Neuromuscular diseases that affect the respiratory system are a major cause of morbidity and mortality in both acute and long-term settings. This conference examined the pathophysiology and management of neuromuscular diseases in both settings. Presentations by experts representing respiratory, physiologic, pediatric, neurologic, and intensive-care disciplines covered a broad range of topics. This summary of the conference briefly describes the main points of each presentation and highlights areas that need addressing in the future. Major topics covered include the basic respiratory pathophysiology of neuromuscular disease; respiratory complications and management of amyotrophic lateral sclerosis; techniques of noninvasive ventilation and secretion removal; and evaluation and management of neuromuscular-induced respiratory failure in the acute-care setting, including Guillain-Barré syndrome, myasthenic crisis, and critical-illness myoneuropathy. Keywords: neuromuscular disease, respiratory, myasthenia gravis, Guillain-Barré syndrome, spinal-cord injury, noninvasive ventilation, tracheostomy, secretions, pulmonary, amyotrophic lateral sclerosis, ventilator, diaphragm.

Introduction
In recent years, important advances have occurred in the understanding and management of the respiratory and critical care complications of neuromuscular diseases. Most previous symposia have focused on long-term respiratory or critical-care consequences of neuromuscular disease, but few have combined the 2 disciplines. This conference took the perspective that physiologists, respiratory clinicians (therapists and pulmonologists), neurologists, and

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intensivists must talk to one another if the respiratory and critical-care consequences of neuromuscular disease are to be understood. Presenters representing each of these disciplines were invited to share their experience and ideas. The initial presentations dealt mainly with pathophysiology. Amyotrophic lateral sclerosis (ALS) was used as the prototypical disease; other slowly progressive neuromuscular diseases were not discussed specifically. The important advances in pediatric management of respiratory complications of neuromuscular disease were considered, and technical aspects of long-term disease management received attention, particularly secretion management. The remainder of the conference focused on the acute care setting, as we heard talks on critical care-related neuromyopathies. My approach in summarizing the conference is to address 3 simple questions about the topics covered: What were we taught? What was the main message? and Where do we go from here?

Pathophysiology of Respiratory Complications of Neuromuscular Disease

The first presentation, by meeting organizer Josh Benditt, dealt with neuromuscular pathophysiology of the respiratory system, which he described as “the vital pump.” This consists of a chain (Fig. 1), breakage of any link of which can precipitate respiratory failure. The main determinants of the respiratory manifestations of neuromuscular disease are the “big 3” muscular components of the respiratory system: the inspiratory muscles, responsible for ventilation; the expiratory muscles, responsible for coughing and assisting with ventilation when the inspiratory muscles are stressed or weak; and, finally, the bulbar muscles, which are often not thought of as breathing muscles, but have a critical role in airway protection that becomes obvious if they are weakened.

What was the main message? That the neuromuscular component of the respiratory system is highly integrated and regulated, truly a marvel of nature, and that each subcomponent of the chain is key to proper function. We can anticipate the pathophysiologic manifestations of neuromuscular disease by knowing the pattern and severity of respiratory-muscle involvement.

Where do we go from here? Knowledge of molecular mechanisms of injury to the respiratory muscles is very limited. The priority should be to work toward a better understanding of prevention and repair—which requires better appreciation of pathogenesis. Ultimately, effective therapy of the neuromuscular disorder itself will be the best way to prevent respiratory complications. Remarkable advances have occurred in understanding genetic abnormalities associated with neuromuscular diseases, but how these lead to pathology is incompletely understood.

Bob Brown’s presentation on physiologic aspects of spinal-cord injury flowed logically from Benditt’s talk. He complimented the organizers’ brilliance in having invited a physiologist. He pointed out that spinal-cord injury is quite common—mainly occurring in younger males who put themselves in the path of danger. As we might anticipate, the outcomes of spinal-cord injury are dependent on age, neurologic level, and ventilator dependence; the number one cause of death, of course, is respiratory.

One of the interesting physiological abnormalities seen with high spinal-cord lesions is the loss of abdominal elastance due to the reduction in abdominal muscle tone. In this situation, the contracting diaphragm has no fulcrum upon which to act, merely forcing the abdominal contents out without applying as much force to the rib cage, which then fails to expand as it normally would. If the chest wall muscles are paralyzed, such as occurs with C5–6 lesions, the rib cage itself becomes more compliant and may move paradoxically during inspiration. One therapeutic strategy to minimize this effect is to increase abdominal elastance, using an abdominal binder, which can make the sitting position more tolerable for these patients.

Fig. 1. “Links” in the neuromuscular “chain” that drives the respiratory system, with example pathologies.
Brown outlined a number of other therapeutic approaches based on physiologic principles, one being muscle training. Resistance training increases inspiratory-muscle strength in spinal-cord-injury patients, augmenting total lung capacity. Other studies have demonstrated that adding positive end-expiratory pressure and prolonging inspiratory time enhances speech in ventilator users. What was Brown’s main message? Spinal-cord injury is an unfortunate experiment of nature that gives us insight into respiratory pathophysiology, and understanding the pathophysiology opens therapeutic avenues. We have more to learn about the pathophysiology, of course, and future therapeutic approaches will arise from these studies. One promising approach is to pace the paralyzed muscles. Studies are in progress to pace not only the diaphragm directly to enhance inspiration, but also the intercostals to strengthen cough, with encouraging results thus far. Of course, studies aimed at preventing the occurrence of neurologic deficits or to repair or regrow spinal neurons are the ones most likely to bear fruit.

Long-Term Respiratory Management of Neuromuscular Disease: ALS

Noah Lechtzin next addressed the topic of respiratory complications of ALS, which served as a prototypical neuromuscular disease. ALS is not common, but it’s not rare either, affecting about 30,000 people in the United States annually, predominantly males. Outcomes are terrible: average survival is about 3 years, but highly variable. The presentation is remarkably variable as well. Initial manifestations can vary from hand weakness to foot drop to slurring of speech or dyspnea related to diaphragm weakness. But virtually all muscles are affected eventually, and before they die, at least 80% of ALS patients develop bulbar involvement, a cruel aspect of the disease that deprives the victim of the ability to speak or swallow.

Lechtzin talked about some of the newer approaches to diagnosing the disease. Standard pulmonary function studies lack predictive value, so the sniff nasal pressure and the supine vital capacity are being used to detect diaphragm dysfunction earlier, and as predictive indices. The pathophysiology, of course, remains poorly understood. Mutations of the superoxide dismutase gene are responsible for a very small percentage of the cases, and studies are ongoing seeking other genetic or biochemical abnormalities.

Lechtzin reviewed therapies, including noninvasive positive-pressure ventilation (NPPV), an intervention that has improved dyspnea, quality of life, and functional capacity. One randomized controlled trial from England, which raised some ethical issues, showed a slight survival advantage for ALS patients managed with NPPV. Lechtzin emphasized the importance of cough-enhancement techniques, including mechanical insufflation-exsufflation and, possibly, high-frequency chest-wall oscillation in patients with bulbar involvement who are not well-managed by the in-exsufflation. In his recent survey, Lechtzin found that only about 5% of patients elect to have a tracheostomy, depending on the center. When patients are surveyed after a tracheostomy, they usually report a good quality of life, whereas, on average, family-member caregivers have a less favorable quality of life.

So what was the main message? ALS is inarguably a horrible, inexorably progressive disease that robs people of their humanity. NPPV has been the major therapeutic advance in the field. That’s not to say a whole lot, because there’s currently no medical therapy that alters the natural history of the disease in any substantial way. Even though NPPV appears to improve survival, it is still only a temporizing therapy. In addition, bulbar dysfunction is the major therapeutic challenge. NPPV and cough-assistance techniques don’t do as well for patients with bulbar involvement. Nerve pacing strategies are currently limited because of lower-motor-neuron involvement. Thus, although we are very limited in what we can do to slow the relentless progression of ALS, we can still offer help to most patients.

Respiratory Management of Pediatric Neuromuscular Disease

Howard Panitch, discussing the respiratory consequences of pediatric neuromuscular disease, hastened to point out that children are “not just little adults.” They have smaller airways and less elastic recoil of the chest wall. Their airway dynamics are different, and the peak cough flows we talk about for adults probably don’t apply to children. Preserving normal growth is a big concern with children. Growth of facial structures offers a case in point; flattening of facial structures caused by long-term use of ventilation mask occurs in up to 68% of children because the available NPPV interfaces exert pressure on growing facial structures. Applications of NPPV for children have lagged behind those for adults, but they are now catching up. Use of NPPV for infants with bronchopulmonary dysplasia has been increasing rapidly, for example, stimulating the development of interfaces appropriate for infants. Secretion removal has been a problem in some neuromuscular syndromes in children, such as spinal muscular atrophy. High-frequency chest-wall oscillation may have promise, because patient cooperation is not as important as it is with in-exsufflation.

Important messages from Panitch’s presentation are that children need a different approach, chest-wall and facial growth must be considered in equipment design, manufacturers need to pay attention to pediatric applications, and we need better ways of getting children to adhere to NPPV and to assist in secretion mobilization.
Respiratory Muscle Pathophysiology in Non-Neuromuscular Disease

Neil MacIntyre’s task was to use chronic obstructive pulmonary disease (COPD) as a prototype for non-neuromuscular respiratory-muscle dysfunction. He introduced the concept of underloaded versus overloaded muscle fatigue. In COPD, respiratory muscles are overloaded because of the inefficiencies related to mechanical disadvantages, and this contributes to ventilatory limitation. But respiratory muscles are not the sole factor limiting functional capacity in COPD patients. Other factors include deconditioning of the extremities, airway obstruction, and cardiovascular dysfunction. When the respiratory muscles are the limiting factor, many of the underlying mechanisms may be amenable to therapy. Malnutrition, deconditioning, and chronic hypoxia are such contributing factors, although few data are available to guide therapy. Dr MacIntyre also pointed out there is a growing awareness that systemic inflammation is a very early contributor to the development of COPD and affects not only muscle function, but the pulmonary vasculature as well. Many of our traditional concepts about the progression of COPD being related mainly to hypoxemia and hypoventilation are clearly wrong, and newer therapeutic approaches will have to consider the systemic inflammatory component.

What does it mean? The respiratory muscles are affected in COPD and contribute to performance limitation, even when they’re not the primary targets of disease. Understanding respiratory-muscle pathophysiology can lead to new and more effective therapeutic avenues. Many of our current therapies directed at respiratory muscles—muscle training, nutrition, and NPPV—clearly need more evaluation so we know exactly how and how well they work.

Technical Aspects of NPPV for Neuromuscular Disease

Dean Hess discussed technical aspects of ventilatory assistance in neuromuscular diseases. When NPPV was first used to treat neuromuscular-disease patients, the mouthpiece was the most commonly used interface. With the advent of nasal ventilation, use of NPPV expanded enormously, fueling the development of newer masks and ventilators. Now, largely because of the high prevalence of obstructive sleep apnea, there’s an enormous market for interfaces, which has stimulated the development of a wide variety of interface types and sizes. Dr Hess provided an organized framework for this variety and pointed out the crucial importance of selecting a comfortable and well-fit interface, referring to this as the weak link in the successful application of NPPV.

Hess also described ventilators briefly. His bottom line was that almost any ventilator can work effectively to deliver NPPV—but it must be set properly. He advocated starting at low pressures initially and then gradually increasing mainly inspiratory pressure while monitoring tolerance, symptoms, and gas exchange.

His main message was that, although we have made tremendous technical advances, we also need to gain knowledge and experience to optimally apply NPPV. He acknowledged that many questions need more definitive answers: How best to deal with leaks that can disrupt sleep? How do we best adjust pressures? Should we be using sleep laboratories in some patients to more quickly optimize the pressures?

NPPV for Continuous Ventilatory Support

Josh Benditt returned to the podium to describe techniques to provide round-the-clock NPPV to neuromuscular patients who have little or no vital capacity, something that John Bach discussed in detail at a previous conference. Benditt has accrued considerable experience with such patients, and he illustrated his approach of providing sip ventilation (intermittently via mouthpiece) from a wheelchair-mounted portable volume-limited ventilator during the daytime. He then has patients sleep with whatever interface is comfortable for them, whether it be a nasal or oronasal mask or mouthpiece. He acknowledges that his approach is based on experience and not evidence. We had a discussion—I won’t call it a heated discussion, but perhaps a contentious one—on when one resorts to a tracheostomy in long-term ventilated patients. Ultimately, the decision rests on the judgment of the caregivers and patient, based on experience, preferences, comfort, intactness of bulbar function, whether the need for ventilatory assistance is continuous, and so on.

An important message that Dr Benditt conveyed was that, although his experience clearly demonstrates that continuous ventilation can be provided safely using NPPV, there is precious little evidence to guide us. Randomized studies will be difficult to do because of the small numbers of such patients at any given center, and because of ethical issues, but crossover trials may be adequate to answer some questions.

Techniques to Enhance Airway Secretion Removal

Benditt substituted for Louis Boitano RRT, who was unable to attend the conference, in discussing clearance of airway secretions, a topic of paramount importance in managing neuromuscular patients with respiratory insufficiency. His brief background on cough physiology underlined the need for intact function of all of the big 3 respiratory-muscle groups (inspiratory, expiratory, and upper-airway) to have a normal cough. Cough assessment is an inexact science, however, because of the lack of accu-
rate measures. A value of < 270 L/min for peak cough flow has been proposed as a threshold for cough inadequacy, but this has never been prospectively validated, nor does it allow for individual differences in size, sex, and age. The assessment of bulbar function is also problematic. Some patients seem to have more difficulty with aspiration than others, despite severe bulbar involvement, but systematic tools to assess this have not been adequately developed. Benditt described various cough-enhancement techniques, including manually-assisted cough, in-exsufflation, and the electromagnetic stimulator. He pointed out that in-exsufflation, unfortunately, is not very useful in patients with diffuse airway obstruction.

Benditt’s main message here was that secretion-clearance techniques are critically important in managing neuromuscular-disease patients, because secretion retention, which leads to pneumonia, hypoxemia, and ventilatory failure, is the main cause of death. This is the real weak link in long-term respiratory management of neuromuscular diseases—the inability to cough adequately is a very serious problem.

Management of Chronic Tracheostomies in Neuromuscular Disease

Rajiv Dhand next discussed the indications for and technical aspects of chronic tracheostomies. He described many different types of tracheostomy tubes: different brands, flexible or stiff, tubes with different cuffs, and with and without inner cannulas or fenestrations. Once again, little evidence is available to guide choices. Dhand addressed management issues: complications, troubleshooting, and the issues surrounding decannulation. He also raised the question of whether there might be reluctance to place tracheostomies in some neuromuscular patients, leading to undue prolongation of translaryngeal intubation or multiple failed attempts at NPPV.

Although the increasing use of NPPV appears to have reduced the use of tracheostomy ventilation, there is no question that tracheostomies continue to play an extremely important role in the management of respiratory complications of neuromuscular disease. Many questions remain to be addressed, however: When is it advantageous to do a tracheostomy? What type of tracheostomy tube should be used? How best to manage the cuff or to facilitate speech? How should we counsel patients and their families as they face decisions regarding tracheostomy?

Management of Acute Respiratory Failure Due to Neuromuscular Disease

Redirecting our attention to the acute-care setting, Geeta Mehta next reviewed the literature on the evaluation and management of acute respiratory failure due to Guillain-Barre syndrome or myasthenic crisis. She highlighted the potential value of the 20/30/40 rule (vital capacity < 20 mL/kg, peak inspiratory pressure > –30 cm H2O, and peak expiratory pressure < 40 cm H2O) in helping to decide when intubation is necessary. Other indicators of impending need for ventilatory support and airway protection include inability to raise the head and progression to respiratory insufficiency within a week. Mehta stressed the importance of close monitoring of these patients and of anticipating the need for intubation before a respiratory crisis occurs.

Regarding ventilatory management, she pointed out that, with the exception of some patients with myasthenic crises, NPPV plays a small role in patient management, because secretion clearance is often a challenge. Once intubated, though, patients are at risk for a whole array of problems, including ventilator-associated pneumonia, which increases in occurrence with advanced age, decreased bicarbonate level, and prolonged intubation. Early tracheostomy placement has been encouraged if it appears that the patient will require intubation beyond the first 3 weeks; but with the advent of effective therapies, such as plasmapheresis and gamma globulin, some patients reverse rapidly and may extubate successfully. Deciding on when to extubate can also be a challenge, because the usual criteria don’t necessarily apply.

Mehta’s main message was that a proactive approach should be adopted to manage patients with acute respiratory failure due to neuromuscular disease, to minimize the risk of respiratory crisis and complications. Many questions await clarification: How to minimize the duration of respiratory failure? How to predict successful extubation? How to avoid and best manage late sequelae?

Neuromuscular Disease Following Critical Illness

The next 2 presentations dealt with other aspects of neuromuscular disease in the acute-care setting: sequela of critical illness. Upinder Dhand detailed the evaluation of patients with intensive-care-unit-(ICU)-acquired weakness, from the viewpoint of a neurologist. Possible etiologies to consider include central, spinal, and peripheral neurologic involvement, as well as myopathies. Critical-illness polyneuropathies and myopathies are common causes of weakness in the ICU, but Guillain-Barré syndrome, myasthenia gravis, ALS, and porphyria are encountered occasionally. Electromyography and nerve-conduction studies can be helpful but may be difficult to interpret. Serum creatine phosphokinase may be elevated, and serologies—such as for West Nile virus, calcium channel (for Lambert-Eaton syndrome), and muscle-specific kinase antibodies—may also be helpful. Muscle biopsies are usually nonspecific and not often done.
Although it is unreasonable to expect pulmonologists and intensivists to have the sophistication of a neurologist in evaluating ICU weakness, Dhand pointed out that recognition is important. Patients with weakness after a critical illness may have critical-illness-related polymyopathy, which may linger for months; diaphragm involvement is common, and alternative possible etiologies need to be considered.

Steven Deem focused his discussion on critical-illness-related weakness. He characterized the terminology as “messy,” because of the confusing array of overlapping acronyms, such as CIP (critical-illness polyneuropathy), CIM (critical-illness myopathy), and CINMAP (critical-illness neuromuscular abnormality). The problem is very common, reported to occur in 33–82% of patients receiving mechanical ventilation in an ICU for more than 4 days. Risk factors include not only steroids, neuromuscular blockers, and sepsis, but also asthma, COPD exacerbation, and hyperglycemia. The pathophysiology is poorly understood but appears to be a part of the multiple-organ dysfunction associated with the sepsis syndrome. Increased expression of the ubiquitin-proteasome proteolytic pathway has been implicated in the muscle-wasting associated with sepsis.

There is no specific therapy for critical-illness polymyopathy beyond excellent ICU care, although tight glucose control appears to be important. Clearly, more work needs to be directed at understanding the pathophysiology and testing potential therapies, such as intravenous immune globulin and antioxidants.

Ventilator-Induced Diaphragm Dysfunction

The last talk was an elegant dissertation by Amal Jubran on ventilator-induced diaphragm dysfunction (VIDD), which occurs in animals ventilated with controlled mechanical ventilation. Histologic evidence of VIDD can occur within 12–24 hours under these circumstances, but minimal spontaneous breathing appears to reverse the changes. Jubran pointed out that very little evidence exists for a human counterpart to the VIDD that occurs in animals, or that VIDD interferes with weaning, which has been one of the big concerns. Data from her laboratory have identified several mechanisms of weaning failure, including deteriorating lung mechanics and cardiovascular limitations, but respiratory-muscle weakness doesn’t appear to be one of them, because twitch-induced transdiaphragmatic pressure doesn’t change over the course of a failed weaning trial. From a pragmatic point of view, Jubran suggested that we use assisted or spontaneous breathing modes as much as possible. Until there is a reliable test or biochemical marker for a clinical counterpart to the VIDD that we know occurs in animal studies, however, VIDD will remain a theoretical concern in the clinical setting.

Concluding Remarks

In conclusion, this conference covered a broad expanse of topics related to respiratory complications of neuromuscular disease. It reviewed basic physiology and pathophysiology and highlighted advances in the management of long-term mechanical ventilation of neuromuscular diseases, including state-of-the-art noninvasive techniques and methods to optimize secretion clearance. An unusual feature was the inclusion of critical-care aspects of neuromuscular disease in a conference dealing with the pulmonary complications of long-term neuromuscular conditions as well. Several talks dealt with the neuromuscular complications of critical illness, a problem that is being increasingly recognized and that contributes to prolonged debility of many patients recovering from bouts of severe sepsis, but that is incompletely understood at present. Although we have made great progress in the management of respiratory complications of neuromuscular disease, we have numerous knowledge gaps with regard to pathophysiology and clinical management. We have highlighted many of these gaps in this conference and hope that one outcome will be to stimulate attempts to fill them.

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