CASE REPORTS

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Mandibular Osteoma: A Case of Impossible Rigid Laryngoscopy

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THE airway management of a surgical patient is one of the anesthesiologist's primary concerns. The combination of several parameters seems to predict difficult laryngoscopy and intubation: short thyro-mental distance, protruding incisors, micrognathia, small mouth opening, acromegalic features, short neck, morbid obesity, and others.[1] This case report describes another rare and frequently unrecognized physical feature associated with difficult intubation: a mandibular osteoma.

Case Report

A 54-yr-old man was scheduled to undergo general anesthesia so that biopsy of several areas from the base of the tongue could be performed. His medical history was remarkable for 55 pack/years of smoking, osteoarthritis in his hands and knees, and a remote history of hiatal hernia but no current reflux. Physical examination was unremarkable. His neck was thin, and he appeared to have an adequate thyro-mental distance. There was good mobility of his temporomandibular joint and his cervical spine. His teeth appeared to be in good repair and well aligned, he had a Mallampati class III airway.

We decided to proceed with general anesthesia and to secure the airway with an endotracheal tube to prevent aspiration of blood. We were concerned about the Mallampati class III airway and the presence of a lesion at the base of the tongue, which was described as "suspicious" on computed tomographic scans but appeared not to obstruct the pharyngeal airway. Because all features of the airway examination were normal except for the Mallampati airway classification, we decided to proceed with a modified rapid-sequence induction with alternative airway equipment and a surgeon immediately available in the room.

The patient was preoxygenated for 5 min, and anesthesia was induced with 400 mg thiopental (5.1 mg/kg). Cricoid pressure was applied, and 80 mg succinylcholine was administered after adequate mask ventilation was assured (normal tidal volume, carbon dioxide waveform, and peak inspiratory pressure of 15 mmHg). Laryngoscopy was attempted with a Macintosh no. 4 blade, and a second attempt was made with a Miller no. 2 blade after optimization of the patient's head position. The epiglottis could not be visualized with either attempt. Mask ventilation was resumed with 100% O_2 and 2% isoflurane. Another 100-mg dose of thiopental was administered because a slight increase in blood pressure indicated partial recovery from the initial induction dose. Mask ventilation at this point seemed to be more difficult, with peak inspiratory airway pressures between 20 and 25 mmHg. With continued cricoid pressure, laryngoscopy was attempted a third time with the Macintosh no. 4 blade. At this point, only the tip of the epiglottis could be visualized. Because higher inspiratory airway pressures were necessary to maintain adequate mask ventilation, we decided to let the patient recover from his anesthetic induction and perform an awake fiberoptic intubation.

Ten minutes later, with the patient awake and alert, the sequence of events and the changed anesthetic plan was explained to the patient. We then performed an awake nasal fiberoptic intubation after the usual preparations (intravenous antisialagogue, local anesthesia of the pharynx and nasal passages with 4% lidocaine, transtracheal anesthesia and bilateral block of the superior laryngeal branch of the vagus nerve). The fiberoptic intubation was uneventful and proceeded in a timely fashion. The surgical procedure was complicated by the fact that rigid, surgical laryngoscopy was impossible.

After the patient was successfully intubated, we reexamined the airway and discovered prominent, bilateral bony growths extending from the lingual surface of the mandible toward the floor of the mouth. In discussion with the surgeon, we learned that this tumor was an osteoma of the mandible, clearly visible on the preoperative computed tomographic scan (fig. 1). Throughout the surgical procedure, the patient's vital signs and oxygen saturation remained normal, and his recovery was uneventful.

Discussion

Osteoma is a benign bone tumor characterized by proliferation of either compact or cancellous bone in an endosteal or periosteal location. The most common location of osteomas is the skull; however, lesions do occur in the jaw. The mandible is more frequently involved, and the most common sites are the lingual aspect of the body, the angle, and the condyle.[2] The age at which the lesions are first identified range between 15 and 75 yr, the majority being noticed after the age of 25 yr.

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Key words: Airway; intubation; fiberoptic.

Fig. 1. Sagittal slice of the base of the skull and the body of the mandible showing a large hyperdense area (arrow) adjacent to the body of the mandible that extends toward the angle of the mandible on the left.

This lesion prevented any displacement of the tongue and the mouth floor and was the reason that direct laryngoscopy was not possible. Biopsy specimens of the tongue base had to be obtained without direct visualization. Osteomas in the maxillofacial region may be associated with limited mouth opening (osteoma of the mandibular condyle) or difficult laryngoscopy[3,4] (osteoma of the mandibular body or angle). Unfortunately, there are insufficient demographic data to demonstrate risk factors for this tumor.

This case illustrates that adequate compliance of the tongue and mouth floor is an important prerequisite for rigid laryngoscopy. Decreased motility of this structure may be caused by simple induration, infection, or systemic connective tissue disorders such as mucopolysaccharidoses. Decreased compliance of the mouth floor may not be obvious. The mandibular osteoma described here was not obvious by classically used methods of evaluating the airway.

The anesthesiologist should be aware of the entity because mandibular osteomas can be identified easily by sublingual palpation of the mouth and may have a dramatic impact on laryngoscopy and intubation.

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Use of Recombinant Hirudin in Patients with Heparin-induced Thrombocytopenia with Thrombosis Requiring Cardiopulmonary Bypass

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HEPARIN-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia with thrombosis (HITT) are rare but potentially fatal complications of heparin therapy.[1,2] Administration of heparin in patients with HITT causes platelet aggregation, thromboembolism, and thrombocytopenia. Therefore, an alternative anticoagulant to heparin is recommended in these patients. Recombinant hirudin (r-hirudin; Refludan, Hoechst Marion Roussel, Inc., Kansas City, MO) is a direct thrombin inhibitor that has been used in patients with HIT and HITT, and case reports have described its use as an anticoagulant in patients requiring cardiac surgery.[3–5] The ecarin clotting time (ECT) is probably the best marker for anticoagulation with r-hirudin,[6] but this test is not widely available. Furthermore, little information is available on appropriate dosing for patients with renal insufficiency, obesity, or those requiring prolonged cardiopulmonary bypass (CPB). We describe the use of r-hirudin as an anticoagulant in two patients requiring CPB, the first with normal renal function and the second with renal insufficiency. The different dose regimens and the use of activated partial thromboplastin time (aPTT) for monitoring anticoagulation are discussed.

Case Report

A 59-yr-old, 103-kg man with unstable angina after a non–Q wave myocardial infarction was scheduled for a coronary artery bypass grafting procedure. He had been diagnosed with HITT 6 yr previously at an outside hospital, and although the platelet factor 4 enzyme-linked immunosorbent assay was negative on this admission, his clinical history was significant for thrombocytopenia and thrombosis after heparin exposure. Routine intraoperative monitors were placed, and anesthesia was induced with 5 mg midazolam, 50 μg sufentanil, and 100 mg rocuronium and maintained with intermittent bolus doses of the same drugs. Anticoagulation for CPB was achieved with a bolus dose of 25 mg r-hirudin (0.25 mg/kg) before initiation of CPB, followed by an infusion of 0.15 $mg \cdot kg^{-1} \cdot h^{-1}$. In addition, 25 mg r-hirudin was added to the extracorporeal circuit prime. During CPB, the aPTT was monitored every 15 min, and it remained >100 s throughout bypass. However, the perfusionist reported an increase in the blood viscosity during rewarming, as noted by visual inspection of the filter screen of the hard shell venous reservoir, although there was no evidence of clot formation. The patient tolerated separation from CPB on the first attempt without inotropic support, with the total CPB time of 79 min. The r-hirudin infusion was discontinued after separation from CPB, and 5 min later the blood in the extracorporeal circuit was completely clotted. The surgery was completed without any complications, and the patient was transferred to the intensive care unit in stable condition. The aPTT values, blood products administered, and postoperative chest tube output are shown in table 1. The patient was discharged from the intensive care unit on the first postoperative day and discharged home on the ninth postoperative day.

Our second patient was a 62-yr-old, 143-kg man with severe mitral valve regurgitation scheduled for a repeat mitral valve replacement. He had undergone coronary artery bypass grafting and mitral valve replacement 71 days previously that was complicated by prolonged postoperative mechanical ventilation, prolonged inotropic support, and renal insufficiency (serum creatinine, 2.2 mg/ml). In addition, he developed deep vein thrombosis that was initially treated with heparin. The heparin was discontinued because of the development of HITT (platelet count of 36,000/ml and thrombosis of the left axillary, subclavian, popliteal, and common femoral veins), which was confirmed

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Key words: Activated partial thromboplastin time; anticoagulation; complications; ecarin clotting time.

Table 1. Perioperative Activated Partial Thromboplastin Time Values and Blood Products Administered in the Two Patients

	Patient No. 1	Patient No. 2
aPTT values (s)		
Baseline	25	33
After loading dose of r-hirudin	>100	143
During CPB	>100	>200
30 min post-CPB	NA	35
ICU admission	60	147
8 h postoperatively	25	81
Blood products administered (units)		
Intraoperative	None	PRBC 18, FFP 8, platelets 12
Postoperative	PRBC 2	PRBC 6, FFP 7, platelets 6
Autotransfusion at 8 h (ml)	800	0
Chest tube output at 8 h (ml)	900	780

aPTT = activated partial thromboplastin time; CPB = cardiopulmonary bypass; NA = not available; ICU = intensive care unit; PRBC = packed red blood cells; FFP = fresh-frozen plasma.

by the heparin-induced platelet activation assay. He was then anticoagulated with 22 mg r-hirudin followed by a variable infusion titrated to an aPTT ratio of 2.5 until resolution of the thrombi. Because he continued to have multiple episodes of congestive heart failure and severe mitral regurgitation, he was returned to the operating room.

Routine intraoperative monitors were placed, and anesthesia was induced with 3.5 μg/kg fentanyl, 0.03 mg/kg midazolam, and 100 mg rocuronium and maintained with desflurane, fentanyl infusion, midazolam, and pancuronium. Anticoagulation for CPB was achieved with a bolus dose of 25 mg r-hirudin administered approximately 30 min before initiation of CPB. In addition, 25 mg r-hirudin was added to the extracorporeal circuit prime, and an infusion was started at 0.05 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} with initiation of CPB. The aPTT values were monitored every 15 min. Approximately 135 min after the initial bolus dose, the hirudin infusion was decreased to 0.02 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}, and 90 min later, the infusion was discontinued because as the aPTT values were > 200 s. There were no clinical signs of excessive bleeding (*e.g.*, bleeding from venous puncture sites) noted during the operation. Separation from CPB was extremely difficult because of a long bypass time (297 min) and poor left ventricular function. Epinephrine 0.5 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} and milrinone 0.75 μg $\cdot$ kg^{-1} $\cdot$ min^{-1} were required for inotropic support. At the time of chest closure, the surgeons reported that the operative field was dry. The aPTT values, blood products administered, and postoperative chest tube output are shown in table 1. In the postoperative period, the patient continued to have profound cardiovascular compromise refractory to inotropic support and developed generalized multisystem organ failure. He died 24 h postoperatively.

Discussion

The syndromes of HIT and HITT are now well characterized, and the reported incidence of HIT after full-dose heparin therapy approximates 3%.[1] Chong[7] recommends basing the diagnosis of HIT on four criteria: (1) thrombocytopenia during heparin therapy; (2) absence of other causes of thrombocytopenia; (3) resolution of thrombocytopenia after discontinuation of heparin; and (4) confirmation of a heparin-dependent platelet antibody by *in vitro* testing. Approximately 20% of patients with HIT develop HITT, with associated morbidity and mortality rates of 80% and 30%, respectively.[1] Because diagnostic tests are unable to predict which patients with HIT will develop HITT, any patient who becomes thrombocytopenic during heparin therapy should be considered at risk for thrombosis.[1]

The heparin alternatives available in the United States include danaparoid and r-hirudin. The other anticoagulants, argatroban and ancrod, are still under investigation. Danaparoid has a long half-life, requires a complicated dosing regimen, and cross-reacts with heparin antibody in 5–20% of cases; therefore, r-hirudin is the preferred drug.[8] Natural hirudin is produced by the leech *Hirudo medichalis* and is a highly specific direct inhibitor of thrombin; one molecule of hirudin binds to one molecule of thrombin and blocks its thrombogenic activity.[9] Anticoagulant activity of hirudin is independent of antithrombin III or any other plasma cofactors and is not neutralized by platelet-secreted proteins or other plasma components. r-Hirudin is derived from yeast cells. It does not interact with platelets or heparin antibodies, does not have fibrinolytic activity, and has a relatively short half-life that makes chemical neutralization unnecessary.

The elimination half-life of r-hirudin is 30–60 min in patients with normal renal function.[10] Because the systemic clearance of r-hirudin is proportional to the glomerular filtration rate or creatinine clearance, the dose of r-hirudin must be adjusted based on renal function. In addition, antihirudin antibodies are formed in 40% of patients, which may increase the anticoagulant effects of r-hirudin in renal failure because of decreased renal elimination of the active antibody–hirudin complexes. Furthermore, r-hirudin cannot be neutralized or dialyzed. In obese patients with a body mass index of 25–30, the use of high doses of r-hirudin seems to have a rebound effect that might be caused by redistribution from its storage in fat deposits.[11]

The use of r-hirudin for CPB requires careful monitoring of the degree of anticoagulation. Pötzsch *et al.*[6] evaluated three methods of monitoring r-hirudin anticoagulation: activated clotting time (ACT), aPTT, and ECT. Of these three methods, ECT showed a linear correlation

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with plasma hirudin concentrations, whereas both ACT and aPTT had poor correlation with plasma hirudin concentrations.[6] ECT is based on the fact that snake venom enzyme, ecarin, converts prothrombin to meizothrombin, which has weak coagulant activity and is neutralized by r-hirudin, resulting in a dose-dependent prolongation of clotting times.[12] Although ECT is preferable to both ACT and aPTT, it is not widely available, and we were unable to obtain either ECT or plasma hirudin concentrations at our institution. Because both of our patients required urgent surgical management, we had to rely on a less reliable marker of hirudin anticoagulation, aPTT.

The dose of r-hirudin for anticoagulation for thrombosis is 0.4 mg/kg bolus followed by an infusion of 0.15 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} (package insert, Refludan). The dose should not be increased beyond that required for 110 kg of body weight. With CPB, a higher dose is needed to ensure adequate anticoagulation with exposure to the extracorporeal circuit. Pötzsch *et al.*[6] reported successful anticoagulation without thrombotic or bleeding complications using an initial bolus dose of 0.25 mg/kg, 0.2 mg/kg added to the extracorporeal circuit prime, and intermittent bolus doses of 5 mg to maintain plasma hirudin concentrations $>$ 2.5 μg/ml. It is suggested that the infusion rate be adjusted to maintain the aPTT ratio (*i.e.*, aPTT at the time over an aPTT reference value) of $\geq$ 2.5.[13] Reiss *et al.*[3] reported the successful use of r-hirudin in an aortic valve replacement, in which they monitored anticoagulation with both ECT and aPTT. In this patient, the plasma hirudin concentration was kept between 2.5 and 3.2 μg/ml, ECT was between 300 and 456 s, and aPTT was between 90 and 130 s. With our first patient, although the aPTT ratio was $>$4 and the aPTT values remained $>$100 s throughout CPB, the blood viscosity likely increased during rewarming, and the blood clotted in the extracorporeal circuit within 5 min after termination of CPB (possibly suggesting inadequate anticoagulation). There are several explanations for possible inadequate anticoagulation in this patient. Plasma levels of r-hirudin do show a high degree of interindividual variability during continuous infusions, even when the dose is adjusted for body weight.[6] Furthermore, the aPTT is a relatively unreliable marker of r-hirudin anticoagulation.

The concerns in our second patient with regard to r-hirudin dosing included renal insufficiency (serum creatinine, 2.2 mg/ml), obesity (body weight, 143 kg), the possibility of prolonged CPB time, and our previous experience with possible inadequate anticoagulation when maintaining aPTT $>$ 100 s. Although the laboratory routinely does not extend an aPTT beyond 100 s, it can be measured to 200 s if requested. The bolus dose of r-hirudin (*i.e.*, 25 mg) was based on 0.2 mg/kg (up to 110 kg), and the initial infusion rate of 50 μg $\cdot$ kg^{-1} $\cdot$ h^{-1} was based on the serum creatinine levels (as recommended by the manufacturer). The infusion of r-hirudin had to be reduced by more than half of the recommended dosage (20 μg $\cdot$ kg^{-1} $\cdot$ h^{-1}) after approximately 2 h, suggesting cumulation. Although the aPTT values were maintained higher than those suggested, there were no signs of overdose (*i.e.*, excessive bleeding) in this patient. In addition, we were able to achieve adequate hemostasis after CPB. Therefore, we suggest that if ECT is unavailable and aPTT is being used, the aPTT should be maintained at levels higher than previously recommended in patients undergoing cardiac surgery.

In summary, we observed possible signs of inadequate anticoagulation when using an aPTT ratio $>$ 4 (aPTT $>$ 100 s) to guide infusion of r-hirudin, suggesting that higher levels may be necessary to prevent thrombotic complications during CPB. We also report the use of r-hirudin in a patient with renal insufficiency, obesity, and prolonged CPB time in whom higher aPTT values (approximately 200) provided adequate anticoagulation during CPB without hemorrhagic complications or difficulty in reversal of anticoagulation.

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Life-threatening Upper Airway Obstruction Caused by Oxygen Administration with a Nasal Catheter

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OXYGEN therapy is widely used to prevent and treat postoperative hypoxemia. For oxygen supply, the nasal catheter is popular because of its simplicity, patient comfort, economics, and safeness. This report describes a life-threatening upper airway obstruction associated with the development of submucosal emphysema caused by oxygen therapy with a nasopharyngeal catheter. Other complications after oxygen therapy with nasal catheters are reviewed.

Case Report

A 63-yr-old man (weight, 80 kg; height, 160 cm) was admitted in emergency to the surgical department for acute ischemia of his right leg. Preoperative chest radiograph showed cardiomegaly, pulmonary vascular congestion, and a right lower lobe infiltration. Physical examination showed obesity, hypoventilation on the right pulmonary base, and ischemia of his right leg. Thrombectomy with general anesthesia was planned. In addition to standard monitoring, a catheter was placed in the radial artery for blood pressure monitoring. After induction of anesthesia, an uneventful tracheal intubation was performed with a soft-cuffed tube (8.0-mm ID). Anesthesia was maintained with isoflurane in a mixture of nitrous oxide, 60%, in oxygen supplemented with fentanyl and vecuronium. Ventilation was adjusted to obtain end-tidal carbon dioxide at 3.5–4.5%, and the peak airway pressures noted were never >25 cm H_2O. A nasogastric tube was inserted through the right nostril without difficulty and was left in place for the postoperative period. At the end of surgery, neuromuscular blockade was reversed, and the patient was allowed to breath 100% oxygen until recovery of anesthesia. At extubation, the patient was alert, and there was no respiratory distress. In the postanesthesia care unit, oxygen 5 l/min was administered with a nasopharyngeal catheter inserted through the left nostril. Several attempts of blind tracheal suctioning were performed through the left nostril to clear abundant bronchial secretions. The introduction of the suction catheter was technically difficult, and the attempts were performed with resistance. Blood was noticed in the aspiration fluid. After aspiration, the nasal catheter had to be reintroduced through the left nostril for oxygen administration. After a few minutes, the patient became suddenly dyspneic and cyanotic. He was agitated, and inspiratory stridor was noticed. The patient's appearance was puffy and bloated from the top of the head to the neck. The patient was immediately intubated with an orotracheal tube (6.5-mm ID). The intubation was very difficult because of major swelling of the pharyngeal mucosa narrowing the upper part of the respiratory tract. Immediately after intubation, the stridor and cyanosis disappeared, and the patient was maintained on assisted ventilation with an inspired oxygen fraction of 40%. Manual examination of the pharynx aided by direct laryngoscopy showed that the tip of the nasal catheter was under the mucosa in the posterior wall of the pharynx, just below the uvula. Chest radiograph showed subcutaneous emphysema, particu-

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Key words: Complications; emphysema; oxygen therapy; postoperative; respiratory stridor.

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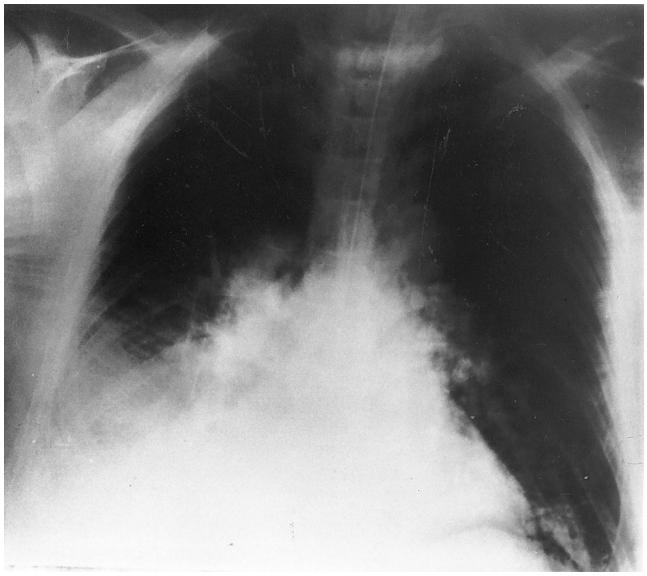

Fig. 1. Postoperative chest radiograph showing subcutaneous emphysema at the level of the pectoralis muscles, the pneumomediastinum, and the infiltration of the right lower pulmonary lobe.

larly at the level of the pectoralis muscles, with pneumomediastinum and infiltration of the right lower lobe already present in the preoperative period; there was no evidence of a pneumothorax (fig 1). Within 6 h after discontinuing nasal oxygen, the subcutaneous emphysema had almost disappeared. Extubation was performed 14 h later and was uneventful. Oral feeding was started on the fourth day after surgery, and no infection of the retropharyngeal space occurred.

Discussion

We report an unusual cause of respiratory distress after oxygen therapy with a nasal catheter. In our case, the use of a suctioning nasotracheal catheter caused laceration of the pharyngeal mucosa and facilitated the submucosal positioning of the catheter. Administration of oxygen was responsible for the development of submucosal swelling of the pharyngeal walls; subcutaneous emphysema of the face, neck, and anterior part of the thorax; and pneumomediastinum. Acute respiratory distress followed the narrowing of the upper part of the respiratory tract caused by submucosal emphysema.

The most common cause of postoperative airway obstruction is pharyngeal obstruction from a sagging tongue in the unconscious patient. Laryngeal obstruction can also occur secondary to a laryngeal spasm or as a result of direct airway injury.[1] In the present case, upper airway obstruction was associated with subcutaneous emphysema. A perforation or erosion of any part of the gastrointestinal tract may result in subcutaneous emphysema, but life-threatening upper airway obstruction is a rare complication associated with subcutaneous emphysema. Golding *et al.*[2] described the development of acute respiratory distress associated with subcutaneous emphysema, pneumomediastinum leading to bilateral pneumothorax after laceration of the pharynx by a nasogastric tube, and subsequent administration of oxygen with a nasal catheter. Respiratory distress ensued 3 h after the end of surgery and was caused by tension pneumothoraces. Golding *et al.* did not describe submucosal emphysema or stridor. Larsen[3] described a similar case, but the respiratory distress was also associated with pneumothorax requiring placement of a chest tube.

Subcutaneous emphysema may be an indicator of barotrauma in patients ventilated with high inflation pressures. Once the alveolar wall has ruptured, gas dissects along the perivascular interstitial spaces to the mediastinum. From there, the gas follows the fascia planes along the trachea and esophagus into the anterior mediastinum and into the subcutaneous tissues of the neck and chest.[4] As the pressure increases, the pleura may rupture and cause pneumothorax. The ventilatory conditions of our patient during surgery were unremarkable, and the subcutaneous emphysema was positively not caused by barotrauma. Pneumothorax did not occur.

Other serious complications have been described after oxygen delivery with a nasal catheter. Gastric rupture has been reported after incidental insufflation in the esophagus caused by inadvertent oxygen administration through the gastric tube[5] or by inadequate positioning of the nasopharyngeal catheter.[6] Pneumocephalus and exophthalmos have also been described using a nasopharyngeal catheter for oxygen administration.[7]

The nasal catheter for routine oxygen supply in the recovery period is widely used as a seemingly noninvasive manner. However, to decrease the incidence of complications associated with this route of administration, the following procedure should be carefully observed. The clinical state of the patient must justify the administration of oxygen by the nasal route. The nasal catheter must be lubricated before insertion. It is important to direct the catheter parallel to the floor of the nose. The catheter must be introduced up to a length corresponding to the distance between the base of the nose and the tragus. Administration of oxygen with a nasal catheter should be avoided when a mucosal tear is suspected either as a result of diagnostic or therapeutic procedures or traumatic lesions. In such cases, the physician should select another oxygen delivery device.

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Hemodynamic and Metabolic Alterations in Response to Graded Exercise in a Patient Susceptible to Malignant Hyperthermia

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MALIGNANT hyperthermia (MH) is characterized by a hypermetabolic response to all commonly used inhalational anesthetics and depolarizing muscle relaxants leading to muscle rigidity, metabolic acidosis, hypercapnia, tachycardia, and fever.[1] Furthermore, it is well known that in certain breeds of swine, MH can be easily triggered by environmental stress. In contrast, MH unrelated to anesthesia occurs rarely in humans. Several investigators have presented case reports of patients suffering from MH during strenuous exercise, excitement, and environmental heat,[2–7] indicating the existence of a human stress syndrome. However, it is still a matter of debate whether stress-induced MH episodes are caused by an increased sympathoadrenergic activity,[1,8] alterations in the serotonergic system,[9,10] or genetic heterogeneity.[11]

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Key words: Caffeine; halothane; stress.

We investigated a young MH-susceptible (MHS) man with a history of MH-like episodes induced by mild physical stress to determine hemodynamic and metabolic responses after graded exercise.

Case Report

A 34-yr-old man (height, 175 cm; weight, 80 kg) was admitted to our MH consultation clinic because of suspicion of a human stress syndrome. In response to mild exercise or emotional stress, he manifested recurrent elevations in body temperature up to 40°C and fatigue associated with muscle cramping and aching. These symptoms disappeared spontaneously after several hours of rest. The patient had noted first signs of a reduced stress tolerance 10 yr earlier. Since that time, the aforementioned stress-associated symptoms had increased in severity and occurred more frequently.

Prior examinations from internists, neurologists, psychiatrists, and dermatologists did not reveal pathologic findings. All blood parameters were within normal limits, and no signs of autoimmune diseases were found. Allergies and cardiac disorders were ruled out. There were no signs of chronic or acute infections. The patient did not take any medication, drugs, or alcohol on a regular basis. There was no history of muscle diseases or of anesthetic complications within the family of the patient. Three months after the patient was tested, his brother and sister were tested, also as MHS, with the *in vitro* contracture test (IVCT)[12]; however, both had no stress intolerance. The patient himself had two uneventful regional anesthesia procedures before our investigations. Because his clinical episodes resembled stress-induced MH, a muscle biopsy specimen for IVCT and muscle histology was obtained, genetic mutation screening was performed, and, in addition to our usual practice, the patient underwent graded exercise on a bicycle ergometer.

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IVCTs and Muscle Histology

The IVCTs with halothane and caffeine were performed according to the protocol of the European MH Group.[12] Muscle bundles, excised from the vastus lateralis muscle, were dissected into eight strips. Only viable muscle samples (twitch response to supramaximal stimulation ≥ 10 mN) were used. Two samples were tested with each drug. The muscle specimens of this patient developed abnormal contracture responses to halothane 0.44 mM and caffeine 1.5 mM, indicating susceptibility to MH. In addition, a ryanodine contracture test with 1 μM ryanodine was performed twice as described previously.[13] After administration of ryanodine, an accelerated and increased contracture development was observed, indicating MH susceptibility.

An additional muscle sample was excised for histologic examination. All investigations performed on this muscle specimen (morphometry, immunohistochemistry, fiber size and ratio analysis, *etc.*) showed normal findings.

Genetic Analysis

Preparation of DNA and oligonucleotides, genotyping, and detection of mutations in the ryanodine receptor gene were performed as described previously.[14] Mutation screening led to the discovery of a substitution of A for G7297. The patient was heterozygous for this mutation. This nucleotide substitution results in the substitution of Arg for Gly2433, which was shown to be associated with MH.[14]

Exercise Tests

The patient was investigated 4 months after the IVCT. A cannula was inserted during local anesthesia for intravenous infusion of 2 ml · kg^{-1} · h^{-1} Ringer's solution. Furthermore, an arterial cannula was inserted into the left radial artery for pressure monitoring and blood sampling, and a Swan-Gantz catheter was inserted into the right cubital vein for measurement of hemodynamic parameters and to obtain blood samples. A standard 12-lead electrocardiogram was monitored continuously and recorded. Room temperature in the laboratory was 18°C, and the patient wore sportswear.

At the end of a 60-min resting period, baseline data were measured (table 1), and the patient started exercise on a bicycle ergometer at a workload of 50 W followed by continuous incremental workloads of 75, 100, and 125 W, with no break between each level. The period spent at each load was 3 min. Electrocardiogram was monitored continuously throughout the experiments. After each period, hemodynamic variables (heart rate, mean arterial pressure, central venous pressure, and mean pulmonary artery pressure), right atrial temperature (°C) *via* the Swan-Gantz catheter, mixed venous and arterial blood gases, lactate levels, and creatine kinase in serum were measured immediately before increasing the work load. After the exercise period, all variables were measured for 360 min. Furthermore, hormone levels such as adrenaline, noradrenaline, and serotonin were determined before and immediately after exercise, as well as 120 and 360 min after the experiments.

Most variables at rest were within normal limits, except blood pressure (mean arterial pressure, 110 mmHg) and creatine kinase with 91 U/l (normal, 30–80 U/l), which showed slight elevations. After starting exercise, heart rate increased from 97 beats/min to 177 beats/min (table 2), mean arterial pressure increased to 130 mmHg at 125 W workload, and mean pulmonary artery pressure increased from 8 mmHg to a maximum of 15 mmHg. Pulmonary capillary wedge pressure increased from 8 to 14 mmHg, whereas central venous pressure remained unchanged at 1 mmHg. Mixed venous oxygen saturation decreased concomitantly from 79% before exercise to a minimum of 49% at 125 W, resulting in an arteriovenous oxygen content difference of 3.2 ml · 100 ml^{-1} before and 10.4 ml · 100 ml^{-1} at the end of exercise (fig. 1A). These values normalized 5 min after the patient stopped exercising. Arterial and mixed venous carbon dioxide concentrations as well as *p*H were stable during the exercise; however, lactate concentration increased from 1 mM to a maximum of 9.9 mM (fig. 1B). Temperature increased from 36.9°C at rest up to 38.9°C at a workload of 125 W.

Table 1. Study Protocol*

Exercise Level	Time Course of Exercise and Resting Periods
Baseline	After 60 min at rest and 5 min before start of the exercise period
50 W	After 3 min of exercise with 50 W
75 W	After 3 min of exercise with 75 W
100 W	After 3 min of exercise with 100 W
125 W	After 3 min of exercise with 125 W
5 min	Resting period of 5 min after exercise
15 min	Resting period of 15 min after exercise
30 min	Resting period of 30 min after exercise
45 min	Resting period of 45 min after exercise
60 min	Resting period of 60 min after exercise
120 min	120 min after exercise
360 min	360 min after exercise

* Exercise was performed on a bicycle ergometer at four incremental workloads followed by a resting period of 6 h.

Serum potassium concentration increased from 3.8 U/l to 4.8 U/l after exercise. Catecholamine levels increased fourfold during the study, adrenaline from 65 ng/l (normal, <60 ng/l) to 233 ng/l, and noradrenaline from 253 ng/l (normal, <260 ng/l) to 930 ng/l, which normalized within 60 min after exercise. Serotonin levels did not change. Creatine kinase concentration reached a maximum of 453 U/l at the last measurement. All other parameters reached the level of the baseline values before this investigation.

Because of these findings and the patient's clinical symptoms, we decided to attempt therapy with dantrolene. This treatment was started 2 weeks later with orally administered dantrolene at a dose of 0.25 mg/kg per day. After 7 days, the dose was increased to 0.5 mg/kg. However, the patient developed migraine, dizziness, and severe muscle weakness. Therefore, dantrolene administration was stopped, and therapy with a β-blocker was started. With this treatment symptoms became a little better, and the patient learned to reduce severity and frequency of such episodes by avoiding stress situations.

Discussion

Physical and emotional stress are triggers of MH in susceptible swine. The role of stress for MH induction in humans is unclear. A large number of reports presented cases of individuals suffering from MH during stressful situations.[2–7] These cases include patients with MH-like symptoms after a long-distance run,[2] after extreme emo-

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Table 2. Changes of Heart Rate, Temperature, Lactate Levels, Creatine Kinase, and Potassium in Serum at Rest and at the Maximum Workload of Exercise in Malignant Hyperthermia–Susceptible and Control Patients Compared with Responses after Graded Exercise in Our Patient

Reference	MH Diagnosis	Exercise Level	HR (beats/min)	Temperature (°C)	Lactate (mM)	CK (U/l)	K^+ (mM)
Green et al., 1987[19]	MHS	At rest	79 ± 5	36.9 ± 0.1	0.5 ± 0.0	—	—
		Maximum workload	122 ± 6	37.4 ± 0.1	0.6 ± 0.1	—	—
	Control	At rest	77 ± 7	36.8 ± 0.1	0.7 ± 0.1	—	—
		Maximum workload	122 ± 7	37.3 ± 0.1	0.8 ± 0.1	—	—
Campbell et al., 1981[17]	MHS	At rest	—	—	1.5 ± 0.2	212 ± 77	4.3 ± 0.1
		Maximum workload	—	—	1.5 ± 0.2	228 ± 96	4.6 ± 0.1
	Control	At rest	—	—	1.1 ± 0.1	83 ± 12	4.2 ± 0.1
		Maximum workload	—	—	1.8 ± 0.4	79 ± 12	4.5 ± 0.1
Campbell et al., 1983[18]	MHS	At rest	—	37.3 ± 0.1	2.3 ± 0.3	—	—
		Maximum workload	—	37.8 ± 0.2	4.2 ± 1.2	—	—
	Control	At rest	—	37.2 ± 0.1	1.6 ± 0.2	—	—
		Maximum workload	—	37.6 ± 0.1	4.0 ± 0.6	—	—
Our patient	MHS	At rest	97	36.9	1.0	91	3.8
		Maximum workload	177	38.9	9.9	453	4.8

MH = malignant hyperthermia; MHS = malignant hyperthermia susceptible; HR = heart rate; CK = creatine kinase; K^+ = serum potassium.

tional[3] and physical stress,[4,5,7,15] or extended car trips.[6] In most of these cases, susceptibility to MH was evaluated with an IVCT; however, the definite trigger mechanisms could not be detected, and exercise tests were not performed. In some patients, dantrolene was shown to be effective in the treatment[3] or prevention[16] of such symptoms. A possible explanation for the variation in clinical expression in stress-induced MH syndromes may be a result of the genetic heterogeneity that is present in humans compared with pigs.

Prior studies systematically investigated the effects of different forms and intensities of exercise in MHS patients compared with control individuals.[17–20] The investigators found no significant differences between MHS and MH-normal patients in response to mild exercise.[17,19] Thermoregulation, plasma catecholamine levels, and metabolic changes in the MHS individuals were comparable with the data from control individuals. In a later study, leg exchange of energy substrates was quantified by measuring leg blood flow and arterial-venous content differences at rest and during different levels of exercise.[20] The results of that study indicated normal sympathetic activity and muscle metabolism in MHS patients during rest, as well as during moderate and severe exercise. In contrast to these findings, free fatty acids, cortisol, and blood lactate levels were significantly increased in MHS but not in MH-normal subjects, indicating an abnormality in the sympathetic activity.[18] Regarding the results of these exercise studies, no differences in heart rate,[19] creatine kinase,[17] temperature,[18,19] lactate[17,19] and K^+[17] were found between MHS subjects and controls. Compared with these data, our patient developed markedly higher values after exercise than controls or other MHS individuals. However, the fundamental problem with all studies is that the investigators used different experimental protocols (type and grade of exercise), study populations (*i.e.*, patients with and without stress syndromes), the condition of patients and control individuals was not proofed before the investigations, and the measurements during exercise were not identical. Therefore, it could be speculated that MHS subjects with a history of stress intolerance would present other reactions in response to exercise, as in our case report.

The sympathetic system has been proposed to play a major role in genesis of porcine stress syndrome.[1] However, activation of the sympathetic nervous system seems to be a secondary response to stress, because it has been shown that total spinal anesthesia failed to attenuate the course of porcine MH, whereas the expected catecholamine increases were prevented.[21] In a considerable number of case reports, the possibility of triggering MH-like episodes in humans by stress has been demonstrated[2–7]; however, whether these responses were caused by an overactivity of the sympathetic nervous system remained unclear. Furthermore, *in vitro* studies on skeletal muscles from MHS patients showed no effect of adrenaline and noradrenaline on halothane-induced contractures.[22] In our patient, catecholamine levels were increased fourfold during exercise, which is comparable to the changes during porcine MH,[8] but this might be a physiologic response to the applied workloads.

Serotonin, which is also an important stress hormone, can be a trigger agent of MH in susceptible pigs.[9] Furthermore, it has been shown that serotonin levels in

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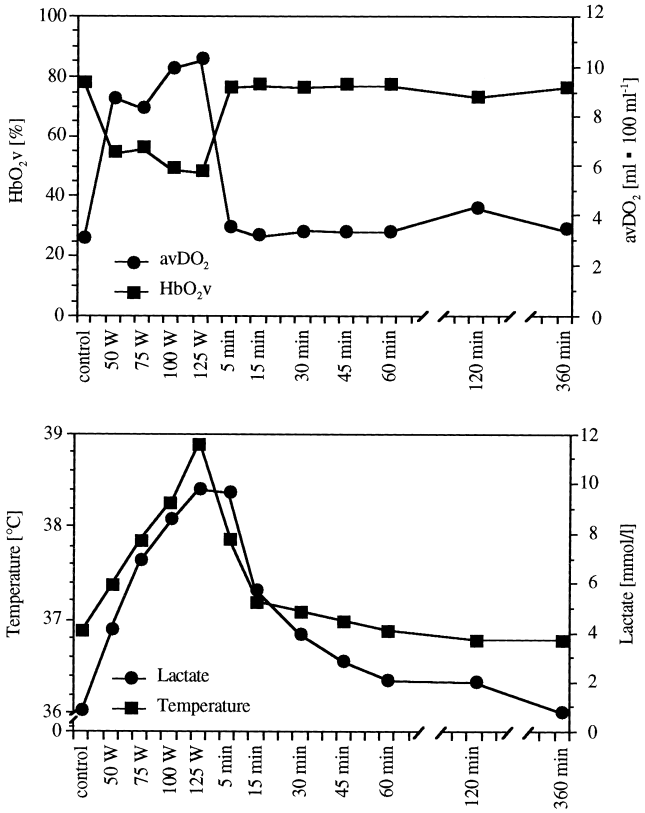

Fig. 1. Changes in mixed venous oxygen saturation (%) and arteriovenous oxygen content difference (ml/100 ml) (*top*) and in temperature (°C) and lactate concentrations (mM) (*bottom*) before and during exercise and at rest in this malignant hyperthermia–susceptible patient.

plasma are significantly enhanced during halothane-induced MH.[23] Under *in vitro* conditions, serotonin induced a marked contracture development in muscle specimens from MHS but only small contractures in control samples.[10] Therefore, it could be hypothesized that serotonin might also trigger MH in humans. However, in this patient, serotonin levels in plasma remained stable at a normal level throughout our investigation.

It is well known that special breeding programs led to the genetic selection of swine with muscle hypertrophy and leanness but also to susceptibility for MH, associated with a reduced tolerance to stress.[1,11] Genetic linkage studies showed that a single amino acid mutation (Arg615 to cysteine) in the porcine skeletal muscle ryanodine receptor gene on chromosome 6 is tightly linked to the MH phenotype. The corresponding mutation in the human ryanodine receptor gene is localized on the chromosome 19q13.1–13.2 region.[11] At present, 17 different single-point mutations have been identified in the human ryanodine receptor gene in MH families. Furthermore, recent studies demonstrate linkage to DNA markers from chromosomes 1, 3, 5, 7, and 17 with the MHS phenotype.[11] It can be hypothesized that these genetic differences in humans and swine are associated with diverging properties or sensitivities with respect to MH trigger. Furthermore, it is tempting to speculate that different genetic mutations in the human ryanodine receptor gene are responsible for an enhanced sensitivity to stress, explaining the existence of a human stress syndrome in some patients. Moreover, heterogeneity could be a satisfactory explanation for the complex pharmacology in MH as well as for different clinical MH presentations (*i.e.*, mild and fulminant forms, rhabdomyolysis).

Heterogeneity in humans may lead to different expressions of symptoms and probably sensitivity to MH trigger, including stress. It would therefore be desirable to standardize test protocols for exercise studies and to select MHS patients with a history of stress intolerance for these experiments. These attempts could be interesting contributions in our understanding of trigger mechanisms in MH. Although treatment with dantrolene failed in this case report because of severe side effects, this treatment was shown to be beneficial in other patients with stress symptoms[3,16]; therefore, a therapy attempt with dantrolene should be recommended in patients with MH episodes unrelated to anesthesia.

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Use of Intravenous Cosyntropin in the Treatment of Postdural Puncture Headache

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POSTDURAL puncture headache (PDPH) is a complication of spinal anesthesia and unintentional dural puncture during attempted epidural anesthesia. We describe a case of PDPH after unsuccessful epidural placement, followed by successful combined spinal–epidural placement. Conventional treatment of PDPH failed. Successful treatment was obtained by administering intravenous cosyntropin, a synthetic form of adrenocorticotropic hormone (ACTH).

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Key words: ACTH; combined spinal–epidural anesthesia; complication; steroids.

Case Report

A healthy 19-yr-old term parturient (gravida II, para 0) was admitted to the hospital in active labor after spontaneous rupture of membranes. She requested epidural analgesia. Preassessment showed a healthy

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individual (weight, 80 kg; height, 168 cm; American Society of Anesthesiologists physical status, 2) with an uneventful pregnancy. The patient denied any significant medical history, specifically headaches or chronic back problems.

Epidural catheter placement was attempted using an 18-gauge Weiss epidural needle inserted perpendicular to the dural fibers at L3–L4 without success. Two attempts were made at L3–L4 using a loss of resistance to air technique. There was no loss of resistance or evidence of unintentional dural puncture. A successful combined spinal–epidural was then placed at L4–L5 using an 18-gauge Weiss epidural needle with the bevel inserted perpendicular to the dural fibers and using the loss of resistance to air technique. A Sprotte 24-gauge spinal needle was then placed through the Weiss needle, and free-flowing cerebrospinal fluid was obtained. Satisfactory analgesia was achieved with intrathecally administered bupivacaine 2.5 mg and fentanyl 25 μg. An epidural closed-end, multiorifice, nonstyleted, 19-gauge catheter was inserted 5–6 cm through the Weiss needle and left in place. A test dose of 3 ml xylocaine 1.5% with epinephrine 1:200,000 was administered through the catheter to rule out intrathecal or intravascular catheter placement. Analgesia was maintained with a continuous epidural infusion of bupivacaine 0.125% and fentanyl 2.5 μg/ml at 10 ml/h. The patient remained comfortable throughout labor and had a spontaneous vaginal delivery 4 h later. The epidural catheter was removed immediately after delivery.

Approximately 12 h after delivery, the patient began to complain of an occipital headache that radiated to her shoulders. An anesthesiologist was consulted for evaluation of possible PDPH. The headache worsened when the patient was in the upright position. The patient reported associated nausea. She denied vomiting, photophobia, tinnitus, or symptoms of cranial nerve involvement. Physical examination and vital signs were within normal limits. A diagnosis of PDPH was made. She was treated with Ringer's lactate 125 ml/h, acetaminophen with codeine as needed for pain, and caffeine sodium benzoate 500 mg in 1 l intravenous fluids per day. The patient reported mild relief of symptoms. She refused further treatment for her headache was discharged home with a prescription for analgesics and instructions to return should her headache worsen.

The patient returned on day 2 complaining of severe headache. Neurologic/physical examination was unchanged from the previous day, except that the severity of the headache had worsened. An epidural blood patch with 15 ml autologous blood injected through an 18-gauge Weiss needle inserted at L3–L4 was performed. The patient had minimal relief of her headache but refused further treatment. She was sent home with instructions to return if her headache worsened. The patient returned on day 3 complaining of severe headache with nausea and vomiting. A presumptive diagnosis of refractory PDPH was made. An intravenous infusion of Ringer's lactate was begun secondary to nausea and vomiting and probable dehydration. Epidural blood patch was performed with 20 ml autologous blood injected at L4–L5 using an 18-gauge Weiss needle. The patient stated that her headache was significantly improved. She was sent home with analgesics and instructions to drink as much fluid as possible and to return if the headache worsened. On day 5 she returned, stating that her headache was worse. It remained occipital and postural in nature. She denied nuchal rigidity, nausea and vomiting, fever, or visual changes. Neurologic examination was normal. She was admitted to the hospital for further evaluation. Her evaluation included consultation with neurologists, hematologic testing for evidence of sepsis, and magnetic resonance imaging of the brain to rule out mass lesion or cortical vein thrombosis. All examinations (complete blood count, magnetic resonance imaging) were normal. The neurologists concurred with the diagnosis of PDPH. Intravenous caffeine, hydration, analgesics, amytriptyline, and muscle relaxants were administered with some transient relief. Over the next 48 h the patient's headache increased in intensity despite all measures. A third epidural blood patch with 20 ml sterilely obtained autologous blood was performed at L4–L5 using an 18-gauge Weiss needle. The patient again stated that the headache was better and was discharged home. Eight days after the combined spinal–epidural analgesia was administered, the patient reported that the headache was worse and was now most intense when she was supine. Because of the patient's complaint of increasing severity of the headache in the supine position and lack of response to epidural blood patch, cortical vein thrombosis was again considered. A repeat magnetic resonance imaging examination of the brain was obtained and was unremarkable.

Based on literature reports of success in treating refractory PDPH with ACTH, a decision was made to offer this steroid treatment to the patient.[1,2] On day 10, the patient agreed to the treatment, and after informed consent was obtained, an intravenous infusion of cosyntropin 0.5 mg in 1 l Ringer's lactate was administered over 8 h. The patient had complete relief of her symptoms. She was able to ambulate without recurrence of her headache. She was discharged the following day asymptomatic and remained asymptomatic at 3 days and 1 week later.

Discussion

The typical PDPH is frontal–occipital and may radiate to the neck or shoulders. It is aggravated by sitting or standing and is lessened or relieved when the patient is in the supine position. Associated symptoms include photophobia, nausea and vomiting, tinnitus, deafness, and abducens nerve palsy.[3] The differential diagnosis for PDPH includes meningitis, sinus headache, tension headache, cerebral hemorrhage, cerebral infarction, preeclampsia, migraine headache, and cortical vein thrombosis.[4,5] Although preeclampsia and meningitis are included in the differential diagnosis of PDPH, these possibilities were unlikely because of the lack of hypertension, fever, or nuchal rigidity.

Our decision to use steroid treatment was based on correspondence by Collier,[1] who described the use of 20 U long-acting ACTH administered intramuscularly to relieve PDPH. Because ACTH is not commonly available, Collier used a synthetic form of 1 mg ACTH administered intramuscularly in his treatment of PDPH. He speculated that ACTH may stimulate the adrenal gland to increase cerebrospinal fluid production and possibly also increase β-endorphin output. In a separate letter, Foster[2] reported using 1.5 U/kg ACTH infused for >1 h in 1 or 2 l Ringer's lactate solution for treatment of PDPH. Final relief was established 6–12 h after the infusion was

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completed. He reported that this treatment for PDPH was 70% effective, without reporting the number of cases used to determine this percentage.

Adrenocorticotropic hormone is not available in our pharmacy, but a similar drug, cosyntropin, is available. Cosyntropin shows the full corticosteroidogenic activity of natural ACTH. Cosyntropin is an α 1-24 corticotropin, a synthetic subunit of ACTH. It contains the first 24 of 39 amino acids of natural ACTH. It may be given as an intravenous infusion over a 4–8-h period to provide a greater stimulus to the adrenal glands. Doses of 0.25–0.75 mg have been used in clinical studies of adrenal function.[6] Our patient was treated with an intravenous infusion of 0.5 mg cosyntropin administered in 1 l Ringer's lactate over 8 h. She had complete relief of her headache without recurrence.

Adrenocorticotropic hormone stimulates the adrenal cortex to secrete glucocorticoids, mineralocorticoids, and weak androgens. ACTH activates adenylyl cyclase and increases intracellular cyclic adenosine monophosphate, which is the second messenger for most, if not all, of the effects of ACTH. Corticosteroids exert a number of indirect effects on the central nervous system. Most patients respond with mood elevation, which may impart a sense of well-being despite the persistence of underlying disease. In addition, corticosteroids profoundly alter the immune responses of lymphocytes, which is important in the antiinflammatory actions of the glucocorticoids. The risk of cosyntropin administration is low. Aside from the rare hypersensitivity reactions, the toxicity of ACTH is primarily limited to the increased secretion of corticosteroids. Cosyntropin is generally less antigenic than native ACTH and is thus the preferred agent for clinical use.[6]

The positive result of our treatment of this patient with cosyntropin does raise many questions. Is it possible that the headache had simply run its course (11 days) and that it was coincidental that the cosyntropin gave positive results? If the basis for conservative treatment of PDPH is to increase cerebrospinal fluid production, and the possible benefit from cosyntropin is also to increase cerebrospinal fluid production, why would cosyntropin work and epidural blood patch fail? Could the positive results we experienced with cosyntropin be secondary to its antiinflammatory or mood-elevation effects? We have no clear answers to these questions. However, because the treatment of PDPH with cosyntropin is noninvasive and may be beneficial, we believe it should be considered in the treatment of PDPH. Future studies are warranted to determine precisely the role of synthetic ACTH analogs in the treatment of PDPH.

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Detection of Basophil Activation by Flow Cytometry in Patients with Allergy to Muscle-relaxant Drugs

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ALLERGIC or pseudoallergic reactions that occur during anesthesia have been increasing over the last few years.[1] Muscle-relaxant drugs are responsible for at least half of these life-threatening adverse reactions.[1,2] The diagnosis of drug allergy is mainly based on a detailed clinical history, positive skin tests, and detection of specific immunoglobulin E (IgE). Nevertheless, the biologic results are not always closely correlated with clinical assessment of the disease, and discrepancies between skin tests and specific IgE are reported.[2,3] In these cases, *in vitro* investigations to identify the responsible drug are needed, and the histamine release (HR) test is usually performed.[2] HR reflects basophil degranulation, but the very small number of circulating basophils is a limitation to this test, and its clinical benefit remains controversial. Because flow cytometry is a valuable tool for identifying cell populations even at low concentrations, we developed a tricolor flow cytometric method (FCM) for the study of allergen-induced basophil activation.[4] Briefly, identification of basophils is based both on CD45 expression (a common leukocyte antigen) and on the presence of IgE on the cell surface, because basophils express high-affinity receptor for IgE. Cell activation on allergen or drug challenge is assessed by the expression of CD63 on the plasma membrane.[5] After the publication of preliminary data (only focused on usual allergens), we initiated studies to evaluate the usefulness of the method in the diagnosis of drug allergy. We report here results of the first four cases of allergy to muscle-relaxant drugs since this FCM was introduced in our laboratory.

The patients were recruited from different associated hospitals in Lyon, France, and rapidly developed clinical features evocative of anaphylactic reaction after induction of anesthesia, *e.g.*, hypotension, bronchospasm, and cutaneous signs. Investigations of the responsible drug were performed in the outpatient unit of the Department of Anesthesia (screening for drug allergy unit) at least 2 months after the allergic reaction. Skin prick and intradermal reaction (IDR) tests[3] were performed using various dilutions of drug solutions, specific IgE antibodies (against ammonium group) were measured using radioallergosorbent techniques (Capsystem; Pharmacia, Uppsala, Sweden), histamine was measured using a radioimmunoassay (Immunotech, Marseille, France), and HR test was considered positive when superior to 10% of total HR. Basophil degranulation by FCM was detected by CD63 expression on the cell surface. A positive threshold is defined with a negative control without any drug. Results are positive when >10% of basophils express CD63.

Case Reports

Patient 1

A 54-yr-old woman presented for coeloscopic treatment of a hiatal hernia. Anesthesia was induced with rocuronium, propofol, alfentanyl, and midazolam. A few minutes after induction, the patient developed cardiovascular collapse accompanied by bronchospasm and general flushing. The patient was transferred to the intensive care unit, and surgery was cancelled. At this time, tryptase level was 188 μg/l (RIA kit, Pharmacia). Two months later, prick test (dilution 1/1) and IDR test (dilution 1/10) with rocuronium were positive. IDR tests (dilution 1/10) were negative for all other drugs: propofol, fentanyl, and midazolam. Specific IgE and HR (36%) tests were positive. The diagnosis of IgE-mediated allergy caused by rocuronium was made.

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Key words: CD63; histamine release; IgE.

Table 1. Results of Prick Tests, Intradermal Reactions, Specific Immunoglobulin E Antibodies Research, Histamine Release, and Flow Cytometry in Four Patients with Anaphylactic Shock during Induction of Anesthesia

	Prick Test	IDR	IgE	HR	FCM/CD63
Patient 1					
Propofol	nd	−	nd	nd	nd
Alfentanil	nd	−	nd	nd	nd
Midazolam	nd	−	nd	nd	nd
Rocuronium	+	+	+	+	+
Patient 2					
Propofol	nd	−	nd	nd	nd
Alfentanil	nd	−	nd	nd	nd
Midazolam	nd	−	nd	nd	nd
Atracurium	−	−	+/−	+	nd
Suxamethonium	nd	+	+/−	+	+
Patient 3					
Thiopental	nd	−	nd	nd	nd
Suxamethonium	+	+	−	−	+
Patient 4					
Propofol	nd	−	nd	nd	nd
Atracurium	−	−	+/−	−	nd
Suxamethonium	+	+	+/−	−	+

Responsible drug is in boldface type.

nd = not done; IDR = intradermal reactions; IgE = immunoglobulin E antibodies research; HR = histamine release; FCM = flow cytometry.

Patient 2

A 46-yr-old woman presented for surgery of dehiscence in the abdominal wall. Anesthesia was induced with atracurium, propofol, alfentanil, and midazolam. A few minutes after induction, the patient developed bronchospasm accompanied by urticaria and flushing. Three months later, prick test with atracurium (dilution 1/10) and IDR test with atracurium (dilution 1/1,000) were negative, whereas IDR test with suxamethonium (dilution 1/100) was positive. The patient had no response to all other drugs: propofol, alfentanil, and midazolam (dilution 1/10 for IDR test). Specific IgE was found in the gray zone near the positive threshold. HR test was positive with atracurium (15%) and suxamethonium (18%). The diagnosis was IgE-mediated allergy caused by suxamethonium with cross-reaction to atracurium.

Patient 3

In 1983, a 24-yr-old woman underwent multiple tooth extraction; anesthesia was induced with suxamethonium and thiopental. After induction, the patient rapidly developed cardiovascular collapse with bronchospasm. Fifteen years later, during a preoperative screening for drug allergy, prick tests were positive with suxamethonium (dilution 1/1) and negative with rocuronium (dilution 1/1) and mivacurium (dilution 1/10); IDR tests with suxamethonium (dilution 1/100), rocuronium (dilution 1/10), and mivacurium (dilution 1/1,000) were positive. The patient had no response to thiopental (dilution 1/10 for IDR test). Tests for specific IgE were negative. HR tests were negative with the aforementioned drugs. The diagnosis was IgE-mediated allergy caused by suxamethonium with cross-reaction to rocuronium and mivacurium.

Patient 4

A 44-yr-old woman presented for surgery in the ear, nose, and throat unit. Anesthesia was induced with suxamethonium, atracurium, and propofol. A few minutes after induction, the patient developed cardiovascular collapse. Five months later, prick tests were positive with suxamethonium (dilution 1/1) and negative with atracurium (dilution 1/10). IDR test with suxamethonium (dilution 1/100) was positive, whereas that with atracurim was negative (dilution 1/1,000). The patient had no response to propofol (dilution 1/10 for IDR test). Specific IgE was found in the gray zone. HR test was negative with all drugs tested. The diagnosis was IgE-mediated allergy caused by suxamethonium.

All biologic data are summarized in table 1.

Discussion

During anesthesia, anaphylactic shock is mainly caused by muscle relaxants. Among the four patients for whom clinical signs were strongly evocative of drug allergy, the detection of basophil degranulation by flow cytometry was the only biologic test to give positive results in each case. Although skin and specific-IgE tests remain the more reliable methods to investigate a suspected drug allergy, in case of discrepant results, we suggest performing the CD63 test by FCM. This method seems to be more sensitive, even if HR test and CD63 by FCM assess the same process, *i.e.*, basophil degranulation. The HR test is based on histamine (entrapped in secretion granules) measurement, whereas FCM detects CD63 on basophil surface

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before and after drug-induced activation. CD63 is anchored in the basophilic granule membrane, and its exposure to the outside of the cells demonstrates cell degranulation.[5] Furthermore, the HR test is costly in terms of both reagents and laboratory technician time.[2]

Thus, CD63 detection by FCM seems to be a more reliable method in the clinical immunology laboratory and is a useful additional test to identify a drug causing anaphylactic shock during anesthesia. Additional data are needed to validate these first results (sensitivity and specificity, especially in atopic patients) and to assess the interest of the method to investigate drug allergy caused by other types of molecules.

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Oropharyngeal Burn in a Newborn Baby: New Complication of Light-bulb Laryngoscopes

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TRACHEAL intubation is commonly performed on sick babies in the neonatal intensive care unit (NICU). Direct laryngoscopy before tracheal intubation can cause complications, including bradycardia, increased intracranial pressure, desaturation, trauma to the pharynx, injuries to the gum, and perturbances of cardiorespiratory measurements.[1,2] Here we describe a previously unreported complication that was most likely caused by overheating in a laryngoscope during intubation of a newborn baby.

Case Report

A term baby weighing 3.6 kg was born covered in thick meconium. The Apgar score was 5 and 7 at 1 and 5 min, respectively. Gentle suction of the mouth was performed, and the baby was tracheally intubated at approximately 1 min of age using a Welch Allyn light-bulb laryngoscope (model WA 685; Welch Allyn, Skaneateles Falls, NY). The findings on chest radiograph were supportive of a diagnosis of meconium aspiration. A septic screen that included blood culture did not suggest infection. The baby needed positive pressure ventilation for pulmonary hypertension caused by aspiration of meconium. On day 2 of life, the baby had blood-stained secretions from the mouth. Examination of the oropharynx revealed a 5-mm ulceration (fig. 1). The doctor who intubated the baby was surprised because the procedure was easy and did not involve any force or repeated attempts. These comments were supported by the nurse who was present at the time. The baby made an uneventful recovery and was discharged home on day 7.

During resuscitation of a baby in our NICU 6 months later, we left a Welch Allyn light-bulb laryngoscope accidentally switched on for a few minutes. On picking up the laryngoscope, the light bulb on the blade of the laryngoscope was noted by the specialist (T. H. H. G. K.) to be so hot that he dropped it. On questioning, the resident involved in the aforementioned case recalled that the Welch Allyn laryngoscope was left switched on for a while before the baby was intubated. We therefore suspect that the lesion in the case reported here may have been caused by a burn sustained from an overheated light bulb of the laryngoscope.

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Key words: Fiberoptic; intubation; NICU; overheating.

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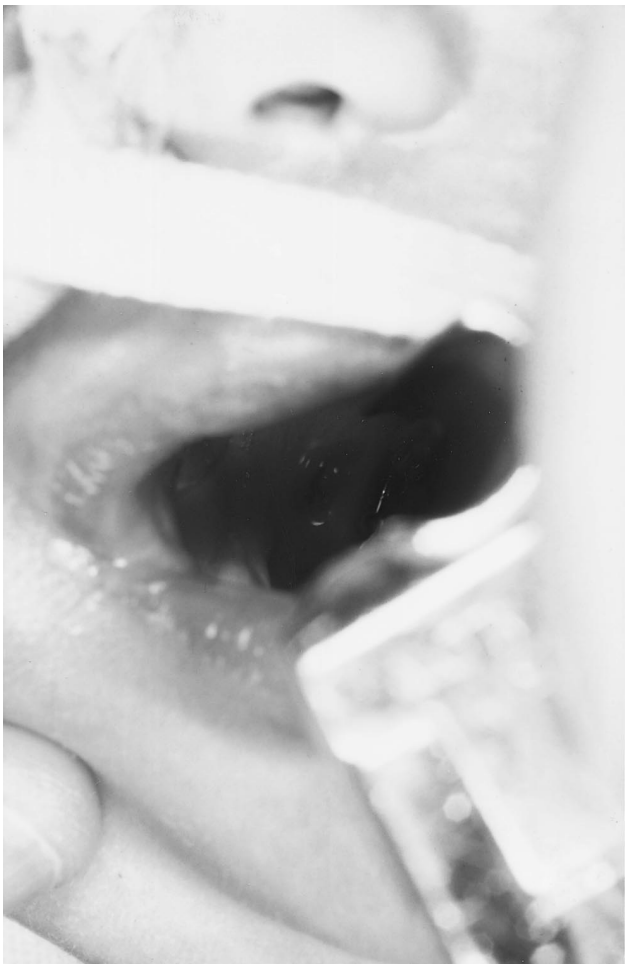

Fig. 1. The 5-mm ulceration in the oropharyngeal mucosa suggestive that the injury was likely caused by the overheated bulb of the light-bulb laryngoscope.

Methods and Results

We performed a telephone survey of the 22 NICUs in Australia to ascertain the incidence of use of laryngoscopes with a light bulb and laryngoscopes with fiberoptic-conveyed light source. We found that 18 of 22 NICUs use light laryngoscopes only, one unit uses fiberoptic laryngoscopes only, and three units use a combination of the two.

Ten laryngoscopes (nine Welch Allyn 68470 and one Atom Medical fiberoptic "O" [Mitcham, Australia]) in current use in the delivery suites and the NICU of our hospital were assessed. The laryngoscope blade and a thermocouple were held in separate bench vices that were positioned such as to bring the thermocouple tip into contact with the surface of the laryngoscope light bulb. Thermal contact was optimized by the application of a small spot of transistor heat-sink compound at the point of contact. A regulated power supply was used to apply 2.5 V to the laryngoscope lamp. Each laryngoscope light source was activated, and the temperature at the face of the light source was recorded every 30 s for 7 min.

We measured the temperature of the light bulb at 1-min intervals for 3 min from when the laryngoscopes were switched on. For one light-bulb laryngoscope, there was an increase in temperature at 1 min to a maximum recorded temperature of 70°C and a further increase at 2 min to 78°C (fig. 2); this was hot enough to evoke a painful withdrawal when placed on the palms of the investigators. It was then confirmed that the bulbs that overheated drew more than the normal current. This suggests that the filaments may have become partly overlapped, resulting in a greater current consumption and hence greater heating. Our findings were confirmed by the manufacturer (Michael Lynch, Product Manager, Welch Allyn Medical Division). In contrast, the temperature of the distal end of the fiberoptic bundle in the blade of the fiberoptic laryngoscope remained unchanged (the bottom line in fig. 2).

Discussion

One of the challenges facing the neonatal team is to minimize iatrogenic problems. Tracheal intubation is a common procedure performed in delivery suites and NICUs. Unusual complications associated with laryngoscopes include tracheal perforation[3] and ingestion of the laryngoscope light bulb.[4]

We have shown that a light-bulb laryngoscope, in contrast to a fiberoptic laryngoscope, can reach temperatures that could result in burns to the oropharynx. This is the first reported case of oropharyngeal burns caused by an overheated light-bulb laryngoscope. The preterm newborn baby with an immature mucosa may be at increased risk from such burns. Such injuries may have easily passed undetected because examination of the oropharynx in intubated newborn babies is not routinely performed. Our case emphasizes the importance of routine examination of the oropharynx to identify both congenital abnormalities but also iatrogenic lesions in the palate of babies who have been intubated. It may be argued that the lesion in our baby was caused by the suction catheter; however, this is unlikely because the doctor did not perform any suctioning of the oropharynx.

There is one report of thermal skin burn from a laryngoscope that was switched on while leaning against the flank of a 5-month-old infant during orthopedic surgery.[5] The laryngoscope used was a Harris-Lake Miller-1, and temperature measurements from three laryngoscopes showed an increase of up to 55°C at 1 min after the laryngoscope has been switched on. Malposition of the blade on the laryngoscope handle can produce a short circuit that leads to rapid heating of the handle.[6]

We recommend that all light-bulb laryngoscopes be switched on for <1 min. If left switched on, the temperature of the bulb should be checked with the hand before usage. We would advise that all light-bulb laryn-

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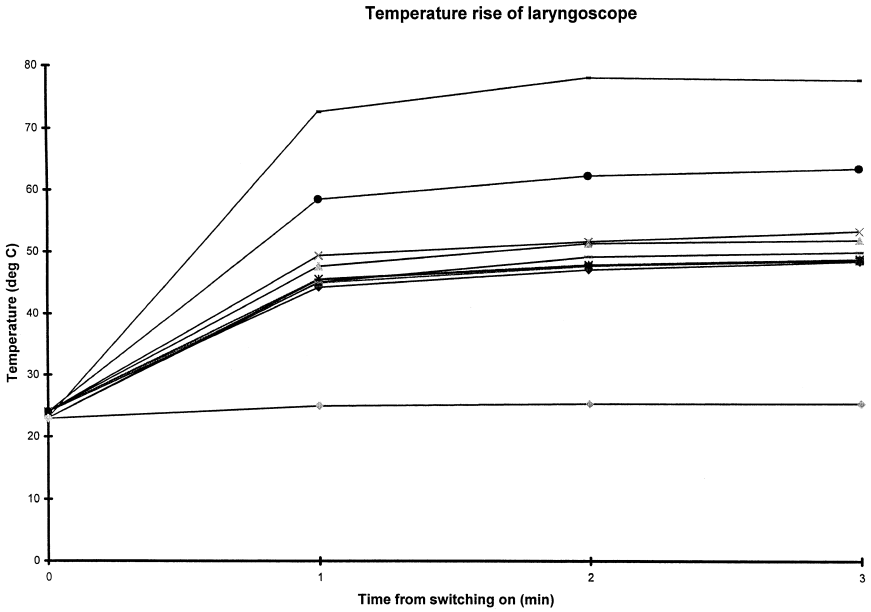

Fig. 2. Graph showing the increase in temperature for the light-bulb laryngoscope. The bottom line shows the temperature measurements from the time the fiberoptic laryngoscope was switched on.

goscopes in use undergo an annual check for overheating tendencies. We recommend that only fiberoptic laryngoscopes be used in NICUs. However, fiberoptic laryngoscopes also have a light bulb located in the handle. If the blade is disconnected from the handle and pressure is placed on the connection adjacent to the light bulb, the light bulb is activated and can become hot. Although heat generated from a handle of the fiberoptic laryngoscope can cause burns to the limbs or torso,[5] we believe that it is unlikely in the context of injury to the orophraynx.

The authors thank Welch Allyn for their report on light-bulb testing.

In Reply:—To the best of my knowledge, the article and Mr. Lynch's response accurately describe the event and our subsequent findings. By the nature of their operation, lamps get hot during illumination. As they approach end of life, the filament relaxes, and it is common for two or more of the coils to touch. This reduces the resistance of the lamp, and the current, in turn, increases, thereby increasing the operating temperature further. Some institutions have made recommendations that only fiberoptic laryngoscopes be used in neonatal intubation procedures. To the best of my knowledge, this is the only report of such an incident that we have ever received. However, the potential of a patient burn from a laryngoscope lamp is recognized, and there is now a requirement in the ISO standard for laryngoscopes: the instructions for use contain a warning that "lamps in an exposed position may generate heat sufficient to burn human tissue."

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