The Neuromuscular Respiratory System: Physiology, Pathophysiology, and a Respiratory Care Approach to Patients

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The neurorespiratory system includes the central nervous system control centers and feedback mechanisms, spinal cord, motor nerves, and the respiratory muscles that affect chest-wall and lung movement, causing air to enter the lungs and carbon dioxide to be excreted into the environment. Without this "vital pump" the body is unable to function, which explains why a major cause of morbidity and mortality in those with neuromuscular disease is respiratory failure. This paper reviews the anatomy and physiologic function of the neurorespiratory system, details some of the more important diseases seen in clinical practice, and proposes a practical "respiratory approach" to individuals with neuromuscular disease. *Key words: neuromuscular disease, respiratory failure, control of breathing, diaphragm, noninvasive ventilation, spinal-cord injury, muscular dystrophy*. [Respir Care 2006;51(8):829–837. © 2006 Daedalus Enterprises]

Introduction: Historical Overview

The first understanding of the mechanical function of the respiratory system began with Galen (131–201 AD), a Greek physician, who realized that the lungs filled the chest cavity and were moved by the actions of the thorax.[1] He cut the phrenic and intercostal nerves in animals and described the effects of these interventions on breathing.[2] He also hypothesized that air passing upward from the lungs causes the vocal cords to move and sound to occur. In addition, he noted that gladiators or animals injured below the neck continued to breathe, whereas those injured high in the neck immediately ceased breathing movement, thus beginning our understanding of the localization of the central nervous system centers that control breathing.[3] Further elucidation of the neuro-mechanical respiratory system awaited the beginning of the Renaissance, when dissections of the human body (banned during the middle ages) began in Padua, Italy.[4] Vesalius was the first to draw the phrenic nerves[2] and daVinci drew the human diaphragm and spinal nerves.[5] In the 1600s, Mayow, an Oxford physiologist, built a model of the chest as bellows, with the lungs contained as a bladder inside.[6] He postu-

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lated that a negative intrathoracic pressure caused by contraction of the diaphragm and chest muscles led to air being drawn into the lungs through the upper airway. In the mid-1800s, Donders differentiated between the expansile properties of the inspiratory muscles and the elastic properties of the lungs and chest.[7] Wirz and von Neergard measured pleural pressure to determine the elastic recoil of the lung and chest wall in normal humans, and this led to the a scientific evaluation of the mechanical respiratory system.[7]

The central-nervous-system control of the respiratory system was first described by Whytt, a neurologist, who observed an unconscious reflex breathing action.[2] He noted that, although basically an unconscious action, breathing was also subject to willful control. He described diseases with periodic apnea. In 1760, Lorry described the persistence of breathing movements in the rabbit after the cerebrum and cerebellum were removed, and postulated that the rhythmic breathing was directed by areas in the brainstem.[8] Further localization of the brainstem breathing centers were described, with localization of both inspiratory and expiratory centers.[4] In 1887, Frenchman François-Franck described the finding of cortical control of respiration when he stimulated changes in breathing by stimulating the cortex of experimental animals.[9]

Descriptions of the reflex control of breathing began in the late 1800s.[4] Herring and Breuer described mechanoreceptors in 1868, when they made the discovery that inflation of the lungs stopped inspiration and promoted expiration during the breathing cycle; conversely, they noted that lung deflation stimulated inspiration and suppressed expiration. Miescher-Ruesch first describe chemical stimulation of the respiratory centers by carbon dioxide in humans, and, in 1905, Haldane, Priestly, and Douglas further clarified the role of CO_2 in the control of breathing. Jacobs played a key role in unifying the understanding of the chemical control of breathing by CO_2 and O_2 in both the central and the more recently described peripheral chemoreceptors.[10] More recent work on control of respiration has further clarified the locations of the centers of respiratory control and evaluated function on a cellular level. However, a good deal about the intricacies of the system remains incompletely understood.

Functional Anatomy of the Neurorespiratory System

The ventilatory system is designed to bring oxygen into the body, to fuel energy-generation and remove carbon dioxide, which is a waste product of cellular metabolism. The system can flexibly respond to the variable metabolic demands that result from the activities of living. The system is made up of the cortex of the brain, which controls voluntary breathing; the brainstem, which is involved with automatic breathing; the spinal cord and motor neurons, which transmit nerve impulses; the respiratory muscles, which are the effectors of the system; and a complex system of feedback receptors and nerves that regulate ventilation precisely (Fig. 1). The following is a discussion of each of the components of this complex network.

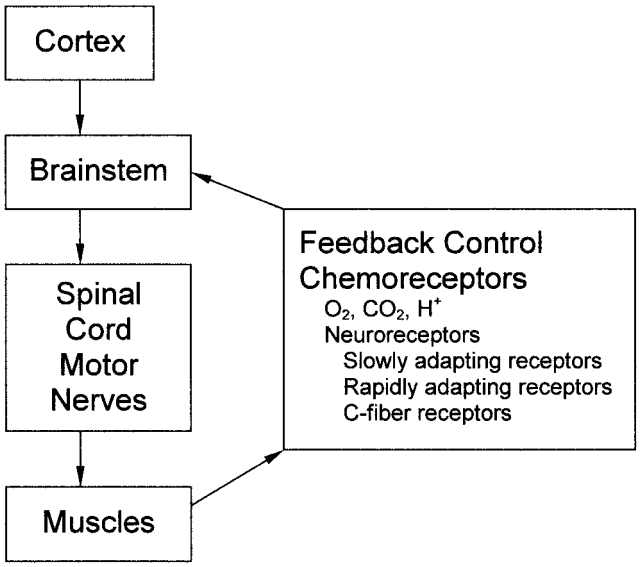

Fig. 1. Schematic of the neurorespiratory system.

Central Nervous System

Voluntary-Breathing Controllers. The signals for voluntary breathing originate in the cerebral cortex. There are centers within the parietal cortex that send the signals for inspiration and expiration to occur (Fig. 2).[11] These cortical areas project to the motor neurons in the spinal cord via the corticospinal tracts. These tracts are separate pathways from those that connect the central automatic-breathing centers to the motor neurons (reticulospinal pathways), although there are probably interconnections between the 2 pathways that are at this time poorly understood. Diseases have been described that can affect one or the other of the pathways, and these are described below.

Automatic-Breathing Controllers. Automatic breathing is controlled by a complex system that includes respiratory centers in the pons and medulla, nerve tracts in the lower brainstem, and the feedback mechanisms that are both chemical and mechanical in nature. There are thought to be 3 centers that generate the rhythm and drive to breathe: one located in the pons and two in the medulla (Fig. 3). The pontine respiratory group (also known as the pneumotaxic center) lies in the dorsal lateral pons and contains both inspiratory and expiratory neurons.[12] It is not essential for respiratory-impulse generation but appears to allow fine control of the respiratory pattern.[4] The medullary con-

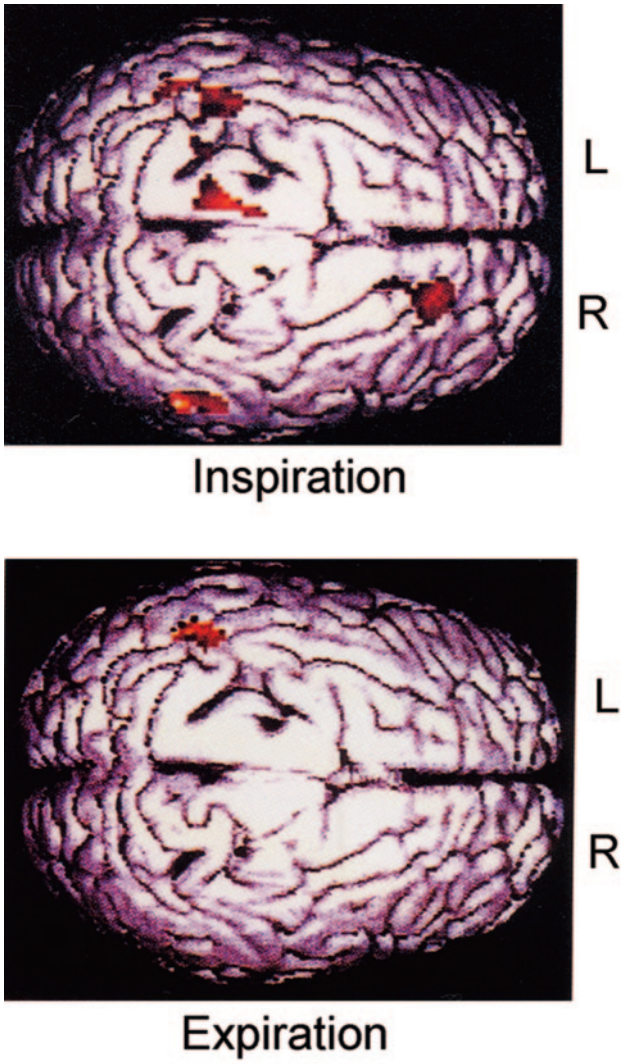

Fig. 2. Functional magnetic resonance imaging in a human, during a breathing maneuver. View is from above, with the frontal lobes on the right and the occipital lobes on the left. The colored areas are active during the specified activity. (From Reference 11, with permission.)

trollers fall into 2 main groups, on either side of the central neuro-axis, that are known as the ventral respiratory group and the dorsal respiratory group.[13] The ventral respiratory group has the neurons that generate the respiratory rhythm.[14] The centers that are thought to be the major sites of respiratory-rhythm generation are the Botzinger complex and the pre-Botzinger complex.[15] Rhythmic neuron firing in these regions acts much like a "pacemaker" for the respiratory system. The genesis of the rhythmic firing of the neurons is thought to result from either an intrinsic "pacemaker" capability of cells within the pre-Botzinger complex[16] or the interaction of neurons within several of the respiratory centers.[17]

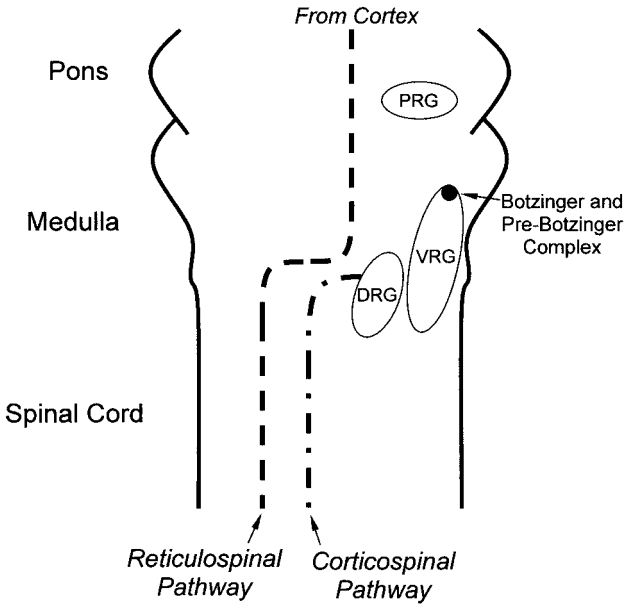

Fig. 3. Schematic of the brainstem and upper spinal cord, showing the centers that control automatic breathing and nerve pathways. PRG = pontine respiratory group. VRG = ventral respiratory group. DRG = dorsal respiratory group. For simplicity, the figure shows structures on only one side of the brainstem. Symmetrical structures are present in the contralateral brainstem.

Spinal Cord. The spinal cord and the motor nerves conduct the nerve impulses from the cortex and brainstem to the anterior horn cells of the motor neurons that supply the respiratory muscles. As noted above, the nerve-fiber tracts in the spinal cord responsible for voluntary (corticospinal tract) and automatic (reticulospinal tract) breathing are separate within the spinal cord.[18,19] The fibers in these tracts project to the lower portion of the spinal cord, where they synapse with the lower motor neurons.

Peripheral Nervous System

Lower Motor Neurons. The lower motor neuron has its cell body in the spinal cord (anterior horn cell) but exits the spinal cord to become the spinal nerve roots and the nerves that supply the respiratory muscles. When the nerves arrive at the muscle, they divide into branches (known as "twigs"), which, upon reaching the muscle fiber, further divide into bulbous projections called "boutons" that apply themselves to the muscle membrane at specialized anatomical junctions called the motor endplates. These boutons contain the acetylcholine that is the chemical transmitter that excites the muscle to contract. With nerve firing, there is release of acetylcholine at the motor endplate into the cleft between the nerve and muscle. The acetylcholine binds to receptors on the muscle side of the motor endplate, which results in a "suprathreshold excitatory endplate potential," depolarization of the muscle membrane,

and a muscle action potential that results in contraction of the muscle fiber.[20]

Respiratory Muscles. The respiratory muscles are the mechanical effectors of the breathing system. The respiratory muscles are often divided into 3 major groups: the inspiratory muscles, the expiratory muscles, and the accessory muscles of respiration. The muscles of the upper airway that maintain patency during the respiratory cycle are often also considered muscles of respiration.

The diaphragm is the major muscle of inspiration; it contributes approximately 70% to inspiratory tidal volume in the normal individual.[21] The innervation of the diaphragm is via the phrenic nerve, which originates from cervical nerve roots 3 through 5. The intercostal muscles are thin sheets of muscular fibers that run between the ribs, in the costal spaces.[22] There are 2 sheets of muscle fibers: the external and internal intercostals. The external intercostals expand the rib cage during inspiration. The internal intercostals are deeper and have an important role during expiration. Innervation of the intercostals is via the intercostal nerves, which originate from the thoracic spinal nerve roots.

The abdominal muscles (rectus abdominus, internal oblique, external oblique, and tranversus abdominus) serve a number of inspiratory and expiratory functions. The internal and external obliques and the transversus abdominus result in an inward movement of the abdominal wall, which displaces the diaphragm into the thoracic cavity and assists exhalation. The rectus abdominus, as well as the internal and external obliques, result in downward movement of the lower rib cage, an increase in pleural pressure, and exhalation. The abdominal muscles may also play a minor role in inspiration.[22] Below function residual capacity, abdominal-muscle contraction stores elastic recoil energy in the chest wall, which assists during the next inspiration.

The accessory muscles of respiration (sternocleidomastoid, scalenes, trapezii, latissimus dorsi, pectoralis major and minor muscles, and platysma) may assist inspiration during situations of ventilatory demand, such as during exercise in a normal person, or in disease states in which other inspiratory muscles are impaired, such as quadriplegia and chronic obstructive pulmonary disease. These muscles expand the rib cage during inspiration, and it is now clear that some of them function during minimal exertion and even at rest.[23]

The muscles of the upper airway are also considered muscles of respiration, because they maintain patency of the upper airway during respiration and allow air to flow into and out of the lungs without interruption.[24] These muscles include the abductors of the vocal cords, the palatal elevators, retractors of the tongue, and dilators of the nares. These muscles are innervated by cranial nerves V, VII, IX, X, XI, and XII, and many of the central control centers are the same as those described above for the more commonly considered ventilatory muscles.

Feedback Control. The respiratory control mechanisms depend on both chemical and neural receptors found in peripheral and central sites. An excellent discussion of this topic is available.[25] The automatic respiratory centers in the brainstem described above respond to inputs from the feedback receptors and adjust neural output to the muscles that control ventilation and upper-airway patency.

Neural receptors fall into a number of different classes and are present in the upper airway, respiratory muscles, lungs, and pulmonary vessels (Fig. 4A).[25] Activation of these receptors signals the central respiratory centers via the vagus nerve. The respiratory centers then adjust respiratory drive and output to the respiratory muscles to affect ventilation and reflexes such as cough and sneeze. The neural receptors include muscle spindles and slowly adapting pulmonary stretch receptors, which predominantly respond to changes in lung and thoracic-cage volume. These are the receptors involved in the Hering-Breuer reflex, in which inspiration is halted as higher lung volume is approached; the stretching of muscle and chest-wall receptors feed back negatively to inspiratory centers in the medulla. Rapidly acting irritant receptors respond to changes in lung volume and react to chemical stimuli such as histamines, noxious stimuli, and prostaglandins. C-fiber endings in the airways and lung are stimulated by chemical stimuli in the local environment. These neural receptors are probably the ones that mediate the hyperventilation and hypocapnia that occur despite administration of oxygen in various pulmonary disorders, such as asthma, pulmonary embolism, pneumonia, and pulmonary edema.[4]

Chemoreceptors are found peripherally and in the central nervous system (see Fig. 4B).[25] The peripheral chemoreceptors include the carotid and aortic bodies. These receptors are the primary sites for sensing of the P_{aO_2}, but they also respond to a lesser extent to P_{aCO_2} and pH. They increase their neural firing in response to P_{aO_2} (when it falls below 75 mm Hg) and to increasing P_{aCO_2} and decreasing pH. The aortic chemoreceptors are more important in infancy, whereas the carotid receptors are key in adults.[26] Once stimulated, the impulses from the carotid bodies travel through the 9th cranial nerve to the nucleus tractus solitarius, where neurotransmitters are released that increase ventilation.[27] There may be other peripheral receptors that are as yet unidentified, as the carotid bodies do not mediate the hyperventilation seen in exercise.[28]

Central-nervous-system chemoreceptors are crucial in the adjustments of ventilation to acid-base disturbances. There are 4 groups of chemosensitive neurons in the brainstem: the locus ceruleus, the nucleus tractus solitarius, the midline raphe, and ventrolateral quadrant of the medulla.

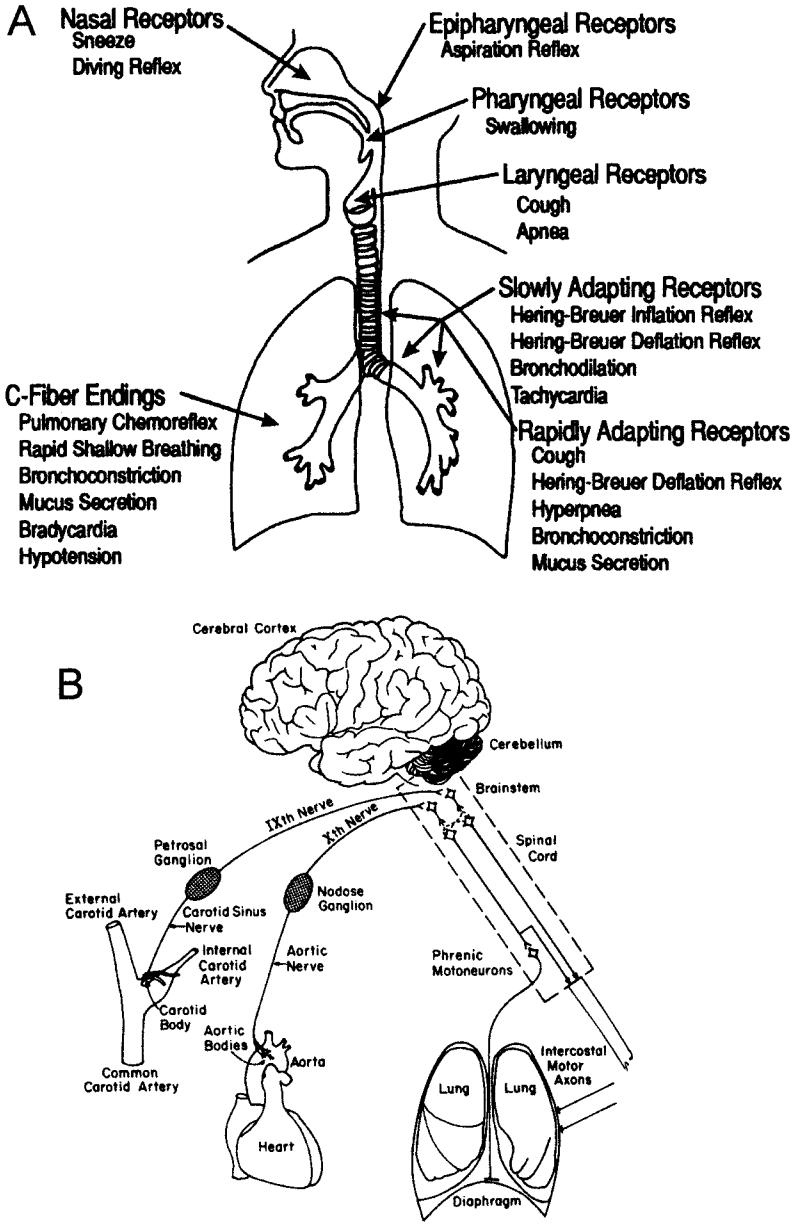

Fig. 4. A: Mechanical receptors involved in respiratory feedback. B: Chemical receptors and feedback loops that control automatic respiration. (Both diagrams from Reference 25, with permission.)

The central chemoreceptors are responsible for most of the response to carbon dioxide, which is mediated through the detection of a fall in the pH of the cerebrospinal fluid associated with an increase in cerebrospinal-fluid P_{CO_2}.[29]

CO_2 is lipid-soluble and moves rapidly into the central nervous system with responses, and it appears that the parasympathetic nervous system is important in the response mechanism of cerebrospinal-fluid pH changes. This is supported by data from animal experiments that show that chemical inhibition of acetylcholine transmission can abolish the ventilatory response to change in central pH.[27]

Diseases That Affect the Respiratory System

The diseases of the neurorespiratory system can be organized most logically by examining them in the frame of reference of the functional anatomic analysis described above. Table 1 lists diseases of the central nervous system that affect the respiratory system. Table 2 lists diseases of

Table 1. Diseases of the Central Nervous System Associated With Respiratory Dysfunction

Cerebral Cortex	Brainstem	Basal Ganglia	Spinal Cord
Stroke	Infarction ("locked-in syndrome")	Parkinson disease	Trauma
Neoplasm	Neoplasm	Chorea	Infarction or hemorrhage
Cerebral degeneration	Drugs	Dyskinesias	Dymyelinating disease
Seizures	Hemorrhage		Disc compression
	Progressive bulbar palsy		Syringomyelia
	Multiple-system atrophy		Tetanus
	Poliomyelitis		Strychnine poisoning
	Anoxic encephalopathy		Neoplasm
	Encephalitis		Motor neuron disease
	Multiple sclerosis		Epidural abscess
	Primary alveolar hypoventilation		

Table 2. Diseases of the Peripheral Nervous System Associated With Respiratory Dysfunction

Motor Nerves	Neuromuscular Junction	Myopathies
Motor-neuron disease	Drugs	Myotonic dystrophy
Amyotrophic lateral sclerosis	Antibiotics	Muscular dystrophies
Spinal muscular atrophy	Neuromuscular-junction blockers	Polymyositis and dermatomyositis
Guillain-Barré syndrome	Anticholinesterase inhibitors	Thick-filament myopathy
Critical-illness neuropathy	Corticosteroids	Glycogen-storage diseases
Vasculitides	Lidocaine	Pompe disease
Toxins (eg, lithium, arsenic, gold)	Quinidine	McArdle disease
Metabolic	Lithium	Tarui disease
Diabetes	Antirheumatics	Severe hypokalemia
Porphyria	Toxins	Hypophosphatemia
Uremia	Botulism	Mitochondrial myopathy
Lymphoma	Snake venom	Nemaline body myopathy
Diphtheria	Scorpion sting	Acid maltase deficiency
	Shellfish poisoning	
	Crab poisoning	
	Myasthenia gravis	
	Lambert-Eaton myasthenic syndrome	

the peripheral nervous system that affect the respiratory system.

Central-Nervous-System Diseases

Diseases of Voluntary Breathing: A number of disorders can affect the pathways (corticospinal tracts) that connect the voluntary respiratory centers of the cortex to the spinal motor neurons. A mid-pontine stroke can affect the corticospinal tracts and cause what is know as the "locked-in syndrome," first described by Plum and Posner in 1966.[30] In this syndrome, caused by injury to the basilar pons, the patient is nearly totally paralyzed, with the exception of eye movement. Injury to the reticulospinal tracts causes lost of volitional, but not automatic, breathing. There is preserved response to automatic breathing and changes in P_{aCO_2}, but no ability to voluntarily control breathing.[31] This syndrome is most commonly due to ischemic stroke, but it can be due to pontine tumor, central pontine myelinolysis, high cervical demyelination, syphilitic arteritis of the medulla, or head injury.[4]

Extrapyramidal disorders such as Parkinsonism can also affect voluntary breathing.[32] In these disorders, patients are unable to voluntarily affect the breathing pattern, and they may also show a Cheyne-Stokes respiratory pattern and other breathing abnormalities. Hemispheric lesions can also affect breathing. In hemiplegia following stroke, chest-wall and diaphragm movements on the contralateral side of the cortical injury can be decreased.[33]

Diseases of Automatic Breathing. The classic disruption of automatic but not voluntary breathing is that of "Ondine's curse."[34] Injury to the automatic respiratory centers in the brainstem leads to central sleep apnea when the patient falls asleep and loses voluntary triggering of respiration. This can be seen in unilateral and bilateral med-

ullary infarction, bulbar poliomyelitis, bilateral cervical tractotomy (for chronic pain), and congenital central alveolar hypoventilation, which is a rare genetic disorder of infants.[4] Many of the disorders of all parts of the neuro-respiratory system lead to hypoventilation and the need for ventilatory support. However, this is not always the case. Hyperventilation can be caused by abnormalities in the central controllers of breathing. Central-nervous-system infection and tumor can result in hyperventilation.[35] In a number of conditions the central controllers are normal but are driven to produce hyperventilation by disease within the body, drugs, or environmental stimuli. These include fever, sepsis, pain, pregnancy, medications (such as progesterone and salicylates), and high altitude. A variety of irregular breathing patterns are also associated with central-nervous-system disease, including Cheyne-Stokes respiration and ataxic breathing.[30]

Diseases of the Spinal Cord. Diseases of the spinal cord often dramatically affect breathing because of their direct impact on control of motor nerves that lead to respiratory muscles. Although traumatic injury is the major cause of spinal-cord pathology, some other causes include tumor, vascular accident, transverse myelitis, syringomyelia, and epidural abscess (see Table 1). High (cervical) spinal-cord injury is a common cause of a requirement for long-term ventilation. Because the diaphragm is the major muscle of inspiration and ventilation (C3–C5 spinal nerve roots), the level of the spinal-cord injury or pathology determines the effect on ventilatory function. For lesions at C3 and above, ventilatory support is almost invariably required. Injuries between C3 and C5 will differ in the requirement for ventilatory support. Injuries below C5 are almost always independent of continuous ventilator support. Because cough function largely depends on abdominal and intercostal muscle function (spinal nerve roots T1–L1), cervical, thoracic, and even some high lumbar spinal-cord injury can affect the ability to cough and clear secretions.

Diseases of the Motor Nerves and the Neuromuscular Junction. Disorders of the motor nerves and the neuromuscular junction can occur acutely, such as in Guillain-Barré syndrome or botulinum toxicity, or more chronically, such as in motor-neuron disease or myasthenia gravis (see Table 2). Again, the level of the motor-nerve root or neuromuscular junction predominantly affected will dictate the effect on the respiratory system. More detailed descriptions of acute and chronic motor-neuron disorders will appear in other papers from this Journal Conference.

Phrenic-nerve dysfunction is a common problem encountered in various in-patient and out-patient clinical scenarios (Table 3). One or both of the phrenic nerves can be affected. In the case of unilateral phrenic-nerve injury only one of the diaphragm leaflets is affected. These patients may have no symptoms and relatively normal pulmonary function, or they may have symptoms and vital-capacity reduction of up to 75%.[36] In patients with bilateral phrenic-nerve involvement the vital capacity is always reduced, and these patients are almost always symptomatic. Orthopnea and dyspnea on immersion and with exertion are reported symptoms,[37] and the vital capacity is often as low as 45% of predicted. Noninvasive positive-pressure ventilation is often used with these patients. Phrenic-nerve pacing is generally not an option for these patients, as an intact nerve is necessary for the pacemaker to function.

Table 3. Causes of Phrenic Neuropathy

Trauma
Cardiac surgery with cold cardioplegia
Blunt trauma
Radiation injury
Cervical manipulation
Scalene and brachial nerve block
Tumor compression
Metabolic
Diabetes
Vitamin deficiency (B6, B12, folate)
Hypothyroidism
Inflammatory neuritis
Idiopathic (neuralgic amyotrophy, Parsonage-Turner syndrome)
Mononeuritis multiplex
Vasculitis
Cervical spondylosis
Poliomyelitis
Amyotrophic lateral sclerosis

Diseases of the Respiratory Muscles. A large number of disorders, both acute and chronic, can affect the respiratory muscles (see Table 3). In the intensive-care setting, critical illness neuropathy/myopathy is a very common and potentially devastating complication of intensive care. A full discussion of this topic will be presented in Steven Deem's contribution to this Journal Conference, which will appear in the September 2006 issue of RESPIRATORY CARE.[38]

There are many causes of chronic muscle disease that result in respiratory-muscle dysfunction, including genetic muscular dystrophies, myopathies, and myotonias, as well as inflammatory myopathies and those associated with systemic diseases. A prototype for chronic muscular diseases is Duchenne muscular dystrophy, in which there is slow progressive loss of muscle function, with respiratory-muscle dysfunction occurring later in the course of the disease. The condition is due to a genetic defect that occurs in approximately 1 in 3,300 live male births and causes a deficiency or absence of dystrophin, which is an important structural protein in the muscle myofibril. Although con-

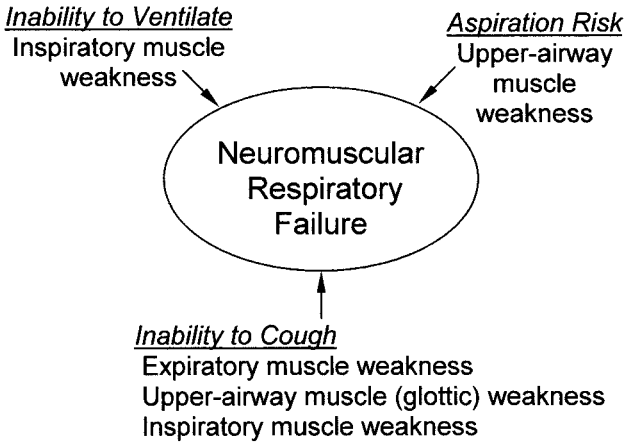

Fig. 5. The 3 main components of neuromuscular respiratory failure.

sidered a lethal disease, due ultimately to respiratory or cardiac failure, great strides have been made in prolonging the lives of individuals with Duchenne muscular dystrophy, with the advent of noninvasive positive-pressure ventilation.[39]

Summary: A Respiratory Approach to the Individual With Neuromuscular Disease

Establishing the location of the impairment in an individual with neurologic disease is critical for the healthcare team in establishing the cause, treatment, and prognosis. However, the respiratory effects of a wide range of neurologic diseases with various etiologies can be surprisingly similar. Therefore, a logical "respiratory approach" focusing on the known effects of neurologic impairment on breathing can be extremely fruitful in treating patients and preventing the respiratory complications of neurologic disease. There are 3 potential respiratory disabilities we need to consider in a patient with neurologic disease: inability to ventilate, inability to cough, and risk of aspiration. Figure 5 shows the respiratory muscles that are involved with each of those disabilities. Ventilatory insufficiency is mainly related to weakness or failure of the inspiratory muscles. Cough insufficiency is related to inspiratory, expiratory, and upper-airway dysfunction. And the risk of aspiration is related predominantly to upper-airway-muscle issues. Each of these disabilities can be assessed individually at clinic visits or in the hospital. Appropriate interventions can then be undertaken in advance of overt failure and respiratory emergency, to support each of the 3 areas that may be affected. Later papers from this Journal Conference will further discuss these measurements and interventions for each of the 3 areas of dysfunction. It is important to note that many of these measurements and interventions are entirely within the scope of the respiratory therapist. In fact, successful implementation of a program of care for individuals with neurorespiratory disease depends in large part on the respiratory therapist.

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Discussion

Giordano:* I read something about the H5N1 virus, and I understand that bird flu has an important neural component. Could you comment on that, Josh?

Benditt: I'm going to defer to my neurologist colleague, Dr Dhand.

Upinder Dhand: I haven't come across any report with regard to avian influenza causing neuromuscular problems, but West Nile virus infection is associated with neuromuscular paralysis, which is very similar to poliomyelitis, presenting as asymmetric flaccid paralysis. I am not aware of any reports of that with avian flu.

Brown: I want to suggest that you consider including information in your paper about shortness of breath, which is often left out in discussions of the neurophysiology of the respiratory system. As you noted about inspiratory and expiratory motor neurons, the shortness-of-breath center has now been discovered, using functional MRI [magnetic resonance imaging], and it's in the insula, near pain centers. And perhaps it's not surprising that the "cosmic committee" put it there, since shortness of breath is a discomfort. You might refer to the work of Banzett et al[1] and Evans et al.[2]

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Hill: I was surprised to hear you mention how frequently you see phrenic nerve palsies. In the late 1980s and early 1990s I saw a high frequency of those patients after open-heart-surgery. These were usually older women who had large hearts with valvular disease, and they had phrenic nerve injuries. Studies around that time found that the pathophysiology was probably what we referred to as "phrenic frostbite."[1] It was the cardioplegia (iced saline lavage) that was damaging the nerves, and when they started using insulators, the rate went down. I haven't seen a case in over 10 years now. Do you use insula tors in Seattle?

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Benditt: I think the frequency that I see is related to my practice rather than the skill level of the cardiac surgeons, because, yes, in Seattle we use insulators, and the frequency of the post-heart-surgery problems has gone way down. At our institution we have a lot of pretty complex elderly patients, and I would say I see perhaps three a year who have that condition. And it's probably not the technique, but the underlying protoplasm. ButI see tons of other causes. The Parsonage-Turner syndrome or the brachial plexopathy is much more common than I ever would have thought. I see them be-

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cause my practice focuses on neuromuscular disease, and people send me their problem patients. One thing I've noted is that most physicians think that you can use phrenic pacemakers for injury to the phrenic nerve. So I get a lot of referrals for that, and, unfortunately, I have the bad luck to have to tell them that they can't do that. But I see a lot of other causes. I agree with you that the frequency of the cardiac-surgery-related phrenic-nerve injury has gone down.

Brown: I have unpublished observations regarding cold cardioplegia. Years ago at the West Roxbury Veterans Affairs Hospital, in Boston, where I used to work, I saw a number of patients after open-heart surgery who had bilateral phrenic-nerve lung dysfunction, and I wondered whether something was going on in the procedure. At the time, the surgeons at that hospital were using saline slush for cold cardioplegia, putting it in the pericardium. Well, that's pretty cold stuff. We went into the operating room and put thermistor probes into the pericardium region where the saline slush was being placed, and, more often than not, the diaphragm dysfunction was on the left, not on the right, not always bilateral, and the temperature in the region of the left phrenic nerve reached 4°C, which I subsequently learned is sufficient to cause frostbite.

So we did a controlled trial with about 30 patients, whom we randomly assigned to receive insulator or not. One of the radiologists got involved and read the postoperative chest radiographs of these patients, thinking that he would be able to tell who had had an insulator by looking at the radiographs and the number of abnormalities in the left and right lung. Well, the insulator was effective only inasmuch as the lowest temperature recorded was now not 4°C, but 10°C, which is still pretty darned cold. The radiologist, it turned out, after we "broke the code," could not tell any difference in the chest radiographs. We thought then that we should have put in 2 insulators to see if it made a difference, but we never got around to that. Soon thereafter the surgeons abandoned using saline slush, and just used cold saline, and we stopped seeing the problem.

I understand that there are cardiac surgery centers (I think developed at the University of Toronto) in which cold cardioplegia is no longer used; instead they use other methods, in which the temperature of the heart isn't reduced like that. So I think it is a function of the temperature—and a function of the change in the methods used for cold cardioplegia—that has caused us to stop seeing this disorder.

Panitch: We also see traumatic phrenic-nerve injury, typically after repair of congenital heart defects. The incidence in pediatrics ranges widely among the reports, and probably has a lot to do with the type of repairs being done at different institutions. The other instance in which we see phrenic-nerve damage is from traumatic birth injury. About 75% of the time it's associated with an ipsilateral Erb palsy, and 25% of the time it's an isolated phrenic-nerve injury.

Upinder Dhand: The bilateral phrenic neuropathy can also have multiple causes: not just ALS [amyotrophic lateral sclerosis]. One of the very important etiologies is chronic inflammatory demyelinating polyneuropathy, which should always be kept in mind, especially because it is treatable. The distinction is easy with phrenic-nerve conduction, which shows markedly prolonged latencies for the diaphragm compound muscle-action potential. Patients with neuralgic amyotrophy (also called Parsonage-Turner syndrome) may also present with isolated phrenic neuropathy, without the weakness in the shoulder girdle or other muscles.[1]

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Lechtzin: I've seen a fair number of patients who have bilateral phrenic-nerve involvement, and the neurologists tell me it's brachial amyotrophy. I take their word for it. Have you had the same experience?

Benditt: I have seen them sequentially. That is, I recently had a patient who came in with one, and then again maybe 6 months later, with one on the other side. I personally haven't seen a patient present initially with both phrenic nerves involved at once. I can't tell you why that is. Upinder, do you have experience with that?

Upinder Dhand: Usually with neuralgic amyotrophy it's going to be unilateral. But there are incidences of bilateral (more often one after the other) or simultaneous involvement resulting in bilateral brachial neuritis or Parsonage-Turner syndrome. These patients have hereditary neuralgic amyotrophy. So if one looks further, there will be a positive family history in them.

Pierson:[†] Following up on Bob Brown's reminder to us about dyspnea as an important aspect of your topic, I want to bring up the hyperventilation syndromes, which are a complicated and incompletely understood collection of conditions that I suspect we won't have a chance to talk about more at this conference. These syndromes surely must have to do with ventilatory drive and its integration at some level.

Just for interest's sake, the other comment I would like to make is a

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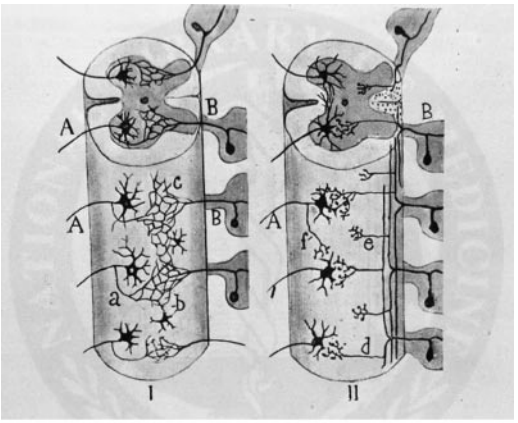
reflection on the complexity of the ventilatory drive system in having both voluntary and involuntary components. In the world of comparative physiology there are examples of other involuntary, non-gas-exchange functions in addition to those you discussed in humans, such as panting for temperature-control in dogs, and purring to indicate contentment in cats.

Benditt: Thank you all for those comments and great suggestions. Obviously it's a very complicated system, and in my talk I didn't include things about the limbic system, dyspnea centers, and so forth.

Mehta: I was interested in your last slide, when you talked about inspiratory muscle weakness—how hypoxemia didn't even come up. I think it's important to emphasize that in neuromuscular disease, hypoxemia may be a very late finding or may not exist at all, whereas all the other problems you mentioned (hypercapnia, aspiration, and airway protection) are much more important.

Benditt: I did not mention hypoxemia, but I'll talk about that tomorrow. A very common problem we see in treating people with chronic neuromuscular disease is that a finger oximeter will indicate that the patient may be hypoxemic, and they're treated in the typical fashion for hypoxemic respiratory failure, not hypercarbic. And it leads to all types of complications. So when I'm talking with residents and students, I try to separate out hypoxemia, and although it may be a finding, it is the least important of the findings. So, I agree.

Brown: This came as a surprise to me. In the respiratory-acute-care unit at Massachusetts General Hospital, we've been operating for 5 years and have seen 15 cases of bilateral diaphragm paralysis, only one of which was recognized prior to the patient arriving in the unit. I think one of the odd problems is that patients develop respiratory failure from bilateral diaphragm dysfunction, and it's not generally recognized in intensive care units, on general wards, and so on. It's a very easy diagnosis to make, right at the bedside. The causes in the respiratory-acute-care unit have been extremely variable: neuropathies of various sorts; commonly, diabetes seems to be an etiologic factor, and then trauma, surgical complications, and the like—the myriad of causes you referred to. So I think a problem for us is to teach others how to think about this diagnosis and how to make the diagnosis, even at the bedside.



Schematic illustration of a section of the spinal cord
Santiago Ramón y Cajal
Madrid, 1923
Courtesy National Library of Medicine