

Inductive Warming of Intravenous Fluids: Overheating of the Toroid Heating Element during Rapid Infusion

Casey S. Husser, M.D.,* Brian Chamblee, M.D.,* Michael J. Brown, M.D.,† Timothy R. Long, M.D.,†
C. Thomas Wass, M.D.‡

REFRIGERATION of stored packed erythrocytes at 1°–6°C prolongs the shelf life up to 42 days.¹ In an attempt to avoid transfusion-related hypothermia, conductive, convective, radiant, and inductive fluid warming techniques have been used with varying success. We report a unique observation in which an inductive fluid warming device overheated during rapid infusion.

Case Report

A 42-yr-old, 80-kg male with chondrosarcoma of the left pelvis was scheduled to undergo elective left internal hemipelvectomy. His medical history and physical examination results were unremarkable. After placing standard American Society of Anesthesiologists monitors, general anesthesia was induced and maintained without incident. Based on historic precedent, large fluid shifts were anticipated, which prompted placement of a right radial arterial catheter as well as 8.5-French and 14-gauge antecubital intravenous catheters. Central venous pressure was continuously monitored *via* the distal port of a right internal jugular 9-French multilumen cordis. A Belmont FMS 2000 Rapid Infusion Device (Belmont Instrument Corporation, Billerica, MA) was connected to the 8.5-French antecubital catheter to deliver warmed fluids throughout the procedure.

The case proceeded uneventfully through the first 9.5 h of the operation. Despite receiving 12 units packed erythrocytes, 11 l crystalloid, 12 units fresh frozen plasma, 6 units platelets, and 2.5 l albumin, 5%, the patient remained warm (36.9°C at the conclusion of pelvic resection) and hemodynamically stable. During fascial closure of the wound, the surgeon observed a “dusky” left leg. Doppler examination disclosed absence of a femoral pulse, necessitating emergent femoral artery exploration and bypass.

Despite having just completed a highly invasive orthopedic surgical procedure, 5,000 units intravenous heparin was administered, as requested by the vascular surgeon, resulting in an activated clotting time of more than 300 s. Ten minutes after heparin administration, hemostasis became increasingly difficult, and hemorrhage was evident in the surgical field. Despite fulminant hemorrhage, central venous and systemic arterial blood pressures were maintained within 20% of baseline using the Belmont FMS 2000 to deliver an additional 8 units of packed erythrocytes and 3 l saline, 0.9% (flow rate ranged from 100 to 500 ml/min). However, near the conclusion of the resuscitative effort (and after the surgeons had regained hemostasis), we noted an acrid smell reminiscent of burning plastic that coincided with an abrupt profound hypotensive (blood pressure 110/50 → 50/30 mmHg) and tachycardic

(heart rate 97 → 130 beats/min) episode that was readily treated with 200 µg intravenous phenylephrine. Both the blood pressure and the heart rate returned to preevent levels in less than 2 min. At the nadir of this brief but dramatic hemodynamic change, the overheat alarm sounded and automatically shut off the Belmont warming unit. The disposable tubing insert was removed, was noted to be disfigured, and seemed to have charred material in one half of the heating coil (figs. 1A and B). The warming unit itself appeared grossly undamaged, but it was promptly replaced with another Belmont FMS 2000 with a new disposable insert.

Subsequent fluid warming proceeded uneventfully, and the patient remained hemodynamically stable and warm (esophageal temperature 37.0°C at the time of discharge from the operating room). He was transferred to the intensive care unit, where serum electrolytes and urine output remained within normal limits. He was extubated on the second postoperative day and discharged to a rehabilitation facility on postoperative day 8, without adverse sequelae.

Discussion

Rapid resuscitation with large volumes of unwarmed intravenous fluid and blood products may result in life-threatening hypothermia. In response to this concern, the medical equipment industry has developed several fluid warming devices that are capable of delivering large volumes of temperature-specific intravenous fluids at high rates of infusion. Unlike conductive warming, which requires physical contact between the intravenous fluid and the warming device, inductive warming occurs in the absence of physical contact between the intravenous fluid and warming element. The Belmont FMS2000 is an inductive fluid warmer capable of heating intravenous fluids to 37.5°C at flow rates ranging from 60 to 500 ml/min and to 39°C at rates of less than 60 ml/min.² With this device, intravenous fluid passes through a toroidal-shaped (donut-shaped) heat exchanger by a built-in peristaltic pump.² A magnetic field is created by a coil at the center of the heat exchanger.² Energy from the magnetic field is transferred to the steel rings of the heat exchanger and then to the intravenous fluid.² Infrared temperature sensors are located on both the input and output ports of the heat exchanger.² If the output sensor detects a fluid temperature of 42°C or greater, the system is designed to—and did so in our case—shut down and alarm, thereby preventing thermal-related injury.²

Malfunction of fluid warming devices has previously been reported.^{3–6} However, regional overheating of the toroid is a unique observation. In hope of elucidating the etiology of malfunction, we sent the disposable warming

* Resident in Anesthesiology, † Assistant Professor of Anesthesiology, ‡ Associate Professor of Anesthesiology.

Received from the Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota. Submitted for publication December 22, 2003. Accepted for publication March 12, 2004. Support was provided solely from institutional and/or departmental sources.

Address reprint requests to Dr. Wass: Department of Anesthesiology, Mayo Clinic, 200 First Street, Southwest, Rochester, Minnesota 55905. Address electronic mail to: wass.thomas@mayo.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

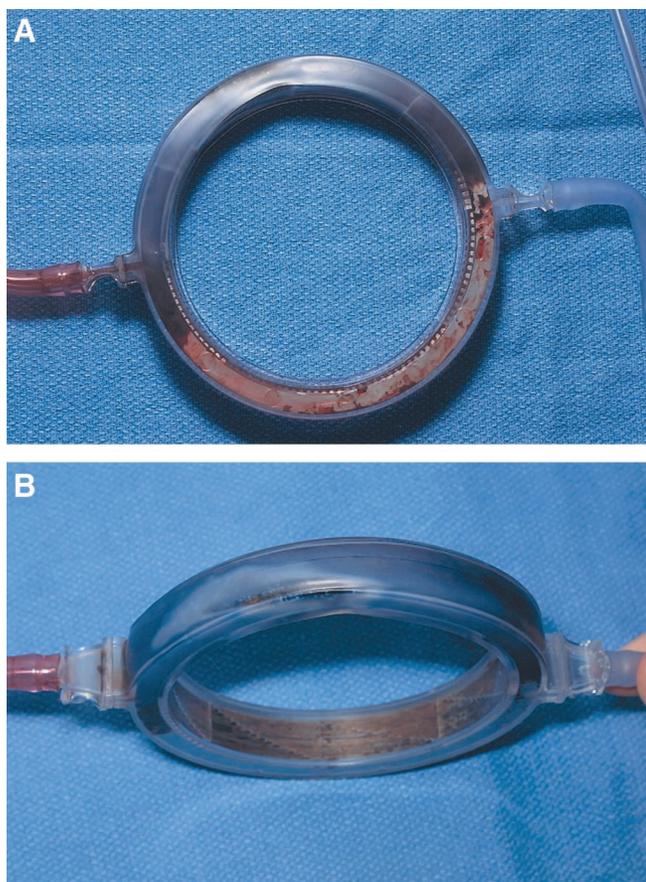


Fig. 1. Anterior (A) and oblique (B) views of the Belmont FMS 2000 disposable tubing insert (Belmont Instrument Corporation, Billerica, MA). Charred, deformed toroidal shaped heating element suggests exposure to temperatures exceeding 100°C (*i.e.*, the melting point of the plastic used to manufacture this device).

element to the manufacturer for evaluation. They too noted charred material in one half of the heating coil (*i.e.*, in the vicinity of melted plastic; figs. 1A and B), whereas other areas were devoid of obvious abnormality. Uncertain as to the composition of the discolored material noted in the toroid, the manufacturer undertook studies to determine whether clot formation could have occurred. They reported such an occurrence was only possible when procoagulant solutions (*e.g.*, calcium, clotting factors, cryoprecipitate, or platelets) were administered through their device. However, being cognizant of this potential pitfall, procoagulant solutions were administered through an alternate fluid warming device (*i.e.*, Hotline fluid warmer, Model REFHL-90DC; Smiths Industries Medical Systems, Rockland, MA) during the above-mentioned operation. Such practice is in keeping with the clinical guidelines at our institution. Therefore, we doubt that the charred material resulted from clot formation or improper use. Also, under extreme testing conditions, the manufacturer determined that the melting point of the plastic housing was 100°C. Aside from providing this information, the manufacturer

was unable to clearly identify the cause of overheating in our case.

Because the damaged portion of the toroid was likely exposed to temperatures of 100°C or greater (*i.e.*, at or beyond the melting point of the toroid), another consideration for the source of toroidal discoloration was thermal injury to formed elements in transfused blood. In regard to the latter, human erythrocytes are capable of withstanding temperatures near 45°C (*i.e.*, a value significantly greater than the maximal output temperature of commercially available fluid warmers) for prolonged periods of time with little effect on cellular integrity.⁷ Denaturation of erythrocyte membrane proteins is responsible for increased osmotic fragility and hemolysis after exposure to temperatures exceeding 45°C.⁸⁻¹³ The percentage of hemolyzed blood cells increases linearly as a function of exposure duration and temperature magnitude.^{8,10,12} Of interest, on review of the patient's laboratory studies, two arterial blood gas samples were noted to be hemolyzed during and soon after the period of hemodynamic instability. Ironically, all other samples drawn from the same arterial line either before or thereafter were not reported as hemolyzed specimens.

Unless leukocyte filtration is performed before or during transfusion, leukocytes are also present in units of packed erythrocytes. To our knowledge, the temperature of leukocyte lysis has not been reported. However, there is concern that thermal-mediated leukocyte free-radical production, complement activation, and release of vasoactive mediators (*e.g.*, prostaglandins, leukotrienes, interleukins, bradykinins, tumor necrosis factor, oxygen free radicals, and cytokines) from thermally lysed or degranulated leukocytes may contribute to physiologic perturbations such as hypotension.¹⁴

As stated above, when the output sensor detects temperatures of 42°C or greater, the device shuts down, thereby preventing thermal injury. However, temperature within the toroid itself is not monitored. Therefore, it is plausible that formed elements in blood exposed to nonphysiologic extreme temperatures (*i.e.*, $\geq 100^\circ\text{C}$ in malfunctioning half of the warming element) lysed, releasing vasoactive mediators. We speculate this may have been the cause of the brief, but profound hypotensive episode rather than an abrupt change in preload, as the central venous pressure was maintained within 20% of baseline and surgical control of hemorrhage had already been achieved. We envision that prevention of this vasoactive mediator exposure was not possible because the output sensor detects temperature of fluid mixed from both halves of the toroid. That is, admixture of fluid within the distal toroid resulted in effluent temperatures of less than 42°C until the temperature within the malfunctioning half of the toroid was so extreme that "cooler" fluid (from the normal functioning region of the toroid) was no longer able to moderate outgoing fluid temperature. Accordingly, up to this endpoint, flow

through the toroid may have flushed vasoactive mediators into the patient's circulation, resulting in hemodynamic instability.

In summary, we report a unique observation in which the heating element of an inductive fluid-warming device experienced overheating (*i.e.*, temperature $\geq 100^\circ\text{C}$) during rapid infusion. Without prompt intervention, such an occurrence could result in patient injury.

References

1. Miller RD: Transfusion therapy, Anesthesia, 5th edition. Edited by Miller RD. Philadelphia, Churchill Livingstone, 2000, pp 1613-44
2. Belmont Fluid Management System FMS 2000 Operator/Service Manual. Billerica, Massachusetts, Belmont Instrument Corporation, 2000
3. Anonymous: Hazard report: Using Baxter ThermaCyl blood/fluid warmer with manual pumps may cause warming cuffs to burst. Health Devices 2001; 30:147-8

4. Hegarty M, Turner T, Yentis SM: FW-537-1 fluid warmer. Anaesthesia 2000; 55:402-3
5. Anonymous: Hazard report: Greater vigilance urged in use of SIMS Level 1 Hotline fluid warmers to detect leaks in warming set. Health Devices 2000; 29:478-80
6. Hartmannsgruber MWB, Gravenstein N: Very limited air elimination capability of the Level 1 fluid warmer. J Clin Anesth 1997; 9:233-5
7. Eastlund T, Van Duren A, Clay ME: Effect of heat on stored red cells during non-flow conditions in a blood-warming device. Vox Sang 1999; 76:216-9
8. Chalmers C, Russell WJ: When does blood haemolyse? A temperature study. Br J Anaesth 1974; 46:742-6
9. Van der Walt JH, Russell WJ: Effect of heating on the osmotic fragility of stored blood. Br J Anaesth 1978; 50:815-20
10. Checcucci A, Olmi R, Vanni R: Thermal haemolytic threshold of human erythrocytes. J Microwave Power 1985; 20:161-3
11. Gershfeld NL, Murayama M: Thermal instability of red blood cell membrane bilayers: Temperature dependence of hemolysis. J Membr Biol 1988; 101:67-72
12. Lepock JR, Frey HE, Bayne H, Markus J: Relationship of hyperthermia-induced hemolysis of human erythrocytes to the thermal denaturation of membrane proteins. Biochim Biophys Acta 1989; 980:191-201
13. Tsong TY, Kingsley E: Hemolysis of human erythrocyte induced by a rapid temperature jump. J Biol Chem 1975; 250:786-9
14. Hatherill JR, Till GO, Bruner LH, Ward PA: Thermal injury, intravascular hemolysis, and toxic oxygen products. J Clin Invest 1986; 78:629-36

Anesthesiology 2004; 101:1021-2

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Inductive Warming of Intravenous Fluids

In Reply:—The case report by Husser *et al.* describes a situation involving massive transfusion of crystalloid, packed erythrocytes, and platelets in a crisis situation. During the case, our rapid infusion/warmer, the FMS 2000 (Belmont Instrument Corporation, Billerica, MA), detected an over-temperature situation, alarmed, and stopped the infusion. A portion of the heat exchanger seemed to have become very hot, and a portion of the housing seemed to have softened. The authors attribute a brief episode of hypotension, and tachycardia, to the incident.

The FMS 2000 monitors the true temperature of the infusate (not that of a water bath or plate) and alarms whenever the fluid exiting the heat exchanger reaches 42°C , well below the temperature at which blood can be damaged. When the alarm occurs, the system immediately closes the line to the patient and stops the pump and heater, and an alarm message instructs the user to discard the disposable set. There is a substantial volume (45 ml) in our disposable set downstream of the heat exchanger, at lower temperature, so that it is impossible for any fluid above 42°C to reach the patient. When the system involved in the incident was returned to us for evaluation, it was thoroughly tested, and it performed according to specification. The disposable set was returned to us, and the heat exchanger was found to be partially occluded with what seemed to be clotted blood. There was no charred plastic. Blood clots had become trapped in the fine channels of the heat exchanger, preventing blood from flowing through them, and also preventing much of the clot material from being infused into the patient. When sufficient clot material is trapped in the heat exchanger, a portion of the heater can be occluded, trapping infusate fluid, which can get very hot. However, the trapped fluid cannot reach the patient. As soon as any fluid at 42°C or higher exits the heat exchanger, the over-temperature alarm activates, closing off flow to the patient as described above.

The heat exchanger in our system consists of a series of specially treated stainless steel annular rings that are heated indirectly by magnetic induction and are enclosed in plastic housing. The system has been tested multiple times by an independent, university-affiliated laboratory using packed human erythrocytes from a blood bank. Hemolysis and erythrocyte osmotic fragility have been measured both for test samples at all flow rates and for control samples that did not pass through the system. In all measurements, which were repeated on several occasions using different blood samples, no difference between the test samples and

controls was ever found. As to the origin of the clots, we know that they were formed downstream of the reservoir filter of our disposable set, which removes all gross particulate matter, suggesting the involvement of a soluble factor. The pore size of the reservoir filter is $160\ \mu\text{m}$ ($0.16\ \text{mm}$), which is much smaller than the heat exchanger channel spacing, $760\ \mu\text{m}$ ($0.76\ \text{mm}$). At some institutions, lactated Ringer's solution (containing Ca^{2+} ions) has been infused with citrated blood products, which, in a few cases, has led to clotting within the disposable set. However, in this case report, the authors state that lactated Ringer's solution was never added to the FMS.

The only way in which we are able to reproduce such high heat as to soften the heat exchanger housing is to completely occlude a section of the heat exchanger with epoxy cement. This causes no flow to occur in the blocked section, which leads to dramatic overheating. (The annular rings of the heat exchanger divide the flow into a series of parallel fine channels. Occluding approximately two thirds of the fluid path for all 17 channels in the heat exchanger and monitoring the fluid temperature just downstream of the blockage with a small thermocouple probe showed only a small increase in temperature to between 42° and 46°C , which does not damage stored erythrocytes.¹ This makes the scenario in the second to last paragraph of the case report, regarding vasoactive mediators, very unlikely. It is only when several channels were completely blocked that dramatic overheating occurred. This was due to a region of trapped, stagnant fluid being continually heated by the rings. The temperature in the adjacent unblocked channels stayed near normothermic temperature.) If the flow path changes slightly, and some of the overheated fluid can reach the output temperature probe, the system alarms as soon as the output temperature reaches 42°C . In the disposable set returned to us, the occlusion was located very close to the output of the heat exchanger, so that the response would have been very quick.

The authors speculate that the hypotensive incident could have been caused by damage to the small amount of leukocytes contained in the packed erythrocytes. However, the high temperature in the heat exchanger results from complete lack of flow in an area of occlusion. Furthermore, leukocytes in packed erythrocyte suspensions stored under standard conditions are already degraded and are known to release numerous cytokines.²⁻⁴ In this case report, no laboratory measurements were made relating to leukocytes or cytokines, and no conclusion regarding the involvement of these factors can be made. As

for the transient hypotensive incident, Elia and Kang,⁵ in their comprehensive review of rapid transfusion devices, state that "hypotension may occur during massive transfusion because the heart is exposed to a large amount of acidic, hyperkalemic, hypocalcemic, and desaturated blood." As for the hemolyzed blood in the arterial blood gas samples, many factors are known to produce hemolysis during transfusion, including 5% dextrose-containing solutions,⁶ the effects of massive transfusion, and the process of drawing the blood sample for the measurement.

This incident describes a situation in which our infusion-warming device, the FMS 2000, overheated during a massive transfusion crisis. However, the device alarmed when it sensed 42°C infusate and protected the patient by shutting off the patient line, while maintaining a margin of safety of 45 ml between the device and the patient. We attribute the problem to gross blood clots within the heat exchanger. Our examination of the disposable set indicated that there was no charred plastic, as alleged by the authors. There is no evidence for the involvement of damaged leukocytes or cytokines.

More than 20,000 patients have been helped with the FMS 2000, including a number of cases that involved much higher transfused fluid

volumes than that described here, including several in which more than 100 l was transfused.

George Herzlinger, Ph.D., Belmont Instrument Corporation, Billerica, Massachusetts. gherzlinger@belmontinstrument.com

References

1. Van der Walt J, Russell W: Effect of heating on the osmotic fragility of stored blood. *Br J Anesth* 1978; 50:815-20
2. Zallen G, Moore E, Ciesla D, Brown M, Biffi W, Silliman C: Stored red blood cells selectively activate human neutrophils to release IL-8 and secretory PLA2. *Shock* 2000; 13:29-33
3. Chin-Yee I, Keeney M, Krueger L, Dietz G, Moses, G: Supernatant from stored red cells activates neutrophils. *Transfus Med* 1998; 8:49-56
4. Frabetti F, Musiani D, Marini M, Fanelli C, Coppola S, Ghibelli L, Tazzari PL, Bontadini A, Tassi C, Conte R: White cell apoptosis in packed red cells. *Transfusion* 1998; 38:1082-9
5. Elia E, Kang Y: Rapid transfusion devices for hemorrhagic cardiothoracic trauma. *Sem Cardiothoracic Vasc Anesth* 2002; 6:105-12
6. Vengelen-Tyler V: *Technical Manual*, 13th edition. Bethesda, American Association of Blood Banks, 1999, p 489

(Accepted for publication March 12, 2004.)

Anesthesiology 2004; 101:1022-4

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Vasopressin for Hemodynamic Rescue in Catecholamine-resistant Vasoplegic Shock after Resection of Massive Pheochromocytoma

John G. Augoustides, M.D.,* Marc Abrams, M.D.,† Darryl Berkowitz, M.D.,† Douglas Fraker, M.D.‡

PERIOPERATIVE management of pheochromocytoma remains an anesthetic challenge.^{1,2} Acute variations in serum catecholamine levels may present as hypertensive or hypotensive crises, depending on tumor type and stage of the procedure. Major advances in perioperative management included preoperative catecholamine blockade and adequate preoperative volume resuscitation.²

We present a case of massive pheochromocytoma that required urgent surgical resection. The urgency of the case and tumor mass precluded complete preoperative catecholamine blockade. The major perioperative challenge was profound vasoplegic shock after tumor resection.

The unusual feature in this case was that vasopressin therapy was required to reverse the catecholamine-resistant vasoplegic shock that persisted after tumor resection. Although this application of vasopressin has recently been reported, it was in a case of pheochromocytoma that was complicated by massive blood loss.³ Our case is unique

because it illustrates the successful application of vasopressin in pheochromocytoma resection, complicated not by hypovolemia but by severe acute catecholamine deficiency resulting from the resection of a giant tumor.

Case Report

Preoperative Presentation

A 47-yr-old man presented to the emergency room in respiratory distress. His vital signs included heart rate of 166 beats/min, blood pressure of 212/153 mmHg, respiratory rate of 45 breaths/min, and a systemic oxygen saturation of 75% on room air. Chest auscultation revealed bilateral rales. The electrocardiogram was remarkable for sinus tachycardia and widespread ST-segment depression. His chest radiograph revealed pulmonary edema.

The patient was placed on mechanical ventilation, and vasodilator therapy with nitroprusside was instituted. He was transferred to cardiac catheterization laboratory for emergent angiography that revealed normal coronary and renal arterial anatomy. Transthoracic echocardiography revealed an ejection fraction of 20%, global left ventricular hypokinesis, and no significant valvular disease.

The patient was admitted to the intensive care unit. His hemoglobin was 19 g/dl, and his creatinine was 3.7 mg/dl. His blood pressure was gradually controlled with both nitroprusside and labetalol. Plasma free normetanephrine was 88.1 nM (range, 0-0.89 nM) and plasma free metanephrine was 35.3 nM (range, 0-0.49 nM). A computed tomographic scan of the abdomen revealed a 10 cm left adrenal mass. He was referred to our institution with a diagnosis of left adrenal pheochromocytoma.

In the intensive care unit there was complete resolution of his cardiomyopathy and acute renal failure. Mechanical ventilation was successfully withdrawn. Repeat transthoracic echocardiography re-

* Assistant Professor of Anesthesia, † Senior Anesthesia Resident, Department of Anesthesia. ‡ Professor of Surgery, Department of Surgery.

Received from the Department of Anesthesia and the Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. Submitted for publication January 30, 2004. Accepted for publication March 29, 2004. Supported by the Department of Anesthesia, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

Address reprint requests to Dr. Augoustides: Assistant Professor of Anesthesia, (Cardiothoracic Section), Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA, 19104-4283. Address electronic mail to: yiandoc@hotmail.com. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

vealed normal left ventricular size and function with no regional wall abnormalities.

The patient was volume resuscitated and commenced on oral phenoxybenzamine. Oral labetalol and nifedipine were then added to achieve a blood pressure of 100/60–120/80 mmHg, complicated by breakthrough hypertensive spells. The hemoglobin was 11.5 g/dl, and serum creatinine was 1.2 mg/dl. Despite breakthrough hypertension, surgery was scheduled because complete preoperative catecholamine blockade was unlikely given the tumor mass and the extreme catecholamine production.

Intraoperative Management

After placement of routine monitors (as recommended by the American Society of Anesthesiologists) and adequate intravenous sedation, a thoracic epidural (T10-T11) was placed without hemodynamic consequence. General anesthesia was induced with propofol 2 mg/kg and fentanyl 10 μ g/kg. Vecuronium 0.1 mg/kg was added for neuromuscular blockade (goal train-of-four ratio was less than 25%). The hemodynamic response to tracheal intubation was attenuated with esmolol 1 mg/kg (maximum blood pressure, 128/75 mmHg; maximum heart rate, 100 beats/min). Anesthesia was maintained with isoflurane in oxygen and titrated fentanyl. There was no epidural drug administration.

Invasive hemodynamic monitoring consisted of a left radial arterial line and a pulmonary arterial catheter (*via* the right internal jugular vein). The baseline hemodynamic profile was as follows: blood pressure 95/65 mmHg, heart rate 70 beats/min (sinus rhythm), central venous pressure 15 mmHg, pulmonary arterial pressure 25/16 mmHg, cardiac index 2.2 l/min/m², systemic vascular resistance 900–1000 dynes·s·cm⁻⁵, and mixed venous saturation 70% (F_{IO₂}, 1.0).

Incision, dissection, and tumor manipulation were continuously associated with baseline mean arterial pressure and systemic vascular resistance. Close communication with the surgical team was maintained during the entire procedure. Intravascular volume expansion with crystalloid was titrated to the following goals: central venous pressure of 12–15 mmHg and urine output of at least 1 ml·kg⁻¹·h⁻¹. Blood loss was 0.2 l and crystalloid replacement was 6.0 l in total.

Systemic vascular resistance was maintained at 900–1200 dynes·s·cm⁻⁵ with the following agents: isoflurane (1.5–2.5%, end-tidal concentration), fentanyl (intraoperative total of 40 μ g/kg), nicardipine infusion (2–4 mg/h), and labetalol (total 400 mg).

After tumor mobilization, all vasodilators were terminated in anticipation of tumor venous ligation. The patient was mechanically ventilated with pure oxygen, and scopolamine (0.4 mg) was administered for amnesia. Immediately after tumor venous ligation, profound vasoplegic shock developed. The blood pressure was 55/30 mmHg, and the systemic vascular resistance was 300–400 dynes·s·cm⁻⁵.

Despite aggressive intravascular volume expansion, norepinephrine (bolus of 50–100 μ g; infusion of 10–30 μ g/min) and epinephrine (bolus of 50–100 μ g; infusion of 10–20 μ g/min), the blood pressure only rose to 65/45 mmHg. The profound vasoplegia responded to bolus vasopressin in doses of 10–20 units. The blood pressure steadily increased to 90/60 mmHg, and the systemic vascular resistance increased to the low normal range of 800–900 dynes·s·cm⁻⁵. A vasopressin infusion at 0.1 units/min was added to maintain systemic vascular resistance.

After skin closure, the patient followed simple commands and had no focal neurologic deficit. His extremities were warm and his urine output greater than 1 ml·kg⁻¹·h⁻¹. The following infusions maintained his blood pressure of 90/55 mmHg and a systemic vascular resistance of 800–900 dynes·s·cm⁻⁵: norepinephrine 13 μ g/min, epinephrine 4 μ g/min, and vasopressin 0.1 units/min. The central venous pressure was 12 mmHg, and his cardiac index was 2.0–2.5 l/min/m².

Postoperative Management

The patient was admitted to the intensive care unit. Tracheal extubation was performed 16 h later. The vasopressor infusions were gradually withdrawn over 24 h: epinephrine first, norepinephrine second, and vasopressin last. Patient-controlled epidural analgesia was begun thereafter. The patient was discharged from the intensive care unit within 48 h. The rest of the hospital stay was uneventful.

Discussion

This case of massive pheochromocytoma illustrates a clinical approach to catecholamine blockade and catecholamine replacement at the appropriate stages of the procedure. An unusual feature of this case is the application of vasopressin to complete the pharmacologic support of vasomotor tone after tumor resection. Tan *et al.* recently described vasopressin in the treatment of catecholamine-resistant hypotension after resection of a pheochromocytoma that was complicated by significant intraoperative blood loss.³ The unique feature of our case is that vasopressin restored vascular tone after pheochromocytoma resection that was uncomplicated by hypovolemia. There was no significant blood loss in this case. Euvolemia was always maintained, as evidenced by a high normal central venous pressure and brisk urine output.

The main etiology of the catecholamine-resistant vasoplegia was the severe abrupt catecholamine deficiency induced on tumor removal. This was exaggerated because of the massive tumor catecholamine secretion. Aggressive exogenous catecholamine replacement did not restore vascular tone. Vasopressin provides an alternative pharmacologic route to reverse catecholamine-resistant vasoplegia. Vasopressin should be readily available as an adjunctive agent for vascular rescue, given that there is almost always a degree of catecholamine-tolerance after resection of a pheochromocytoma.

The ability of vasopressin to reverse catecholamine-resistant vasoplegia has also been described in vasodilatory shock associated with sepsis,^{4,5} insertion of ventricular-assist devices,⁶ cardiopulmonary bypass,^{7,8} and organ donation.⁹ Vasopressin levels in these types of vasodilatory shock are low. The mechanism of this deficiency is unclear, although several hypotheses have been proposed.^{10,11} The proposals include central depletion of neurohypophyseal stores, decreased stimulation of vasopressin release, and inhibition of vasopressin release.¹⁰ A possible explanation for vasopressin deficiency in our case may be the excessive circulating norepinephrine levels that are known to inhibit vasopressin release.¹² Chronic increase of circulating norepinephrine would thus chronically inhibit vasopressin release and ultimately down-regulate neurohypophyseal vasopressin synthesis. Thus, after tumor removal, the neurohypophysis is unable to acutely release high levels

of vasopressin to restore adequate vasopressin levels and restore vascular tone. This hypothesis requires further investigation, including serum vasopressin assays during the perioperative management of pheochromocytoma.

A limiting factor in this case was the persistent α -blockade because of phenoxybenzamine.¹ Although phenoxybenzamine is the standard for preoperative α -blockade, its effects persist for 48 h postoperatively. Doxazosin may be a superior alternative to phenoxybenzamine because it is a specific α_1 -blocker with a shorter half-life: its effects disappear within 12 h postoperatively.¹³ Prys-Roberts and Farndon concluded that doxazosin was a safe and effective alternative to perioperative phenoxybenzamine.¹³ As experience with doxazosin increases, nonspecific long-acting α -blockade with phenoxybenzamine may no longer be the standard for preoperative preparation of pheochromocytoma.

A second limiting factor in this case was the lack of preoperative blockade of catecholamine synthesis with methyl-para-tyrosine, the competitive inhibitor of tyrosine hydroxylase.¹⁴ Tyrosine hydroxylase is the rate-limiting enzymatic step in endogenous catecholamine production. Synergistic preoperative therapy with methyl-para-tyrosine and α -blockade results in superior perioperative hemodynamic management.¹⁵ Although our preoperative protocol for pheochromocytoma typically includes this synergistic combination, this patient was better served with prompt tumor removal. The symptomatic profile of this giant tumor mandated urgent resection, allowing insufficient time to achieve perfect preoperative catecholamine blockade.

A third limiting factor in this case was the choice of labetalol for catecholamine blockade because its half-life of 4–6 h complicates the vasoplegia after tumor removal. Labetalol was chosen because it was part of the preoperative regimen that had achieved near adequate catecholamine blockade. The advantage of this choice was that intraoperative catecholamine excess was asymptomatic. Given that the postoperative vasoplegia lasted 24 h (four times the half-life of labetalol), labetalol

was not a major factor in the profound vasoplegia after tumor removal.

In summary, this case highlights vasopressin for hemodynamic rescue in the management of vasoplegic shock after complicated resection of symptomatic pheochromocytoma. The anesthesiologist should have a low threshold to initiating therapy with vasopressin in this setting, especially when the vasoplegia is catecholamine-resistant and hypovolemia has been corrected.

References

1. Kinney MAO, Narr BJ, Warner MA: Perioperative management of pheochromocytoma. *J Cardiothor Vasc Anesth* 2002; 16:359–69
2. Bogdonoff DL: Pheochromocytoma: Specialist cases that all must be prepared to treat. *J Cardiothor Vasc Anesth* 2002; 16:267–9
3. Tan SG, Koay CK, Chan ST: The use of vasopressin to treat catecholamine-resistant hypotension after pheochromocytoma removal. *Anaesth Intensive Care* 2002; 30:477–80
4. Landry DW, Levin HR, Gallant EM, Ashton RC Jr, Seo S, D'Alessandro D, Oz MC, Oliver JA: Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997; 95:1122–5
5. Landry DW, Levin HR, Gallant EM, Ashton RC Jr, Seo S, D'Alessandro D, Oz MC, Oliver JA: Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med* 1997; 25:1279–82
6. Argenziano M, Choudri AF, Oz MC, Rose EA, Smith CR, Landry DW: Prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. *Circulation* 1997; 96:286–90
7. Argenziano M, Chen JM, Choudri AF, Cullinane S, Garfein E, Weinberg AD, Smith CR Jr, Rose EA, Landry DW, Oz MC: Management of vasodilatory shock after cardiac surgery: Identification of predisposing factors and use of a novel pressor agent. *J Thorac Cardiovasc Surg* 1998; 116:973–80
8. Rosenzweig EB, Starc TJ, Chen JM, Cullinane S, Timchak DM, Gersony WM, Landry DW, Galantowicz ME: Intravenous arginine-vasopressin in children with vasodilatory shock after cardiac surgery. *Circulation* 1999; 100:182–6
9. Chen JM, Cullinane S, Spanier TB, Artrip JH, John R, Edwards NM, Oz MC, Landry DW: Vasopressin deficiency and pressor hypersensitivity in hemodynamically unstable organ donors. *Circulation* 1999; 100:244–6
10. Holmes CL, Patel BM, Russell JA, Walley KR: Physiology of vasopressin relevant to the management of septic shock. *Chest* 2001; 120:989–1002
11. Reid IA: Role of vasopressin deficiency in the vasodilation of septic shock. *Circulation* 1997; 95:1108–10
12. Day TA, Randle JC, Renaud LP: Opposing alpha and beta-adrenergic mechanisms mediate dose-dependent actions of norepinephrine on supraoptic vasopressin neurons *in vivo*. *Brain Res* 1985; 358:171–9
13. Prys-Roberts C, Farndon JR: Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. *World J Surg* 2002; 26:1037–42
14. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS: Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. *Ann Intern Med* 2001; 134:315–29
15. Steinsapir J, Carr AA, Prisant LM, Bransome ED Jr: Metyrosine and pheochromocytoma. *Arch Intern Med* 1997; 157:901–6

Anaphylactic Shock: Is Vasopressin the Drug of Choice?

Wolfram Schummer, M.D., D.E.A.A., E.D.I.C.,* Claudia Schummer, M.D.,† Jens Wippermann, M.D.,‡ Juergen Fuchs, M.D.*

ANAPHYLAXIS is one of the few remaining causes of mortality that is directly due to general anesthesia. It is particularly tragic when death occurs in American Society of Anesthesiologists class I and II patients undergoing elective procedures—despite all available treatment. The most important requirements in the treatment of anaphylaxis are prompt diagnosis and the maintenance of coronary and cerebral perfusion, but these can be difficult or even impossible to accomplish. In the case described, rapid diagnosis was made easier by the invasive monitoring and transesophageal echocardiography. Evidence has recently emerged for the use of vasopressin in cardiopulmonary resuscitation.¹ In septic shock, the application of vasopressin in varying concentrations and combinations with other inotropic or vasoactive agents has resulted in conflicting conclusions.²⁻⁴ To our knowledge, we are the first to report the successful treatment of anaphylactic shock with vasopressin.

Case Report

A 59-yr-old woman with coronary artery disease was scheduled for minimally invasive direct coronary artery bypass grafting for her anterior descending artery stenosis (80%). Her arterial hypertension was well controlled with 2×40 mg propranolol, and she was taking 10 mg atorvastatin daily. She had undergone appendectomy as a child, hysterectomy in 1986, and adenectomy in 1993. Otherwise, her medical history was unremarkable, with no reports of drug or food allergies, hay fever, or bronchial asthma.

One hour before surgery, 40 mg propranolol and 7.5 mg midazolam were administered orally for premedication. General anesthesia was induced using 100 μ g sufentanil, 10 mg midazolam, and 8 mg pancuronium and was maintained with 25 μ g/h sufentanil. After intubation with a Univent endotracheal tube (Fuji Systems Corp., Tokyo, Japan), the patient was ventilated with sevoflurane in oxygen-air (inspiratory oxygen fraction, 0.5; tidal volume, 550 ml; 12 breaths/min; positive end-expiratory pressure, 5 cm H₂O). Continuous monitoring included electrocardiography; monitoring of pulse, oxygen saturation, end-tidal carbon dioxide, invasive arterial blood pressure, and central venous pressure; and transesophageal echocardiography.

After induction, vital signs were stable, with a blood pressure of 130/70 mmHg, a heart rate of 70 beats/min, a central venous pressure

of 11 mmHg, a pulse oxygen saturation of 99% and an end-tidal carbon dioxide of 32 mmHg.

After starting one-lung ventilation, the inspiratory oxygen fraction was increased to 0.7, and vital signs remained stable while the surgeon prepared the left internal mammary artery. To optimize cardiac preload, an infusion of succinylated gelatin solution (Gelafulsol[®]; molecular weight, 30,000 Da; Serumwerk Bernburg AG, Bernburg, Germany) was started. Less than 50 ml had been given when the patient's blood pressure decreased suddenly to 50/25 mmHg, with a heart rate of 90 beats/min, an oxygen saturation of 96%, and an end-tidal carbon dioxide of 28 mmHg. Anaphylaxis was immediately suspected. Transesophageal echocardiography of transgastric mid short axis view showed a hyperkinetic empty left ventricle with a decrease in end-diastolic area without any signs of dyskinesia and without mechanical disturbance due to a surgical compression system. The diagnosis of distributive shock caused by anaphylaxis was made after excluding significant bleeding. There was neither an increase in airway pressure nor evidence of wheezing, urticaria, or erythema.

The gelatin solution was thought to be the trigger agent, and its infusion was stopped. Inspiratory oxygen fraction was increased to 1.0. Resuscitation included intravenous administration of 1000 ml hydroxyethyl starch, 10% (HAES-steril[®]; molecular weight, 200,000 Da; Fresenius Kabi, Bad Homburg, Germany), as well as repeated doses of 100 μ g epinephrine (totalling 1.5 mg), norepinephrine with a maximum rate of 1 μ g \cdot kg⁻¹ \cdot min⁻¹, and 1 g methylprednisolone *via* the central venous catheter. Twenty minutes after the beginning of the anaphylactic reaction, the patient's blood pressure was 80/40 mmHg, her heart rate was 116 beats/min, and she still required increasing doses of vasopressor support. The decision was made to add a bolus of 2 U vasopressin (Pitressin[®]; Monarch Pharmaceuticals, Bristol, United Kingdom) *via* the central venous catheter. Within 5 min, the patient stabilized; after an additional 10 min, blood pressure and heart rate returned to normal (100/60 mmHg and 80 beats/min, respectively), while epinephrine and norepinephrine were discontinued (fig. 1). The patient was successfully extubated in the intensive care unit 2 h after completion of the minimally invasive direct coronary artery bypass grafting. Medical progress was uneventful, and the patient was discharged from the hospital 6 days later. During follow-up, skin testing for gelatin solution was performed: 1 ml of the gelatin solution was diluted in 100 ml normal saline. A positive response was produced in less than 15 min by 0.05 ml of this solution injected intracutaneously. The wheal was greater than 1 cm in diameter, and the flare approximately 2 cm.

The temporal sequence of events during anesthesia and the positive skin test later confirmed that the gelatin infusion caused the anaphylactic shock.

Discussion

The predominant reasons for acute cardiovascular collapse in anaphylaxis are vasodilatation and leakage of plasma from capillaries due to increased permeability. Although multiple mediators such as prostanooids, leukotrienes, and kinins can all promote vasodilatation, histamine seems to play a major role in the pathomechanism.⁵ The heart is not typically the primary target organ in most cases of anaphylaxis, and cardiac dysfunction is

* Consultant, † Resident, Department of Anesthesiology and Intensive Care Medicine, ‡ Consultant, Department of Cardiothoracic and Vascular Surgery, Friedrich-Schiller University Jena.

Received from the Department of Anesthesiology and Intensive Care Medicine, Friedrich-Schiller University Jena, Jena, Germany. Submitted for publication February 4, 2004. Accepted for publication April 29, 2004. Support was provided solely from institutional and/or departmental sources.

Address reprint requests to Dr. Schummer: Department of Anesthesiology and Intensive Care Medicine, Friedrich Schiller-University of Jena, Erlanger Allee 103, 07747 Jena, Germany. Address electronic mail to: cwsm.schummer@gmx.de. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

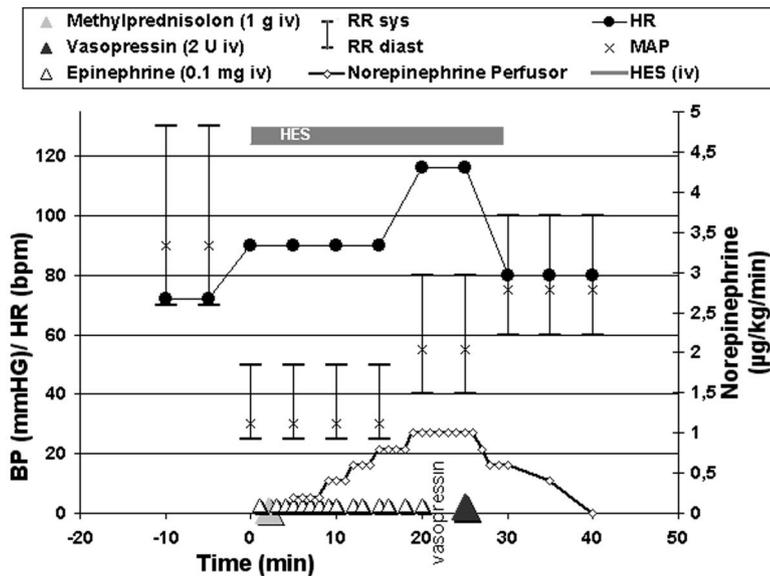


Fig. 1. Hemodynamic response to therapy. BP = blood pressure; diast = diastolic; HES = hydroxyethyl starch; HR = heart rate; iv = intravenous; MAP = mean arterial pressure; RR = Riva Rocci (blood pressure); sys = systolic.

usually related to underlying disease.⁶ The heart has histamine receptors⁷ and contains drug-specific immunoglobulin E.⁸ Cardiac abnormalities in anaphylaxis mediated by immunoglobulin E are more often due to underlying cardiac disease or the arrhythmogenic effects of epinephrine than the anaphylaxis itself.⁶ Stimulation of endothelial H₁ receptors releases nitric oxide and prostacyclin.⁹ Blockade of the target enzyme of the nitric oxide pathway, guanylate cyclase with methylene blue, or use of vasopressin may represent additional therapeutic options in the treatment of anaphylactic shock.^{9,10}

Although questioned by some,¹¹ standard therapy to reverse the vascular collapse in anaphylaxis is epinephrine,¹² a catecholamine with both α - and β -adrenergic effects. Epinephrine inhibits further vasodilating mediator release from basophils and mast cells, reduces bronchoconstriction, increases vascular tone, and improves cardiac output. Nevertheless, human studies on the utility of epinephrine in improving hemodynamic recovery from anaphylactic or anaphylactoid reactions have not been totally supportive.^{13,14} Furthermore, prospective studies to determine the best possible therapy to reverse the vascular collapse are nearly impossible because the occurrence of anaphylactic reactions is rare and unpredictable. Therefore, therapy with epinephrine remains empirical and may not always effectively reverse the vasodilation.¹⁴ Patients with ischemic heart disease are especially vulnerable to the undesired effects associated with epinephrine, *e.g.*, increased myocardial oxygen consumption, ventricular arrhythmia, and myocardial dysfunction during the period after resuscitation.⁵ Individuals who use β blockers—as was the case in the current patient (and possibly angiotensin-converting-enzyme inhibitors, although such evidence is incomplete)—may not respond completely to epineph-

rine.^{15,16} This is in accordance with the observations from a retrospective survey on anaphylaxis during anesthesia in France. Of eight cases involving long-term treatment with β blockers, seven had a grade III anaphylactic reaction, and one had grade IV with cardiac arrest.¹⁷

The current patient did not respond adequately to volume expansion and epinephrine infusions. To maintain cerebral¹⁸ and coronary perfusion pressure, we added norepinephrine at an increasing dosage (fig. 1).¹⁹ The use of vasopressin to treat shock is well established, and the use of vasopressin for resuscitation of septic and vasodilatory shock is not new and has been well studied.²⁰ Anaphylaxis is one form of vasodilatory shock. Therefore, the application of vasopressin in such a situation seems to be logical. Vasopressin plays an important role in cardiovascular homeostasis through both its vasoactive and antidiuretic actions. *In vitro* studies have shown that epinephrine only partially reverses histamine-induced vasodilatation in human internal mammary arteries, whereas vasopressin, methylene blue, and drugs involved in the inhibition of nitric oxide and prostaglandin generation lead to a complete reversal of the vascular relaxation.²¹ Vasopressin is also known to reduce heart rate,²² whereas epinephrine induces tachycardia that might be deleterious in patients with ischemic heart disease or aortic stenosis.

Our case report suggests that adding vasopressin to standard therapy should be considered as a potential therapeutic approach for mediator-induced vasodilatory shock, such as in anaphylactic/anaphylactoid reactions, especially when catecholamines do not restore vascular tone.

The authors thank Don Bredle, Ph.D. (Professor for Kinesiology, Department of Kinesiology, University of Wisconsin-Eau Claire, Eau Claire, Wisconsin), for his helpful suggestions in preparation of the manuscript.

References

- McIntyre KM: Vasopressin in asystolic cardiac arrest. *N Engl J Med* 2004; 350:179-81
- Klinzing S, Simon M, Reinhart K, Bredle DL, Meier-Hellmann A: High-dose vasopressin is not superior to norepinephrine in septic shock. *Crit Care Med* 2003; 31:2646-50
- Sun Q, Dimopoulos G, Nguyen DN, Tu Z, Nagy N, Hoang AD, Rogiers P, De Backer D, Vincent JL: Low-dose vasopressin in the treatment of septic shock in sheep. *Am J Respir Crit Care Med* 2003; 168:481-6
- Patel BM, Chittock DR, Russell JA, Walley KR: Beneficial effects of short-term vasopressin infusion during severe septic shock. *ANESTHESIOLOGY* 2002; 96:576-82
- Paradis NA, Wenzel V, Southall J: Pressor drugs in the treatment of cardiac arrest. *Cardiol Clin* 2002; 20:61-78
- Fisher MM: Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intensive Care* 1986; 14:17-21
- Bristow MR, Ginsburg R, Harrison DC: Histamine and the human heart: The other receptor system. *Am J Cardiol* 1982; 49:249-51
- Assem ES, Ghanem NS: Demonstration of IgE-sensitized mast cells in human heart and kidney. *Int Arch Allergy Appl Immunol* 1988; 87:101-4
- Lindner KH, Prengel AW, Pfenninger EG, Lindner IM, Strohmenger HU, Georgieff M, Lurie KG: Vasopressin improves vital organ blood flow during closed-chest cardiopulmonary resuscitation in pigs. *Circulation* 1995; 91:215-21
- Prengel AW, Lindner KH, Keller A: Cerebral oxygenation during cardiopulmonary resuscitation with epinephrine and vasopressin in pigs. *Stroke* 1996; 27:1241-8
- Waldhausen E, Keser G, Marquardt B: [Anaphylactic shock]. *Anaesthesist* 1987; 36:150-8
- McLean-Tooke AP, Bethune CA, Fay AC, Spickett GP: Adrenaline in the treatment of anaphylaxis: what is the evidence? *BMJ* 2003; 327:1332-5
- Oliveira Neto AM, Duarte NM, Vicente WV, Viaro F, Evora PR: Methylene blue: An effective treatment for contrast medium-induced anaphylaxis. *Med Sci Monit* 2003; 9:CS102-6
- Smith PL, Kagey-Sobotka A, Bleecker ER, Traustman R, Kaplan AP, Gralnick H, Valentine MD, Permutt S, Lichtenstein LM: Physiologic manifestations of human anaphylaxis. *J Clin Invest* 1980; 66:1072-80
- Ellis AK, Day JH: Diagnosis and management of anaphylaxis. *CMAJ* 2003; 169:307-11
- Part 8: Advanced challenges in resuscitation. Section 3: Special challenges in ECC. 3D: Anaphylaxis. European Resuscitation Council. *Resuscitation* 2000; 46:285-8
- Laxenaire MC, Mertes PM: Anaphylaxis during anaesthesia: Results of a two-year survey in France. *Br J Anaesth* 2001; 87:549-58
- Fox AJ, McLaren IM, Naylor AR: Cerebral perfusion monitored using transcranial Doppler during acute anaphylaxis. *Anaesthesia* 1999; 54:678-82
- Muller-Werdan U, Werdan K: [Anaphylactic shock]. *Anaesthesist* 1997; 46:549-63
- Dunser MW, Mayr AJ, Ulmer H, Knotzer H, Sumann G, Pajk W, Friese-necker B, Hasibeder WR: Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. *Circulation* 2003; 107:2313-9
- Tsuda A, Tanaka KA, Huraux C, Szlam F, Sato N, Yamaguchi K, Levy JH: The in vitro reversal of histamine-induced vasodilation in the human internal mammary artery. *Anesth Analg* 2001; 93:1453-9
- Nuyt AM, Segar JL, Holley AT, O'Mara MS, Chapleau MW, Robillard JE: Arginine vasopressin modulation of arterial baroreflex responses in fetal and newborn sheep. *Am J Physiol* 1996; 271:R1643-53

Anesthesiology 2004; 101:1027-30

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Intraneural Injection during Anterior Approach for Sciatic Nerve Block

Xavier Sala-Blanch, M.D.,* Jaume Pomés, M.D.,† Purificación Matute, M.D.,* Josep Valls-Solé, M.D.,‡ Anna Carrera, M.D.,§ Xavier Tomás, M.D.,† Anna I. García-Diez, M.D.†

DESPITE the technological advances in nerve approach and neurostimulation techniques, the percentage of nerve block procedure associated neuropathies has not decreased significantly. It is still between 1.7% and 1.9%.^{1,2} Use of nerve stimulation techniques do not guarantee avoidance of nerve puncture.^{3,4} Bearing these questions in mind, we devised a research protocol, which was approved by the Ethical Committee of our Hospital, in which we included a computerized tomographic (CT) scan examination with the aim of having better chances of avoiding vulnerable structures in the path of the needle from the skin to the nerve when using the anterior approach for sciatic nerve block. We describe two cases in which, after localizing the nerve with

nerve stimulation, CT scanning revealed that the needle has been placed intraepineurally.

Case Report

A 75-year-old woman, 75 kg, 158 cm, American Society of Anesthesiologists physical status III having a history of noninsulin-dependent diabetes mellitus treated with oral hypoglycemic agents was scheduled for transmetatarsal amputation of the right foot because of a severe vasculopathy. The patient gave her written informed consent to perform a continuous sciatic nerve block using the anterior approach.⁵ A CT image confirmed possible access to the sciatic nerve along an anatomical path that avoided contact with other significant structures (fig. 1). After setting up a peripheral blood access line, administering oxygen at a rate of 4 l/m, sedating the patient with 1 mg of midazolam, and anesthetizing the injection site with 3 ml of 1% mepivacaine we inserted the 100 mm stimulation needle (Plexolong®; Pajunk GmbH, Geisingen, Germany). Final position of the needle tip was determined by nerve stimulation. Nerve stimulation (Stimuplex® HNS 11; B Braun Melsungen AG, Melsungen, Germany) performed at a frequency of 2 Hz and pulse duration of 300 μ s. The initial stimulation current intensity was set at 1.5 mA, and the needle was advanced until we observed a plantar flexion at a depth of 9 cm. Further advancement of the needle allowed a decrease in intensity to 0.3 mA, an intensity commonly used for administration of anesthetic near the nerve. After needle stabilization, we first administered 2 ml of 1.5% mepivacaine, which induced no pain or discomfort, followed by another 18 ml of mepivacaine to which we had added 1 ml of nonionic, iso-osmolar iodine contrast medium (Iohexol-Omnipaque® 300; Nycomed Ireland, LTD., Cork, Ireland) without resistance or pain. CT images showed contrast medium around the nerve and between nerve fascicles with a

* Staff Anesthesiologist, Especialista Senior, Department of Anesthesiology, Hospital Clínic, † Staff Radiologist, Especialista Senior, Unitat de Radiologia osteomuscular, CDI, Hospital Clínic, ‡ Staff Neurologist, Consultor Senior, Unitat d' Electromiografia, Hospital Clínic, § Associate Professor, Department of Anatomy and Human Embriology, University of Barcelona, Barcelona, Spain.

Received from the Department of Anesthesiology, the Unitat de Radiologia, and the Unitat d' Electromiografia osteomuscular, Hospital Clínic, and the Department of Anatomy and Human Embriology, University of Barcelona, Barcelona, Spain. Submitted for publication December 5, 2003. Accepted for publication April 26, 2004. Support was provided solely from institutional and/or departmental sources.

Address reprint requests to Dr. Sala-Blanch: Anesthesiology Department, Hospital Clínic, C/ Villarroel 170, 08036-Barcelona, Spain. Address electronic mail to: xsala@clinic.ub.es. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.



Fig. 1. Computed tomographic image of the lesser trochanter region for injection planning; a metallic marker shows the access to the normal flat sciatic nerve (white arrows).

small bubble of entrapped air intraepineurally (fig. 2). Contrast medium showed along the entire 9.5-cm length of nerve explored (fig. 3). Normal flat nerve morphology before needle puncture changed to

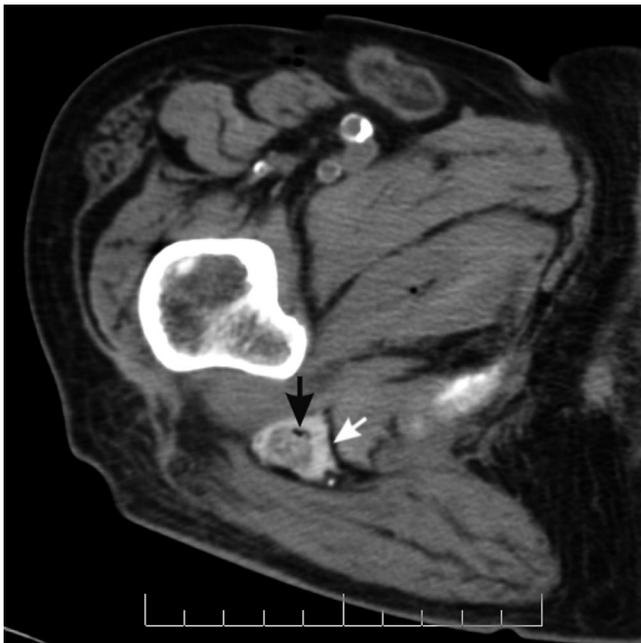


Fig. 2. Computed tomographic image of the lesser trochanter region after injection of the anesthetic plus contrast medium. The contrast medium can be seen in the perineurium (white arrow) and between the nerve fascicles. A small air bubble can be seen inside the nerve (black arrow). The anterior-posterior and transversal diameter of the nerve is increased compared to that before injection.

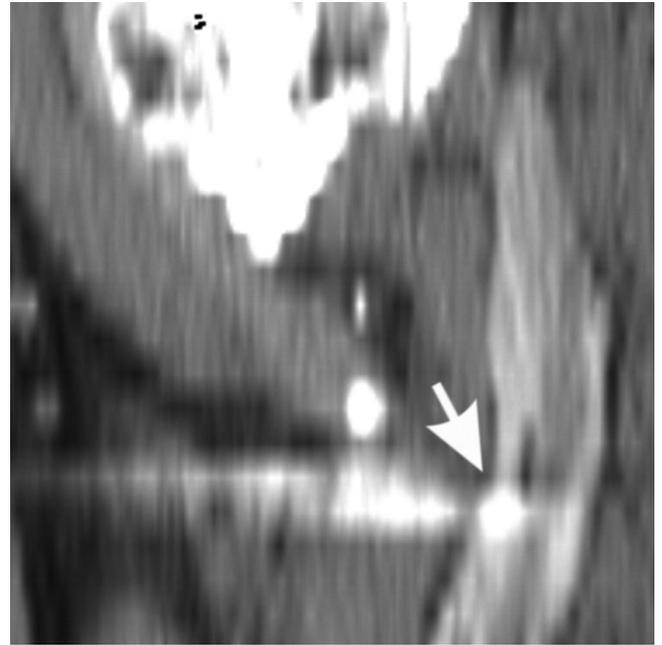


Fig. 3. Sagittal reformation showing the needle path from the anterior of the muscle to the nerve; the tip of the needle is marked with an arrow. The diffusion of the anesthetic plus contrast medium is also shown.

circular morphology after the injection (fig. 2). A catheter was inserted through the needle to a depth of 3 cm. A further dose of 10 ml of 1.5% mepivacaine mixed with 0.5 ml of iodine contrast medium was administered. Further scan sequences showed the catheter inside the epineurium (fig. 4). The catheter was left in place for 3 days after the surgical procedure to administer a continuous infusion of 0.2% ropi-

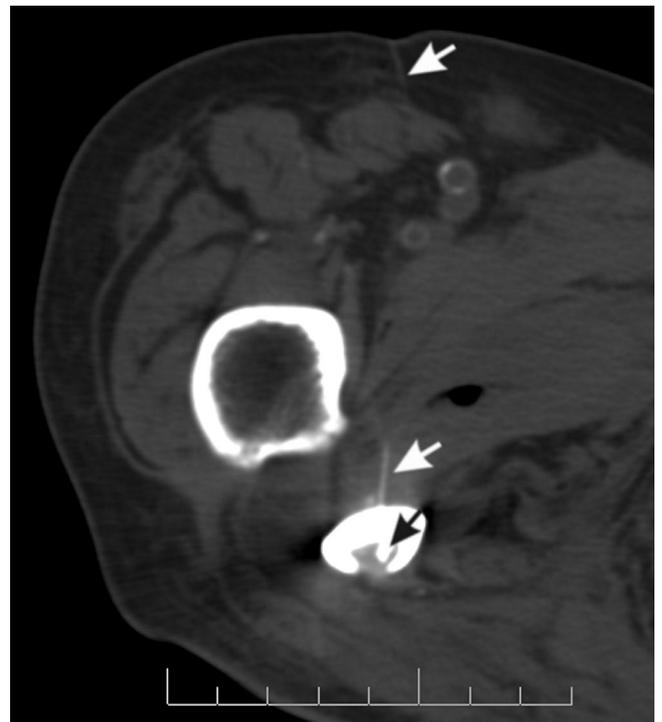


Fig. 4. Location of catheter (white arrows). Injection of anesthetic plus contrast medium confirms that the catheter is inside the epineurium (black arrow).

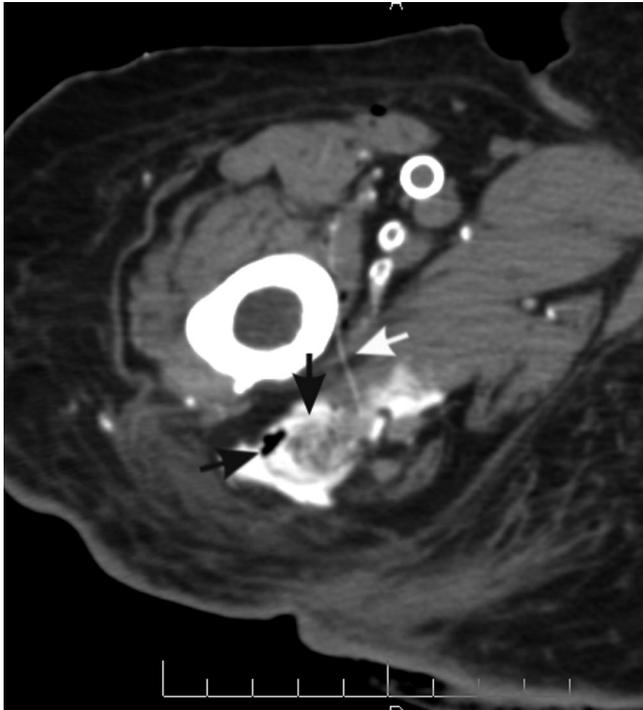


Fig. 5. Catheter (white arrow), epineurium (black arrows), and air bubble inside the epineurium, shown after catheter placement.

vacaine at a rate of 5 ml/h. Motor and sensory functions of the foot recovered when the infusion was discontinued.

Similar observations were made in another noninsulin-dependent diabetic woman with distal diabetic polyneuropathy and vasculopathy. She was 69 yr old, 53 kg, 152 cm, and ASA physical status III. In this patient, the depth of the needle was 9.5 cm, and the minimal stimulation intensity was 0.56 mA at pulse duration of 300 μ s. The local anesthetic and contrast medium were administered following the same protocol as in the previous patient. A CT scan confirmed the diffusion of the contrast medium inside the nerve and along the entire length of 10 cm of explored nerve. The final administration through the catheter of 10 ml dose of 1.5% mepivacaine mixed with 0.5 cm of iodine contrast medium showed its intraneural diffusion (fig. 5). At the end of the surgical procedure, motor and sensory functions recovered fully.

Discussion

Several factors may contribute to postoperative nerve damage after performing peripheral nerve block anesthesia. Modern current nerve stimulators, such as those used in our case studies, allow for the more precise positioning of the needle electrodes and minimize the risk of errors resulting from a possible malfunction of the equipment during nerve stimulation. The electrical current applied to the nerve (electrical charge = nC) will depend on two settings controlled by the nerve stimulator: current intensity and duration of the stimulus (measured in mA and μ s, respectively).^{1,6} In the above cases, stimulus duration of 300 μ s was used and current intensity was varied. Minimal current intensities to produce motor responses in our patients were 0.3 mA

(90 nC) and 0.56 mA (168 nC), which, according to the literature, are in the range of intensities used for infusion of the anesthetic near the nerve.⁶ Finally, a disappearance of muscular twitch with 2 ml of local anesthetic without inducing paresthesia or discomfort and the re-appearance with increased voltage (negative Raj test⁷) indicates correct performance of the technique. However, several tests confirmed that the nerve was punctured and that the anesthetic was actually administered intraepineurally in both patients. CT images showed contrast medium inside the nerve. The contrast occupied the interfascicular space, and the catheter inserted through the stimulator needle was positioned inside the nerve.

The fact that these two patients were diabetic should be taken into account. However, diabetic polyneuropathy would affect the excitability of distal more than proximal parts of the nerve.⁸ Therefore, a proximal approach to the sciatic nerve in a diabetic patient might not be expected to theoretically significantly alter the response to stimulation.⁸

Nerve stimulation can induce specific motor responses. Nevertheless, because of the random distribution of nerve fibers into fascicles, the specific muscle group activated may vary among patients. Induction of specific movements may also be the consequence of selective stimulation of nerve fascicles if the needle has been placed intraneurally through the epineurium.

The structure of the sciatic nerve is different from other nerves. It has a thick, well-formed epineurium that covers two main nerve branches, the tibial and the peroneal nerves.⁹ These two nerves are functionally and structurally separate but share a common epineurium. These structural characteristics may explain why, for this specific nerve, to achieve nerve stimulation at the usual clinical intensities, the needle may have to go through the epineurium. As Vloka *et al.*⁹ suggest, injecting the anesthetic within the epineural adventitia causes the contrast medium to spread into the epineurium around the perineurium that surrounds the fascicles. This procedure is different from an "intrafascicular" injection, which could indeed induce nerve damage. Vloka *et al.*⁹ performed their studies in embalmed cadavers, in which the neural fascia might have suffered structural changes. This intraepineural adventitial administration explains the diffusion of the contrast medium observed in our two patients. The study by Reina *et al.*¹⁰ suggested that by inserting the needle into the epineurium of the sciatic nerve, nerve damage may occur because the fascicles can be "easily touched." However, the strong sheath of the perineurium is different from the loose tissue framework of the interfascicular epineurium. After puncture of the epineural adventitia the needle probably enters the nerve but separates the fascicles rather than punctures them. CT images showed that the local anesthetic diffused within the intraneural space as well as

outside the epineurium. This may be the result of a partial administration of the anesthetic inside and outside because of needle displacement or of the retrograde flow from intraneural space.

The two cases described here demonstrate that, when using a nerve stimulation guided approach, puncture of the sciatic nerve can occur and the local anesthetic can be injected intraneurally (inside the epineurium). Although such procedure did not induce any noticeable nerve damage in the reported patients, intraneural administration of local anesthetic should be avoided. More extensive studies on the sciatic nerve as well as other peripheral nerves are indicated to improve our understanding of this phenomenon.

References

1. De Andres J, Sala-Blanch X: Peripheral nerve stimulation in the practice of brachial plexus anesthesia: a review. *Reg Anesth Pain Med* 2001; 26:478-83
2. Fanelli G, Casati A, Garancini P, Torri G: Nerve stimulator and multiple injection technique for upper and lower limb blockade: Failure rate, patient acceptance, and neurologic complications. Study Group on Regional Anesthesia. *Anesth Analg* 1999; 88:847-52
3. Urmey WF, Stanton J: Inability to consistently elicit a motor response following sensory paresthesia during interscalene block administration. *ANESTHESIOLOGY* 2002; 96:552-4
4. Choyce A, Chan VWS, Middleton WJ, Knight PR, Peng P, McCartney CJL: What is the relationship between paresthesia and nerve stimulation for axillary brachial plexus block? *Reg Anesth Pain Med* 2001; 26:100-4
5. Beck GP: Anterior approach to sciatic nerve block. *ANESTHESIOLOGY* 1963; 24:222-4
6. Koscielniak-Nielsen ZJ, Rassmussen H, Jepsen K: Effect of impulse duration on patient's perception of electrical stimulation and block effectiveness during axillary block in unsedated ambulatory patients. *Reg Anesth Pain Med* 2001; 26:428-33
7. Raj P, Rosenblatt R, Montgomery SJ: Use of nerve stimulator for peripheral blocks. *Reg Anesth* 1980; 5:14-21
8. Patel J, Tomlinson DR: Nerve conduction impairment in experimental diabetes-proximodistal gradient of severity. *Muscle Nerve* 1999; 22:1403-11
9. Vloka JD, Hadzic A, Lesser JB, Kitain E, Geatz H, April EW, Thys DM: A common epineural sheath for the nerves in the popliteal fossa and its possible implications for sciatic nerve block. *Anesth Analg* 1997; 84:387-90
10. Reina MA, López A, De Andrés JA, Machés F: Posibilidad de lesiones nerviosas relacionadas con los bloqueos nerviosos periféricos. Un estudio en nervio ciático humano con diferentes agujas. *Rev Esp Anestesiol Reanim* 2003; 50:274-83