

## Intrathecal Catheter Tip Inflammatory Mass: A Failure of Clonidine to Protect

James D. Toombs, M.D.,\* Kenneth A. Follett, M.D., Ph.D.,† Richard W. Rosenquist, M.D.,‡ Lisa M. Benton§

INTRATHECAL drug infusions are being used more frequently to treat spasticity and chronic pain. More than 95,000 intrathecal drug administration devices have been implanted in the United States since their development in the 1980s. When opioids are part of the intrathecal infusion solution, catheter tip granulomas are emerging as an important potential complication. More than 90 cases of catheter tip granuloma have been reported since 1992.<sup>1</sup> Complication reporting is currently on a voluntary basis, and this number is likely understated. The granuloma is typically a collection of acute and chronic inflammatory cells derived from the arachnoid layer. This reactive tissue does not seem to directly involve the neural parenchyma<sup>1</sup> but has the potential to compress the spinal cord and produce permanent neurologic deficits, including paralysis, sensory loss, and impairment of bowel and bladder function. In sheep and dog studies, intrathecal morphine infusions reliably produce catheter tip granulomas.<sup>2,3</sup> Within the human population, their development is less predictable. Morphine concentration and total daily dosage seem to influence the development of granulomas. The incidence increases with the duration of intrathecal therapy and has been reported as 0.4% after 2 yr of therapy and 1.16% after 6 yr of therapy.<sup>1</sup> The incidence of asymptomatic lesions may be much higher. In a cohort of seven patients, identification of a single symptomatic lesion led to imaging and identification of two additional asymptomatic lesions.<sup>4</sup> In a small canine study, combination therapy with morphine and clonidine was found to prevent granuloma development when the clonidine infusion was greater than 250  $\mu\text{g}/\text{day}$ .<sup>1</sup> On this basis, some physicians who manage patients with intrathecal analgesic infusion systems recommend the routine use of clonidine as an adjunct with opioid to inhibit granuloma

formation (personal observation, Kenneth Follett, M.D., Ph.D., Professor, Department of Neurosurgery, University of Iowa, Iowa City, Iowa, verbal communication, June 2004).

We describe a case in which continuous infusion of intrathecal clonidine did not prevent granuloma formation after subsequent addition of morphine to the intrathecal infusate. This observation suggests that clonidine may not have the same granuloma-inhibiting effect in humans that has been described in animal models.

### Case Report

After falling in 1995, a woman developed complex regional pain syndrome type I involving her left leg. Extensive conservative measures did not provide adequate relief of her pain, and consideration was given to intrathecal analgesic therapy. In April 1999, she underwent a successful trial (80–90% reduction of pain) with intrathecal clonidine, infused continuously over several days *via* temporary intrathecal catheter. Intrathecal opioid was not tested because of our previous experience that pain with a strong neuropathic component tends not to respond well to long-term intrathecal opioid administration. After this successful trial, an intrathecal catheter and infusion pump were implanted in the patient in August 1999 (Medtronic model 8627-18, Medtronic catheter 8709 [89-cm catheter implanted]; Medtronic Neurologic, Minneapolis, MN). Initially, clonidine (1,000  $\mu\text{g}/\text{ml}$ ) was infused at 150  $\mu\text{g}/\text{day}$ . This dose was selected based on the patient's dose requirement during the trial. This rate was progressively increased, and after 6 months, she was receiving 950  $\mu\text{g}$  clonidine per day. In March 2000, morphine was added to her infusion. Morphine (10 mg/ml) was infused at 1 mg/day because of inadequate pain relief with clonidine alone. Clonidine was continued, however, and the rate was reduced to 100  $\mu\text{g}/\text{day}$ . During the next several months, the infusion rate of morphine was gradually increased to 10 mg/day with a parallel increase in clonidine. In June 2000, the infusion solution was changed to increase the concentration of morphine and clonidine to allow further titration and extend the period between pump refills. The new solution contained 17.5 mg/ml morphine and 1,300  $\mu\text{g}/\text{ml}$  clonidine. After this change, the infusion rate was progressively increased until the patient reached a maximum dose of 15 mg morphine and 1,114  $\mu\text{g}$  clonidine per day in April 2001 (table 1).

During the next year, the patient's pain remained stable. Results of physical and neurologic examinations remained stable. In February 2002, she began having left lateral thigh pain. A lumbar radiculopathy was considered, and magnetic resonance imaging studies were obtained that demonstrated no significant findings. Physical examination revealed findings consistent with meralgia paresthetica. The patient was subsequently treated with a series of lateral femoral cutaneous nerve blocks, and her symptoms resolved. She continued with periodic pump refills until July 2003, when her left thigh pain returned. Again, she was diagnosed with meralgia paresthetica and treated with nerve blocks in July and September 2003. Her symptoms improved after each block.

In February 2004, the patient reported thigh pain during a pump refill visit and was referred to the Center for Pain Medicine and

\* Staff Physician, Pain Medicine and Primary Care, Harry S. Truman Veterans' Memorial Hospital, Columbia, Missouri. † Professor, Department of Neurosurgery, ‡ Professor, Department of Anesthesia, University of Iowa Hospitals and Clinics. § Pharmacy Student, University of Iowa College of Pharmacy, Iowa City, Iowa.

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Address reprint requests to Dr. Toombs: Harry S. Truman Veterans' Memorial Hospital, 800 Hospital Drive, Columbia, Missouri 65201. Address electronic mail to: jctoomb@earthlink.net. Individual article reprints may be purchased through the Journal Web site, [www.anesthesiology.org](http://www.anesthesiology.org).

Srinivasa N. Raja, M.D., acted as Handling Editor for this Case Report.

|| Medtronic Patient Registration Data, Medtronic Neurological, Minneapolis, Minnesota. Available at: <http://www.medtronic.com>. Accessed November 5, 2004.

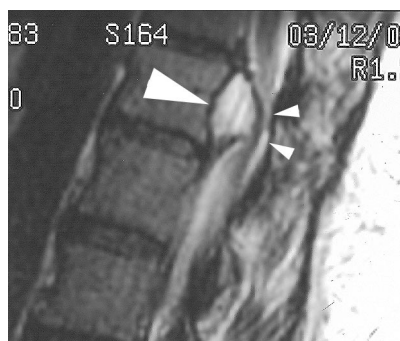
**Table 1. Infusion Solutions and Rates**

Date	Solution	Rate
August 1999	1,000 $\mu\text{g/ml}$ clonidine	150 $\mu\text{g/day}$ clonidine
March 2000	10 mg/ml and morphine and 1,000 $\mu\text{g/ml}$ clonidine	1 mg/day morphine and 100 $\mu\text{g/day}$ clonidine
June 2000	17.5 mg/ml morphine and 1,300 $\mu\text{g/ml}$ clonidine	11 mg/day morphine and 817 $\mu\text{g/day}$ clonidine
April 2001	17.5 mg/ml morphine and 1,300 $\mu\text{g/ml}$ clonidine	15 mg/day morphine and 1,114 $\mu\text{g/day}$ clonidine

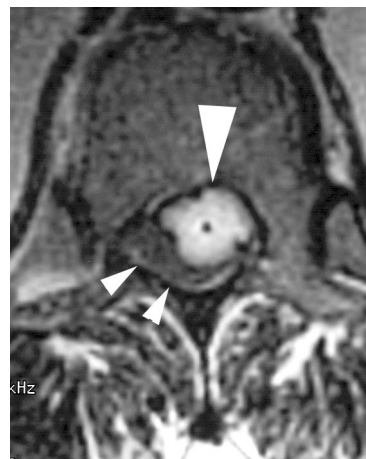
Regional Anesthesia for presumed recurrence of her meralgia paresthetica. In contrast to the pain she reported with her previous episodes of meralgia paresthetica, this pain was bilateral and was located more anteriorly on the thighs. She also reported bilateral leg weakness and increased pain with hip flexion. Physical examination at this time revealed no changes in her strength, sensation, or reflexes. However, given these new symptoms, lumbar and thoracic magnetic resonance imaging studies were completed.

These magnetic resonance imaging studies revealed a contrast-enhancing mass at the tip of the intrathecal catheter, consistent with intrathecal granuloma (figs. 1 and 2). The mass was located anterior to the spinal cord at the T11 level. It compressed the spinal cord and caused cord deformity. A neurosurgical evaluation was completed; given the absence of neurologic deficit and the anterior location of the lesion in relation to the cord (which would have made surgical resection of the mass difficult), conservative management was elected.

During the course of 15 days, the intrathecal morphine-clonidine dose was progressively reduced, and then the morphine-clonidine solution in the pump was replaced with preservative-free normal saline. Concurrent with the reduction in intrathecal analgesics, oral analgesic medications were increased. The lumbar and thoracic magnetic resonance imaging studies were repeated approximately 4 weeks after initiation of intrathecal saline infusion and revealed near complete resolution of the mass with restoration of the spinal cord to normal dimensions (figs. 3 and 4). At this time, the patient reported complete resolution of her leg weakness and leg pain. Retrospectively, the patient reported a history of intermittent urinary urgency and incontinence in the 6 months before discovery of the intrathecal mass that resolved entirely.



**Fig. 1.** Sagittal T2-weighted magnetic resonance imaging scan obtained at the time of initial presentation of the presumed granuloma showing a hyperintense mass anterior to the spinal cord, behind the T11 vertebral body (*large arrowhead* overlying T11 body, pointing toward granuloma). The thecal sac and spinal cord are compressed and distorted by the mass. *Small arrowheads* indicate the posterior margin of the thecal sac at the level of the granuloma.

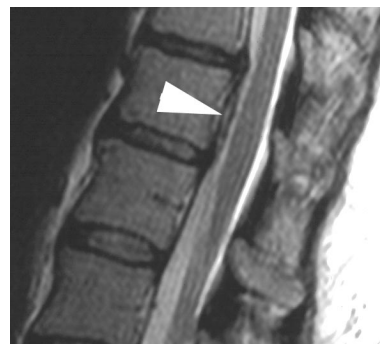


**Fig. 2.** Axial T2-weighted magnetic resonance imaging scan obtained at the time of initial presentation of the presumed granuloma showing a hyperintense mass anterior to the spinal cord, behind the T11 vertebral body (*large arrowhead* overlying the T11 body, pointing toward granuloma). The tip of the intrathecal catheter can be seen as a *small, dark spot* in the center of the lesion. The mass causes significant posterolateral compression and distortion of the thecal sac and spinal cord. *Small arrowheads* indicate the posterolateral margins of the thecal sac.

## Discussion

In most ways, this patient represents a typical granuloma patient. She had been seen frequently in the clinic for refilling of her infusion pump. She did not report significant change in her “regular” complex regional pain syndrome pain during her scheduled follow-up visits, her daily activities remained stable, and her neurologic examination results remained normal except for long-standing allodynia associated with her complex regional pain syndrome. The evaluation that revealed the intrathecal mass was prompted by new subjective changes in physical symptoms that were not accompanied by objective change in physical findings.

At the time the intrathecal mass was identified, the catheter had been present for 55 months; morphine had



**Fig. 3.** Sagittal T2-weighted magnetic resonance imaging scan obtained approximately 4 weeks after replacement of intrathecal analgesic with saline. The mass anterior to the spinal cord has resolved almost completely; only a thin layer of residual tissue remains. The spinal cord is relieved of compression, and only minor distortion of the anterior aspect of the thecal sac remains. The *arrowhead* overlies the T11 vertebral body.



**Fig. 4.** Axial T2-weighted magnetic resonance imaging scan obtained approximately 4 weeks after replacement of intrathecal analgesic with saline. The presumed granuloma is nearly gone (*large arrowhead* overlying T11 vertebral body, pointing at residual granuloma). The tip of the catheter can still be seen as a *small, dark spot* within the residual hyperintense lesion. Resorption of the granuloma is accompanied by almost complete resolution of compression of the thecal sac and spinal cord (posterolateral margins of thecal sac indicated by *small arrowheads*).

been infused for 48 months. This is somewhat longer than the average duration of therapy in patients described in the literature. In a case series of 41 patients, the median duration of therapy at the time of discovery was 24 months (range, 0.5–72 months).<sup>5</sup> Clonidine was the only component of the infusion for the first 7 months of therapy in the current patient. After morphine was added to the infusion, clonidine remained present continuously with the opioid infusion. The morphine was increased to a maximum of 15 mg/day (17.5 mg/ml) and continued for 35 months at this rate. In reviewing other case reports, this rate does not seem unusually large in either dose or concentration.<sup>1,4</sup> Sheep studies have shown the absence of granuloma formation at low morphine concentrations.<sup>3</sup> There is an apparent dose-response curve in dogs with higher doses and concentrations of morphine consistently producing granulomas. However, these studies are of short duration, and it remains unclear whether there is a safe (*i.e.*, non-granuloma-inciting) intrathecal dose of morphine for humans. Fully 30% of granulomas noted in the series of Yaksh *et al.*<sup>2</sup> developed in patients receiving less than 10 mg morphine per day; 40% were using morphine concentrations less than 25 mg/ml. Limiting the infusion concentration and daily dose could potentially delay or prevent granuloma formation. Most patients require an increase in intrathecal dosing over time to maintain pain control.<sup>6</sup> If intrathecal opioids are limited, additional oral medications or the addition of adjunct nonopioid intrathecal agents will likely be required.

In dog studies, combination therapy with morphine and clonidine has been found to prevent granuloma development.<sup>1</sup> The protective effect of clonidine is dose

dependent. At a morphine:clonidine ratio of 6:1 (1.5 mg morphine:250  $\mu$ g clonidine), the incidence of granuloma development was the same as without clonidine. However, at a 3:1 ratio (1.5 mg morphine:500  $\mu$ g clonidine), the incidence of granuloma formation is decreased. In this patient, clonidine was not protective against formation of a mass that is presumed to be an inflammatory granuloma. Clonidine was infused as a single agent before administration of opioid, and clonidine was administered continuously with infusion of opioid. Although the rate of clonidine infusion was variable, it was infused at the rate of 1,114  $\mu$ g/day when the morphine infusion was at the maximum 15 mg/day. There are several possible explanations for the occurrence of a granuloma in this patient despite the prediction, based on animal models, that clonidine may protect against granuloma formation. The absolute dose of clonidine given to this patient was higher than that used in the dog studies, but the cerebrospinal fluid volume and flow in humans may be sufficiently different to require a much higher dose to be “protective.” The morphine:clonidine ratio in our patient was 13.5:1 (15 mg morphine:1,114  $\mu$ g clonidine). To achieve the same “protective” 3:1 ratio noted in the canine studies and to continue a 15-mg/day morphine infusion, a 448% increase (5,000  $\mu$ g) in the clonidine component would have been necessary. In absolute terms, this is far in excess of what is commonly used in clinical practice. It is possible that clonidine partially mitigated the granuloma-inciting effects of the opioid, given the fact that the patient’s granuloma was discovered after 48 months of opioid therapy, double the median duration of therapy at the time of discovery described in other case reports. In this case, the granuloma was not examined histologically. Clonidine may have affected the composition of the granuloma by alteration of inflammatory mediators or prevention of fibrosis. Additional studies are necessary to determine whether clonidine inhibits the formation of intrathecal opioid-induced granulomas and whether it might be a useful adjunct in intrathecal opioid therapy.

We elected, in consultation with the patient, to treat this mass nonsurgically. Our rationale for conservative management was based on the absence of frank neurologic deficit, the ventral location of the granuloma in the spinal canal (rendering surgical resection somewhat risky), the patient’s understanding of the situation and willingness to report any worsening of symptoms (with immediate return for follow-up evaluation, if necessary), and her reliability in monitoring her status and reporting changes to us. The granuloma was treated by ceasing intrathecal analgesic infusion, and within 6 weeks, the mass had resolved, with no residual sequelae. Surgical resection would have been undertaken if this patient had manifested clear-cut neurologic deficit, if symptoms had progressed despite cessation of intrathecal drug therapy, if radiographic improvement of the lesion did not occur



after cessation of intrathecal drug therapy, or if we believed she would be unreliable or unable to report worsening of symptoms. Our patient's good outcome should not be taken as approval for nonsurgical treatment of all granulomas. Neurologic deficit can develop and progress rapidly. Any patient with progressive neurologic symptoms or signs should be evaluated urgently or emergently for surgical treatment of the mass lesion.

Recommendations for detection, evaluation, and management of intrathecal opioid-induced granulomas have been published in a consensus statement.<sup>7</sup> This case supports the recommendations of the consensus panel, underscoring the need for a low threshold for evaluation and intervention in patients receiving intrathecal drug therapy with opioids who are suspected of harboring an intrathecal granuloma. It also highlights the importance of obtaining an interval history and examining the patient at the time of each pump refill, with special attention paid to eliciting symptoms of new pain, change in "usual" pain, or change in neurologic function. In addition,

this case report demonstrates that the addition of clonidine to an intrathecal infusion of morphine does not obviate the need for clinical vigilance in regard to catheter tip inflammatory masses.

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## Diaphragmatic Paralysis after Endovascular Stent Grafting of a Thoracoabdominal Aortic Aneurysm

Harish S. Lecamwasam, M.D.,\* Dean Hess, R.R.T., Ph.D.,† Robert Brown, M.D.,‡ Christopher J. Kwolek, M.D.,§ Luca M. Bigatello, M.D.¶

OPEN repair of thoracoabdominal aortic aneurysms (TAAs) is associated with significant respiratory morbidity. Predisposing factors include older age, preexisting lung disease, duration of aortic cross clamping, and the development of diaphragmatic dysfunction.<sup>1-3</sup> Endovascular Stent graft implantation has been advocated as an alternative treatment of TAAs in high-risk patients.<sup>4</sup> We describe a patient in whom diaphragmatic paralysis and ventilator dependence developed after endovascular Stent grafting of a TAA. We discuss the possible pathogenesis of this finding and its implications on our

understanding of diaphragmatic dysfunction after surgical TAA repair.

## Case Report

A 71-yr-old woman with history of cigarette smoking, hypertension, and hypercholesterolemia was admitted to our hospital with the diagnosis of a small, contained rupture of a TAA. She had recently undergone endovascular Stent grafting of an infrarenal aortic aneurysm at another institution and wished to have her TAA also repaired through an endovascular approach. After approval by our institutional review board (Massachusetts General Hospital, Boston, Massachusetts) for compassionate release of a thoracic Medtronic AVE (Santa Rosa, CA) aortic Stent graft system, she underwent endovascular TAA repair during general anesthesia. Five Stent graft components were positioned through the right femoral artery to extend from 4-5 cm distal to the left subclavian artery to the suprarenal abdominal aorta. A completion aortogram revealed no endovascular leaks and satisfactory blood flow to the celiac, superior mesenteric, and renal arteries.

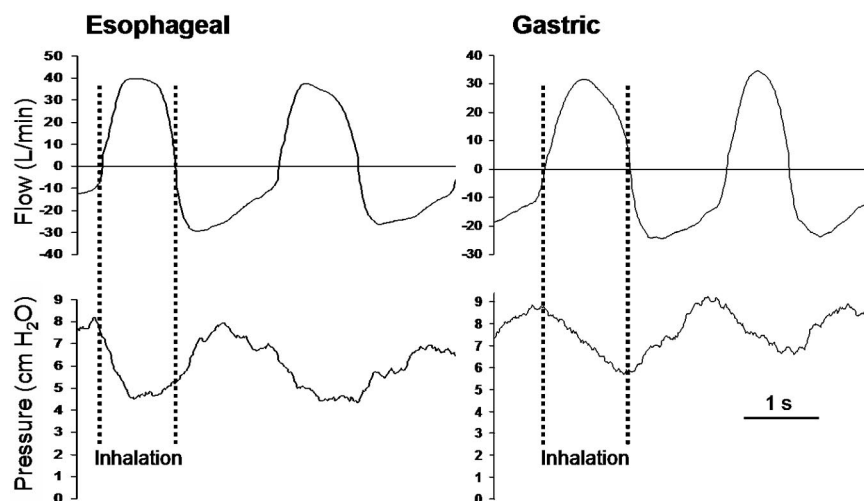
The postoperative course was complicated by atrial fibrillation, renal failure necessitating hemodialysis, nosocomial pneumonia, and respiratory failure necessitating prolonged mechanical ventilation and a tracheostomy. After approximately 4 weeks, the patient's pneumonia resolved, and she was tolerating pressure support ventilation. However, her tidal volumes seldom exceeded 250-300 ml with a pressure support of 12-14 cm H<sub>2</sub>O, and she persistently had dyspnea. Her maximum inspiratory pressure was -30 cm H<sub>2</sub>O. On physical examination, she used the accessory muscles of breathing. On discontinuation of ventilatory support, inward retraction of the abdomen during

\* Instructor in Anesthesia, Harvard Medical School; Department of Anesthesia and Critical Care, Massachusetts General Hospital. † Assistant Professor of Anesthesia, Harvard Medical School; Respiratory Care Services, Massachusetts General Hospital. ‡ Associate Professor of Medicine, Harvard Medical School; Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital. § Assistant Professor of Surgery, Harvard Medical School; Division of Vascular and Endovascular Surgery, Massachusetts General Hospital. ¶ Associate Professor of Anesthesia, Harvard Medical School, Department of Anesthesia and Critical Care, Massachusetts General Hospital.

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Address reprint requests to Dr. Bigatello: Department of Anesthesia and Critical Care, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114. Address electronic mail to: lbigatello@partners.org. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

**Fig. 1.** Esophageal (*left*) and gastric (*right*) pressures. Positive flow represents inhalation, and negative flow represents exhalation. Both esophageal and gastric pressure decrease during inhalation, consistent with diaphragmatic paralysis.



inspiration developed immediately, suggestive of diaphragmatic paralysis. Electromyography and nerve conduction studies excluded a sensorimotor polyneuropathy, neuromuscular junction dysfunction, and a spinal cord lesion.

To confirm our clinical diagnosis of diaphragmatic paralysis, we placed two balloon-tipped catheters (SmartCath<sup>®</sup> Esophageal Catheter; VIASYS Healthcare, Palm Springs, CA) during local anesthesia from the nose into the esophagus and stomach to evaluate changes in intrathoracic and intraabdominal pressure during unsupported breathing.<sup>5</sup> A pneumotachometer (Novamatrix Medical Systems, Wallingford, CT) was attached to the tracheostomy tube. Flow and pressures signals were recorded with a VenTrak Respiratory Mechanics Monitoring System (Novamatrix Medical Systems) using waveform acquisition software (Analysis-Plus; Novamatrix Medical Systems). As shown in figure 1, during unsupported breathing, both esophageal and gastric pressures had a negative deflection during inspiration, a finding suggestive of diaphragmatic paralysis.<sup>6–8</sup>

Because of the patient's wish to avoid prolonged respiratory and renal support, mechanical ventilation and hemodialysis were eventually withdrawn, and she died on the 53rd postoperative day. A post-mortem examination was denied by the family.

## Discussion

Diaphragmatic dysfunction after open TAA repair has been generally attributed to the surgical dissection of the diaphragm. A "diaphragmatic-sparing" technique has been developed in an attempt to limit damage to the diaphragm by preserving its central tendinous portion.<sup>9</sup> However, even its use has not decreased the long-term pulmonary morbidity after open TAA repair, which remains between 20 and 40%.<sup>2,3</sup> Our report is important because it describes the occurrence of diaphragmatic paralysis after endovascular Stent grafting of a TAA in the absence of any surgical manipulation of the lung or chest wall.

With endovascular Stent grafting, avoidance of the lung and chest wall trauma associated with an open approach should minimize perioperative respiratory morbidity. However, acute respiratory failure still occurs in 5–14% of patients undergoing this procedure, and its etiology is unclear.<sup>4,10</sup>

Based on our current report, we postulate that acute

respiratory failure after endovascular Stent grafting of a TAA may result from compromised perfusion to the diaphragm. The blood supply to the diaphragm derives from branches of the internal mammary arteries, the lower thoracic aorta, and the upper abdominal aorta or celiac trunk.<sup>11</sup> A decreased blood supply from one or more of these sources may significantly compromise diaphragmatic function, as has been reported after harvesting of bilateral internal mammary arteries for coronary bypass surgery.<sup>12</sup> In the current patient, the extent of Stent grafting could have occluded the phrenic arteries originating from the thoracic or upper abdominal aorta or both. It is also possible that the blood supply to the phrenic nerves was compromised; however, such large nerves are well vascularized by their vasa vasorum and should be less susceptible to selective ischemic damage.

Phrenic nerve injury has also been described as a complication of central venous cannulation. The current patient had both internal jugular veins cannulated at different times. However, we do not believe that either cannulation caused her complication because (1) she never showed signs of phrenic nerve paralysis such as acute dyspnea or elevation of a hemidiaphragm immediately after central line placement; (2) nearly all cases reported in the literature occurred after traumatic placements, whereas our placements were uneventful; and (3) the current patient had unequivocal evidence of bilateral diaphragmatic paralysis (see below), and it is unlikely that she sustained two separate occurrences of phrenic nerve paralysis after line placement.<sup>13</sup>

The possibility of ischemic injury to the diaphragm after TAA repair is significant not only as an unexpected complication of endovascular Stent grafting, but also because it would have implications regarding open repair. Similar to ischemic injuries to the spinal cord, ischemic injury to the diaphragm could occur during prolonged thoracic aortic cross clamping, independent of the technique used to dissect the diaphragm. This

possibility is supported by the finding of Engle *et al.*<sup>2</sup> that the diaphragmatic-sparing technique does not decrease the long-term rate of reintubation, tracheostomy, and prolonged mechanical ventilation after open TAA repair.

Diaphragmatic paralysis is a clinical diagnosis based predominantly on an accurate physical examination. In a spontaneously breathing patient with a patent airway, diaphragmatic paralysis produces a paradoxical inward retraction of the abdomen during inspiration. This phenomenon must be distinguished from similarly dyssynchronous breathing patterns that can be seen with upper airway obstruction and with the active contraction of the expiratory muscles at end-exhalation that can occur during respiratory distress of various causes.<sup>14</sup> Although a careful physical examination, including palpation of the abdomen to detect contraction of the oblique muscles, should suggest the correct diagnosis, measurement of the gastric pressure, as we report here, is useful in the diagnosis of diaphragmatic paralysis by demonstrating the occurrence of a negative deflection of the gastric pressure during inhalation.

Confirmation of diaphragmatic paralysis can be attempted using direct fluoroscopy, electromyography, measurement of the transdiaphragmatic pressure, or measurement of the individual intrathoracic and intraabdominal pressures. We chose intrathoracic and intraabdominal pressure measurement because it is simple, has been clinically validated,<sup>7,8</sup> and can be used in patients who are able to maintain spontaneous breathing only for a short time.

In summary, we have described a patient in whom ventilator dependence developed with diaphragmatic paralysis after endovascular Stent grafting of a TAA. We postulate that this complication resulted from ischemic injury to the diaphragm at the time of Stent graft place-

ment. This case report is clinically significant because (1) it describes a risk factor for respiratory failure and ventilator dependence after endovascular Stent grafting of a TAA, and (2) it proposes a mechanism of diaphragmatic dysfunction (vascular compromise) that may pertain to both endovascular and open TAA repair.

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