chromatin, and enlargement and condensation of nucleolar elements (results not shown).

Immunohistochemical Studies

Light Microscopy. Trifluoroacetyl-modified proteins were detected in liver sections using a well-described procedure.[9] Briefly, slides were incubated with affinity-purified rabbit anti-trifluoroacetyl immunoglobulin G (IgG; 2 μg/ml, 1 h) in 1.5% (vol/vol) normal goat serum, followed by biotinylated, affinity-purified goat anti-rabbit secondary antibody (Vector Laboratories, Inc., Burlingame, CA). TFAMPs were visualized with a peroxidase reagent (Vector Laboratories, Inc.) and developed with a diaminobenzidine peroxidase substrate kit (Vector Laboratories, Inc.). Infiltrating cells in the liver biopsy were immunohistochemically characterized using an automated immunostainer. In short, an antigen retrieval method was used with a standard pressure cooker. $CD4^+$ lymphocytes were detected with 1:20 monoclonal mouse anti-human clone IF6 (Novocastra, Newcastle upon Tyne, United Kingdom); $CD8^+$ lymphocytes with 1:20 mouse anti-human IgG1, clone C8/144B, (DAKO Corp., Carpinteria, CA); B lymphocytes with 1:200 mouse anti-human IgG2a κ, clone L-26 (DAKO Corp.); and macrophages with 1:50 monoclonal mouse anti-human CD68 IgG1, clone KP-1 (DAKO Corp.). The secondary antibody was a biotinylated anti-rabbit/mouse globulin supplied by Ventana ES (Tucson, AZ). Diaminobenzidine was used as the chromogen throughout. Incubation times were according to the manufacturer's recommendations.

Trifluoroacetyl-modified proteins were detected in intact and necrotic hepatocytes in zones 1 and 2 adjacent to zones of steatosis (figs. 3A and B). No adducts were detected when purified normal rabbit IgG (2 μg/ml) was used in place of the anti-trifluoroacetyl IgG (fig. 3C) or when the trifluoroacetyl hapten was removed from the tissue proteins with 1 M monoethanolamine before the addition of anti-trifluoroacetyl IgG (results not shown).[10] Immunochemically identified $CD4^+$ and $CD8^+$ T cells and B lymphocytes in zones 1 and 2 adjacent to the zones of steatosis were few in number, whereas macrophages found in the same regions did not seem to differ in number from those found in normal liver tissues (results not shown).

Electron Microscopy. Tissue from the patient's liver biopsy and from the normal liver biopsy of an individual

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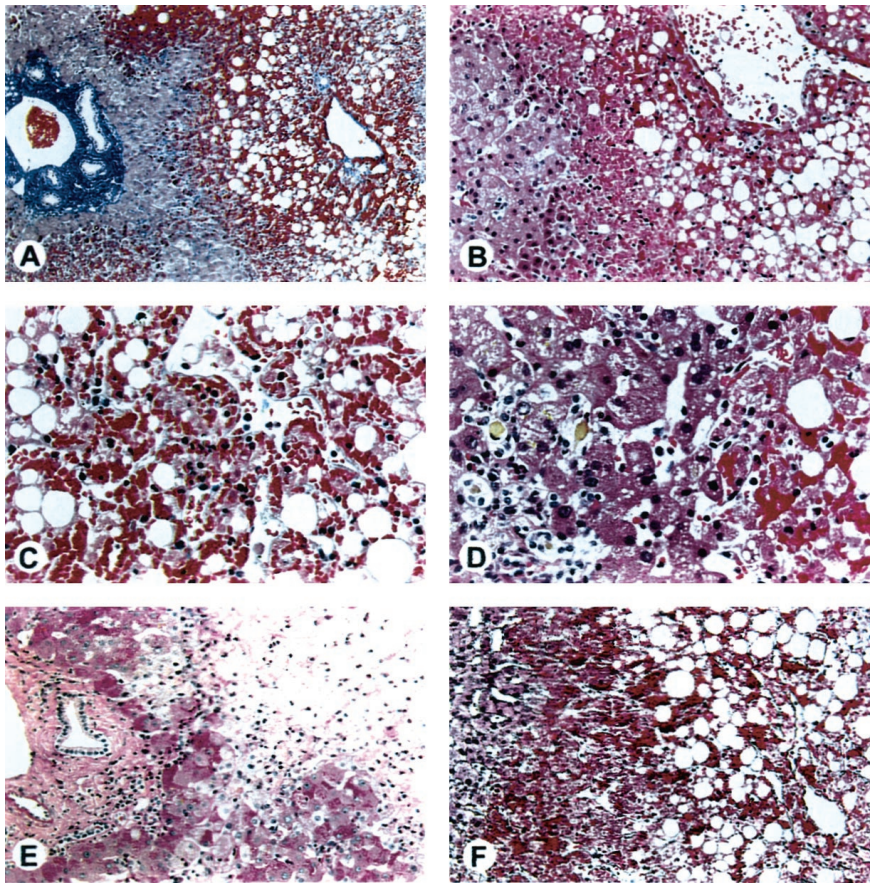

Fig. 2. Histopathology of the liver biopsy obtained 72 h after surgery. (*A*) Zones 2 and 3 (*right*) show steatosis and severe congestion with preservation of hepatocytes in zone 1 (*left*) (Masson trichrome, 65×). (*B*) Central vein with perivenular steatosis surrounded by a rim of hepatocytes showing coagulative necrosis (hematoxylin and eosin, 125×). (*C*) Erythrocytes in zone 3 are trapped in the liver cords with debris of degenerated hepatocytes and fat droplets (Masson trichrome, 250×). (*D*) Bilirubinostasis in zone 1 (*left*) (hematoxylin and eosin, 250×). (*E*) Cytoplasmic glycogen (mauve staining) is present in hepatocytes of zone 1 but is absent in zones 2 and 3 (Periodic acid Schiff without diastase, 125×). (*F*) Reticulin pattern is preserved in zones 2 and 3 (Gordon and Sweet reticulin stain, 125×).

not recently exposed to volatile anesthetics were removed from the paraffin blocks, deparaffinated in xylene, placed in absolute ethanol, and embedded in LR White (SPI, West Chester, PA). Ultrathin sections were mounted on 150-mesh uncoated nickel grids. Grids were floated on blocking solution (20 min, phosphate-buffered saline, 0.1% Tween 20, 0.5% cold water fish gelatin; Ted Pella, Inc., Redding, CA) and incubated with anti-trifluoroacetyl IgG (2 μg/ml, 1 h), or with normal rabbit IgG (2 μg/ml, negative control). The grids were then rinsed in blocking buffer (5 min), incubated with 10 nm gold-conjugated goat anti-rabbit antiserum (1:1,000; Ted Pella, Inc.), rinsed in phosphate-buffered saline, and air dried. Sections were counterstained with uranyl acetate and examined with a Phillips CM10 electron microscope (Phillips/FEI Co., Hillsboro, OR).

Although the use of paraffin-embedded material did not allow ideal tissue preservation, TFAMPs were always associated with cytoplasmic organelles and absent from lipid droplets and from the extracellular spaces (fig. 4). The labeling was most intense in the mitochondria and the endoplasmic reticulum and to a lesser extent in the nuclear membrane and the nucleus. The normal liver tissue exhibited only minimal background labeling, similar to the section in which the primary antibody was replaced by normal rabbit IgG (results not shown).

Discussion

The use of volatile anesthetics, including halothane, enflurane, isoflurane, and desflurane, has been associated with a severe form of idiosyncratic liver injury that is believed to be caused, in many cases, by immune-mediated processes.[11–13] This theory is supported by clinical evidence and immunochemical evidence. For example, in the case of halothane hepatitis, patients often have received multiple halothane anesthetics and have had fever, rash, arthralgia, and eosinophilia, which are signs and symptoms suggestive of an immune-mediated process. In addition, most halothane hepatitis patients have serum antibodies that recognize one or more liver microsomal proteins either in their native state (antigens) or after they have been covalently trifluoroacetyl modified by the trifluoroacetyl chloride metabolite of halothane (neoantigens).[12,14] These antibodies, and possibly antigen-specific T cells, have been suggested to have an immunopathological role not only in halothane hepatitis but also in hepatitis caused by other volatile anesthetics.[9] In fact, anti-trifluoroacetyl antibodies have been detected in the sera of three patients diagnosed with isoflurane hepatitis.[15,16] Serum antibodies from another isoflurane hepatitis patient were found to react with a trifluoroacetyl-labeled 60-kd protein antigen in rat liver microsomes.[17] Unfortunately, by the time isoflurane was

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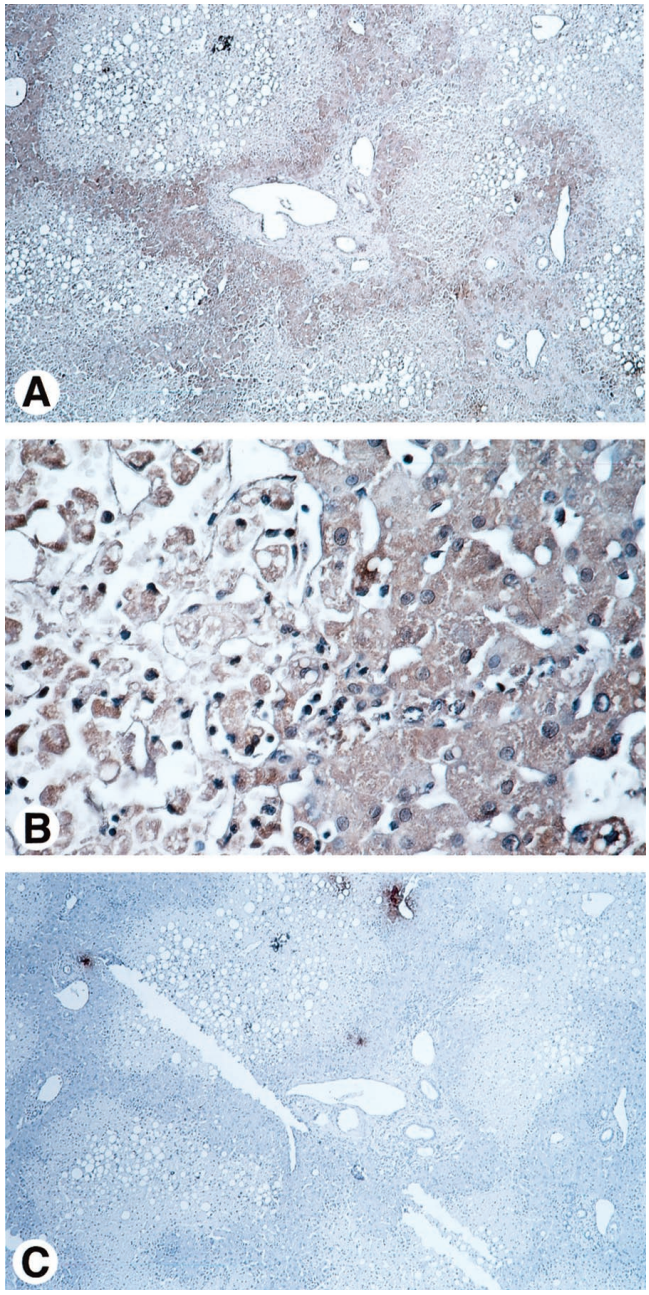

Fig. 3. Immunohistochemical detection of trifluoroacetyl-modified proteins in the liver biopsy. (*A* and *B*) Trifluoroacetyl-modified proteins were detected in zones 1 and 2 of the patient's liver with the use of anti-trifluoroacetyl immunoglobulin G (37.5 and 300×, respectively). (*C*) No trifluoroacetyl-modified proteins were observed in the liver using the control immunoglobulin G (37.5×).

implicated in the current case, a serum sample could not be obtained to determine whether anti-trifluoroacetyl antibodies were present. Nevertheless, we were able to demonstrate TFAMPs in the patient's liver, an important finding not previously reported in the liver of a patient diagnosed with isoflurane-induced liver injury.

The finding of TFAMPs in the liver of the patient was surprising because isoflurane is oxidatively metabolized to form TFAMPs approximately two orders of magnitude less than halothane.[9,18] This result suggests that the patient may have had an increased concentration of cytochrome P450 2E1 in the liver because this isoform of cytochrome P450 is predominantly responsible for the oxidative metabolism of halothane,[19] enflurane,[20] and isoflurane.[21] In this regard, if the patient had a preexisting condition of nonalcoholic steatohepatitis before anesthesia, this could have accounted for this enzyme being increased.[22] Alternatively, the patient may have had increased concentrations of cytochrome P450 2A6, which can also oxidatively metabolize halothane to form TFAMPs.[19,23]

The lack of massive infiltration of T or B lymphocytes or macrophages in the zones of necrosis suggests that the pathophysiologic mechanism of isoflurane hepatitis may not involve a significant contribution by cellular immune reactions but instead could be mediated by other mechanisms. The finding of TFAMPs for the first time in the mitochondria, nucleus, nuclear membranes, and rough endoplasmic reticulum after isoflurane anes-

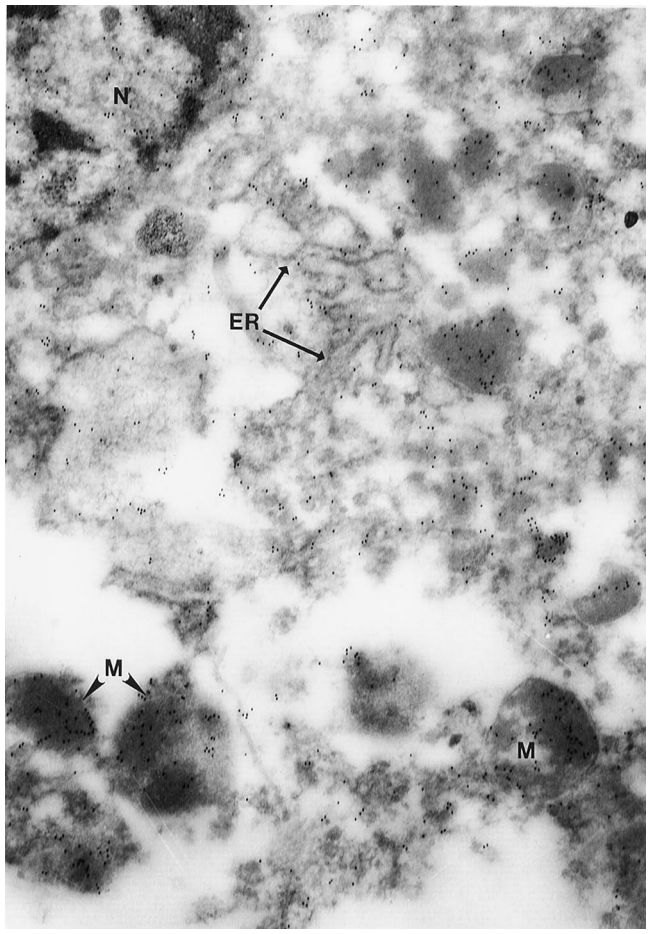

Fig. 4. Immuno-electronmicroscopic detection of trifluoroacetyl-modified proteins in hepatocyte organelles. Trifluoroacetyl-modified proteins were present in the mitochondria (M), the endoplasmic reticulum (ER), and to a lesser extent the nuclear membrane and the nucleus (N). Trifluoroacetyl-modified proteins were absent from lipid droplets and from the extracellular spaces (14,000×).

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thesia is consistent with this idea (fig. 4) because it suggests that liver injury may have been initiated at one or more of these sites by TFAMPs. For example, microvesicular steatosis may have been initiated by the TFAMPs inhibiting β oxidation and respiration in the mitochondria.[24] In this regard, a recent case report of fatal hepatotoxicity after isoflurane exposure was also associated with microvesicular fatty changes in the liver.[7] Moreover, the finding of an active form of cytochrome P450 2E1 in the mitochondria of hepatocytes[25] suggests that TFAMPs may have been formed at this site. Alternatively, the TFAMPs in the endoplasmic reticulum may have led to a humoral-based liver injury after they were released from damaged hepatocytes, as has been proposed as a possible mechanism of halothane hepatitis.[13]

In summary, we present a man who developed fulminant hepatic failure after a second exposure to isoflurane for general anesthesia. There was no evidence that the liver injury was caused by hypotension, hypoxia, viral hepatitis, or sepsis. It is unlikely that his liver injury is attributable to the glyburide, which has rarely been associated with hepatitis[26–28] or any of his other medications because he had been taking them for many months without adverse effect. The demonstration of TFAMPs in intact and necrotic hepatocytes associated with subcellular organelles suggests that the hepatitis may have been caused by isoflurane, possibly by both immune- and nonimmune-mediated mechanisms of toxicity.

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Bilateral Continuous Interscalene Block of Brachial Plexus for Analgesia after Bilateral Shoulder Arthroplasty

Konrad Maurer, M.D., Georgios Ekatodramis, M.D.,† Jürg Hodler, M.D.,‡ Katharina Rentsch, M.D.,§ Henry Perschak, M.D.,‖ Alain Borgeat, M.D.#*

CONTINUOUS interscalene block of the brachial plexus is a common technique for analgesia after total shoulder arthroplasty because it provides good postoperative analgesia. Paresis of the ipsilateral hemidiaphragm is a well-described side effect of this technique.[1] Bilateral interscalene block is generally considered an absolute contraindication because total paresis of the diaphragm could lead to respiratory insufficiency. We report a case of bilateral continuous interscalene block of the brachial plexus after bilateral total shoulder arthroplasty.

Case Report

A 61-yr-old woman with American Society of Anesthesiologists physical status II was admitted for bilateral total shoulder replacement. Her medical history was remarkable for a systemic lupus erythematosus for 27 yr without clinically apparent lung involvement. She had a spine decompression in 1998 with untreatable nausea and vomiting during the first three postoperative days because of opioids. Results of preoperative clinical investigations (chest radiography, electrocardiography, and blood test) were all unremarkable. Because of her past experience with morphine, the patient asked not to receive, if possible, any opioids for analgesia. After written informed consent was obtained from the patient, a regional analgesia technique was chosen. The day before surgery, spirometry was assessed using a Cardiovit AT 6 recorder (Schiller Reomed AG, Dietikon, Switzerland) in its spirometry configuration with the patient placed in a 45° semirecumbent position. Diaphragm excursion was assessed by ultrasonography using a Sonoline Prima ultrasonograph (Siemens Medical, Erlangen, Germany). With the patient lying supine in a 45° semirecumbent position, a 3.5-MHz convex transducer was placed posterolaterally at the midclavicular line, using the usual subcostal approach. The procedure was always repeated at the same location on both sides. After identifying the dome of the hemidiaphragm (right and left separately), its excursion was measured in the M mode during rest and maximal forced inspiration. Spirometry and diaphragmatic excursion measurements were repeated according to the same procedure at 8, 24, and 72 h after the first interscalene block (figs. 1 and 2). The patient was premedicated with 7.5 mg oral midazolam 60 min before anesthesia. Monitoring included a continuous three-lead electrocardiography, noninvasive blood pressure measurement, and pulse oximetry. A peripheral venous catheter was inserted on the left foot. On both sides (right side first, left side 15 min later), interscalene brachial plexi were identified by using a nerve stimulator (Stimuplex-HNS II; B.Braun Melsungen AG, Melsungen, Germany) connected to the proximal end of the metal inner needle (Stimuplex A; B.Braun Melsungen AG). Contraction of the triceps was elicited with a threshold stimulation of 0.34 mA/0.32mA, right and left sides, respectively. The impulse duration was 0.1 ms. A catheter (Polymedic, 22-gauge with stylet; Te me na, Bondy, France) was introduced distally between the anterior and middle scalene muscles for 3 cm without producing dysesthesia or pain according to the cannula-over-needle technique. Then, the catheters were subcutaneously tunneled over 4 cm through an 18-gauge intravenous cannula and fixed to the skin with adhesive tape (Tegaderm; 3 M Health Care, Borken, Germany). The interscalene blocks were performed with 30 ml ropivacaine, 0.5% (right side, time t = 0; left side, t = 15 min). At t = 40 min, the patient had complete bilateral sensory block (inability to recognize cold temperature) and motor block (inability to extend the arms). General anesthesia was performed with propofol using the target-controlled infusion technique (TCI Deltec Graseby 3500, Laubscher Basel, Basel, Switzerland, and Diprifusor subsystem, AstraZeneca Ltd., Macclesfield, Cheshire, United Kingdom). Tracheal intubation was performed after injection of 40 mg rocuronium and 0.1 mg fentanyl. Surgery was uneventful and lasted 280 min. The patient underwent extubation 5 min after the end of surgery. Clinically, the patient was ventilating adequately with auxiliary breathing muscles (muscle intercostales, muscle scaleni, muscle sternocleidomastoidei) at a respiratory rate between 12 and 18 breaths/min. In the supine position, pulse oximetry without supplementary oxygen was 94%, and respiratory rate was 17 breaths/min. The patient did not subjectively have "shortness of breath," and visual analog scale score was 0 (0 = no pain, 100 = worst pain imaginable). A continuous perfusion of 0.2% ropivacaine was started in the recovery room 6 h after the first block at a rate of 7 ml/h on each side (total volume administered = 14 ml/h) *via* the interscalene catheters by two perfusion pumps (PERFUSOR® secura; B.Braun Melsungen AG). Plasma concentrations of total and free fraction of ropivacaine and α-1-acid glycoprotein were measured at t = 0, 0.5, 1, and 1.5 h and at t = 8, 24, 48, and 72 h (fig. 3). The total concentration of ropivacaine in plasma was determined by gas chromatography with a nitrogen-sensitive detector. The free concentration of ropivacaine was determined by coupled-column liquid chromatography with mass spectrometric detection using electrospray ionization, after ultrafiltration of the plasma samples. The concentration of α-1-acid glycoprotein was determined by an immunoturbidimetric method. The patient received supplementary oxygen, 2 l/min, *via* a nasal tube while asleep. Pulse oximetry over the whole period was always 92% or greater, and the patient at no time reported shortness of breath. Respiration rate was assessed every 4 h and remained within 10–18 breaths/min during the whole study period. Physical rehabilitation was started from the first postoperative day with visual analog scale score = 0. With this analgesic regimen, the visual analog scale score remained 0 until the end of the observation term (72 h). During the first 48 h, the patient was cared for in the intensive care unit, and then he was transferred to the ward. No nausea or vomiting occurred during the first 72 postoperative hours, significantly increasing patient satisfaction.

* Resident, † Consultant, # Chief of Staff, Department of Anesthesiology, ‡ Chief of Staff, Department of Radiology, § Consultant, Department of Clinical Chemistry, ‖ Consultant of Internal Medicine.

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Address reprint requests to Dr. Borgeat: Orthopedic University Clinic of Zurich/Balgrist, Forchstrasse 340, CH-8008 Zurich, Switzerland. Address electronic mail to: aborgeat@balgrist.unizh.ch. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

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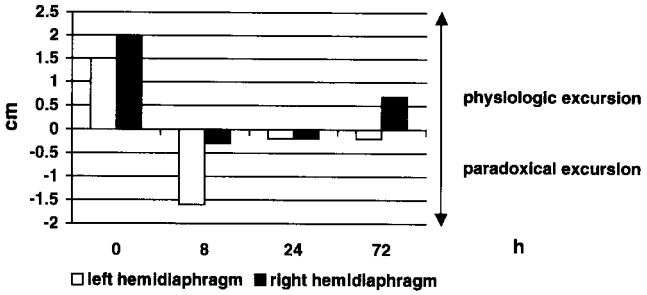

Fig. 1. Time course evolution of diaphragmatic excursion. h = time in hours after application of first interscalene block. The arrow shows the direction and maximal width of excursion of the diaphragm during forced respiration, measured on a defined position of the ultrasound sensor.

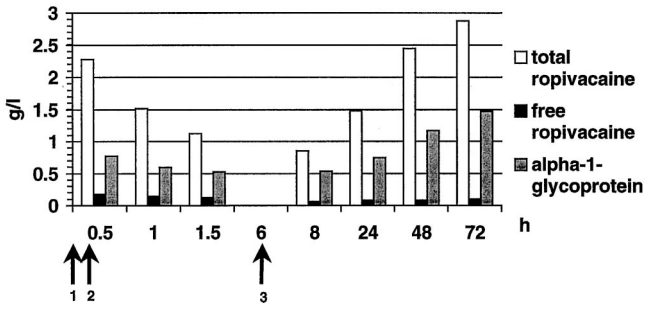

Fig. 3. Time course evolution of venous ropivacaine and α-1-acid glycoprotein concentrations. h = time in hours after application of first interscalene block. Arrow 1 shows the application of right interscalene block; arrow 2 shows the application of left interscalene block; arrow 3 shows the start of continuous perfusion of 0.2% ropivacaine with 7 ml/h right side, 7 ml/h left side (total 28 mg/h) *via* interscalene catheter.

Discussion

Total shoulder arthroplasty is known to be associated with severe pain, hindering early rehabilitation. Continuous interscalene block of the brachial plexus is therefore an effective technique for analgesia. However, bilateral interscalene block of the brachial plexus is considered contraindicated because it could lead to acute bilateral phrenic nerve paralysis[1] with respiratory insufficiency. It has been demonstrated that paralysis of the phrenic nerve is only partial when 0.2% ropivacaine is administered through the indwelling interscalene catheter,[2] and therefore, in the current case, a bilateral interscalene catheter could be chosen.

In the current case, the hemidiaphragm motions were paradoxical in forced respiration on both sides at t = 8 h and still slightly paradoxical at t = 24 h, probably because of some residual effect of the initial block consistent with the results of our previous study.[2] On the left side, the excursion of the hemidiaphragm was still slightly paradoxical after 72 h, which could be explained by the more proximal location of the interscalene catheter on that side. At t = 72 h, the right hemidiaphragm showed a diminished physiologic excursion (fig. 1). Despite a marked decrease of the forced vital capacity by 60% from 2,670 ml preoperatively to 1,100 ml postoperatively (fig. 2), the postoperative respiratory course of this patient was uneventful and well-tolerated. This is mainly explained by the help of the auxiliary breathing muscles (muscle intercostales, muscle scaleni, muscle sternocleidomastoidei), which were able to provide sufficient ventilation even in the supine position, as demonstrated by a physiologic respiratory rate and the oxygen saturation of more than 92% at all times.

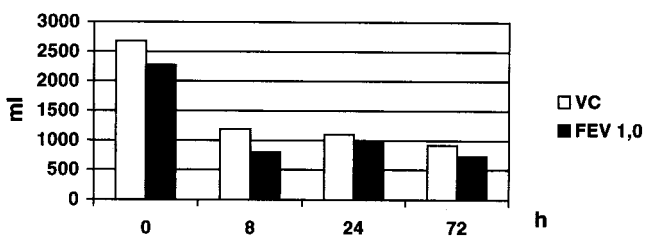

Fig. 2. Time course evolution of spirometry. VC = vital capacity; FEV 1.0 = forced 1-s expiratory volume; time = time in hours after application of first interscalene block.

There are few data that show the effect of acute diaphragm paralysis on ventilation caused by isolated bilateral phrenic nerve paralysis in humans. Wiebel *et al.*[3] found a reduced vital capacity by 50% in six patients with bilateral phrenic nerve paralysis. Camfferman *et al.*[4] reported a case of normal ventilation in an awake patient, even in the supine position. Stradling *et al.*[5] showed that acute diaphragm paralysis in awake dogs did not impair ventilation because of a marked increase in rib cage expansion, reflecting intercostal and accessory muscle activity. In the current case, a decrease in pulse oximetry was at no time observed during the whole controlled period. This could be explained by an incomplete phrenic nerve paralysis—unilateral or bilateral—as already shown by Borgeat *et al.*[2] The difference in diaphragm motion amplitude between the right and left sides at t = 72 h could eventually be explained by more proximal placement of the tip of the catheter on the left side.

Total and free venous ropivacaine concentration reached a peak (2.27 and 0.18 g/l, respectively) 15 min after application of the second interscalene block and then constantly decreased (1.12 and 0.12 g/l, respectively) within the first 90 min. With the start of continuous perfusion of 0.2% ropivacaine (14 ml/h), total ropivacaine concentrations steadily increased in parallel with the increase of α-1-acid glycoprotein (acute phase protein), whereas the free ropivacaine concentration, responsible for toxic reactions, remained stable until the end of the continuous perfusion (fig. 3). This confirms earlier results with continuous epidural infusion of ropivacaine[6] and is in accordance with the knowledge that regional anesthesia or analgesia does not block the inflammatory reaction mediated mainly by the liberation of interleukin 6, responsible in part for the steady increase

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of α-1-acid glycoprotein.[7,8] This acute phase protein increase has the potential advantage to buffer the free concentration of ropivacaine, providing in the context of a continuous infusion of local anesthetics a protective mechanism against toxic reactions.

Conclusions

Although bilateral interscalene block of the brachial plexus is generally considered contraindicated, this technique can be performed in some selected patients. An acute paresis of the diaphragm causing a decrease in spirometry of 60% was well-tolerated in this case. However, this practice should be reserved for selected patients who do not have pulmonary disease jeopardizing ventilatory function in particular. It is imperative that the patient is closely monitored in an intensive care unit or equivalent facility for at least the first 48 postoperative hours to assess patient's tolerance and enable prompt reaction in the event of major complications.

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Delayed Postoperative Rhabdomyolysis in a Patient Subsequently Diagnosed as Malignant Hyperthermia Susceptible

Kevin A. McKenney, M.D., Stephen J. Holman, M.D.†*

WE report an unusual case of myoglobin-induced acute renal failure occurring on the third postoperative day in a patient receiving a general anesthetic.

Case Report

A 48-yr-old man (weight, 109 kg; height, 182 cm) presented for elective umbilical hernia repair. His medical history was significant for gastroesophageal reflux and mild mitral valve prolapse. There was no personal or family history for myopathy or malignant hyperthermia (MH). The patient reported having a tonsillectomy performed when he was a child during general anesthesia without incident. He was not taking any outpatient medications and had no history of drug allergies. The results of preoperative laboratory testing, including a complete blood count, coagulation studies, and a chemistry panel, were within normal limits.

The patient was taken to the operating room, and a rapid sequence induction was performed. The patient received 180 mg succinylcholine and 200 mg propofol for induction. A defasciculating dose of a nondepolarizing muscle relaxant was not administered, and no fasciculations were observed. His trachea was easily intubated, with no evidence of increased masseter tone. The patient was maintained with oxygen–isoflurane–nitrous inhalational anesthesia in addition to fentanyl. The concentration of isoflurane administered was approximately 0.5 minimum alveolar concentration. Muscle relaxation was maintained with rocuronium after 4/4 twitches with normal height returned.

The patient remained in the supine position for the surgical procedure, which lasted approximately 1 h. No urinary catheter was placed intraoperatively. The patient remained hemodynamically stable throughout the procedure with no dysrhythmias. His heart rate ranged from 62–75 beats/min, and his blood pressure ranged from 85/50 mmHg immediately after induction to a maximum of 140/82 mmHg, with a mean reading of 120/72 mmHg. His nasal temperature remained constant at 35.9 ± 0.2°C. He received a total of 1 l Ringer's lactate during the procedure, with minimal surgical blood loss. Muscle relaxation was reversed, and the patient underwent extubation while awake in the operating room without incident. An arterial blood gas measurement was not obtained perioperatively in this patient.

The patient recovered uneventfully in the postanesthetic care unit. His vitals signs throughout his stay in the postanesthesia care unit were unremarkable. He was discharged to home within 4 h of completion of the surgery, with no complaints.

The patient returned to the hospital on the third postoperative day, reporting general malaise, myalgias, and nausea and vomiting of 2 days' duration. He denied fevers, sweats, palpitations, or rigidity. He did report that his urine was dark in color on the evening of surgery but reported that this had improved over the next 2 days. He maintained normal urinary output until the day of presentation, when he noted a moderate decrease. A routine chemistry panel performed in the emergency room revealed a serum creatinine concentration of 7.8 mg/dl

* Assistant Professor of Anesthesiology, National Naval Medical Center. † Associate Professor of Anesthesiology, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

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Address reprint requests to Dr. McKenney: Department of Anesthesiology, National Naval Medical Center, Bethesda, Maryland 20889. Address electronic mail to: Mckmail2@yahoo.com. Individual article reprints may be purchased from the Journal Web site, www.anesthesiology.org.

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and a blood urea nitrogen concentration of 56 mg/dl. The patient's urine tested positive for myoglobin.

The patient was admitted to the intensive care unit with a preliminary diagnosis of rhabdomyolysis with myoglobin-induced acute renal failure. Examination of his extremities revealed no evidence of compartment syndrome. The concentration of creatine kinase taken on the evening of his readmission was 12,041 U/l. The calcium concentration was 8.7 mg/dl, phosphate was 6.3 mg/dl, and uric acid was 13.4 mg/dl. Liver function test results revealed an aspartate aminotransferase concentration of 195 U/l, an alanine aminotransferase concentration of 128 U/l, and a lactate dehydrogenase concentration of 1,411 U/l. Nephrology was consulted, and the patient was hydrated and alkalinized to maintain a urine pH of 7.5–7.8. A urinary catheter was placed. The creatine kinase concentration decreased to 4,049 U/l within 24 h and was down to 757 U/l 72 h after readmission.

Over the next 14 days, the patient's renal function eventually recovered, and he was discharged to home with normal blood urea nitrogen and creatinine concentrations. The remainder of his electrolyte panel and liver function test results were normalized. Dialysis was not required.

Approximately 4 months later, the patient underwent vastus lateralis muscle biopsy during spinal anesthesia. Muscle samples underwent caffeine–halothane contracture testing (CHCT) at the Uniformed Services University of the Health Sciences Malignant Hyperthermia Testing Center in Bethesda, Maryland. Diagnosis of MH was performed according to the North American CHCT protocol.[1] Individuals are considered MH susceptible if any one of the six muscle strips exceeds diagnostic criteria (3% halothane—increased basal contracture of at least 0.7 g; 2 mM caffeine—increased basal tension of at least 0.3 g).

All three muscle strips tested with 3% halothane exhibited an abnormal response: 1.1, 0.9, and 1.3 g. At 2.0 mM caffeine concentration, another three strips exhibited an abnormal increase in tension: 0.5, 0.5, and 1.0 g.

Histopathologic and histoenzymatic analyses for myopathies were conducted at the Armed Forces Institute of Pathology in Washington, DC. Adenosine monophosphate deaminase, myofibrillary adenosine triphosphatase at pH 10.4, nicotinamide adenine dinucleotide tetrazolium reductase, alkaline phosphatase, and nonspecific esterase test results were all normal. Modified Gomori trichrome, periodic acid-Schiff, and hematoxylin and eosin stains performed on the frozen muscle sample were normal.

The formalin-fixed tissue was processed in paraffin, and sections were stained with hematoxylin and eosin and trichrome. Under microscopy, the sections revealed normal fiber size and configuration without evidence of atrophy, degeneration, regeneration, inflammation, or fibrosis. Oxidative enzyme stains revealed no abnormalities of the intermyofibrillary network. The perimysium and its neurovascular contents were unremarkable.

Genetic analysis of 18 known mutations in the ryanodine receptor (RYR) type 1 was conducted at the Uniformed Services University of the Health Sciences. The presence or absence of mutations was determined by the polymerase chain reaction–based restriction fragment polymorphism method using genomic DNA extracted from stored muscle tissue. None of the 18 mutations screened for was identified in this patient.[2]

Discussion

Classically, MH presents perioperatively with tachycardia, tachypnea, fever, rigidity, metabolic acidosis, cardiac dysrhythmias, cyanosis, or mottling. Although none of these signs were evident, myoglobinuria developed in the patient, leading to nonoliguric, acute renal failure postoperatively. Case reports of patients with rhabdomyolysis postoperatively after administration of succinylcholine, inhalation agents, or both are usually associated with undiagnosed myopathies in children rather than MH.[3] However, histologic–histochemical analysis of the patient's muscle was normal. Further, his increased creatine kinase concentration and myoglobinuria returned to normal rapidly with treatment, making the diagnosis of latent myopathy unlikely. Lack of significant fasciculations or myalgias does not support a diagnosis of succinylcholine-induced rhabdomyolysis.

The patient's lack of clinical signs may be explained by the relatively short exposure to isoflurane. MH triggering with isoflurane has been associated with a delayed onset of MH triggering.[4]

Phenotypically, MH presents in a highly variable fashion. Some perioperative episodes have only subtle signs, and up to 50% of MH-susceptible patients have been exposed to triggering agents without development of any clinical signs of MH.[5] A recently published genetic study of patients with exertional rhabdomyolysis found 3 of 10 CHCT-positive patients had RYR type I mutations typical of MH.[6] A possible link between exertional heat stroke and MH has also been reported.[7] CHCT using North American guidelines is reported to be 97% sensitive and 78% specific.[8] Although the differential diagnosis of rhabdomyolysis is extensive,[9] in light of the history, test results, and recent publications mentioned, we diagnosed this patient as MH susceptible.

In summary, the nature of this subacute but clinically significant presentation of MH suggests that the incidence of MH may be higher than currently reported.[10] This patient did not have an acute MH episode; however, given his CHCT results, perioperative myoglobinuria, and acute renal failure, there is little doubt that another exposure to volatile anesthetics, depolarizing muscle relaxants, or both would be unwise.

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Ventilatory Failures with the Datex-Ohmeda 7900 SmartVent

Joaquin Cantillo, M.D., Richard Domsky, M.D.,† Irwin Gratz, D.O.,‡ Michael E. Goldberg, M.D.§*

THE Datex-Ohmeda 7900 SmartVent (Madison, WI) is a microprocessor-controlled ventilator that is supplied with the Aestiva 3000 (Datex-Ohmeda) and the Excell 210 SE anesthesia machine (Datex-Ohmeda). It allows ventilation in two ventilatory modes: volume and pressure control. The ventilator is therefore capable of handling a wide range of patients, from neonates to patients with challenging procedures, such as thoracic and neurosurgical. With a wide range of control and alarm settings, it can compensate for small leaks in the breathing circuit and compression losses. Recently, we had three cases in which the Datex-Ohmeda SmartVent failed to maintain the ventilatory settings, requiring swift intervention.

Case Reports

Case 1

A 60-yr-old man with American Society of Anesthesiologists physical status class III and cervical spinal stenosis was scheduled to undergo a C3–C6 posterior cervical fusion. After an uneventful intravenous induction of anesthesia and orotracheal intubation, the SmartVent ventilator was set to deliver a tidal volume of 850 ml, with a respiratory rate set at 10 min. The gas flows were set at a 1-l/min combination of air and oxygen. The ventilator was attached to an Excell 210 SE and a Fisher & Paykel MR-720 Anesthesia Humidifier (Panmure, Auckland, New Zealand) in the breathing circuit.

Anesthesia was maintained with a continuous infusion of propofol, rocuronium, and fentanyl. Concentrations of isoflurane were maintained below 0.5% end-tidal because of a request from the electrophysiologist who was monitoring the somatosensory evoked potentials. Adequate muscle relaxation was maintained during the procedure. The patient was turned to the prone position. A few minutes after positioning the patient, we noticed that the patient's chest was not rising adequately. The tidal volume was found to be only 425 ml. Peak inspiratory pressures decreased from mid 20s to high teens (cm H_2O). The ventilator displayed the following alarms: expiratory reverse flow and unable to drive bellows. The bellows was not empty and the bag–vent switch was set at the vent position.

Despite changing the flow sensors, the same alarms were still present. Heavy condensation was found at this point on the expiratory valve dome. The patient was disconnected from the circuit and underwent ventilation with an Airlife Resuscitator Bag (Allegiance Healthcare, McGaw Park, IL), and the expiratory valve was dissembled and dried. The ventilator was now delivering a tidal volume of 500 ml. We then changed the ventilation mode to pressure control of 24 cm H_2O from volume control of 850 ml, which solved the problem of inadequate ventilation previously experienced.

The case proceeded uneventfully for the next 6 h with the ventilator set in the pressure mode. The patient emerged from anesthesia without complications.

Additional material related to this article can be found on the ANESTHESIOLOGY Web site. Go to the following address, click on Enhancements Index, and then scroll down to find the appropriate article and link. http://www.anesthesiology.org

Case 2

A 38-yr-old woman with American Society of Anesthesiologists physical status class II and a diagnosis of endometriosis was scheduled to undergo laparoscopic ablation of endometriosis with a carbon dioxide laser and hysteroscopy. The breathing circuit had a heat and moisture exchanger (Intersurgical Inc., Liverpool, NY). Maintenance was achieved by using a 3-l/min fresh gas flow of 33% oxygen in the balance of nitrous oxide, and isoflurane was titrated to hemodynamic response. A tidal volume of 650 ml was set on the Datex-Ohmeda Smart Vent with a respiratory rate of 10 breaths/min. The ventilator was attached to an Excell 210SE.

Approximately halfway into the procedure, the following alarms were displayed by the ventilator: expiratory reverse flow, tidal volume not achieved, low minute ventilation (Ve), and check sensor. The tidal volume being delivered was 420 ml. Peak inspiratory pressure decreased from low 20s to mid teens (cm H_2O). The ventilator was changed to pressure control mode from volume control mode. Despite this change, the following alarms were displayed while in the pressure control mode: low Ve, expiratory reverse flow, and check sensors. Inspection of the expiratory and inspiratory sensors revealed that they were both dry. However, we changed the expiratory sensor, and this solved the problem. The procedure was finished with the ventilator set in the volume mode without further problems.

Case 3

A 52-yr-old woman with American Society of Anesthesiologists physical status class II and a history of pseudomeningocele who had previously undergone a suboccipital decompression with duraplasty presented for a wound revision of duraplasty. After an uneventful induction of anesthesia and orotracheal intubation, a tidal volume of 750 ml was set on the Datex-Ohmeda 7900 SmartVent with a respiratory rate of 10 breaths/min. The patient's anesthetic was maintained with desflurane in a mixture of oxygen and nitrous oxide at a total flow of 2 l/min. The breathing circuit had a heat and moisture exchanger inserted.

Immediately after induction and intubation, difficulty with ventilation was noted by alarms displayed in the ventilator. The alarm read: expiratory reverse flow, unable to drive bellows. The ventilator was changed to the pressure control mode without improvement. Inspection of the sensors revealed no condensation on them. The patient

* Assistant Professor of Anesthesiology, § Professor of Anesthesiology, Robert Wood Johnson Medical School, The University of Medicine and Dentistry of New Jersey, Department of Anesthesiology, The Cooper Health System. † Instructor of Anesthesiology, ‡ Associate Professor of Anesthesiology, Department of Anesthesiology, The Cooper Health System.

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Address reprint requests to Dr. Cantillo: Robert Wood Johnson Medical School, The University of Medicine and Dentistry of New Jersey, Department of Anesthesiology, The Cooper Health System, One Cooper Plaza, Camden, New Jersey 08103. Address electronic mail to: jjcantillo@cs.com. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

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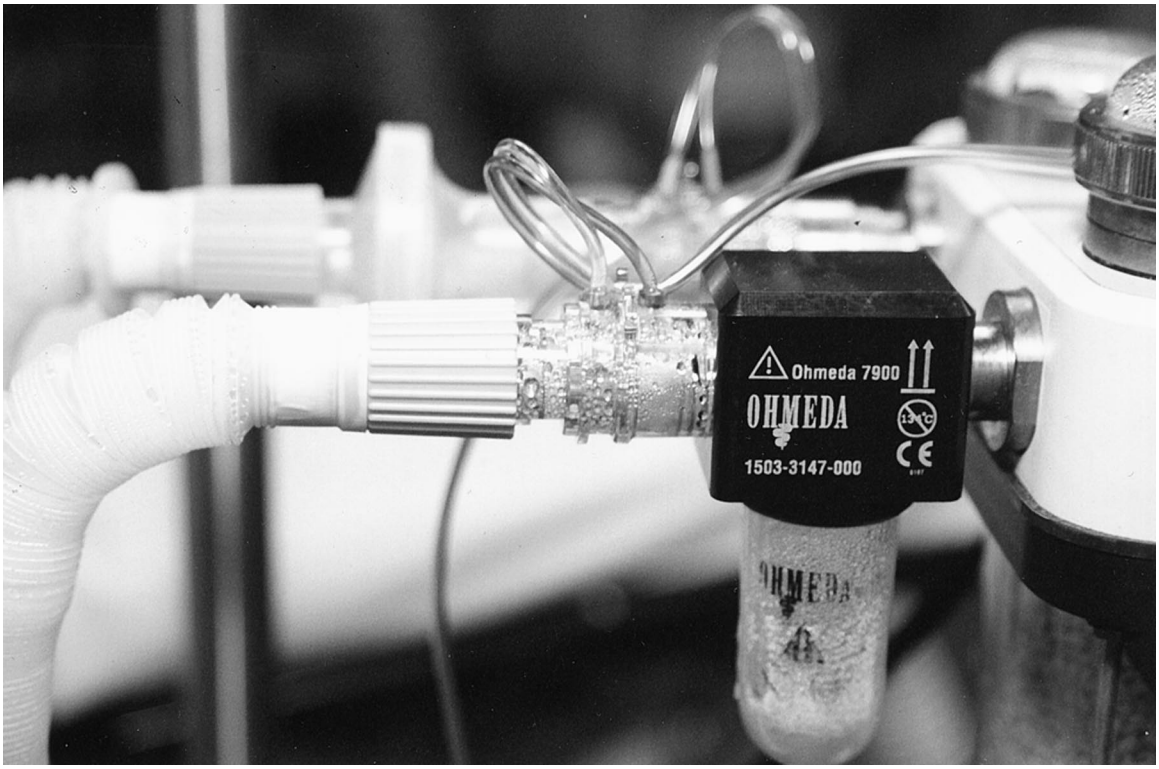

Fig. 1. Datex-Ohmeda Flow Sensor with water condensation.

underwent ventilation with an Ambu bag while the sensors were changed without improvement.

As a result, the machine was removed from the room and replaced. The case proceeded uneventfully, and the patient awakened without complication.

Discussion

Mechanical ventilation during anesthesia has evolved from simple oxygen-powered breathing devices to complex microprocessor-controlled systems capable of providing a variety of ventilatory techniques. The 7900 Datex-Ohmeda ventilator incorporates the latest technological advances to provide ventilatory control of the anesthetized patient. It has the capability of delivering both pressure and volume control ventilation. Sensors in the breathing circuit allow for compensation of compression loses, fresh gas contribution, and small leakage in the breathing circuit. Positive end-expiratory pressure is electronically regulated. The software for the ventilator is upgraded, with the latest version being 3.3 (installed at our institution). It is a useful ventilator for neonates and children, and the controls are easy to use and understand.

The expiratory flow sensor measures expiratory flow (used for volume monitoring and alarms). Electrical connections of the sensors to the ventilator are monitored. Each sensor also contains calibration data stored at the time of manufacture. If the data cannot be read, the system shows "Flow Sensor Failure." The flow sensors use a change in internal diameter to generate a pressure decrease that is proportional to the flow through the sensor. Clear tubes connect to pressure transducers inside the anesthesia machine. During volume control mode, the ventilator calculates the flow per second that will supply the required tidal volume. It applies current to the flow valve needed to supply this flow. The inspiratory flow sensor measures the actual volume, and the valve current is adjusted until the actual volume equals the desired tidal volume. It can compensate for air leaks proximal to the inspiratory flow sensor. It does not compensate for losses distal to this sensor. Volume compensation stops if the sensor fails.[1]

The flow sensors on the 7900 Datex-Ohmeda ventilator seem to be very sensitive to humidity. The presence of water in the flow sensor above a certain threshold causes failure of the sensor and results in general ventilator failure and inadequate tidal volumes. Even when the sensor seems dry, humidity from previous use can find its way inside the anesthesia machine *via* the flow sensors to the interface board of the ventilator and can cause the ventilator to fail.

The above cases all illustrate failure of one of the sensors, interface boards of the sensors, or both with the rest of the mechanical and electronic components of the ventilator. The use of a heated humidified circuit worsens the situation because of its constant water output, allowing humidity to track into the ventilator interface and control boards. Before these incidents, the use of heated humidifiers was common at our institution.

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Although some of the incidents do not involve the use of heated humidifiers, each of these anesthesia machines had been used with a heated humidifier earlier that day or the day before. Because the sensor is sensitive to humidity, we suspected this as the most logical cause in all of the cases.

On all instances, the Datex-Ohmeda service representative found no problem with the ventilator when he tested it. The test by the service representative consisted of a test lung, total fresh gas flow of 2 l/min, and no humidification.

Usually, the first sensor to fail is the expiratory sensor because of the presence of higher humidity in exhaled gases. One of the first alarms to appear was "Exp. Reverse Flow." If not acted on quickly, this can interfere with the patient's ventilation. We contacted the manufacturer and were surprised to find that they were aware of the problem. This is important because they do not provide any warnings about this problem in the instruction manual for this ventilator. We believe that new guidelines should be set on the preoperative checklist of this ventilator until a new sensor that is less sensitive to water is designed.

Increased failure rate with the use of heated humidifiers has prompted us to evaluate our policy regarding their use. We have previously demonstrated that the heat and moisture exchanger does not prevent temperature decreases but may possibly maintain humidity in outpatients undergoing laparoscopic procedures.[2] Heat loss from the respiratory system represents only a small fraction of the total heat lost during anesthesia and surgery in adults. Airway temperature may increase 2–8°C when using a heat and moisture exchanger, and heat conserved by these filters represents 5.51–7.2% of the estimated total metabolic heat production during anesthesia.[3] It seems that heated humidifiers offer little advantage over moisture exchangers.[4] A moisture exchanger may also prevent some of the humidity from reaching the flow sensor.

At our institution, the mentioned problems were isolated to one machine. The manufacturer replaced the interface and control board of the ventilator. They seemed to think that water had found its way to the board because of their sensor design and our constant use of humidified circuits.

We propose that as a part of the preoperative checklist, the sensor be inspected. If presence of condensation is found (fig. 1), this sensor should be removed from the machine and replaced with a dry sensor (a color image of fig. 1 is available in the Web Enhancement). The old sensor can be sterilized and dried between cases. We also propose that the manufacturer issue a warning about using heated humidified circuits on these ventilators because they increase the probability of humidity tracking into the control board of the ventilator. All of our cases were handled appropriately, and potentially devastating consequences were prevented by quick intervention.

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In Reply:—We appreciate the opportunity to respond to the article "Ventilatory Failures with the Datex-Ohmeda 7900 SmartVent." The authors point out some issues of topical importance in the ever-changing worlds of both anesthesia practice and the design and manufacture of anesthesia equipment. In addition, the authors have correctly provided a brief explanation of the internal workings of the 7900 SmartVent, the function of the flow sensors, and the interaction of active humidification on the ventilator functions.

The 7900 SmartVent is designed around a flow sensor technology that provides ventilation to a broad spectrum of patients and addresses specific pressure control ventilation requirements. These specific requirements include an extremely short response time necessary for precise pressure control ventilation. Such precision prevents pressure overshoot. To accomplish these goals, the 7900 SmartVent depends on flow-sensor interface tubing that has an extremely narrow diameter and is constructed from nondistensible material. As a result, although humidity is not of concern, the presence of condensed water within the flow sensor, where the flow sensor interface tubing is attached, may migrate into and along the tubing. This water may migrate as far as the sensor interface board on the 7900 SmartVent. The cases described in the accompanying article most probably are the result of such events.

The fact that these events have prompted the authors to evaluate their policy regarding the use of active humidifiers is a tribute to the dynamic nature of their particular anesthesia practice. As the practice of anesthesia has trended from fresh gas flows of 3 l or more toward flows measured in milliliters, Datex-Ohmeda has continued to improve the 7900 SmartVent in general, as well as the flow sensors and software used in the ventilator. This evolution has produced flow sensors that exhibit a much greater tolerance to excessive humidity and discourage the formation of water at the openings to the flow sensor interface tubing.

Another concern raised by the authors was the Reverse Flow alarm that prompted the dismantling and drying of the expiratory valve. Although this alarm may be a false-positive alarm, which is most likely in the case presented, Datex-Ohmeda decided to err on the side of safety by presenting this alarm and asking the user to evaluate the situation.

We agree with the authors that additional user-level information is needed that addresses active humidification, humidity, and water. We are exploring alternate methods, beyond operations manual updates, to both heighten the awareness of and educate the user in these areas of concern. The presentation of cases in ANESTHESIOLOGY is an excellent forum for both.

Michael Mitton, Datex-Ohmeda, North America, Madison, Wisconsin. michael.mitton@us.datex-ohmeda.com

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