

# Paroxysmal Apnea and Vasomotor Instability Following Medullary Infarction

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**Background:** Central hypoventilation and paroxysmal hypertension are uncommon complications of medullary infarction. To our knowledge, the combination of these autonomic complications of medullary stroke has not previously been reported.

**Objective:** To describe a patient who experienced life-threatening paroxysmal attacks of central apnea and vasomotor instability 3 months after medullary infarction, a combination of symptoms that is unusual.

**Patient, Methods, and Results:** Following a right lateral medullary infarction, an otherwise stable 70-year-old woman developed recurrent episodes of apnea ( $PCO_2$ ,  $>100$  mm Hg), blood pressure instability (systolic blood

pressure,  $>200$  to  $<100$  mm Hg), and mental status changes (from agitation to coma) within hours of removal from mechanical ventilation. These attacks occurred repeatedly after removal from mechanical ventilation and were prevented by diaphragm pacing with a phrenic nerve pacemaker and nocturnal mechanical ventilation via a tracheostomy.

**Conclusions:** A syndrome of life-threatening central hypoventilation and vasomotor instability can occur after medullary infarction. Placement of a phrenic nerve pacemaker can prevent these complications, without the functional limitations imposed by continuous mechanical ventilation.

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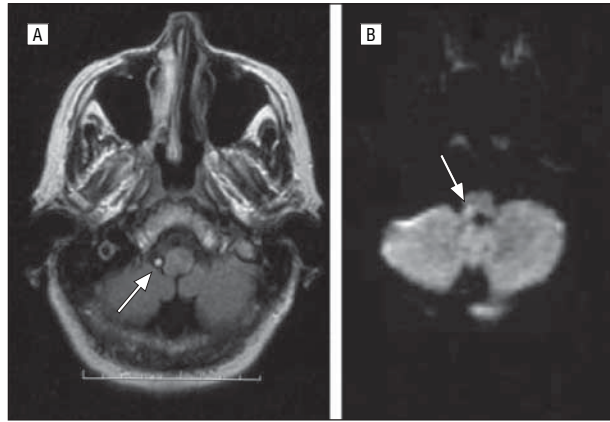
**O**NDINE CURSE, FIRST DESCRIBED in 1962, refers to the syndrome of sleep apnea with preserved voluntary control of respiration.<sup>1</sup> Although it can result from injury to the brain in different locations, it occurs most commonly following infarction of the medulla.<sup>2,3</sup> Medullary infarction can also induce combined loss of automatic and voluntary respiration,<sup>4,5</sup> as well as loss of voluntary respiratory control with preserved automaticity.<sup>6,7</sup> Stroke is not the only cause of such syndromes; central hypoventilation also has been reported following damage to the medulla from poliomyelitis, neoplasm, multiple sclerosis, syringobulbia, trauma, and other causes.<sup>3,8,9</sup> The medulla also contains vasomotor centers that control resting peripheral vascular tone and blood pressure, and syndromes of paroxysmal neurogenic hypertension after medullary infarction have been described.<sup>10,11</sup> In this report, we describe a patient who experienced life-threatening paroxysmal attacks of central apnea and vasomotor instability 3 months after medullary infarction, a combination of symptoms that is unusual. These attacks were successfully eliminated with placement of a phrenic nerve pacemaker.

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## REPORT OF A CASE

A 70-year-old right-handed woman with a history of thyroidectomy, mastectomy, hysterectomy, depression, and action tremor presented with the acute onset of headache and nausea. Examination revealed a right partial Horner syndrome (ptosis and miosis), right palatal paresis, right hemiataxia, and right face and left body sensory loss to pain and temperature. Magnetic resonance imaging revealed a small right lateral medullary infarction (**Figure 1**), and magnetic resonance angiography demonstrated nonvisualization of the distal intracranial right vertebral artery, presumably from atherothrombotic occlusion. Results of an echocardiogram and electrocardiogram were normal, and she was treated with aspirin. She required a prolonged course of mechanical ventilation for pneumonia, and a tracheostomy and percutaneous gastrostomy tube were placed. After she was weaned from mechanical ventilation, she was discharged to a short-term rehabilitation facility.

Three months after her stroke, she was hospitalized for repeated paroxysmal episodes of apnea, coma, and hypertension followed by hypotension. All of these episodes resolved with the reinstatement of mechanical ventilation. After 4

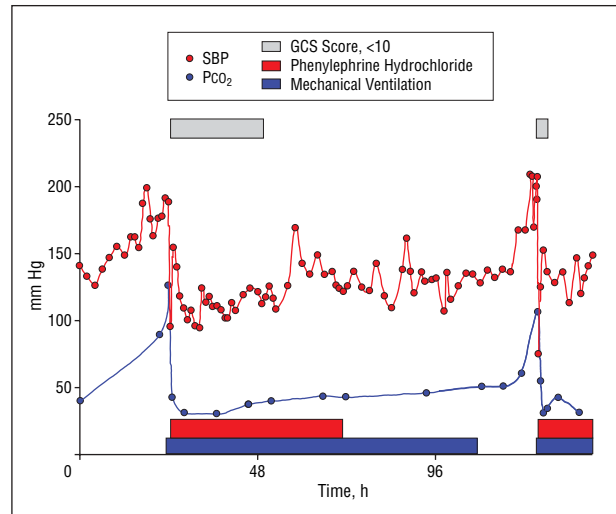


**Figure 1.** Magnetic resonance imaging findings, with arrows indicating high signals. A, T1-weighted image demonstrating thrombotic occlusion (high signal) of the right vertebral artery. B, Diffusion-weighted image revealing a small right lateral medullary infarction (high signal).

episodes occurred during 4 weeks, she was transferred to the neurological intensive care unit of Columbia University Medical Center, New York, with a working diagnosis of “brainstem seizures.”

On admission, she was mechanically ventilated with synchronized intermittent mandatory ventilation at a rate of 10 breaths per minute via a tracheostomy. Her mental status was normal, she was afebrile, and her vital signs were stable. Physical examination revealed mild diffuse muscle wasting, and neurological examination showed resolving deficits consistent with her original stroke syndrome. On the second day of her intensive care unit stay, she was disconnected from the ventilator after demonstrating the ability to breath spontaneously for 12 hours on continuous positive airway pressure with pressure support of 5 cm H<sub>2</sub>O. At baseline, her mental status was normal and she was breathing independently by means of a tracheostomy collar with 40% inspired oxygen, with a pH of 7.51, PCO<sub>2</sub> of 40 mm Hg, and PO<sub>2</sub> of 109 mm Hg. After 24 hours, during a period of quiet rest, her respiratory rate fell from 16 to 4 breaths per minute. She became agitated, tremulous, and confused, in conjunction with an increase in her blood pressure from 140/72 mm Hg at baseline to 200/101 mm Hg at the onset of this change in mental status. She then abruptly deteriorated from lethargy to coma with apnea, and after a period of fluctuation and instability, her blood pressure plummeted to 95/46 mm Hg, requiring treatment with phenylephrine hydrochloride (**Figure 2**). Before the reinstatement of mechanical ventilation, measurement of arterial blood gas levels revealed a pH of 7.10, PCO<sub>2</sub> of 126 mm Hg, and PO<sub>2</sub> of 150 mm Hg on 50% inspired oxygen through a tracheostomy collar. Her blood gas levels, blood pressure, and mental status normalized during the next several hours after the reinstatement of mechanical ventilation. Thereafter, she remained alert and conversant, with a stable PCO<sub>2</sub> and blood pressure as long as she was mechanically ventilated.

After 2 subsequent trials of disconnection from the ventilator, an identical sequence of events occurred 14 and 7 hours after being removed from mechanical ventilation (Figure 2). Continuous electroencephalographic monitoring during these events showed no epileptiform activity, and treatment with phenytoin had no effect.



**Figure 2.** Systolic blood pressure (SBP) and PCO<sub>2</sub> during the first and second trials of removal from mechanical ventilation in the neurological intensive care unit. The first episode occurred 24 hours and the second episode 14 hours after removal from mechanical ventilation. In each instance, hypertension (SBP, >200 mm Hg) and respiratory acidosis (PCO<sub>2</sub>, >100 mm Hg) occurred in parallel, before the onset of coma (Glasgow Coma Scale [GCS] score, <10) and acute hypotension (SBP, <100 mm Hg).

Evaluations for sepsis, pheochromocytoma, and hyperthyroidism were also negative.

The patient was maintained on synchronized intermittent mandatory ventilation for the following 4 weeks until a phrenic nerve pacemaker (Dobelle Institute, New York) was placed. After implantation, she was more comfortable and was able to move from the bed to a chair, ambulate with assistance, and engage in physical therapy. The episodes of apnea and the autonomic instability did not recur, and she was discharged to home. The tracheostomy was left in place to allow nocturnal mechanical ventilation with the phrenic nerve pacemaker shut off, which she stated was more comfortable. By day, she was able to speak with a Passy-Muir valve off the ventilator. She died in her sleep 11 months after her stroke, presumably from a cardiac arrhythmia or myocardial infarction. A request for autopsy was refused.

#### COMMENT

Our patient developed recurrent episodes of central apnea, coma, and blood pressure instability that were consistently provoked by removal from mechanical ventilation 3 months after a left lateral medullary infarction. These attacks were successfully prevented by placement of a phrenic nerve pacemaker, which allowed for liberation from mechanical ventilation and improved functional independence.

The original use of the term *Ondine curse* related to 3 patients who developed symptoms following surgery in the brainstem or high cervical spinal cord.<sup>1</sup> The neuroanatomical pathways that control respiration likely originate in the pons and medulla, with descending connections into the upper segments of the cervical spinal cord. The 2 main collections of neurons that regulate respiration in the medulla are the dorsal respiratory group near the solitary tract and the ventral respiratory group near

the nucleus ambiguus.<sup>9</sup> There is also a collection of neurons in the dorsal pons that participate in the control of automatic respirations.<sup>12</sup> All 3 groups of neurons are paired bilaterally. Originally, it was thought that bilateral damage was necessary to induce central hypoventilation, because each side was believed to have the ability to independently drive diaphragmatic activity. However, autopsy-proved unilateral ischemic infarction of the lateral medullary tegmentum demonstrated unequivocally that unilateral damage can cause the syndrome.<sup>2</sup> In such cases, damage to crossing fibers connecting the paired medullary nuclei has been proposed as an explanation.<sup>12</sup>

In our patient, a remarkably small dorsolateral infarct (Figure 1) resulted in a delayed syndrome of central hypoventilation and apnea, with gradual diminution of automatic and voluntary respiration during quiet rest followed by apnea. The infarct presumably damaged the ventral respiratory group, which has been implicated in maintaining automatic respiratory drive. The pre-Bötzinger region of the ventral respiratory group has been hypothesized to be the source of intrinsic pacemaker activity that drives respiration; lesions of this region in adult anesthetized animals result in apnea.<sup>13</sup> In our patient, the delayed development of the syndrome after several months is unusual and implicates some form of secondary neuronal degeneration, or an abnormality of local synaptic interconnections related to plasticity and remodeling, in the pathogenesis of her disorder.

Tonic and reflex activity of medullary neurons that mediate sympathetic and parasympathetic cardiovascular reflexes is affected by respiration, and these vasomotor centers are located in close proximity to the ventral respiratory group and dorsal respiratory group. Instability of blood pressure and heart rate has been reported after lateral medullary infarction in association with central hypoventilation, but in that case bradycardia and hypotension resulted.<sup>14</sup> Others have reported episodic hypertension and tachycardia following damage to the solitary nucleus and the intermediate reticular zone in the lateral medulla, areas that receive chemoreceptor and baroreceptor synaptic inputs from the glossopharyngeal and vagus nerves.<sup>10</sup> Similarly, animal studies<sup>13,15</sup> have demonstrated that damage to these structures can result in abnormally large changes in blood pressure in response to various stimuli. Sympathoexcitatory neurons of the rostroventrolateral medulla are known to contain neurons that primarily respond to changes in pH and PCO<sub>2</sub> in the cerebrospinal fluid. In our patient, it seems plausible that central hypoventilation and respiratory acidosis triggered an exaggerated reflex sympathetic surge as a result of damage to modulatory inputs, followed by hypotension resulting from vasomotor instability and worsening acidosis.

As long as our patient was maintained on mechanical ventilation in the hospital, preventing the initial respiratory acidosis, her mental status, blood pressure, and heart rate remained normal. We excluded other causes of transient autonomic dysfunction, including seizures, pheochromocytoma, thyroid storm, and sepsis. We did not perform a follow-up magnetic resonance scan at the time of her readmission and, hence, cannot formally rule out the possibility that she experienced a recurrent brainstem infarct. In the absence of any new focal neu-

rological signs, however, we believe that this possibility was unlikely. Similarly, the strict temporal relationship between her symptoms and removal from mechanical ventilation makes recurrent transient ischemic attacks as the proximate cause of her paroxysmal symptoms unlikely.

The patient was referred for implantation of a phrenic nerve pacemaker to provide ventilatory support for intermittent apnea and to prevent the associated episodes of life-threatening autonomic instability. Diaphragmatic pacing has been used successfully for Ondine's curse from various causes, including trauma, poliomyelitis, and stroke.<sup>16</sup> In our patient, the technology provided her with a degree of independence and quality of life that would have been impossible with continued mechanical ventilation, and it successfully prevented the episodic autonomic instability. Placement of a phrenic nerve pacemaker can prevent these complications, without the functional limitations imposed by continuous mechanical ventilation.

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