REVIEW

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Respiratory disorders in neurologic diseases

ABSTRACT

Various neurologic diseases such as multiple sclerosis and Parkinson disease can cause pulmonary complications. Pulmonary disorders often manifest late in a neuromuscular disease, but occasionally a respiratory problem may be the first sign. Often the first signs are sleep disturbances and nocturnal desaturation. Although the diseases are diverse, common principles apply in their management.

KEY POINTS

In neurologic diseases, the forced vital capacity is a simpler and more sensitive marker of restrictive pulmonary impairment than is total lung capacity and is an important tool for follow-up.

Adequate pulmonary management should aim to support inspiratory and expiratory muscle function, as this has been found to decrease hospitalization rates and improve survival.

Noninvasive positive-pressure ventilation via a nasal mask is often effective for the support of inspiratory muscle function, though it may be contraindicated in some patients.

Other treatments include respiratory muscle training and theophylline in select patients.

To avoid worsening hypercapnia, oxygen supplementation should probably be limited to patients already on some form of ventilatory support, or to patients in whom hypoventilation has been excluded.

MANY NEUROLOGIC DISEASES, including multiple sclerosis and Parkinson disease, can progress to the point where they compromise respiratory function (**TABLE 1**).[1–23] Although the diseases have variable causes and clinical courses, in many cases it is a pulmonary complication that is the cause of death or other serious adverse event.

This review addresses the pathophysiology of pulmonary impairment in diverse neurologic diseases and reviews the clinical evaluation, the role of pulmonary function testing, and management, including medical therapy and support of inspiratory and expiratory function.

PATHOPHYSIOLOGY

Central respiratory control may be normal

Patients with neuromuscular diseases tend to have either a normal or increased central respiratory drive.[24–27] However, patients who develop nocturnal hypercapnia may have a reduced central drive and reduced daytime ventilatory responses, possibly because progressive accumulation of CO_2 in the cerebrospinal fluid (CSF) raises the pH of the CSF in relation to the partial pressure of CO_2 ($P_{CO})_2$ of the CSF.[28]

Abnormalities in central respiratory control may play a more direct role in the pathogenesis of respiratory dysfunction in central neurologic diseases such as multiple sclerosis and Parkinson disease.

Howard et al[29] found that 6 of 19 patients with multiple sclerosis and respiratory complications had abnormal respiratory control. Patients with multiple sclerosis can develop voluntary or autonomic respiration, diaphrag-

TABLE 1

Clinical and pulmonary course in representative neurologic diseases

SITE AND REPRESENTATIVE DISEASES	CLINICAL COURSE	PREVALENCE OF RESPIRATORY INVOLVEMENT AND PROGNOSIS
Central nervous system		
Multiple sclerosis	Relapsing	Pulmonary function is impaired in 63%[1]; respiratory failure or infection causes death in 5%[2]
Parkinson disease	Slowly progressive	Pneumonia accounts for 20% of deaths,[3,4] possibly from involvement of upper airway muscles and impaired cough[5–7]
Spinal cord		
Trauma	Permanent	High lesions (C1–C3) usually create a need for long-term mechanical ventilation[8]
Motor neuron		
Postpolio syndrome	Very slowly progressive	Respiratory impairment is limited to those with breathing muscle involvement in the initial infection[9]
Amyotrophic lateral sclerosis	Progressive	Death almost uniformly due to respiratory complications[10]
Motor nerves		
Guillain-Barré syndrome	Slowly reversible	Respiratory failure in 28%[11]
Charcot-Marie-Tooth disease	Very slowly progressive	96%–100% have prolonged phrenic nerve conduction[12–14]; 30% have forced vital capacity < 80%[12,15]
Neuromuscular junction		
Myasthenia gravis	Reversible	Aspiration pneumonia can cause crisis episodes with 6% mortality[16]
Botulism	Slowly reversible	Mortality is 8%, due to respiratory failure; some pulmonary impairment may persist for over 1 year in survivors[17]
Muscle		
Duchenne muscular dystrophy	Progressive	Respiratory failure is the major cause of death[18]
Polymyositis/dermatomyositis	Variable	Pulmonary function tests tend to be normal,[19] diaphragm dysfunction reported[20,21]
Postparalysis myopathy	Slowly reversible	30% of asthma patients on steroids and paralyzed patients in intensive care had muscle weakness, which was associated with prolonged ventilation[22,23]

matic paralysis, paroxysmal hyperventilation, apneustic breathing (characterized by a pause after inspiration), and neurogenic edema; the pattern depends on the location of the lesions in the brain.[30]

In Parkinson disease, abnormalities of ventilatory control are more common in parkinsonism associated with autonomic dysfunction than in idiopathic parkinsonism, possibly because the susceptible areas in the brain are close to the areas involved in central respiratory control.[31] Patterns of respiratory dysfunction in Parkinson disease include dysrhythmic breathing, central apneas, Cheyne-Stokes patterns, cluster breathing, apneustic breathing, and central hypoventilation.[31]

Respiratory muscle impairment

Pulmonary symptoms often manifest late in the course of a neurologic illness. Occasionally, they may be precipitated by a fever or infection that increases ventilatory demands and weak-

ens respiratory muscles,[32] or that triggers an exacerbation of the neurologic illness, as can be seen in multiple sclerosis.[33]

At first, the brain adapts to respiratory muscle impairment and maintains normal arterial carbon dioxide and oxygen tensions by increasing central respiratory output so that the patient breathes faster. However, as the disease progresses, a subsequent central adaptive response allows hypoventilation to occur in order to avoid dyspnea or fatigue.[34] Low vital capacity, impaired airway clearance, and a decrease in sighs also contribute to the development of atelectasis and hypoxemia, which further increase ventilatory demands.[35] The eventual development of muscle fatigue may be followed by tachypnea, worsening alveolar hypoventilation, and acidemia.[36]

Weakness of expiratory and bulbar muscles

Although expiration is predominantly a passive process that does not require muscle exertion, expiratory muscles must be actively recruited to clear respiratory secretions adequately, eg, during coughing.[37] In some neurologic disorders, expiratory muscles may be more severely impaired than inspiratory muscles.[38–41]

Additionally, neurologic diseases may affect the bulbar muscles (controlled by cranial nerves VII, IX, X, and XII, which originate in the medulla or "bulb"), the masticatory muscles (controlled by cranial nerve V, trigeminal motor nucleus), and the larynx (controlled by the C1 root). Although not directly involved in expiratory function, these muscles play an essential role in speech, swallowing, and airway protection, and their dysfunction may lead to dysarthria, dysphonia, dysphagia, choking, ineffective cough, and susceptibility to atelectasis and aspiration pneumonia.

Bulbar or expiratory function may be impaired in central as well as peripheral diseases, including multiple sclerosis, Parkinson disease, amyotrophic lateral sclerosis, Guillain-Barré syndrome, and myasthenia gravis. For example, in Parkinson disease, the upper airway muscles are often involved and there is evidence of airflow limitation,[5] and impairment in the motor and sensory component of cough may be responsible for the high risk of aspiration and its associated mortality in this disease.[6,7]

Sleep disorders

Patients with neurologic disease and early diaphragmatic or bulbar involvement are vulnerable to respiratory events during sleep, especially during the rapid eye movement (REM) phase, even if they have no daytime symptoms.[42,43] Sleep testing can detect early respiratory muscle involvement and the need for early ventilatory support.[44] For example, some patients with amyotrophic lateral sclerosis have nocturnal desaturations even though their forced vital capacity is more than 50% of their predicted value.[45]

Several mechanisms underlie these observations. For instance, the normal shift of the burden of respiration to the diaphragm during REM sleep[46] may lead to nocturnal desaturation in patients with impaired diaphragmatic function.[47] Additionally, patients with bulbar involvement may develop hypopnea (shallow, slower breathing) during REM sleep.[48–50] Lastly, the withdrawal of the wakefulness drive to breathing during sleep may lead to hypercapnic central apnea.[51]

Central mechanisms of sleep disturbances can be seen in patients with central nervous system disorders such as multiple sclerosis and Parkinson disease. Specifically, obstructive apneas can occur with multiple sclerosis affecting the medullary tegmentum[30] and in Parkinson disease with autonomic disturbance and laryngeal obstruction.[31] Additionally, central apnea and central hypoventilation syndrome (Ondine's curse) have been reported in parkinsonism associated with autonomic disturbances.[52]

Orthopnea is the rule in neurologic diseases

CLINICAL EVALUATION

Signs and symptoms

Symptoms that should prompt an evaluation of pulmonary function in patients with neurologic disease include new-onset sleep disturbances, unrefreshed feeling on awakening, morning headaches, disappearance of snoring, or development of orthopnea.

Percussion of the chest wall can detect impaired diaphragmatic movement with inspiration.

Orthopnea (shortness of breath when lying down) is the rule in neurologic disease, but an exception may be seen in tetraplegic

Lung volumes and capacities in neurologic diseases

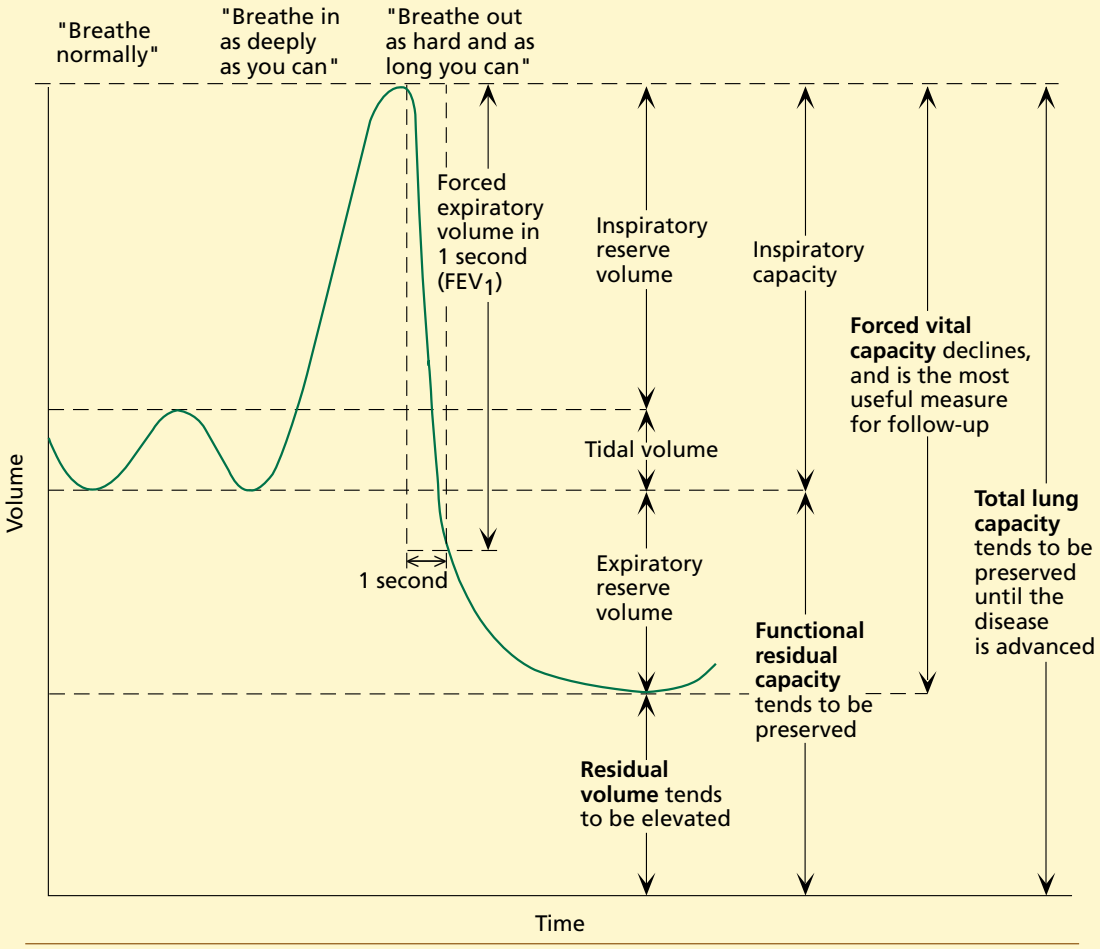

FIGURE 1. Pulmonary function testing in neurologic diseases generally shows a restrictive pattern, with a decreased forced vital capacity. Total lung capacity tends to be preserved until late in the course of the disease.

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Generally, neuromuscular diseases cause a restrictive pattern on testing

patients with lower cervical cord lesions (C4–C6), who may have shortness of breath and hypoxemia while upright (platypnea and orthodeoxia), presumably because gravity-dependent flattening of the diaphragm places it at a mechanical disadvantage.[53]

Indicators of bulbar muscle involvement include slurred speech, trouble swallowing liquids, aspiration manifesting as a new-onset cough, or frank choking spells.

Progression to inspiratory muscle fatigue can present as an increase in respiratory rate, followed by alternating abdominal and rib cage breathing (respiratory alternans), and paradoxical inward abdominal motion during inspiration (abdominal paradox).[36]

Although pulmonary complaints often manifest after neurologic disease has already been diagnosed, they can occasionally be the initial presentation of the illness. If a patient presents with respiratory failure after a bout of pneumonia, one might easily look no further than the pneumonia and thus miss the underlying, unsuspected neurologic disease.[54] Clinical features that should raise suspicion of a neurologic disorder as the cause of respiratory insufficiency include absence of a chronic cardiopulmonary disorder; relatively normal

TABLE 2

Pulmonary function tests in a patient with amyotrophic lateral sclerosis

TEST	PREDICTED	BASELINE		5 MONTHS LATER	
		MEASURED	% PREDICTED	MEASURED	% PREDICTED
Forced vital capacity (FVC)	4.01 L	1.86 L	46	1.52 L	38
Forced expiratory volume in 1 second (FEV_1)	3.02 L	1.66 L	55	1.17 L	39
FEV_1/FVC ratio	0.76	0.89	—	0.76	—
Total lung capacity	6.68 L	5.52 L	83	—	—
Residual volume	2.55 L	3.50 L	137	—	—
Functional residual capacity	3.60 L	4.33 L	120	—	—

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physical, electrocardiographic, and chest radiographic findings; and rapid improvement with ventilatory support with subsequent difficulty in weaning.[55–57]

Pulmonary function testing

Pulmonary function testing in neurologic diseases generally reveals:

- Reduced measures of maximal inspiratory and expiratory muscle pressures
- A restrictive pattern on spirometry with preserved total lung capacity until the disease is advanced (**FIGURE 1**)
- Elevated residual volume
- Reduced vital capacity
- Preserved functional residual capacity.[40,58]

The sigmoid shape of the relaxation curve of the respiratory system is such that higher lung volumes are at a flatter portion of the volume-pressure relationship and dictates that any decrease in inspiratory muscle strength due to a neuromuscular disease is accompanied by a much smaller decrease in total lung capacity.[40] Total lung capacity therefore may be preserved until the neurologic disease is well advanced, and decreases in maximal inspiratory pressure do not correlate,[59] or correlate weakly,[60] with changes in total lung capacity and vital capacity.

Alternatively, the residual volume is often increased in neurologic diseases affecting the expiratory muscles, and there is a strong negative correlation between maximum static expiratory pressure and residual volume.[40,58,61] Accordingly, the vital capacity (the difference between total lung capacity and residual volume) is decreased, predominantly from an increase in residual volume and to a lesser degree, from a decrease in total lung capacity. It follows that vital capacity can be reduced before total lung capacity.

Of note, the American Thoracic Society interpretative strategies, which specify a decrease in total lung capacity as a criterion for restrictive lung disease, may therefore not always apply in patients with neurologic diseases.[62] The forced vital capacity is one of the most important tools for the longitudinal follow-up of pulmonary function in neurologic disease.

Forced vital capacity is one of the most important tools for follow-up

The functional residual capacity is predominantly determined by a balance between the elastic recoil of the chest wall and that of the lung, rather than expiratory muscle strength, and it tends to remain normal in neurologic diseases. This feature differentiates restrictive lung diseases from other causes in which the functional residual capacity tends to be decreased. Some exceptions include a generally decreased functional residual capacity in myasthenia gravis due to decreased outward elastic recoil of the chest wall,[63] and increased functional residual capacity in Parkinson disease due to a rightward shift of the chest wall pressure-volume curve.[64]

TABLE 2 shows sequential pulmonary function test results from a real patient with amyotrophic lateral sclerosis.[65] On the earlier test,

TABLE 3

When and when not to use noninvasive positive pressure ventilation in neurologic disease

Indications (any of the following)
- Forced vital capacity < 50% predicted
- Nocturnal desaturation ≤ 88% for ≥ 5 consecutive minutes during sleep
- Maximal inspiratory pressure < 60 cm H_2O
- Awake partial pressure of CO_2 (arterial) ≥ 45 mm Hg at the patient's usual fraction of inspired oxygen

Contraindications (any of the following)
- Upper airway obstruction
- Assisted peak cough flows < 2.7 L/second with failure to clear secretions
- Inability to achieve mask fit
- Intolerance of the intervention

note the relatively preserved total lung capacity (83%) despite a severely reduced vital capacity (46%), high-normal functional residual capacity (120%), and elevated residual volume (137%). The test obtained only 5 months later demonstrates how rapidly this disease can progress.

Sitting and supine spirometry can be useful in the evaluation of diaphragmatic dysfunction.[66] In normal subjects, the forced vital capacity is 5% to 10% less in the supine position than in the sitting position, with larger decrements in the range of 10% to 20% in people who are obese or have unilateral diaphragmatic paralysis. Decreases larger than 20% are seen in bilateral diaphragmatic weakness, and patients with bilateral diaphragmatic paralysis have a 40% to 50% decrement in forced vital capacity between the sitting and supine positions.[67]

We test pulmonary function every 2 months in patients with ALS and a FVC < 60%

MANAGEMENT OF RESPIRATORY DYSFUNCTION

Support and monitoring of inspiratory function

Noninvasive ventilation usually consists of positive-pressure ventilation via a nasal or facial mask.

Several studies have suggested that, in patients with progressive neurologic diseases, this treatment can prolong survival,[68–70] improve quality of life,[38,71,72] enhance cognitive function,[73] and reduce pneumonia and hospitalization rates.[74] However, one randomized study has shown a survival disadvantage with noninvasive ventilation in patients with Duchenne muscular dystrophy, possibly due to overreliance on the device at the expense of regular monitoring.[75]

Other noninvasive ventilation techniques using rocking beds, "pneumobelt" (intermittent abdominal pressure respirator), and negative-pressure ventilation are much less frequently used.

While some authors concerned about airway protection discourage the use of positive-pressure ventilation in patients who have upper airway dysfunction,[76] about 30% of patients with moderate to severe bulbar symptoms from amyotrophic lateral sclerosis may benefit from the intervention.[68] Proposed indications[47,77,78] and contraindications[8,79] to the use of noninvasive positive-pressure ventilation are outlined in TABLE 3.

How often to monitor pulmonary function depends on how fast the disease tends to progress.

For instance, we perform spirometry, measure inspiratory and expiratory pressures, and obtain arterial blood gases every 2 months in patients with amyotrophic lateral sclerosis and a forced vital capacity lower than 60%.[68] This helps identify indications for noninvasive ventilation, as outlined in TABLE 3, and needed adjustments to the setup for those already on noninvasive ventilation. A similar monitoring interval can be used in the occasional patient with myasthenia gravis who requires chronic noninvasive ventilatory support despite optimal medical management.

Other slowly progressive diseases can be followed at longer intervals. For instance, we test patients with Charcot-Marie-Tooth disease once a year.

In more rapidly progressive and potentially reversible diseases such as decompensated myasthenia gravis and Guillain-Barré syndrome, early detection of respiratory muscle weakness and respiratory failure requires close monitoring of vital capacity and maximal static inspiratory pressures, preferably in an intensive care unit with potential elective intubation at vital capacities less than 10 to 15 mL/kg in order to support inspiratory function and protect the airway.[35,63] Maximal inspiratory pressures can also be helpful, with values greater than 30 cm H_2O usually being adequate for unassisted breathing, and values less than 20 cm H_2O usually indicating inability to maintain an adequate partial pressure of CO_2 (arterial) ($PaCO_2$).[35]

Pulmonary function may need to be assessed as often as every 2 hours in hospitalized patients with myasthenia gravis.[80] Similarly, measurements of vital capacity and maximal inspiratory pressures every 4 to 6 hours have been recommended in hospitalized patients with Guillain-Barré syndrome, though more frequent determinations are not recommended due to the development of fatigue and decreasing endurance.[35]

Invasive ventilation should also be considered in patients in whom noninvasive ventilatory options have failed, are contraindicated, or are not tolerated.[8] When considering more permanent invasive mechanical ventilation via tracheostomy, one should consider the patients' and caregivers' attitudes, the diagnosis, and the prognosis.

Support of expiratory function

The use of expiratory aids to clear secretions in conjunction with support of inspiration was found in retrospective studies to significantly decrease hospitalization rates for respiratory complications of neurologic diseases[81] and to improve survival.[79]

Expiratory aids consist of suction devices, assisted cough techniques (either manually or mechanically through an insufflator-exsufflator),[82] high-frequency oscillation techniques,[83] training to improve maximum insufflation capacity,[84] and air stacking.[85] The mechanical insufflator-exsufflator combines air stacking and cough enhancement by manual or mechanical cycling, from a positive pressure to enhance lung volumes, to a negative pressure to facilitate secretion clearance.[82]

Management of oral secretions

Complementary to the support of expiratory muscles is control of excessive saliva, drooling, and inability to cope with secretions in the presence of bulbar symptoms.[78]

Pharmacologic options include anticholinergic agents such as glycopyrrolate, benztropine mesylate, amitriptyline, and transdermal scopolamine.[78] Surgical interventions to reduce or divert salivary flow are occasionally used in slowly progressive neurologic diseases.[8]

Sialorrhea should be distinguished from excessive and thick mucous production, which requires the mechanical clearance options discussed above.[78] Nebulized *N*-acetylcysteine can also be used to liquefy thick mucus and is often given with a bronchodilator to prevent bronchospasm.[86] There are also anecdotal reports of the use of papain (the same substance found in papaya juice or meat tenderizer) to coat the mouth or tongue and liquefy thick secretions.

Sialorrhea should be distinguished from excessive and thick mucous production

Respiratory muscle training

Inspiratory muscle training has been shown to improve maximal inspiratory pressures, and possibly endurance, in several neurologic diseases.[87–90] Although the protocols differed markedly, outcomes were achieved by training at inspiratory threshold loads targeted to 40% to 80% of a patient's maximal inspiratory pressure.[8,87]

Expiratory muscle training has also been used in some studies. For instance, one approach capitalizes on the fact that the clavicular head of the pectoralis muscle contributes to cough and expiratory muscle function,[91,92] and training of the pectoralis muscle improves expiratory muscle strength and reduces the residual volume in tetraplegic patients.[93] In studies of patients with multiple sclerosis, expiratory muscle training through a resistive device improved expiratory muscle strength and cough for up to 3 months after cessation of training.[94,95]

Medical therapy

Theophylline has been found to have beneficial effects on the contractility of the diaphragm, although larger studies have had mixed results.[96] In patients with amyotrophic lateral sclerosis, theophylline was found to increase negative inspiratory pressure and vital capacity after breathing through a resistive load.[97] In experimental animal models of cervical cord injury, theophylline has been shown to have beneficial effects on phrenic nerve and diaphragm activation, though it may be more effective in the acute phase of injury.[98] Concern remains as to whether any therapeutic benefit would come at the expense of toxicity, given the narrow therapeutic window of this agent.[96]

Limited role for oxygen. To avoid worsening hypercapnia, oxygen supplementation should probably be limited to patients already on some form of ventilatory support, or those in whom hypoventilation has been excluded. In a retrospective review of patients with neurologic disease, there was a mean increase in $PaCO_2$ by 28 torr after initiation of low-flow oxygen.[99] Additionally, one study of patients with neurologic disease found a higher rate of pneumonia and hospitalization in patients receiving oxygen therapy compared with untreated patients or those using other types of ventilatory support.[74]

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