Airway Clearance Applications in the Elderly and in Patients With Neurologic or Neuromuscular Compromise

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Summary

Respiratory compromise is the leading cause of morbidity and mortality in patients with neuromuscular and neurologic disease, and in elderly patients, who have a reduced pulmonary reserve from deterioration of the respiratory system associated with the normal aging process. Although the otherwise healthy older patient is normally asymptomatic, their pulmonary reserve is further compromised during stressful situations such as surgery, pneumonia, or exacerbation of a comorbid condition. The inability to effectively remove retained secretions and prevent aspiration contribute to this compromise. Although no secretion-management therapies are identified as having specific application to the elderly, clinicians must be attentive and understand the needs of the elderly to prevent the development of respiratory compromise. Patients with neuromuscular disease often cannot generate an effective cough to mobilize and evacuate secretions. Respiratory muscle training, manual cough assistance, mechanical cough assistance, high-frequency chest wall compression, and intrapulmonary percussive ventilation have each been suggested as having potential benefit in this...
population. Although strong evidence supporting the benefit of these therapies is lacking, clinicians must be guided as to whether there is a pathophysiologic rationale for applying the therapy, whether adverse effects are associated with the therapy, the cost of therapy, and whether the patient prefers a given therapy. Key words: aging process, airway clearance, cough mechanics, Duchenne muscular dystrophy, high-frequency chest wall compression, high-frequency chest wall oscillation, intrapulmonary percussive ventilation, manually assisted cough, mechanical insufflation-exsufflation, neurologic disease, neuromuscular disease, respiratory muscle training, peak cough flow. [Respir Care 2007;52(10):1362–1381. © 2007 Daedalus Enterprises]

Introduction

Respiratory compromise is the leading cause of morbidity and mortality in patients with neuromuscular and neurologic disease.1–3 It can also contribute to increased morbidity and mortality in the elderly.4 The ability to prevent aspiration and to evacuate secretions via coughing is reduced as a consequence of changes to respiratory mechanisms during the normal aging process and by neuropa-thologies. The objectives of this paper are to review the normal airway clearance process, to describe how the pulmonary system is affected by the aging process, to review how cough mechanics may be affected by neuromuscular conditions, and to review the evidence of therapies specific to those conditions.

The Normal Clearance Mechanisms

The primary purpose of the respiratory system is to facilitate entry of oxygen and to eliminate carbon dioxide from the body. The incoming air must be conditioned—filtered, warmed, and humidified—to maintain this gas-exchange process. The upper airways and lining of the central and lower airways help to serve this purpose.

Normally, airway secretions are continuously produced and cleared by the centripetal movement of the mucocili-ary escalator and with the aid of differential airflow.5 Between 10 mL and 100 mL of respiratory secretions are produced and cleared each day.6,7 When this mechanism is impaired or the volume of mucus becomes overwhelming, the cough mechanism helps to mobilize and evacuate these excess secretions.

Coughing serves to clear the airway of large amounts of inhaled material, mucus due to excessive secretions or impaired mucociliary clearance, and abnormal material such as edema fluid or pus.8 An effective cough depends on the ability to generate high expiratory gas flow and velocity through the airways. A cough normally consists of 3 phases: an inspiratory phase, a compressive phase, and an expiratory phase.8–10 During the inspiratory phase, a volume, ranging from 50% of tidal volume to 50% of vital capacity, is inspired.8 The goal is to get air behind the mucus and to optimize the time-tension relationship of the expiratory muscles to enable greater expiratory pressure and therefore higher expiratory flow. The compressive phase is characterized by closure of the glottis and simultaneous contraction of the expiratory muscles of the rib cage and abdomen. Within 0.2 seconds, intrathoracic pressure normally reaches 50–100 cm H2O or more.8 The expiratory phase begins with opening of the glottis and continued contraction of the expiratory muscles. Although flow begins, intrathoracic pressure may continue to rise and can reach 150–200 cm H2O.8 This high pressure generates an explosively fast expiratory flow and compresses the central airways. The dynamic airway compression improves cough effectiveness by enhancing expiratory flow velocity.8,9 Velocity is the average speed through a given airway, which is equal to the instantaneous flow divided by the cross-sectional area of the airway.11 For a given flow, a smaller airway has a faster velocity than a larger airway. Clinically, the airflow velocity within an airway cannot be easily measured, so expiratory peak cough flow at the mouth is used. Although normal peak cough flow may be as high as 10–12 L/s, a peak cough flow of <4.5 L/s (270 L/min) has been associated with increased risk of complications from respiratory infection, and <2.7 L/s (160 L/min) probably increases the risk of failed extubation and is a threshold for initiating cough-assist therapy.12–14

The Effect of the Aging Process on Respiratory Function

Part of the normal aging process is decline of lung function.15–17 Although the upper airways and the control of breathing are affected, most of the functional changes are related to a decrease in the static elastic recoil of the lung, a decrease in the chest wall compliance, and a decrease in respiratory muscle strength.18 This is particularly important for patients who undergo surgery, because approximately 40% of perioperative deaths in patients over 65 years of age are related to postoperative respiratory complications.15 Assessing the true impact of the aging process on pulmonary function is difficult because the assessment can be confounded by underlying respiratory illness, the effects
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Table 1. Age-Related Structural Changes in the Respiratory System

<table>
<thead>
<tr>
<th>Change</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased alveolar surface area, due to diminished intra-alveolar</td>
<td>pneumonia</td>
</tr>
<tr>
<td>penetration</td>
<td></td>
</tr>
<tr>
<td>Increased interstitial connective tissue</td>
<td></td>
</tr>
<tr>
<td>Enlarged respiratory bronchioles and alveolar ducts (ductectasis)</td>
<td></td>
</tr>
<tr>
<td>Smaller airway diameter, due to destruction of supporting connective</td>
<td>tissue</td>
</tr>
<tr>
<td>tissue</td>
<td></td>
</tr>
<tr>
<td>Increased proteolysis of elastin, reduced elastin/collagen ratio,</td>
<td></td>
</tr>
<tr>
<td>reduced/alterted surfactant</td>
<td></td>
</tr>
<tr>
<td>Calcification of ribs and vertebral joints</td>
<td></td>
</tr>
<tr>
<td>Loss of respiratory accessory muscle mass</td>
<td></td>
</tr>
</tbody>
</table>

of direct or indirect smoking, and the effects of environmental exposure. The elderly are also more likely to be deconditioned or have comorbidities that impact the respiratory system. Cross-sectional studies that look at changes in function and stratify the results by age categories have not always controlled for these factors. Longitudinal studies that follow individuals over a predetermined time interval are more difficult to conduct, but provide more meaningful information.

Changes to the Lung Parenchyma

Structural changes in the lung parenchyma occur with age (Table 1). Airway size is reduced due to alterations in the supporting connective tissue that normally helps to tether the airways open. Conversely, the alveolar duct size is increased. This air-space enlargement (ductectasis) is not due to alveolar wall destruction, as in emphysema, but most likely to a decrease in elastic tissue and an increase in collagen with age. These anatomic changes result in the following physiologic changes: (1) decreased elastic recoil (ie, increased pulmonary compliance), (2) reduced diffusion capacity for oxygen and carbon monoxide, (3) premature airway closure and associated ventilation-perfusion mismatch and larger alveolar-arterial oxygen difference, (4) small-airway closure and air trapping, and (5) reduced expiratory flow. The term "senile emphysema" has been used to describe these age-related changes because of the functional similarities to emphysema, but these changes are associated with a homogeneous dilatation of air spaces without destruction of tissue (as in emphysema), so the term "senile lung" may be more descriptive.

It has been suggested that cumulative oxidative damage by industrial and environmental factors might be partly responsible for this structural change and functional decline. Also, the lungs' ability to clear particles from small airways appears to decrease with age. The rate of mucociliary clearance is reduced in elderly subjects, as is the lung immune response and the ability to fight infection.

Changes to the Chest Wall and Respiratory Muscles

With increasing age, chest wall compliance decreases due to calcification of intercostal joints and rib-vertebral articulations, as well as a narrowing of intervertebral disk spaces and kyphoscoliosis. These changes, as well as contractures of intercostal muscles, result in rigidity and reduced rib-cage mobility. This shifts the breathing muscle-use pattern toward a smaller contribution from the thoracic muscles and a larger contribution from the diaphragm and abdomen. With age, the diaphragm decreases in strength, which appears not to be related to atrophy or to a change in muscle fiber type. The expiratory intercostal muscles atrophy by approximately 20% after 50 years of age, possibly due to a more sedentary lifestyle. Diaphragm strength is thought to be reduced by approximately 10–20% in healthy elderly individuals compared to younger individuals, and maximum inspiratory and expiratory pressures are reduced by more than 50%. The reduced strength may be associated with reduced expiratory flow and compromised cough, but peak cough flows have not been evaluated in this population.

Pulmonary Function and Gas Exchange

The reduced lung recoil pressure is associated with an increased resting expiratory lung volume or functional residual capacity. In particular, the residual volume is increased at the expense of the expiratory reserve volume. The reduced chest wall compliance and the reduced force of the respiratory muscles make it harder to take in a breath, which is associated with a reduced inspiratory reserve volume and vital capacity. As a result, total lung capacity is not substantially affected. It has been suggested that residual volume increases by approximately 50% and that vital capacity is reduced by 25% between 20 and 70 years of age. Figure 1 shows the relative change in lung volumes associated with age, and Figure 2 depicts these changes over time.

The forced vital capacity (FVC) and forced expiratory volume in the first second (FEV₁) decrease with age, and the rate of decline is greater in men and in persons with asthma. The annual decline of FEV₁ is approximately 20 mL/y in persons 25–39 years old, and increases to 38 mL/y in individuals greater than 65 years of age.

Small-airways close earlier during expiration with increasing age. The site of this small-airway closure moves more distal within the airway and occurs earlier during exhalation, resulting in an increased closing volume of the lung. It has been suggested that closure during tidal breathing, when closing volume is greater than functional residual capacity (see Fig. 2), occurs in the sitting position by 65 years of age, and in the supine position on average by 44 years of age. This closure of the terminal bronchioles...
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1. Relative changes in lung volume associated with aging. IRV = inspiratory reserve volume. VC = vital capacity. TV = tidal volume. ERV = expiratory reserve volume. FRC = functional residual capacity. RV = residual volume. (From Reference 19, with permission.)

2. Changes in lung volume over time. (From Reference 15, with permission.)

in the dependent part of the lung during tidal breathing worsens the ventilation-perfusion relationship and is associated with a reduction in oxygenation and diminished carbon monoxide transfer. Carbon dioxide elimination appears to be unaffected, despite a slight increase in the dead-space ventilation ratio.

This age-related deterioration in lung function is slower in those with a long-term habit of exercise, but it is not abated, even in elite athletes.

Exercise and Ventilatory Response

Younger normal individuals are limited in exercise by circulation, not ventilation. Because of the changes already discussed, the ventilatory reserve is compromised in the elderly, and although not apparent at rest, their ventilatory limitations may become evident during acute illness, surgery, or exercise. During exercise the elderly tend to use their abdominal muscles to a greater degree and to use a rapid shallow breathing pattern because of a rigid rib cage. But, despite these ventilatory changes, the elderly are still usually limited by circulation because of deconditioning or from changes in cardiovascular physiology. During exercise, the incremental increase in tidal volume to increase minute ventilation is primarily due to recruitment of end-inspiratory lung volume, rather than to reducing end-expiratory lung volume as seen in younger individuals.

With aging, the ventilatory response to hypoxia and hypercarbia is blunted, most likely due to a combination of a reduced neural output to the respiratory muscles, a decreased peripheral chemosensitivity, and a lower mechanical efficiency and deconditioning. Minute ventilation response to elevated carbon dioxide during hypoxia is reduced during exercise in the elderly, compared to younger individuals. Respiratory response to both hypoxemia and hypercarbia is decreased by 40–50% in a healthy 70-year-old.

Clinical Implications

Despite the physiologic and functional changes associated with aging (Table 2), the basal function of most organ systems, including the respiratory system, is relatively uncompromised. The healthy elderly individual is asymptomatic at rest, but functional reserve and the ability to compensate for various physiologic stressors is reduced. Stressors that might challenge the elderly beyond their reserve include pneumonia, surgery, and exacerbation of a comorbid condition, such as asthma, chronic obstructive pulmonary disease, or congestive heart failure. Response of the elderly to specific medications and to combinations of medications can also be an issue. Lean body mass and total body water is decreased while body fat is increased in the elderly, which alters the volume of distribution and redistribution and the clearance rates of drugs, so drugs are not eliminated as well as they are in younger patients.

The aging process is also associated with changes in the central nervous system, which increases the sensitivity of the elderly patient to many anesthetic agents. Elderly patients are approximately 30–50% more sensitive to propofol than are younger patients.

A particular respiratory concern is the increased risk of aspiration and pneumonia. Anesthetics and muscle relaxants compromise pharyngeal function and diminish the effectiveness of the cough mechanism, especially in the elderly. The elderly are also more susceptible to drug interactions that can result in respiratory depression (eg, an analgesic that contains codeine with an antihistamine or a β blocker). Because of these issues, the elderly...
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Table 2. Age-Related Changes in Respiratory Function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type of Change</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory muscle strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum inspiratory pressure</td>
<td>Reduced</td>
<td>45, 48–50</td>
</tr>
<tr>
<td>Maximum expiratory pressure</td>
<td>Reduced</td>
<td>49</td>
</tr>
<tr>
<td>Maximum voluntary ventilation</td>
<td>Reduced</td>
<td>21, 51</td>
</tr>
<tr>
<td>Compliance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung compliance</td>
<td>Increased</td>
<td>45, 52–54</td>
</tr>
<tr>
<td>Thoracic/chest wall compliance</td>
<td>Reduced</td>
<td>52, 55</td>
</tr>
<tr>
<td>Total compliance</td>
<td>Reduced</td>
<td>45, 55</td>
</tr>
<tr>
<td>Volumes and Flows</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung capacity</td>
<td>Unchanged</td>
<td>21, 52</td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>Increased</td>
<td>52, 53</td>
</tr>
<tr>
<td>Residual volume</td>
<td>Increased</td>
<td>21, 55, 56</td>
</tr>
<tr>
<td>Closing volume</td>
<td>Increased</td>
<td>21, 38, 54</td>
</tr>
<tr>
<td>Forced vital capacity</td>
<td>Reduced</td>
<td>21, 23, 45, 53, 57, 58</td>
</tr>
<tr>
<td>Vital capacity</td>
<td>Reduced</td>
<td>53, 56</td>
</tr>
<tr>
<td>Inspiratory capacity</td>
<td>Reduced</td>
<td>53</td>
</tr>
<tr>
<td>FEVI</td>
<td>Reduced</td>
<td>20, 21, 23, 58</td>
</tr>
<tr>
<td>Peak expiratory flow</td>
<td>Decreased</td>
<td>51, 59</td>
</tr>
<tr>
<td>Gas Exchange</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shunt</td>
<td>Increased</td>
<td>21</td>
</tr>
<tr>
<td>Diffusing capacity for carbon monoxide</td>
<td>Reduced</td>
<td>60</td>
</tr>
<tr>
<td>$P_{O_2}$</td>
<td>Reduced</td>
<td>39, 61</td>
</tr>
<tr>
<td>$P_{CO_2}$</td>
<td>Unchanged</td>
<td>61</td>
</tr>
<tr>
<td>Maximum oxygen consumption</td>
<td>Reduced</td>
<td>21</td>
</tr>
<tr>
<td>Dead-space ventilation (anatomic, physiologic)</td>
<td></td>
<td>Increased</td>
</tr>
<tr>
<td>Ventilatory Response to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Reduced</td>
<td>45, 47</td>
</tr>
<tr>
<td>Hypercarbony</td>
<td>Reduced</td>
<td>45, 47</td>
</tr>
</tbody>
</table>

FEVI = forced expiratory volume in the first second

have a disproportionate number of respiratory complications. Seymour and Vaz reported a respiratory complication rate of 40% in 288 general surgical patients over 65 years of age. Although 44% of the patients had no complications, the respiratory complications included atelectasis (17%), acute bronchitis (12%), and pneumonia (10%).

An evidence-based approach to prescribing medications for the elderly is challenging, because most clinical trials exclude them. Much of the geriatric practice of drug prescription is therefore based on anecdotal experience or extrapolating results from studies of younger patients.

Regarding secretion management, in the literature we found no therapies specific to the elderly. Realizing that pulmonary reserve is reduced, strength for effective coughing is reduced, risk of aspiration is increased, response to stress may be blunted, and response to medications may be altered, clinicians can be more attentive to the needs of elderly patients in order to help prevent the development of respiratory compromise. Observing some basic tenets, such as maintaining a semi-recumbent position, may help to minimize reflux and aspiration of gastric contents and the negative effects of an increasing closing volume on oxygenation.

Effects of Neurologic and Neuromuscular Disease on Respiratory Function

An inability to remove secretions, and the associated respiratory compromise, significantly increase morbidity and mortality in patients with neurologic and neuromuscular disease. This compromise in respiratory function is primarily the result of weakened inspiratory, upper-airway, and expiratory muscles. The importance of these issues to respiratory therapists and other pulmonary clinicians is evidenced by recent reviews in Respiratory Care.
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Table 3. Respiratory Muscles

<table>
<thead>
<tr>
<th>Inspiratory, primary</th>
<th>Deep Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaphragm</td>
<td></td>
</tr>
<tr>
<td>External intercostals</td>
<td></td>
</tr>
<tr>
<td>Scalenae</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inspiratory, accessory</th>
<th>Deep Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternocleidomastoid</td>
<td></td>
</tr>
<tr>
<td>Trapezius</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Expiratory</th>
<th>Deep Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal intercostals</td>
<td></td>
</tr>
<tr>
<td>Internal and external obliques</td>
<td></td>
</tr>
<tr>
<td>Transverse abdominus</td>
<td></td>
</tr>
<tr>
<td>Rectus abdominus</td>
<td></td>
</tr>
</tbody>
</table>

Upper Airway
Abductors of vocal cords
Palatal elevators
Retractors of tongue
Dilators of nares

The Muscles of Respiration

The muscles of respiration and those involved with cough are often divided into 3 categories: inspiratory muscles, expiratory muscles, and muscles of the upper airways. Table 3 and Figure 3 review these muscles.

The primary inspiratory muscles include the diaphragm, the external intercostals, and the scalene muscles. During exercise and other situations in which additional effort is required, the accessory inspiratory muscles (sternocleidomastoid and trapezius muscles) are recruited.

Expiration is normally a passive maneuver, dependent on the elastic recoil of the lung. During exercise or forced expiration, the abdominal muscles are recruited either to fix or to cause an inward movement of the abdomen and upward displacement of the diaphragm to assist expiration. The expiratory muscles include the rectus abdominus, transverse abdominus, the internal intercostals, and the internal and external obliques.

The muscles of the upper airways help to maintain patency so that air can flow in and out of the lungs without obstruction. Muscles of the upper airway include the abductors of the vocal cords, the retractors of the tongue, the palatal elevators, and the dilators of the nares.

Airway Clearance Techniques for Patients With Neuromuscular Disease

In patients with neurologic and neuromuscular disease, an ineffective cough is the main reason for mucus retention. Ineffective cough is primarily due to (1) weak inspiratory muscles and an inability to take a deep breath, (2) impaired bulbar function and a reduced ability to close the glottis to allow generation of adequate intrathoracic pressure, and (3) weak expiratory muscles and an inability to generate an adequate intrathoracic pressure. The result is a limitation of dynamic airway compression and a failure to generate sufficient peak cough flow.

A recent clinical practice guideline for airway clearance therapies reported by the American College of Chest Physicians presented a list of 10 recommendations for various patient populations. The recommendations primarily focus on patients with chronic secretions problems, such as in cystic fibrosis, chronic bronchitis, bronchiectasis, and chronic obstructive pulmonary disease, but 3 recommendations were specific for patients with neuromuscular disease (Table 4). Note, however, that the 3 recommendations (expiratory muscle strength training, manual cough assist, and mechanical cough assist) have relatively low-grade supporting evidence. The grading scale employed suggests that (1) the support for the recommendations is based on low-level evidence (nonrandomized, case-oriented, or observational studies) or on expert opinion, (2) the net benefit is believed to be small (there is evidence of benefit that may not clearly exceed the minimum clinically important benefit) or intermediate (clear evidence of benefit but with some evidence of harm), and (3) the recommendations have a final evidence grade of C (weak recommendation) or E/C (weak recommendation based on expert opinion).
Before reviewing the therapies related to the recommendations, it should be repeated that there is a lack of high-level evidence to support or disprove therapies in the population of interest. Several articles describe individual case reports or larger case series. Studies that have compared the therapies usually involved small sample sizes and were before-and-after or crossover design rather than randomized controlled trials (RCT). The outcomes measured were usually short-term, such as effect on secretion volume, peak cough flow, or oxygenation, which are easy to measure and thought to be clinically important but may not impact long-term outcomes such as progression of disease, quality of life, or patient satisfaction.

**Respiratory Muscle Strength Training**

The inspiratory and/or expiratory muscles may be weakened by neuromuscular disease. Both muscle groups are necessary for an effective cough, and strengthening them may improve a patient's cough and minimize respiratory complications. Strengthening the inspiratory muscles may allow for a larger inspired volume of air, whereas strengthening the expiratory muscles may allow a greater pressure to be generated and therefore faster peak cough flow. Training the inspiratory muscles may also have the added benefit of prolonging the need for assisted ventilation due to hypoventilation.

Similar to other skeletal muscles, the respiratory muscles can be trained to improve strength and endurance. Typically, in the studies of respiratory muscle training, strength training is accomplished by performing a maximal static maneuver against a closed glottis or a nearly occluded resistance valve, whereas endurance training involves breathing through a variable resistor at a predetermined percent of maximum capacity for a specific period. Nonrespiratory maneuvers, such as sit-ups and bicep curls, can also improve inspiratory and expiratory muscles.

Most reports of respiratory muscle training focus on the inspiratory muscles. In a 2002 meta-analysis of respiratory muscle training in patients with chronic obstructive pulmonary disease, all 15 of the RCTs analyzed involved inspiratory muscle training. In a 2006 meta-analysis of respiratory muscle training in patients with spinal cord injury, 4 of the 6 RCTs analyzed focused on inspiratory muscles. In 1995, McCool and Tzelepis reviewed 8 non-controlled studies of inspiratory muscle training in neuromuscular disease. That review suggested that inspiratory training can improve the respiratory muscle force and endurance in patients with neurologic and neuromuscular disease, especially those who are less severely affected by disease. Table 5 summarizes the respiratory muscle training studies in neuromuscular disease reported since 1995. Of these 9 studies, 4 were randomized, 3 specifically targeted the expiratory muscles, 5 targeted inspiratory muscles, and another trained both muscle groups.

Outcome measures of endurance training are usually reflected in changes in the maximum voluntary ventilation, whereas strength is reflected in the maximum inspiratory pressure and maximum expiratory pressure. Strength can affect the volume of air moved, so pulmonary function tests, such as vital capacity and FEV1, are often assessed. Inspiratory muscle training has been suggested to improve strength and/or endurance in such conditions as Duchenne muscular dystrophy, post-polio, spinal muscular atrophy, and myasthenia gravis. Concern has been raised as to whether such training might harm patients with Duchenne muscular dystrophy by increasing muscle damage during the training session, but 2 studies reported training such patients for up to 9 and 24 months, respectively, without any apparent deterioration in lung function or any other adverse effects. None of the studies of inspiratory muscle training have assessed effects on cough effectiveness, although some have implied that it might be improved. Interestingly, both measures of strength were improved, regardless of the muscle group targeted. For example, both maximum inspiratory pressure and maximum expiratory pressure increased with expiration-targeted training, and with inspiration-targeted training.

Of the 4 studies that targeted the expiratory muscles, only one measured peak cough flow. Although the study by Chiara et al found an increase in...
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Table 5. Studies (1996 to 2006) of Respiratory Muscle Training in Patients With Neuromuscular Disease

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Design</th>
<th>n</th>
<th>Subjects (number in each group)</th>
<th>Muscles Targeted</th>
<th>Interventions</th>
<th>Duration of Training</th>
<th>Duration of De-training</th>
<th>Outcomes</th>
<th>Principle Findings and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenager67</td>
<td>1996</td>
<td>RCT</td>
<td>20</td>
<td>Multiple sclerosis</td>
<td>Expiratory</td>
<td>Threshold load vs sham: adjust for 75% of maximum expiratory pressure; mean 3 wk.</td>
<td>5 mo</td>
<td>None</td>
<td>Maximum inspiratory pressure, maximum expiratory pressure</td>
<td>Increased maximum inspiratory and expiratory pressures</td>
</tr>
<tr>
<td>Gotz15</td>
<td>1999</td>
<td>RCT</td>
<td>42</td>
<td>Duchenne muscular dystrophy (21), matched controls (20) (all children)</td>
<td>Inspiratory and expiratory</td>
<td>Residual load (4 sessions/8)</td>
<td>6 mo</td>
<td>12 mo</td>
<td>Maximum inspiratory pressure, maximum expiratory pressure, inspiratory-load perception</td>
<td>No change in either control group. Improvement in maximum inspiratory and expiratory pressures and decreased respiratory-load perception in trained study group vs untrained study group. Pressure returned to baseline within 3 mo of cessation but respiratory-load perception was still improved after 12 mo.</td>
</tr>
<tr>
<td>Gosselink94</td>
<td>2000</td>
<td>RCT</td>
<td>21</td>
<td>Multiple sclerosis</td>
<td>Expiratory</td>
<td>Threshold load at 60% of maximum expiratory pressure for 15 breaths x 3 sessions x standard care</td>
<td>3 mo</td>
<td>3 mo</td>
<td>Maximum inspiratory pressure, maximum expiratory pressure, FVC, FEV, pulmonary index</td>
<td>Improved maximum inspiratory and expiratory pressures, compared to baseline, but not compared to control. Pulmonary index improved, compared to baseline and control. After 6 mo, pulmonary index remained higher in the trained group.</td>
</tr>
<tr>
<td>Klebuc67</td>
<td>2000</td>
<td>Before-after</td>
<td>10</td>
<td>Prior to using part-time electromiographic positive pressure ventilation for hypoventilation, 7 subjects trained, 3 did not train</td>
<td>Inspiratory</td>
<td>Residual load daily for 20 min (1 min max, 1 min rest X 10 times)</td>
<td>10 wk</td>
<td>13 wk</td>
<td>Maximum inspiratory pressure, maximum expiratory pressure, exercise capacity, respiratory, questions about activities of daily living</td>
<td>Improved inspiratory endurance capacity and activities of daily living</td>
</tr>
<tr>
<td>Wolker68</td>
<td>2004</td>
<td>Before-after</td>
<td>16</td>
<td>Duchenne muscular dystrophy (13), spinal muscular atrophy (5)</td>
<td>Inspiratory</td>
<td>Residual load, 1 breath x 9 mo</td>
<td>Note</td>
<td>Maximum inspiratory pressure, maximum expiratory pressure, ventilation, FVC</td>
<td>In both groups, improved maximum inspiratory pressure and 12-s maximum voluntary ventilation. No significant decrease in VC.</td>
<td></td>
</tr>
<tr>
<td>Koenigs8</td>
<td>2001</td>
<td>Before-after</td>
<td>27</td>
<td>Duchenne muscular dystrophy (13), spinal muscular atrophy (11), Striatal by VC (27-50%, 51-70%, 71-90%)</td>
<td>Inspiratory</td>
<td>Residual load, 1 breath x 24 mo</td>
<td>Note</td>
<td>Maximum inspiratory pressure, 12-s maximum voluntary ventilation, FVC</td>
<td>In all groups, improved maximum inspiratory pressure to 12-s maximum voluntary ventilation until 30th month, then plateau. No significant decrease in VC.</td>
<td></td>
</tr>
<tr>
<td>Klebuc67</td>
<td>2005</td>
<td>RCT</td>
<td>15</td>
<td>Multiple sclerosis</td>
<td>Inspiratory</td>
<td>Threshold load, 2 sessions every other day, 10 min maximum</td>
<td>10 wk</td>
<td>30 d</td>
<td>Maximum inspiratory pressure, maximum expiratory pressure, perception of fatigue</td>
<td>Maximum inspiratory and expiratory pressures increased. Maximum inspiratory pressure remained for at least 10 d. Recommended as a complement to ordinary physical training</td>
</tr>
<tr>
<td>Fregonez7</td>
<td>2005</td>
<td>RCT</td>
<td>27</td>
<td>Myasthenia gravis</td>
<td>Inspiratory</td>
<td>Increasing residual load and breathing retainting x 3 sessions/wk (45 min, 10 min diaphragmatic breathing, 10 min expiratory load, 10 min inspiratory load increased from 20% to 60% of maximum inspiratory pressure)</td>
<td>8 wk</td>
<td>Note</td>
<td>Maximum inspiratory pressure, maximum expiratory pressure, ratio of respiratory rate to tidal volume, upper chest wall expansion and reduction</td>
<td>Improved maximum inspiratory and expiratory pressures, ratio of respiratory rate to tidal volume, upper chest wall expansion and reduction. Improvement in strength, endurance, respiratory pattern, and chest wall mobility</td>
</tr>
<tr>
<td>Chiar26</td>
<td>2006</td>
<td>Before-after</td>
<td>31</td>
<td>Multiple sclerosis (17), healthy matched controls (14)</td>
<td>Expiratory</td>
<td>Residual load x 3 sessions/wk, 6 sets of 6 repetitions/session</td>
<td>8 wk</td>
<td>4 wk</td>
<td>Maximum expiratory pressure, FVC, FEV, peak expiratory flow, peak cough flow</td>
<td>Improved maximum expiratory pressure. No difference in peak cough flow as a whole. Those with mild disability had improved peak cough flow. Those with mild disability had no change</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial
FVC = forced vital capacity
FEV = forced expiratory volume in the first second
VC = vital capacity
maximum expiratory pressure, the peak cough flow was, on the whole, unchanged in these patients with multiple sclerosis. When the group was stratified by severity of disease, peak cough flow was found to be improved in the group that had moderate disease, but not in those with mild disease. Although this is promising, further research is needed before firm recommendations can be made for this therapy.

In summary, respiratory muscle training is associated with (1) increased maximum inspiratory and expiratory pressure, which may increase for at least 10 months and then plateau, (2) improved peak cough flow in patients with more moderate disability, (3) reduced decline of vital capacity in patients with Duchenne muscular dystrophy, and (4) improved abilities to perform activities of daily living. When training is stopped, pressures return toward baseline, but other measures of respiratory-load perception remain improved for an unknown duration. The ideal respiratory muscle training program has not been identified, and the long-term benefits are unknown. Further research is required on respiratory muscle training.

**Manual Cough Assist**

Individuals with neuromuscular disease and weak respiratory muscles or structural defects of the abdominal wall can show an outward motion of the abdomen during coughing. This paradoxical motion contributes to an ineffective cough by not allowing the intrathoracic pressure to increase proportional to the effort put forth. Applying an abdominal binder can fix the diaphragm and minimize the outward abdominal movement during cough. Another method, which also augments the efficiency of the respiratory muscles, is manual application of pressure with both hands to the upper region of the abdomen or lower thorax after the individual has taken a maximal inspiration. This manually assisted cough (or abdominal thrust) is commonly referred to as quad-coughing, because it is often used in patients with spinal cord injuries. It is also effective in patients with weak respiratory muscles.

Table 6 summarizes 8 recent studies that included manually assisted cough. None of the studies were RCTs, although 4 of them did randomly assign the application of various cough-assist techniques. Four of these studies are also included in Table 7, which compares the effects of mechanical cough-assist techniques. Several features are common to the studies in Table 6. In addition to unassisted cough and manually assisted cough, a method of augmenting the inspired volume was assessed for its impact on peak cough flow and in combination with manually assisted cough. One method of augmenting inspiratory volume is to have the patient take a maximal inspiration, then close the glottis, then receive multiple stacked breaths from a manual resuscitation bag until no more volume can be held. This is normally referred to as the maximum inspiratory capacity. A one-way valve and mouthpiece is attached to the bag to allow this method of ventilation. Intermittent positive-pressure breathing has also been used, as has mechanical insufflation-exsufflation (in-exsufflation). Peak cough flow was the primary outcome measure in each study. The results consistently demonstrate that manually assisted cough is effective at increasing unassisted peak cough flow, and can be further enhanced by augmenting the inspired volume prior to manually assisted cough.

Advantages of manually assisted cough include low cost, portability, and the fact that no equipment is needed. Potential disadvantages include that it may be difficult for caregivers to learn the proper technique, and the possibility of injury to internal organs if applied inappropriately. Manually assisted cough may not be effective in patients with chest wall or spinal deformities.

The evidence for manually assisted cough is not of a very high level, but it suggests that (1) manually assisted cough consistently increases unassisted peak cough flow, (2) the effects of manually assisted cough are enhanced by various methods of achieving the maximum inspiratory capacity, such as breath-stacking with a manual resuscitation bag, intermittent positive-pressure breathing, or a volume ventilator, (3) manually assisted cough may not be effective in patients with scoliosis, (4) manually assisted cough may be enhanced by in-exsufflation, and (5) further study is warranted to determine which patients receive the most benefit and long-term benefits.

**Mechanical Cough Assist**

Two of the 3 components of a normal cough can be simulated with a mechanical device, the CoughAssist In-Exsufflator (Respironics, Murrysville, Pennsylvania), which applies a positive pressure to augment inspiration, via face mask or connection to an artificial airway, and then quickly transitions to a negative pressure to create a rapid exsufflation. This can generate peak expiratory flow of > 270 L/min, provided adequate pressure and time settings are used. The in-exsufflation concept was first described in the mid-1950s, by Beck and colleagues, who used it with poliomyelitis patients. In-exsufflation fell out of favor in the 1960s, with the introduction of more invasive techniques. It was reintroduced as the CoughAssist In-Exsufflator (JH Emerson, Cambridge, Massachusetts, which was later purchased by Respironics, Murrysville, Pennsylvania), and reports of its use began appearing in the early 1990s. Table 7 summarizes 10 clinical studies that compared in-exsufflation with other methods of augmenting cough. Unfortunately, only one of the studies was an RCT and...
<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Design</th>
<th>n</th>
<th>Subjects (number in each group)</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Principle Findings</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang</td>
<td>2000</td>
<td>Crossover</td>
<td>108</td>
<td>Neuromuscular disease</td>
<td>Unassisted cough</td>
<td>Peak cough flow</td>
<td>In group 1 (n = 90) maximum inspiratory capacity was &gt; VC in group 2 (n = 18) VC = maximum inspiratory capacity due to bowel involvement and inability to a note right aid. Unassisted peak cough flow increased by 38% in group 1 and by 12% in group 2. VC = balance 70 ml. Subjects improved &gt; 27 L.</td>
<td>When VC is &lt; 1.5 L, manually assisted cough should be preceded by maximum inspiratory capacity. Inflation pressure of 40-50 cm H2O usually required.</td>
</tr>
<tr>
<td>Sivasothy</td>
<td>2001</td>
<td>Randomized</td>
<td>29</td>
<td>Normal (9), COPD (9), respiratory muscle weakness without scoliosis (8); respiratory muscle weaknesses with scoliosis (4)</td>
<td>Unassisted cough</td>
<td>Peak cough flow, patient comfort</td>
<td>Respiratory muscle weakness with scoliosis, peak cough flow: unassisted cough = 28 L/min, manually assisted cough = 193 L/min, in-exsufflation = 231 L/min, combination = 32 L/min. Respiratory muscle weakness without scoliosis, peak cough flow: unassisted cough = 64 L/min, manually assisted cough = 283 L/min, in-exsufflation = 195 L/min, combination = 248 L/min.</td>
<td>Manually assisted cough and in-exsufflation should be considered in patients with respiratory muscle weaknesses without scoliosis, but not those with scoliosis.</td>
</tr>
<tr>
<td>Chatwin</td>
<td>2003</td>
<td>Randomized</td>
<td>41</td>
<td>Study spinal muscle amyotrophy (10), Duchenne muscular dystrophy (6), polio (3), congenital muscular dystrophy (3); Control: age-matched normals (19)</td>
<td>Unassisted cough</td>
<td>Peak cough flow, patient comfort</td>
<td>Peak cough flow: unassisted cough = 169 L/min, manually assisted cough = 181 L/min, BiPAP assist = 182 L/min, mechanical insufflation = 235 L/min, in-exsufflation = 297 L/min.</td>
<td>In-exsufflation predicted peak cough flow than other techniques. Patients prefer in-exsufflation.</td>
</tr>
<tr>
<td>Mustafa</td>
<td>2003</td>
<td>Randomized</td>
<td>57</td>
<td>ALS with bulbar dysfunction (21), ALS without bulbar involvement (26), healthy controls (10)</td>
<td>Unassisted cough</td>
<td>Peak cough flow, VC, maximum inspiratory pressure</td>
<td>Manually assisted cough peak cough flow: in-exsufflation with by 13% in nontubal vs 11% in tubal disease.</td>
<td>Greatest improvement was in patients with weak bulbar cough.</td>
</tr>
<tr>
<td>Svedo</td>
<td>2004</td>
<td>Crossover</td>
<td>26</td>
<td>ALS: amyotrophic (11), bulbar (15)</td>
<td>Unassisted cough</td>
<td>Peak cough flow, maximum inspiratory capacity, VC</td>
<td>Peak cough flow in-exsufflation &lt; maximum inspiratory capacity in patients with minimal lung impairment (peak cough flow maximum inspiratory capacity &gt; 4 L/s; peak cough flow via BiPAP maximum inspiratory capacity &lt; 1 L).</td>
<td>Residual peak cough flow in patients with bulbar involvement, most likely due to dynamic collapse of upper airway.</td>
</tr>
<tr>
<td>Kang</td>
<td>2005</td>
<td>Crossover</td>
<td>51</td>
<td>Duchenne muscular dystrophy</td>
<td>Unassisted cough</td>
<td>Peak cough flow</td>
<td>Peak cough flow: unassisted 218 L/min, manually assisted 25 L/min, maximum inspiratory via stacked breaths 224 L/min, manually assisted cough after inspiratory breathing.</td>
<td>Importance of inspiratory assist should be emphasized.</td>
</tr>
<tr>
<td>Trebbia</td>
<td>2005</td>
<td>Randomized crossover</td>
<td>10</td>
<td>Chronic respiratory failure due to chronic respiratory failure due to Duchenne muscular dystrophy (9) or other neuromuscular disease (4)</td>
<td>Manually assisted cough</td>
<td>Peak cough flow, VC, IPPB pressure &gt; 7 cm H2O. Combined cough: VC with mechanical insufflation = IPPB &gt; manually assisted cough &gt; baseline.</td>
<td>Study suggests that inspiratory assist and manually assisted cough should be used in combination.</td>
<td></td>
</tr>
<tr>
<td>Keating</td>
<td>2006</td>
<td>Crossover</td>
<td>40</td>
<td>Traumatic spinal cord injury</td>
<td>Unassisted</td>
<td>Peak cough flow, maximum inspiratory pressure</td>
<td>Peak cough flow: unassisted 228 L/min, volume-assisted = 277 L/min, manually assisted cough = 326 L/min, volume-assisted plus manually assisted cough = 320 L/min. Maximum inspiratory pressure had better correlation than maximum expiratory pressure in all cough methods.</td>
<td>Management of inspiratory muscle strength is important.</td>
</tr>
</tbody>
</table>

VC = vital capacity  
COPD = chronic obstructive pulmonary disease  
BiPAP = bilevel positive airway pressure  
ALS = amyotrophic lateral sclerosis  
IPPB = intermittent positive-pressure breathing
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Table 7. Clinical Studies of Mechanical Insufflation-Exsufflation in Patients With Neuromuscular Disease

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Design</th>
<th>n</th>
<th>Subjects (number in each group)</th>
<th>Interventions</th>
<th>In-exsufflation Pressures (cm H2O)</th>
<th>Outcomes</th>
<th>Principle Findings and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bach(^{107})</td>
<td>1993</td>
<td>Crossover 21</td>
<td>Unassisted cough</td>
<td>Maximum inspiratory capacity via breath-stacking or glossopharyngeal breathing</td>
<td>Maximum tolerated</td>
<td>VC, maximum inspiratory capacity, peak cough flow</td>
<td>VC = 490 mL, Maximum inspiratory capacity = 1.670 L. Peak cough flow: unassisted cough = 1.8 L, maximum inspiratory capacity via breath-stacking or glossopharyngeal breathing = 3.4 L, manually assisted cough after maximum inspiratory capacity = 4.3 L. In-exsufflation = 72 L. Manually assisted cough and in-exsufflation are safe and effective.</td>
<td></td>
</tr>
<tr>
<td>Sivasothy(^{100})</td>
<td>2001</td>
<td>Randomized crossover 29</td>
<td>Normal (9), respiratory muscle weakness without scoliosis (7), ALS without bulbar involvement (19)</td>
<td>Unassisted cough</td>
<td>VC, maximum inspiratory capacity, peak cough flow</td>
<td>VC = 560 mL, Maximum inspiratory capacity = 1.800 L. Peak cough flow: unassisted cough = 1.4 L, maximum inspiratory capacity via breath-stacking or glossopharyngeal breathing = 3.8 L, manually assisted cough after maximum inspiratory capacity = 4.6 L. In-exsufflation = 7.0 L. Manually assisted cough and in-exsufflation are safe and effective.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chatwin(^{108})</td>
<td>2003</td>
<td>Randomized crossover 41</td>
<td>Study: spinal muscular atrophy (10), Duchenne muscular dystrophy (6), spinal muscular atrophy (2), limb girdle muscular dystrophy (3), Corticospinal motor neuron disease (9), age-matched (19)</td>
<td>Unassisted cough</td>
<td>20–20 Peak cough flow, patient comfort</td>
<td>Respiratory muscle weakness with scoliosis: peak cough flow: unassisted cough = 384 L/min, manually assisted cough = 193 L/min, in-exsufflation = 231 L/min, combination = 322 L/min. Respiratory muscle weakness without scoliosis: peak cough flow: unassisted cough = 106 L/min, manually assisted cough = 187 L/min, in-exsufflation = 156 L/min, combination = 248 L/min. In-exsufflation alone had an effect, but manually assisted cough alone or manually assisted cough with in-exsufflation improved cough clearance.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sancho(^{106})</td>
<td>2003</td>
<td>Crossover 26</td>
<td>ALS without bulbar dysfunction (11), bulbar (5)</td>
<td>Unassisted cough</td>
<td>40±40 Volume of secretions, patient satisfaction</td>
<td>No statistically significant increase in secretions or weight (trend favored in-exsufflation). Patients preferred in-exsufflation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winck(^{103})</td>
<td>2004</td>
<td>Crossover 29</td>
<td>ALS (11), other neuromuscular disease (7), COPD (9), All had max. inspiratory and low Spiq</td>
<td>In-exsufflation at 3 pressures</td>
<td>15±15 Peak cough flow, dyspnea score</td>
<td>Nonneuromuscular disease: peak cough flow at 5.4 cm H2O = 160 L/min vs 220 L/min, % CO2 = 6% vs 8%, Borg score (20 vs 17±3), ALS: peak cough flow at 5.4 cm H2O = 150 L/min vs 260 L/min, % CO2 = 5% vs 8%, Borg score (20 vs 17±3). In-exsufflation can increase peak cough flow and SpO2.</td>
<td></td>
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</tr>
</tbody>
</table>

(Continued)
that study was limited in that the authors did not reportconducting a power analysis to determine proper sample size, nor report the sample size studied. Several studies did randomly select the order in which the techniques were applied. Like the studies of manually assisted cough, the studies of the In-Exsufflator used various methods to accomplish maximum inspiratory capacity, which the patient can do without assistance. Glossopharyngeal breathing (also known as frog breathing) involves a series of gulps, using the lips, tongue, pharynx, and larynx to force air into the lungs. It has been used by patients post-polio, and has also been reported to be useful for increasing maximum inspiratory capacity and peak cough flow in patients with spinal cord injury as well as Duchenne muscular dystrophy, as long as bulbar involvement is not severe.

Although not unanimous in their conclusions, in general the studies of in-exsufflation suggest that (1) the insufflation phase can augment inspired volume at least as well as glossopharyngeal breathing, breath-stacking via manual resuscitation bag, or intermittent positive-pressure breathing; (2) peak cough flow is as fast as or faster than that achieved with manually assisted cough, and is above the 160 L/min (2.7 L/s) threshold; (3) in-exsufflation appears to be safe and well tolerated; and (4) patients seem to prefer in-exsufflation over the other cough aids and suctioning.

In addition to the above-mentioned studies, several retrospective reports described longer periods of experience and provided tips in applying in-exsufflation. Miske et al reported using in-exsufflation with 62 pediatric patients with neuromuscular disease over a 24-month period. Patients in-exsufflation candidates if peak expiratory pressure was < 60 cm H₂O, they had a lower-respiratory-tract infection or atelectasis, or they required long-term mechanical ventilation. Most patients used the device twice a day, but those who produced secretions preferred to use it more often, as frequent as every 1-2 hours. Interestingly, those who did not use it routinely each day were not as comfortable using it during periods of respiratory exacerbation. The therapy was viewed to be effective by the caregivers. Although several families reported a reduction in the frequency of pneumonia, the incidence of respiratory infection was too small to allow a meaningful comparison.

Bach et al have been very prolific in reporting their use of in-exsufflation with 62 pediatric patients with neuromuscular disease over a 24-month period. Patients were in-exsufflation candidates if peak expiratory pressure was < 60 cm H₂O, they had a lower-respiratory-tract infection or atelectasis, or they required long-term mechanical ventilation. Most patients used the device twice a day, but those who produced secretions preferred to use it more often, as frequent as every 1-2 hours. Interestingly, those who did not use it routinely each day were not as comfortable using it during periods of respiratory exacerbation. The therapy was viewed to be effective by the caregivers. Although several families reported a reduction in the frequency of pneumonia, the incidence of respiratory infection was too small to allow a meaningful comparison.

### Table 7. (Continued)

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<th>First Author</th>
<th>Year</th>
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<th>Subjects (number in each group)</th>
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<th>In-exsufflation Pressures (cm H₂O)</th>
<th>Outcomes</th>
<th>Principle Findings and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vianello et al</td>
<td>2005</td>
<td>Prospective vs matched historical controls</td>
<td>27 Study: muscular dystrophy (6), ALS (5), spinal muscular atrophy (3); Control: muscle weakness (5), ALS (6), congenital muscular dystrophy (1); All had upper respiratory tract infection and secretions.</td>
<td>In-exsufflation plus CPI</td>
<td>As tolerated. Mean -19 ± 31 -31 ± 4.6</td>
<td>Treatment failure (artifactifal survey, intubation) based on bronchoscopy</td>
<td>In-exsufflation was associated with fewer airway events (0%) vs 6.3%). Bronchoscopy rate was similar (65% vs 38%), but in-exsufflation to CPI may improve airway mucus clearance.</td>
</tr>
<tr>
<td>Pizzati et al</td>
<td>2006</td>
<td>Randomized controlled trial</td>
<td>NR Spinal and upper respiratory tract infection and secretions</td>
<td>Control:</td>
<td>11 to 45</td>
<td>Asthmatic blood gas values, TV, FEV, PEFR, peak cough flow</td>
<td>In-exsufflation was associated with improved pulmonary function but similar arterial blood gas values.</td>
</tr>
</tbody>
</table>

VC = vital capacity
ALS = amyotrophic lateral sclerosis
COPD = chronic obstructive pulmonary disease
BiPAP = bi-level positive airway pressure
SpO₂ = blood oxygen saturation measured via pulse oximetry
CPT = chest physical therapy
NR = not reported
PEEP = positive end-expiratory pressure
FVC = forced vital capacity
PEF = forced expiratory volume in the first second
TV = tidal volume
FEV₁/FVC = ratio of forced expiratory volume in one second to forced vital capacity

**References:**
1. Bach et al.
2. Miske et al.
3. Vianello et al.
4. Pizzati et al.
5. SpO₂ = blood oxygen saturation measured via pulse oximetry
6. FEV₁/FVC = ratio of forced expiratory volume in one second to forced vital capacity
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Manual resuscitation bag to a maximum inspiratory capacity was prescribed. It was emphasized to the patient that oxygen desaturation was caused by airway mucus accumulation and that each component of therapy should be intensified until arterial oxygen saturation was above 94%. Use of supplemental oxygen was discouraged, so as to be able to detect acute changes in respiratory function. To reach maximum inspiratory capacity, often an insufflation pressure > 25 cm H2O was required. It has been suggested that clinical barotrauma is rare in patients with neuromuscular disease, and in fact they reported no pneumothoraces in their experience with over 1,000 ventilator users, many of whom used insufflation pressure of 40–60 cm H2O.131

For best results with in-exsufflation, the insufflation time should be longer (2–4 s) than the exsufflation time (1–3 s), but the total cycle time should not exceed 7 seconds. In patients with a reduced vital capacity, the manually assisted cough is not considered optimal unless preceded by a maximum inspiratory capacity. Similarly, in-exsufflation is not considered optimal unless an abdominal thrust is applied during exsufflation. Manually assisted cough and in-exsufflation must be applied when the patient has a need to cough, not on a predetermined frequency. It is suggested that family members should be allowed to help provide the therapy while the patient is in the hospital. In addition to providing the therapy when it is indicated, the family also becomes better trained to provide care at home. Given that 90% of pneumonia episodes and respiratory failure occur during what is considered an otherwise benign upper-respiratory-tract infection in patients who have an inability to cough effectively, this aggressive approach seems prudent.1 Bach’s research group reported the ability to maintain many patients who are totally ventilator-dependent on noninvasive positive-pressure ventilation devices, but they suggested that tracheostomy and invasive ventilation can only be prevented by aggressive application of the therapy elements listed in the above protocol.134

The low level of the available evidence suggests that (1) insufflation during in-exsufflation can provide a maximum-inspiratory-capacity volume equal to that of the breath-stack techniques, (2) in-exsufflation augments assisted peak cough flow, (3) in-exsufflation peak cough flow is as fast as or faster than that generated by manually assisted cough, (4) in-exsufflation appears to be safe and well tolerated, and (5) most patients prefer in-exsufflation over suctioning.

Mucus Mobilization Devices

The techniques and devices discussed so far help to extract secretions. Occasionally, patients need assistance in mobilizing the secretions to central airways so they can be coughed out. Traditional percussion and postural drainage techniques may be difficult or impossible to perform because of chest wall or spinal deformities or osteoprotic ribs, so alternatives are desirable. Two devices that have been described as possibly beneficial in patients with neuromuscular disease are high-frequency chest wall compression (HFCWC) and intrapulmonary percussive ventilation.

High-Frequency Chest Wall Compression. HFCWC is administered with any of several different brands of device that surround the patient’s thorax and deliver rapid small compressions to the thorax. HFCWC is often erroneously referred to as high-frequency chest wall oscillation, which is only delivered by one device, the Hayek oscillator, which is a cuirass device that delivers both positive and negative pressure pulses to the chest. The rapid shock waves from an HFCWC device cause small pulses of air to move in and out of the lungs at high velocity, initially designed to facilitate ventilation,135 it was soon appreciated that HFCWC could also enhance tracheal mucous clearance.136,137 HFCWC is thought to enhance mucus clearance by reducing the viscosity of the sputum,136,138 augmenting ciliary beating, and redistributing lung volume.141

The most common method of applying HFCWC is via the Vest (Hill-Rom, St Paul, Minnesota). The device consists of an air-pulse delivery system attached via 2 hoses to a non-stretchable, inflatable vest that covers that thorax. It should be adjusted so that it feels snug when the machine is off and the patient takes a deep breath. When in operation, the vest bladder inflates to compress, then deflates to release the chest wall, at frequencies of 5–20 Hz; 10–15 Hz is the most commonly used range. The Vest pressure can also be adjusted. Although the manufacturer recommends adjusting the pressure to the highest level that the patient can tolerate, to maximize inspired volume, this high background pressure has been associated with reduced end-expiratory lung volume and reduced arterial oxygen saturation.142,143

Several RCTs have compared HFCWC to standard chest physical therapy in patients with cystic fibrosis, and found it to be at least as effective and possibly better.144–147 Patients prefer HFCWC because it can be self-administered. Table 8 reviews the reports on HFCWC in patients with neuromuscular disease. Two of the reports are recent RCTs in patients with amyotrophic lateral sclerosis (ALS). Chaisson et al conducted a single-center study of 9 patients with ALS who were also using bi-level positive airway pressure to determine whether HFCWC prolonged the time to death.15 Each patient received standard therapy, and 5 had the addition of twice-daily HFCWC for 15 min. With this small sample size there was no significant difference in the primary end points of rate of FVC decline or time to death. Chaisson et al noted that the study did not exclude the possibility that HFCWC might be beneficial in selected patients.
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Table 8. Studies of High-Frequency Chest Wall Compression in Patients With Neuromuscular Disease

<table>
<thead>
<tr>
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<th>Design</th>
<th>n</th>
<th>Subjects</th>
<th>Interventions</th>
<th>Duration</th>
<th>Outcomes</th>
<th>Principle Findings and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giarraffa149</td>
<td>2005</td>
<td>Before-after</td>
<td>15</td>
<td>Familial dysautonomia</td>
<td>HFCWC at pressure setting of 3-5, frequency of 10-15 Hz, twice a day</td>
<td>Pre-study 12-mo period vs 12-mo of therapy</td>
<td>(S_{\text{PO}_2}), pulmonary function test results, incidence of pneumonia, hospitalization, antibiotic use, doctor visits, absenteeism</td>
<td>Sustained improvement in (S_{\text{PO}_2}), FVC, and peak expiratory flow. Fewer pneumonias (3/y vs 1/y), hospitalizations (1/y vs 0/y), antibiotics days (85 d/y vs 34 d/y), doctor visits (11/y vs 5/y), and less absenteeism (32 d/y vs 9/d/y).</td>
</tr>
<tr>
<td>Lange50</td>
<td>2006</td>
<td>Multi-center RCT</td>
<td>46</td>
<td>Amyotrophic lateral sclerosis</td>
<td>No therapy</td>
<td>12 wk</td>
<td>Primary: pulmonary function Secondary: safety and tolerance</td>
<td>HFCWC = high-frequency chest wall compression (S_{\text{PO}_2}) = blood saturation measured via pulse oximetry FVC = forced vital capacity RCT = randomized controlled trial</td>
</tr>
<tr>
<td>Chaisson51</td>
<td>2006</td>
<td>Single-center RCT</td>
<td>9</td>
<td>Amyotrophic lateral sclerosis</td>
<td>Standard care</td>
<td>Variable until death</td>
<td>Time to death, arterial oxygen saturation, FVC, adverse events</td>
<td>No difference in rate of FVC decline. No difference in time to death (470 ± 241 d vs 340 ± 247 d). Authors noted that the study did not exclude the possibility of potential benefit in selected patients.</td>
</tr>
</tbody>
</table>

HFCWC = high-frequency chest wall compression
\(S_{\text{PO}_2}\) = blood saturation measured via pulse oximetry
FVC = forced vital capacity
RCT = randomized controlled trial

Lange et al conducted a multicenter RCT with 46 patients with ALS, 35 of whom completed the study.150 After 12 weeks of using either standard therapy or HFCWC twice daily for 15 min, there was less breathlessness, less noisy breathing, and more night coughing associated with HFCWC therapy. For the group as a whole, there were no other significant differences. In a subgroup analysis of patients with a baseline FVC of 40-70% of predicted, HFCWC was also associated with a slower decline in FVC and capnography values than in those who did not receive therapy.

Although the evidence is weak in both the number of studies reported and the sample sizes, the evidence suggests that (1) HFCWC may be effective in mobilizing secretions; (2) two long-term before-and-after studies suggest a lower incidence of pneumonia, antibiotic use, and hospitalization with HFCWC; and (3) HFCWC is well tolerated, but patient preference has not been studied.

Intrapulmonary Percussive Ventilation. Intrapulmonary percussive ventilation (IPV) is a form of chest physical therapy that vibrates the airways internally, via the mouth, as opposed to externally, as in manual percussion or HFCWC. IPV provides small bursts of high-flow gas to the airways, at 100-300 cycles/min, as the patient is allowed to spontaneously breathe. IPV is designed to treat patchy atelectasis and to mobilize secretions. It is as effective as chest physical therapy and HFCWC in patients with cystic fibro-
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Table 9. Studies of Intrapulmonary Percussive Ventilation in Patients With Neuromuscular Disease

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Design</th>
<th>n</th>
<th>Subjects</th>
<th>Interventions</th>
<th>Duration</th>
<th>Outcomes</th>
<th>Principle Findings and Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birnkrant153</td>
<td>1996</td>
<td>Case report</td>
<td>4</td>
<td>Neuromuscular disease (3), atelectasis (1)</td>
<td>IPV</td>
<td>Variable</td>
<td>$S_{PO_2}$, chest radiograph</td>
<td>3 subjects had improved $S_{PO_2}$ and chest radiograph findings quickly; 4th subject had slower improvement; subject decompensated due to airway obstruction from secretions during therapy. IPV is safe with close observation.</td>
</tr>
<tr>
<td>Toussaint154</td>
<td>2003</td>
<td>Randomized crossover trial</td>
<td>8</td>
<td>Duchenne muscular dystrophy, 5 subjects had mucus hypersecretion</td>
<td>Control: assisted cough with suctioning, nebulized NaCl solution, then more assisted cough with suctioning, then, after 45 min, more assisted cough with suctioning. Study: Same except with IPV during nebulization.</td>
<td>3 sessions/d for 5 d = 15 sessions</td>
<td>Secretion weight, heart rate, respiratory rate, $S_{CO_2}$, end-tidal carbon dioxide</td>
<td>No difference in sputum weight in subjects without hypersecretion. IPV is safe and increases effectiveness of assisted mucus clearance techniques.</td>
</tr>
<tr>
<td>Reardon155</td>
<td>2005</td>
<td>Randomized controlled trial</td>
<td>18</td>
<td>Neuromuscular disease</td>
<td>Prophylactic IPV vs incentive spirometry</td>
<td>Variable (study went for 7 months)</td>
<td>Days on antibiotics, hospitalization for respiratory issue, school days lost</td>
<td>IPV associated with less antibiotic use (0 d vs 44 d), shorter hospitalization (0 d vs 8 d), and fewer missed school days (1 d v 2 d). IPV was safe and well tolerated.</td>
</tr>
</tbody>
</table>

$IPV =$ intrapulmonary percussive ventilation  
$S_{PO_2} =$ blood oxygen saturation measured via pulse oximetry.

And has been effective in burn centers, where traditional chest physical therapy may not be appropriate.152 In our literature search we found only 3 reports on IPV in patients with neuromuscular disease (Table 9). The case report by Birnkrant included 3 patients with neurologic and neuromuscular disease, and one with atelectasis.153 Three patients demonstrated improved oxygenation and chest radiograph following IPV. IPV appeared to be so effective in mobilizing secretions that the fourth patient had an apparent airway obstruction due to inability to cough. Toussaint et al studied 8 patients with Duchenne muscular dystrophy, 5 of whom had hypersecretion problems.154 IPV was associated with increased sputum weight in the patients with hypersecretion, but not in those without.

Reardon et al conducted a properly powered RCT of prophylactic IPV versus incentive spirometry with 18 patients with neurologic and neuromuscular disease over a 7-month period.155 Patients in the IPV group had no pneumonias or antibiotic use, compared to 3 infections and 44 days of antibiotic use in the incentive spirometry group. IPV was also associated with fewer hospitalizations and fewer missed school days.

Although the evidence is based on small sample sizes and only one RCT, (1) IPV appears to be safe, as long as it is done with close observation, and (2) prophylactic IPV in patients with ALS at risk for pneumonia may be associated with reduced hospitalization and antibiotic use.

What Are Clinicians To Do?

Without an overwhelmingly strong evidence base favoring any of the therapies discussed above, what are clini-
cians to do? The tables of therapies presented in this paper listed few, if any negative studies, yet there are few positive studies with high-level evidence either. Until additional studies are conducted that provide unequivocal guidance, it is prudent to follow the guidelines presented in recent reviews of secretion clearance therapies. 79–81 Four questions that might be considered when providing therapy are:

1. Is there a pathophysiologic rationale for using the therapy?
2. What is the potential for adverse effects?
3. What is the cost of the equipment for the therapy?
4. What are the patient’s preferences?

Hess has suggested the “n-of-1 trial” as a tool to help evaluate individual patient therapy decisions. 79–81 This tool can help provide an objective basis for identifying the best treatment for an individual patient. 156–160 The general concept involves identifying a list of potentially equal therapies, determining outcomes to be monitored, applying the therapies in a random order for a predetermined period, and monitoring and comparing the outcomes. Although it may not be feasible to conduct such a study with each patient, the basic concept is important to apply. We do not know definitively whether one therapy is better than another, so the therapy should be closely observed as each therapy is applied. Starting with a therapy that is most consistent with the patient’s pathophysiology and is least costly, the therapy is applied for a predetermined period and a set of observations are made. Of most importance is whether the patient, and other caregivers consider the therapy helpful. If the therapy did not help, discontinuation should be considered. If it does help, but there is another similar therapy that might also be beneficial, that therapy should be applied and assessed in a similar manner. Evaluated in this manner, the most appropriate therapy can be applied and those found not to be helpful stopped as soon as possible.

Summary

Respiratory compromise can increase morbidity and mortality in the elderly and in patients with neuromuscular disease. The inability to clear secretions is a major contributor to this compromise.

Although the normal aging process reduces pulmonary reserve, the reduction is usually not enough to be detrimental in the otherwise healthy elderly individual. This respiratory compromise often becomes a more concerning factor following physiologically stressful situations, such as surgery or pneumonia. It is important that clinicians be mindful of some core patient-care tenets, such as elevating the head of the bed to minimize reflux and aspiration, and to minimize the negative effects of an increasing closing volume on oxygenation. Close monitoring is warranted at all times, but particularly when receiving medications that might impact level of consciousness or respiratory drive. No secretion-clearance therapies that differ from routine appropriate care are specific to the elderly.

Patients with neuromuscular disease, on the other hand, do manifest both symptoms and comorbid effects, mainly as the result of not being able to take a deep breath or to generate an effective cough. Therapies such as manual cough assist, mechanical cough assist, HFCWC, and IPV have been used in this population. Although large, well-designed studies have not been conducted to prove any of these therapies beneficial, small studies have suggested benefit in certain circumstances. Being clear on the physiologic rationale for applying a particular therapy and closely monitoring the patient’s response to these interventions are most important when determining which treatment is best for a given patient.

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Discussion

Rubin: We need to be careful about a number of these studies. Many of these studies, especially with devices, were very short-term; they dealt with patient perception of breathlessness as primary outcome. They were crossover or diffi­
cult to mask because of the device being used. And the theoretical basis for these, particularly in patients with pro­foundly impaired cough, may be somewhat shaky. Again, there’s potential risk for reflex, aspiration, and patients who fail to protect their airway. So although a number of different devices have been used in patients with neuromuscular disease, if the patients were weak, the one that appears to be best studied in that population is the insufflator-exsufflator, and from Bach’s studies appears to be safe.2,3

Be very careful about extrapolating that to other devices that are expensive, that are not without risk, particularly in patients who are unable to protect their airways. We just don’t have enough data to recommend their use at this time.


3. Myers: It’s interesting, as you sit here and kind of reflect on this. It’s probably the group that could best uti­lize assisted airway clearance, but it is probably the least studied and least scientific of the studies that were conducted. And it’s an interesting area. I think, that we may want to look at in the future for those people who work with neuromuscular patients.

Haas: Yes, I think that it is a challenge. One of the things that kept coming up in the reviews is that, because a given therapy is being used in this population, is it ethical to conduct a study and withhold a therapy that they use regularly? It is an issue worth discus­sing. We won’t know the answer unless those studies are conducted.

Fink: From your description of the changes in the elderly, that maybe the applications of the techniques that we now reserve for patients with obstruc­tive lung disease might be applied for older patients with acute bronchitis as­sociated with pneumonia. Seeing the rise in closing volumes in the elderly, it strikes me that these look like candi­dates that might benefit from techniques like FET [forced expiration technique] and active cycle of breathing. Perhaps therapists should add these techniques to their armamentarium at the bedside when treating older patients who don’t have COPD [chronic obstructive pul­monary disease] but are having some acute problems clearing secretions.

Haas: I agree. It seems like they might be, but there was nothing in the literature to suggest that they are.

Homnick: Carl, that was a very nice presentation. I think one thing—and I just want to echo what Bruce said too—is that in these trials, especially crossover trials in patients with neu­romuscular disease with degenerative conditions, when crossing them over, they may be a different population, depending on the progression of the disease and the comorbidities that oc­cur during that period. So I’m not sure that crossover trials really are appropriate for this group.