

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 neuro-muscular 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 can not 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

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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 mechanics during the normal aging process and by neuropathologies. 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 mucociliary 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.⁹ 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.⁹ 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.¹⁶ 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

Table 1. Age-Related Structural Changes in the Respiratory System

Decreased alveolar surface area, due to diminished intra-alveolar fenestration
Increased interstitial connective tissue
Enlarged respiratory bronchioles and alveolar ducts (ductectasis)
Smaller airway diameter, due to destruction of supporting connective tissue
Increased proteolysis of elastin, reduced elastin/collagen ratio, reduced/ altered surfactant
Calcification of ribs and vertebral joints
Loss of respiratory accessory muscle mass

of direct or indirect smoking, and the effects of environmental exposure.¹⁸ The elderly are also more likely to be deconditioned or to have comorbidities that impact the respiratory system.¹⁹ 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.^{20–23}

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.¹⁵ 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.¹⁹ The term “senile emphysema” has been used to describe these age-related changes because of the functional similarities to emphysema,^{16,24} but these changes are associated with a homogeneous dilation of air spaces without destruction of tissue (as in emphysema), so the term “senile lung” may be more descriptive.^{25–27}

It has been suggested that cumulative oxidative damage by industrial and environmental factors might be partly responsible for this structural change and functional decline.¹⁵ Also, the lungs’ ability to clear particles from small airways appears to decrease with age.²⁸ The rate of mucociliary clearance is reduced in elderly subjects,^{29–31} as is the lung immune response and the ability to fight infection.^{32,33}

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.³⁴ These changes, as well as contractures of intercostal muscles, result in rigidity and reduced rib-cage mobility.³⁴ 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.^{35,36} The expiratory intercostal muscles atrophy by approximately 20% after 50 years of age, possibly due to a more sedentary lifestyle.³⁵ 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%.³⁷ 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.¹⁶ 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.¹⁶

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.³⁸ This closure of the terminal bronchioles

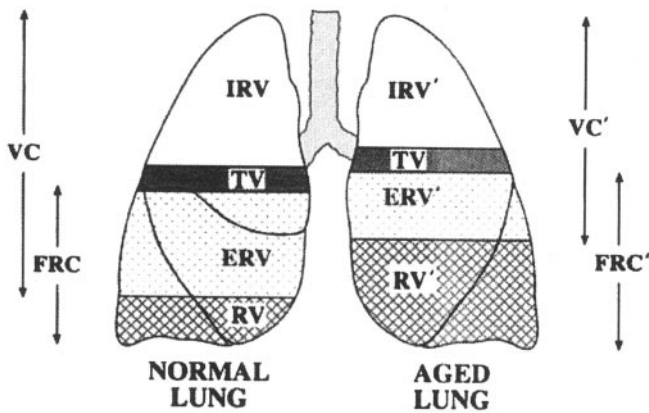


Fig. 1. Relative changes in lung volume associated with aging. IRV = inspiratory reserve volume. VC = vital capacity. TV = tidal volume. ERV = expiratory reserve volume. FRC = functional residual capacity. RV = residual volume. (From Reference 19, with permission.)

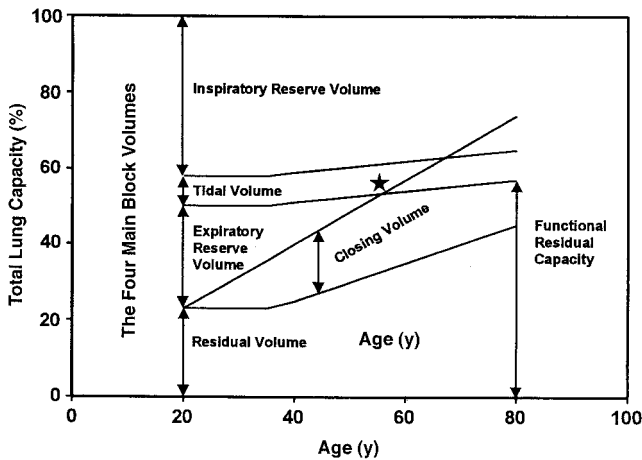


Fig. 2. Changes in lung volume over time. (From Reference 15, with permission.)

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.^{16,39} Carbon dioxide elimination appears to be unaffected, despite a slight increase in the dead-space ventilation ratio.^{40,41}

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.^{42,43}

Exercise and Ventilatory Response

Younger normal individuals are limited in exercise by circulation, not ventilation.^{19,44} 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.¹⁸ 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.¹⁹ But, despite these ventilatory changes, the elderly are still usually limited by circulation because of deconditioning or from changes in cardiovascular physiology.¹⁹ 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.⁴²

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.^{45,46} Minute ventilation response to elevated carbon dioxide during hypoxia is reduced during exercise in the elderly, compared to younger individuals.⁴⁷ Respiratory response to both hypoxemia and hypercarbia is decreased by 40–50% in a healthy 70-year-old.^{45,46}

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.⁶³ The healthy elderly individual is asymptomatic at rest, but functional reserve and the ability to compensate for various physiologic stressors is reduced.¹⁸ 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.⁶⁴ 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.⁶⁵ Elderly patients are approximately 30–50% more sensitive to propofol than are younger patients.^{65,66}

A particular respiratory concern is the increased risk of aspiration and pneumonia.^{19,67} Anesthetics and muscle relaxants compromise pharyngeal function and diminish the effectiveness of the cough mechanism, especially in the elderly.^{63,67,68} 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

Table 2. Age-Related Changes in Respiratory Function

Variable	Type of Change	Reference(s)
Respiratory muscle strength		
Maximum inspiratory pressure	Reduced	45, 48–50
Maximum expiratory pressure	Reduced	49
Maximum voluntary ventilation	Reduced	21, 51
Compliance		
Lung compliance	Increased	45, 52–54
Thoracic/chest wall compliance	Reduced	52, 55
Total compliance	Reduced	45, 55
Volumes and Flows		
Total lung capacity	Unchanged	21, 52
Functional residual capacity	Increased	52, 53
Residual volume	Increased	21, 55, 56
Closing volume	Increased	21, 38, 54
Forced vital capacity	Reduced	21, 23, 45, 53, 57, 58
Vital capacity	Reduced	53, 56
Inspiratory capacity	Reduced	53
FEV ₁	Reduced	20, 21, 23, 58
Peak expiratory flow	Decreased	51, 59
Gas Exchange		
Shunt	Increased	21
Diffusing capacity for carbon monoxide	Reduced	60
P _a O ₂	Reduced	39, 61
P _a CO ₂	Unchanged	61
Maximum oxygen consumption	Reduced	21
Dead-space ventilation (anatomic, physiologic)	Increased	39, 62
Ventilatory Response to		
Hypoxia	Reduced	45, 47
Hypercarbia	Reduced	45, 47

FEV₁ = 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.⁴ 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.⁶⁴ Much of the geriatric practice of drug prescription is therefore based on anecdotal experience or extrapolating results from studies of younger patients.⁶⁴

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*.^{12,69–73}

Table 3. Respiratory Muscles

<i>Inspiratory, primary</i>	
Diaphragm	
External intercostals	
Scalene	
<i>Inspiratory, accessory</i>	
Sternocleidomastoid	
Trapezius	
<i>Expiratory</i>	
Internal intercostals	
Internal and external obliques	
Transverse abdominus	
Rectus abdominus	
<i>Upper Airway</i>	
Abductors of vocal cords	
Palatal elevators	
Retractors of tongue	
Dilators of nares	

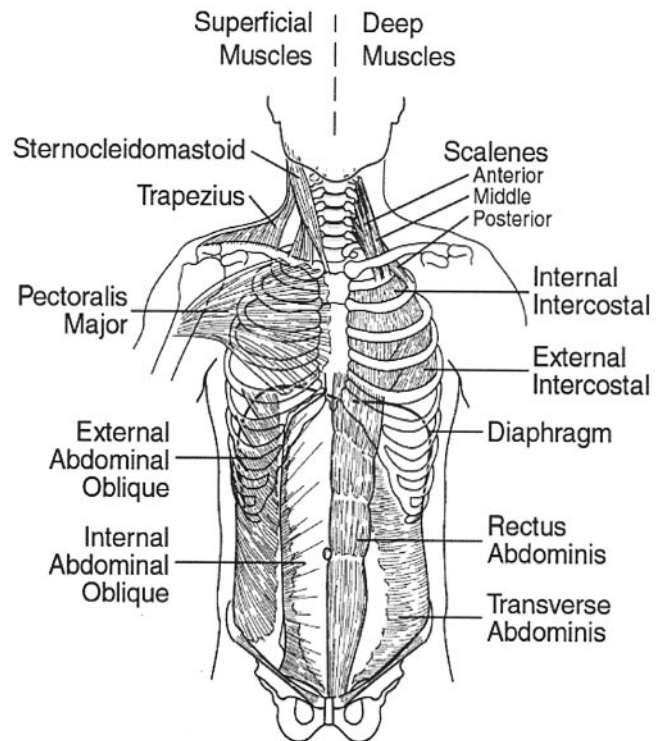


Fig. 3. The muscles of respiration. (From Reference 75, with permission.)

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.⁷⁴ 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.⁷⁵

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.^{70,76}

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.⁷³ 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.⁸

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.⁷⁷ The recommendations primarily focus on patients with chronic secretion 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).⁷⁸

Table 4. American College of Chest Physicians Evidence-Based Recommendations for Airway Clearance Therapies in Individuals with Neuromuscular Impairment

Patient Condition	Therapy	Level of Evidence	Benefit	Evidence Grade
Neuromuscular weakness and impaired cough	Respiratory muscle (expiratory) strength training	Expert opinion	Small	E*/C
Expiratory muscle weakness	Manual cough assist	Low	Small	C
Neuromuscular weakness and impaired cough	Mechanical cough assist	Low	Intermediate	C

*E = based on expert opinion (Adapted from Reference 77.)

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.^{79–81} 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.⁸¹

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.⁸² 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.^{83–85} 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.^{82,86–88} Nonrespiratory maneuvers, such as sit-ups and bicep curls, can also improve inspiratory and expiratory muscles.⁸⁵

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 pul-

monary disease, all 15 of the RCTs analyzed involved inspiratory muscle training.⁸⁹ 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.⁹⁰ In 1995, McCool and Tzelepis reviewed 8 non-controlled studies of inspiratory muscle training in neuromuscular disease.⁹¹ 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,^{86,88,93} post-polio,⁹⁵ spinal muscular atrophy,^{86,88} and myasthenia gravis.⁹⁷ Concern has been raised as to whether such training might harm patients with Duchenne muscular dystrophy by increasing muscle damage during the training session,³ 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.^{86,88} 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,^{92–94,98} only one measured peak cough flow.⁹⁸ Although the study by Chiara et al⁹⁸ found an increase in

AIRWAY CLEARANCE IN THE ELDERLY AND PATIENTS WITH NEUROLOGIC COMPROMISE

Table 5. Studies (1996 to 2006) of Respiratory Muscle Training in Patients With Neuromuscular Disease

First Author	Year	Design	n	Subjects (number in each group)	Muscles Targeted	Interventions	Duration of Training	Duration of De-training	Outcomes	Principle Findings and Conclusions
Smelzer ⁹²	1996	RCT	20	Multiple sclerosis	Expiratory	Threshold load vs sham; adjust for 75% of maximum expiratory pressure; train 5 d/wk.	3 mo	None	Maximum inspiratory pressure, maximum expiratory pressure	Increased maximum inspiratory and expiratory pressures
Gozal ⁹³	1999	RCT	42	Duchenne muscular dystrophy (21), matched controls (20) (all children)	Inspiratory and expiratory	Resistive load (2 sessions/d)	6 mo	12 mo	Maximum inspiratory pressure, maximum expiratory pressure, respiratory-load perception	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.
Gosselink ⁹⁴	2000	RCT	21	Multiple sclerosis	Expiratory	Threshold load at 60% of maximum expiratory pressure for 15 breaths × 3 sessions vs standard care	3 mo	3 mo	Maximum inspiratory pressure, maximum expiratory pressure, FVC, FEV ₁ , pulmonary index	Improved maximum inspiratory and expiratory pressures, compared to baseline, but not compared to control. Pulmonary index improved, compared to baseline and to control. After 6 mo, pulmonary index remained better in the trained group.
Klefbeck ⁹⁵	2000	Before-after	10	Prior polio, using part-time noninvasive positive pressure ventilation for hypoventilation. 7 subjects trained. 3 did not train.	Inspiratory	Resistive load daily for 20 min (1 min train, 1 min rest × 10 times)	10 wk	13 wk	Maximum inspiratory pressure, maximum expiratory pressure, endurance capacity, spirometry, questions about activities of daily living	Improved inspiratory endurance capacity and activities of daily living
Winkler ⁸⁸	2000	Before-after	16	Duchenne muscular dystrophy (13), spinal muscular atrophy (3). Stratified by VC (decline of <10% vs >10% during 12-mo pre-training)	Inspiratory	Resistive load, 10 breaths × 2/d, adjusted every 3 mo to 70–80% of maximum inspiratory pressure; 15 min prior to resistance, 10 maximum static inspiratory efforts of at least 90% of maximum inspiratory pressure	9 mo	None	Maximum inspiratory pressure, 12-s maximum voluntary ventilation, VC	In both groups, improved maximum inspiratory pressure and 12-s maximum voluntary ventilation. No significant decrease in VC
Koessler ⁸⁶	2001	Before-after	27	Duchenne muscular dystrophy (18), spinal muscular atrophy (18). Stratified by %of-predicted VC (27–50%, 51–70%, 71–96%)	Inspiratory	Resistive load, 10 breaths × 2/d, adjusted every 3 mo to 70–80% of maximum inspiratory pressure 15 min prior to resistance, 10 maximum static inspiratory efforts of at least 90% of maximum inspiratory pressure	24 mo	None	Maximum inspiratory pressure, 12-s maximum voluntary ventilation, VC	In all groups, improved maximum inspiratory pressure and 12-s maximum voluntary ventilation until 10th month, then plateau. No significant decrease in VC
Klefbeck ⁹⁶	2003	RCT	15	Multiple sclerosis	Inspiratory	Threshold load, 2 sessions every other day, 10 min/session	10 wk	30 d	Maximum inspiratory pressure, maximum expiratory pressure, perception of fatigue	Maximum inspiratory and expiratory pressures increased. Maximum inspiratory pressure sustained for at least 10 d. Recommended as a complement to ordinary physical training
Fregonezi ⁹⁷	2005	RCT	27	Myasthenia gravis	Inspiratory	Increasing resistive load and breathing retraining × 3 sessions/wk (45 min; 10 min diaphragmatic breathing, 10 min resistance-load, 10 min pursed-lip breathing, 5 min break between) load increased from 20% to 60% of maximum inspiratory pressure	8 wk	None	Maximum inspiratory pressure, maximum expiratory pressure, ratio of respiratory rate to tidal volume, upper chest wall expansion and reduction	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
Chiara ⁹⁸	2006	Before-after	31	Multiple sclerosis (17), healthy matched controls (14)	Expiratory	Resistive load × 5 sessions/wk; 4 sets of 6 repetitions/session	8 wk	4 wk	Maximum expiratory pressure, FVC, FEV ₁ , peak expiratory flow, peak cough flow	Improved maximum expiratory pressure. No difference in peak cough flow as a whole. Those with moderate disability had improved peak cough flow. Those with mild disability had no change.

RCT = randomized controlled trial
 FVC = forced vital capacity
 FEV₁ = 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 expiratory muscles or structural defects of the abdominal wall can show an outward motion of the abdomen during coughing.⁸ 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.⁸ Another method, which also augments the efficiency of the expiratory 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 expiratory 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.^{100–103} 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.¹¹³ 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.^{114,115}

The in-exsufflation concept was first described in the mid-1950s, by Beck and colleagues, who used it with poliomyelitis patients.^{116–119} In-exsufflation fell out of favor in the 1960s, with the introduction of more invasive techniques.¹⁰⁷ 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.^{107,108}

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

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Table 6. Studies of Manually Assisted Cough Techniques in Patients With Neuromuscular Disease

First Author	Year	Design	n	Subjects (number in each group)	Interventions	Outcomes	Principle Findings	Conclusions
Kang ⁹⁹	2000	Crossover	108	Neuromuscular disease	<ul style="list-style-type: none"> Unassisted cough Manually assisted cough after maximum inspiratory capacity with stacked breaths via manual ventilator if VC < 1.5 L 	Peak cough flow	In group 1 (n = 90) maximum inspiratory capacity was > VC. In group 2 (n = 18) VC = maximum inspiratory capacity due to bulbar involvement and inability to a make tight seal. Unassisted peak cough flow increased by 78% in group 1 and by 12% in group 2. 49 of 90 had unassisted peak cough flow < 2.7 L/s. 37 of 49 subjects improved > 2.7 L/min with manually assisted cough.	When VC is < 1.5 L, manually assisted cough should be preceded by maximum inspiratory capacity. Inflation pressure of 40–60 cm H ₂ O usually required.
Sivasothy ¹⁰⁰	2001	Randomized crossover	29	Normal (9), COPD (8), respiratory muscle weakness without scoliosis (8), respiratory muscle weakness with scoliosis (4)	<ul style="list-style-type: none"> Unassisted cough Manually assisted cough In-exsufflation Combination 	Peak cough flow, patient comfort	Respiratory muscle weakness with scoliosis, peak cough flow; unassisted cough = 288 L/min, manually assisted cough = 193 L/min, in-exsufflation = 231 L/min, combination = 362 L/min. Respiratory muscle weakness without scoliosis, peak cough flow; unassisted cough = 104 L/min, manually assisted cough = 185 L/min, in-exsufflation = 156 L/min, combination = 248 L/min	Manually assisted cough and in-exsufflation should be considered in patients with respiratory muscle weakness without scoliosis, but not those with scoliosis.
Chatwin ¹⁰¹	2003	Randomized crossover	41	Study: spinal muscular atrophy (10), Duchenne muscular dystrophy (6), polio (3), congenital muscular dystrophy (3). Control: age-matched normals (19)	<ul style="list-style-type: none"> Unassisted cough Manually assisted cough Inspiratory assist via BiPAP, Mechanical exsufflation Mechanical insufflation Mechanical in-exsufflation 	Peak cough flow, patient comfort	Peak cough flow: unassisted cough = 169 L/min, manually assisted cough = 188 L/min, BiPAP assist = 182 L/min, mechanical exsufflation = 235 L/min, in-exsufflation = 297 L/min	In-exsufflation produced greater peak cough flow than other techniques. Patients preferred in-exsufflation.
Mustfa ¹⁰²	2003	Randomized crossover	57	ALS with bulbar dysfunction (21), ALS without bulbar involvement (26), healthy controls (10)	<ul style="list-style-type: none"> Unassisted cough Manually assisted cough Mechanical exsufflation, Mechanical insufflation, Mechanical in-exsufflation 	Peak cough flow, VC, maximum inspiratory pressure	Manually assisted cough augmented peak cough flow by 13% in nonbulbar vs 11% in bulbar disease.	Greatest improvement was in patients with weakest cough.
Sancho ¹⁰³	2004	Crossover	26	ALS: nonbulbar (11), bulbar (15)	<ul style="list-style-type: none"> Unassisted cough Maximum inspiratory capacity via manual resuscitator (breath-stacking) In-exsufflation Manually assisted cough after maximum inspiratory capacity Manually assisted cough after in-exsufflation 	Peak cough flow, maximum inspiratory capacity, VC	Peak cough flow in-exsufflation < maximum inspiratory capacity in patients with minimal lung impairment (peak cough flow maximum inspiratory capacity > 4 L/s); peak cough flow in-exsufflation > 2.7 L/s in all patients except patients with bulbar dysfunction and maximum inspiratory capacity > 1 L and peak cough flow maximum inspiratory capacity < 2.7 L/s.	Reduced peak cough flow in patients with bulbar involvement, most likely due to dynamic collapse of upper airway.
Kang ¹⁰⁴	2005	Crossover	51	Duchenne muscular dystrophy	<ul style="list-style-type: none"> Unassisted cough Manually assisted cough after maximum inspiration via stacked breaths Manually assisted cough after inspiratory breath-stacking 	Peak cough flow	Peak cough flow: unassisted = 218 L/min, manually assisted = 251 L/min, maximum inspiration via stacked breaths = 258 L/min, manually assisted cough after inspiratory breath-stacking = 286 L/min	Importance of inspiratory assist should be emphasized.
Trebbia ¹⁰⁵	2005	Randomized crossover	10	Chronic respiratory failure due to Duchenne muscular dystrophy (6) or other neuromuscular disease (4)	<ul style="list-style-type: none"> Manually assisted cough Maximum inspiration via IPPB Both the above Compared to baseline 	Peak cough flow, VC	IPPB pressure 31 ± 7 cm H ₂ O. Compared to baseline (per graph): VC with mechanical insufflation > IPPB > manually assisted cough > baseline Peak cough flow with mechanical insufflation > IPPB = manually assisted cough > baseline	Study suggests that inspiratory assist and manually assisted cough should be used in combination.
Kang ¹⁰⁶	2006	Crossover	40	Traumatic spinal cord injury	<ul style="list-style-type: none"> Unassisted Volume-assisted via breath-stacking Manually assisted cough Volume-assisted followed by manually assisted cough 	Peak cough flow, maximum inspiratory pressure, maximum expiratory pressure	Peak cough flow: unassisted = 228 L/s, volume-assisted = 277 L/s, manually assisted cough = 324 L/s, volume-assisted plus manually assisted cough = 362 L/min. Maximum inspiratory pressure had better correlation than maximum expiratory pressure to all 4 cough methods.	Management of inspiratory muscle strength is important

VC = vital capacity
 COPD = chronic obstructive pulmonary disease
 BiPAP = bi-level 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

First Author	Year	Design	n	Subjects (number in each group)	Interventions	In-exsufflation Pressures (cm H ₂ O)	Outcomes	Principle Findings and Conclusions
Bach ¹⁰⁷	1993	Crossover	21	Ventilator-dependent neuromuscular disease: polio (10), muscular dystrophy (5), spinal cord injury (5), myasthenia gravis (1)	<ul style="list-style-type: none"> • Unassisted cough • Maximum inspiratory capacity via breath-stacking or glossopharyngeal breathing • Manually assisted cough after maximum inspiratory capacity • In-exsufflation 	Maximum tolerated	VC, maximum inspiratory capacity, peak cough flow	VC = 490 mL. Maximum inspiratory capacity = 1,670 mL. Peak cough flow: unassisted cough = 1.8 L/s, maximum inspiratory capacity via breath-stacking or glossopharyngeal breathing = 3.4 L/s, manually assisted cough after maximum inspiratory capacity = 4.3 L/s, in-exsufflation = 7.5 L/s. Manually assisted cough and in-exsufflation are safe and effective.
Bach ¹⁰⁸	1993	Crossover	9	Post-polio	<ul style="list-style-type: none"> • Unassisted cough • Maximum inspiratory capacity via breath-stacking or glossopharyngeal breathing • Manually assisted cough after maximum inspiratory capacity • In-exsufflation 	Maximum tolerated	VC, maximum inspiratory capacity, peak cough flow	VC = 540 mL. Maximum inspiratory capacity = 1,880 mL. Peak cough flow: unassisted cough = 1.8 L/s, maximum inspiratory capacity via breath-stacking or glossopharyngeal breathing = 3.8 L/s, manually assisted cough after maximum inspiratory capacity = 4.6 L/s, in-exsufflation = 7.0 L/s. Manually assisted cough and in-exsufflation are safe and effective.
Sivasothy ¹⁰⁰	2001	Randomized crossover	29	Normal (9), respiratory muscle weakness without scoliosis (7 ALS, 1 Becker's muscular dystrophy), respiratory muscle weakness with scoliosis (2 polio, 1 Duchenne muscular dystrophy, 1 spondylometaphyseal dysplasia), COPD (8)	<ul style="list-style-type: none"> • Unassisted cough • Manually assisted cough • In-exsufflation • Combination 	20/-20	Peak cough flow, patient comfort	Respiratory muscle weakness with scoliosis: peak cough flow: unassisted cough = 288 L/min, manually assisted cough = 193 L/min, in-exsufflation = 231 L/min, combination = 362 L/min. Respiratory muscle weakness without scoliosis: peak cough flow: unassisted cough = 104 L/min, manually assisted cough = 185 L/min, in-exsufflation = 156 L/min, combination = 248 L/min. In-exsufflation alone had no effect, but manually assisted cough alone or manually assisted cough with in-exsufflation improved cough clearance.
Chatwin ¹⁰¹	2003	Randomized crossover	41	Study: spinal muscular atrophy (10), Duchenne muscular dystrophy (6), polio (3), congenital muscular dystrophy (3). Control: normal age-matched (19)	<ul style="list-style-type: none"> • Unassisted cough • Manually assisted cough • Inspiratory assist via BiPAP • Mechanical exsufflation • Mechanical insufflation • Mechanical in-exsufflation 	Subjects: 15/-15 Control: 17/-8	Peak cough flow, patient comfort	Peak cough flow for study group: unassisted cough = 169 L/min, manually assisted cough = 188 L/min, inspiratory assist via BiPAP = 182 L/min, mechanical exsufflation = 235 L/min, mechanical in-exsufflation = 297 L/min. Subjects claimed greatest cough assistance with mechanical in-exsufflation. In-exsufflation produced greatest increase in peak cough flow and is well tolerated.
Sancho ¹⁰⁹	2003	Crossover	6	ALS with severe bulbar dysfunction. All ventilator-dependent and tracheostomized	<ul style="list-style-type: none"> • Deep tracheal suctioning • In-exsufflation with superficial tracheal suctioning 	40/-40	Volume of secretions, patient satisfaction	No statistical difference in sputum volume or weight (trend favored in-exsufflation). Patients preferred in-exsufflation.
Mustfa ¹⁰²	2003	Randomized crossover	57	ALS with bulbar dysfunction (21), ALS without bulbar involvement (26), healthy controls (10)	<ul style="list-style-type: none"> • Unassisted cough • Manually assisted cough • Mechanical exsufflation • Mechanical insufflation • Mechanical in-exsufflation 	Maximum tolerated	Peak cough flow, VC, maximum inspiratory pressure	Peak cough flow, bulbar: unassisted cough = 178 L/min, manually assisted cough = 197 L/min, mechanical exsufflation = 225 L/min, mechanical insufflation = 188 L/min, in-exsufflation = 212 L/min. Peak cough flow, nonbulbar: unassisted cough = 217 L/min, manually assisted cough = 244 L/min, mechanical exsufflation = 279 L/min, mechanical insufflation only = 226 L/min, mechanical in-exsufflation = 264 L/min. Greatest improvement was in those with weakest cough.
Winck ¹¹⁰	2004	Crossover	29	ALS (13), other neuromuscular disease (7), COPD (9). All had secretions and low S _p O ₂	In-exsufflation at 3 pressures	15/-15 30/-30 40/-40	Peak cough flow, S _p O ₂ , Borg dyspnea score	Neuromuscular disease: peak cough flow at ± 40 cm H ₂ O = 180 L/min vs 220 L/min, S _p O ₂ = 94% vs 98%, Borg score (2.0 vs 0.75). ALS: peak cough flow at ± 40 cm H ₂ O = 170 L/min vs 200 L/min, S _p O ₂ = 94% v 98%. In-exsufflation can increase peak cough flow and S _p O ₂ .
Sancho ¹⁰³	2004	Crossover	26	ALS: nonbulbar (11), bulbar (15)	<ul style="list-style-type: none"> • Unassisted cough • Maximum inspiratory capacity via manual resuscitator (breath-stacking) • In-exsufflation • Manually assisted cough after maximum inspiratory capacity • Manually assisted cough after in-exsufflation 	40/-40	Peak cough flow, maximum inspiratory capacity, VC	Peak cough flow with in-exsufflation < with maximum inspiratory capacity in patients with minimal lung impairment (peak cough flow with maximum inspiratory capacity > 4 L/s); peak cough flow with in-exsufflation > 2.7 L/s in all subjects except those with bulbar dysfunction and maximum inspiratory capacity > 1 L and peak cough flow maximum inspiratory capacity < 2.7 L/s (most likely due to dynamic upper-airway collapse).

(Continued)

Table 7. (Continued)

First Author	Year	Design	n	Subjects (number in each group)	Interventions	In-exsufflation Pressures (cm H ₂ O)	Outcomes	Principle Findings and Conclusions
Vianello ¹¹¹	2005	Prospective vs matched historical controls	27	Study: muscular dystrophy (6), ALS (2), spinal muscular atrophy (3). Control: muscular dystrophy (9), ALS (6), congenital muscular dystrophy (1). All had upper-respiratory tract infection and secretions.	· In-exsufflation plus CPT · CPT only	As tolerated. Mean 19 ± 3/ -33 ± 4.6	Treatment failure (artificial airway, intolerance). Need for bronchoscopy	In-exsufflation was associated with fewer treatment failures (18% vs 63%). Bronchoscopy rate was similar (45% vs 38%). Adding in-exsufflation to CPT may improve airway mucus clearance.
Pillastrini ¹¹²	2006	Randomized control trial	NR	Spinal cord injury (C1-C7) with tracheostomy and hypersecretion. Number of subjects not reported.	Control: · CPT · PEP · Bag-valve-mask suction Study: · In-exsufflation	15 to 45/ -15 to -45	Arterial blood gas values, FEV ₁ , FEV ₁ /FVC, peak cough flow	In-exsufflation was associated with improved pulmonary function but similar arterial blood gas values.

VC = vital capacity

ALS = amyotrophic lateral sclerosis

COPD = chronic obstructive pulmonary disease

BiPAP = bi-level positive airway pressure

S_pO₂ = blood oxygen saturation measured via pulse oximetry

CPT = chest physical therapy

NR = not reported

PEP = positive expiratory pressure

FEV₁ = forced expiratory volume in the first second

FVC = forced vital capacity

that study was limited in that the authors did not report conducting a power analysis to determine proper sample size, nor report the sample size studied.¹¹² 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. The reports by Bach et al also describe the use of glossopharyngeal breathing to achieve maximum inspiratory capacity, which the patient can do without assistance.^{107,108} 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.¹²⁰ It has been used by patients post-polio,^{120,121} and has also been reported to be useful for increasing maximum inspiratory capacity and peak cough flow in patients with spinal cord injury^{122,123} and Duchenne muscular dystrophy, as long as bulbar involvement is not severe.¹²⁴

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.¹²⁵ 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.

Bach et al have been very prolific in reporting their use of this and other therapies for patients with neuromuscular disease, and have reported several retrospective reviews of a protocol that was introduced in 1993,^{13,107,108,126,127} as well as insightful editorials^{128–131} and reviews.^{132,133} Before 1993, their patients were treated, apparently, with noninvasive positive-pressure ventilation and manually assisted cough. In 1993, they changed their practice to include home pulse oximetry monitoring and use of a manual resuscitation bag to give deep breaths prior to manually assisted cough. When the peak cough flow dropped below 270 L/min and an increased risk of a respiratory infection was noted, in-exsufflation and a portable volume ventilator were made available. At that point, most of the patients had a vital capacity of < 1.0 L, so breath-stacking with the

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-stacking 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 osteoporotic 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 mucus clearance.^{136,137} HFCWC is thought to enhance mucus clearance by reducing the viscosity of the sputum,^{136,138} augmenting cephalad mucus shearing at the air-mucus interface,^{136,139,140} enhancing ciliary beating,¹³⁶ 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.¹⁵¹ 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

First Author	Year	Design	n	Subjects	Interventions	Duration	Outcomes	Principle Findings and Conclusions
Plioplys ¹⁴⁸	2002	Before-after	7	Quadriplegic cerebral palsy with frequent pulmonary infection	HFCWC	Variable	Hospitalization and pneumonia rate	Fewer pneumonias that required antibiotics (36/y vs 18/y). Fewer hospitalizations for pneumonia (9/y vs 3/y). Improved effectiveness of suctioning.
Giarrappa ¹⁴⁹	2005	Before-after	15	Familial dysautonomia	HFCWC at pressure setting of 3–5, frequency of 10–15 Hz, twice a day	Pre-study 12-mo period vs 12-mo of therapy	S _{pO₂} , pulmonary function test results, incidence of pneumonia, hospitalization, antibiotic use, doctor visits, absenteeism	Sustained improvement in S _{pO₂} , 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).
Lange ¹⁵⁰	2006	Multi-center RCT	46	Amyotrophic lateral sclerosis	· No therapy · HFCWC at 10–12 Hz for 10–15 min, twice a day	12 wk	Primary: pulmonary function Secondary: safety and tolerance	HFCWC users had less breathlessness and coughed more at night. In subjects with baseline FVC of 40–70% of predicted, HFCWC was associated with less decline in FVC and capnography values. HFCWC had high patient satisfaction (79%). Nonsignificant trend toward better peak expiratory flow with HFCWC.
Chaisson ¹⁵¹	2006	Single-center RCT	9	Amyotrophic lateral sclerosis	· Standard care · Standard care plus HFCWC twice daily for 15 min	Variable, until death	Time to death, arterial oxygen saturation, FVC, adverse events	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.

HFCWC = high-frequency chest wall compression

S_{pO₂} = 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 sug-

gest 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

First Author	Year	Design	n	Subjects	Interventions	Duration	Outcomes	Principle Findings and Conclusion
Birnkrant ¹⁵³	1996	Case report	4	Neuromuscular disease (3), atelectasis (1)	IPV	Variable	S _{pO₂} , chest radiograph	3 subjects had improved S _{pO₂} and chest radiograph findings quickly; 4th subject had slower improvement; 1 subject decompensated due to airway obstruction from secretions during therapy. IPV is safe with close observation.
Toussaint ¹⁵⁴	2003	Randomized crossover trial	8	Duchenne muscular dystrophy, 5 subjects had mucus hypersecretion	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.	3 sessions/d for 5 d = 15 sessions	Secretion weight, heart rate, respiratory rate, S _{pO₂} , end-tidal carbon dioxide	Among subjects with hypersecretion, greater sputum weight with IPV (3.9 g vs 6.5 g). No difference in sputum weight in subjects without hypersecretion. No difference in other measures. IPV is safe and increases effectiveness of assisted mucus clearance techniques.
Reardon ¹⁵⁵	2005	Randomized controlled trial	18	Neuromuscular disease	Prophylactic IPV vs incentive spirometry	Variable (study went for 7 months)	Days on antibiotics, hospitalization for respiratory issue, school days lost	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 5 d). IPV was safe and well tolerated.

IPV = intrapulmonary percussive ventilation
S_{pO₂} = blood oxygen saturation measured via pulse oximetry.

sis¹⁴⁶ 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 pa-

tients 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 patient 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.

REFERENCES

1. Bach JR, Rajaraman R, Ballanger F, Tzeng AC, Ishikawa Y, Kulesa R, Bansal T. Neuromuscular ventilatory insufficiency: effect of home mechanical ventilator use v oxygen therapy on pneumonia and hospitalization rates. *Am J Phys Med Rehabil* 1998;77(1):8–19.
2. Kang SW. Pulmonary rehabilitation in patients with neuromuscular disease. *Yonsei Med J* 2006;47(3):307–314.
3. Finder JD, Birnkrant D, Carl J, Farber HJ, Gozal D, Iannaccone ST, et al. Respiratory care of the patient with Duchenne muscular dystrophy. ATS consensus statement. *Am J Respir Crit Care Med* 2004;170(4):456–465.
4. Seymour DG, Vaz FG. A prospective study of elderly general surgical patients: II. Post-operative complications. *Age Ageing* 1989;18(5):316–326.
5. Warwick WJ. Mechanisms of mucous transport. *Eur J Respir Dis Suppl* 1983;127:162–167.
6. Rubin BK. Physiology of airway mucus clearance. *Respir Care* 2002;47(7):761–768.
7. Wanner A. Mucociliary and mucus secretory function. *Am Rev Respir Dis* 1985;131(Suppl):S36–S38.
8. Irwin RS, Boulet LP, Cloutier MM, Fuller R, Gold PM, Hoffstein V, et al. Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. *Chest* 1998;114(2 Suppl Managing):133S–181S.
9. Leith DE. The development of cough. *Am Rev Respir Dis* 1985;131(5):S39–S42.
10. McCool FD. Global physiology and pathophysiology of cough. ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(1 Suppl):48S–53S.
11. Leith DE. Cough. *Phys Ther* 1968;48(5):439–447.
12. Boitano LJ. Management of airway clearance in neuromuscular disease. *Respir Care* 2006;51(8):913–922.
13. Bach JR, Ishikawa Y, Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. *Chest* 1997;112(4):1024–1028.
14. Bach JR, Saporito LR. Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure: a different approach to weaning. *Chest* 1996;110(6):1566–1571.
15. Zaugg M, Lucchinetti E. Respiratory function in the elderly. *Anesthesiol Clin North America* 2000;18(1):47–58.

16. Janssens JP, Pache PC, Nicod LP. Physiological changes in respiratory function associated with ageing. *Eur Respir J* 1999;13(1):197–205.
17. Rosenthal RA, Kavic SM. Assessment and management of the geriatric patient. *Crit Care Med* 2004;32(Suppl):S92–S105.
18. Zeleznik J. Normative aging of the respiratory system. *Clin Geriatr Med* 2003;19(1):1–18.
19. Chan ED, Welsh CH. Geriatric respiratory medicine. *Chest* 1998;114(6):1704–1733.
20. Burrows B, Lebowitz MD, Camilli AE, Knudson RJ. Longitudinal changes in forced expiratory volume in one second in adults. Methodologic considerations and findings in healthy nonsmokers. *Am Rev Respir Dis* 1986;133(6):974–980.
21. McClaran SR, Babcock MA, Pegelow DF, Reddan WG, Dempsey JA. Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. *J Appl Physiol* 1995;78(5):1957–1968.
22. Weiss ST, Ware JH. Overview of issues in the longitudinal analysis of respiratory data. *Am J Respir Crit Care Med* 1996;154(6 Pt 2):S208–S211.
23. Van Pelt W, Borsboom GJ, Rijcken B, Schouten JP, Van Zomeren BC, Quanjer PH. Discrepancies between longitudinal and cross-sectional changes in ventilatory function in 12 years of follow-up. *Am J Respir Crit Care Med* 1994;149(5):1218–1226.
24. Gillooly M, Lamb D. Airspace size in lungs of lifelong non-smokers: effect of age and sex. *Thorax* 1993;48(1):39–43.
25. Verbeke EK, Cauberghs M, Mertens I, Clement J, Lauweryns JM, Van de Woestijne KP. The senile lung: comparison with normal and emphysematous lungs, part 1. Structural aspects. *Chest* 1992;101(3):793–799.
26. Verbeke EK, Cauberghs M, Mertens I, J C, Lauweryns JM, Van de Woestijne KP. The senile lung: comparison with normal and emphysematous lungs, part 2. Functional aspects. *Chest* 1992;101(3):800–809.
27. Teramoto S, Ishii M. Aging, the aging lung, and senile emphysema are different. *Am J Respir Crit Care Med* 2007;175(2):197–198.
28. Svartengren M, Falk R, Philipson K. Long-term clearance from small airways decreases with age. *Eur Respir J* 2005;26(4):609–615.
29. Puchelle E, Zahm JM, Bertrand A. Influence of age on bronchial mucociliary transport. *Scand J Respir Dis* 1979;60(6):307–313.
30. Ho JC, Chan KN, Hu WH, Lam WK, Zheng L, Tipoe GL, et al. The effect of aging on nasal mucociliary clearance, beat frequency, and ultrastructure of respiratory cilia. *Am J Respir Crit Care Med* 2001;163(4):983–988.
31. Incalzi RA, Maini CL, Fuso L, Giordano A, Carbonin P, Galli G. Effects of aging on mucociliary clearance. *Compr Gerontol [A]* 1989;3(Suppl):65–68.
32. Meyer KC. The role of immunity in susceptibility to respiratory infection in the aging lung. *Respir Physiol* 2001;128(1):23–31.
33. Meyer KC. Lung infections and aging. *Ageing Res Rev* 2004;3(1):55–67.
34. Teale C, Romaniuk C, Mulley G. Calcification on chest radiographs: the association with age. *Age Ageing* 1989;18(5):333–336.
35. Mizuno M. Human respiratory muscles: fibre morphology and capillary supply. *Eur Respir J* 1991;4(5):587–601.
36. Polla B, D'Antona G, Bottinelli R, Reggiani C. Respiratory muscle fibres: specialization and plasticity. *Thorax* 2004;59(9):808–817.
37. El Solh AA, Ramadan FH. Overview of respiratory failure in older adults. *J Intensive Care Med* 2006;21(6):345–351.
38. Leblanc P, Ruff F, Milic-Emili J. Effects of age and body position on "airway closure" in man. *J Appl Physiol* 1970;28(4):448–451.
39. Cardús J, Burbos F, Diaz O, Roca J, Barberà JA, Marrades RM, et al. Increase in pulmonary ventilation-perfusion inequality with age in healthy individuals. *Am J Respir Crit Care Med* 1997;156(2 Pt 1):648–653.
40. Janssens JP. Aging of the respiratory system: impact on pulmonary function tests and adaptation to exertion. *Clin Chest Med* 2005;26(3):469–484.
41. Tenney SM, Miller RM. Dead space ventilation in old age. *J Appl Physiol* 1956;9(3):321–327.
42. Chaunчайyakul R, Groeller H, Clarke JR, Taylor NA. The impact of aging and habitual physical activity on static respiratory work at rest and during exercise. *Am J Physiol Lung Cell Mol Physiol* 2004;287(6):L1098–L1106.
43. Pollock ML, Mengelkoch LJ, Graves JE, Lowenthal DT, Limacher MC, Foster C, Wilmore JH. Twenty-year follow-up of aerobic power and body composition of older track athletes. *J Appl Physiol* 1997;82(5):1508–1516.
44. Lone AA. Respiratory disorders of the elderly. *J Pharm Pract* 2000;13(4):297–307.
45. Peterson DD, Pack AI, Silage DA, Fishman AP. Effects of aging on ventilatory and occlusion pressure responses to hypoxia and hypercarbia. *Am Rev Respir Dis* 1981;124(4):387–391.
46. Kronenberg RS, Drage CW. Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. *J Clin Invest* 1973;52(8):1812–1819.
47. Poulin MJ, Cunningham DA, Paterson DH, Kowalchuk JM, Smith WDF. Ventilatory sensitivity to CO₂ in hyperoxia and hypoxia in older aged humans. *J Appl Physiol* 1993;75(5):2209–2216.
48. Harik-Khan RI, Wise RA, Fozard JL. Determinants of maximal inspiratory pressure. The Baltimore Longitudinal Study of Aging. *Am J Respir Crit Care Med* 1998;158(5 Pt 1):1459–1464.
49. Enright PL, Kronmal RA, Manolio TA, Schenker MB, Hyatt RE. Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. *Am J Respir Crit Care Med* 1994;149(2 Pt 1):430–438.
50. Hautmann H, Hefele S, Schotten K, Huber RM. Maximal inspiratory mouth pressures (PIMAX) in healthy subjects—what is the lower limit of normal? *Respir Med* 2000;94(7):689–693.
51. Delorey DS, Babb TG. Progressive mechanical ventilatory constraints with aging. *Am J Respir Crit Care Med* 1999;160(1):169–177.
52. Turner JM, Wohl MA. Elasticity of human lungs in relations to age. *J Appl Physiol* 1968;25(6):664–671.
53. Cohen JE, Donoso HD. Mechanical properties of lung in normal men over 60 years old. *J Clin Invest* 1963;42(9):1406–1410.
54. Begin R, Renzetti AD, Bigler AH, Wantanabe S. Flow and age dependence of airway closure and dynamic compliance. *J Appl Physiol* 1975;38(2):199–207.
55. Mittman C, Edelman NH, Norris AH, Shock NW. Relationship between chest wall and pulmonary compliance and age. *J Appl Physiol* 1964;20(6):1211–1216.
56. Permutt S, Martin HB. Static pressure-volume characteristics of lungs in normal males. *J Appl Physiol* 1960;15(5):819–825.
57. de Bisschop C, Marty ML, Tessler JF, Bargerger-Gateau P, Dartigues JF, Geunenard H. Expiratory flow limitation and obstruction in the elderly. *Eur Respir J* 2005;26(4):594–601.
58. Dockery DW, Ware JH, Ferris BG, Glicksberg DS, Fay ME, Spiro III A, Speizer FE. Distribution of forced expiratory volume in one second and forced vital capacity in healthy, white, adult never smokers in six U.S. cities. *Am Rev Respir Dis* 1985;131(4):511–520.
59. Sprung J, Gajic O, Warner DO. Age related alterations in respiratory function—anesthetic considerations. *Can J Anesth* 2006;53(12):1244–1257.

60. Stam H, Hrachovina V, Stijnen T, Versprille A. Diffusing capacity dependent on lung volume and age in normal subjects. *J Appl Physiol* 1994;76(6):2356–2363.
61. Sorbini CA, Solinas VG, Muiestas G. Arterial oxygen tension in relation to age in healthy subjects. *Respiration* 1968;25(1):3–13.
62. Raine JM, Bishop JM. A-a difference in O₂ tension and physiological dead space in normal man. *J Appl Physiol* 1963;18(2):284–288.
63. Cook DJ, Rooke GA. Priorities in perioperative geriatrics. *Anesth Analg* 2003;96(6):1823–1836.
64. McLean AJ, Le Couteur DG. Aging biology and geriatric clinical pharmacology. *Pharmacol Rev* 2004;56(2):163–184.
65. Tsui BC, Wagner A, Finucane B. Regional anaesthesia in the elderly: a clinical guide. *Drugs Aging* 2004;21(14):895–910.
66. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ. The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999;90(6):1502–1516.
67. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med* 2001;344(9):665–671.
68. Aviv JE. Effects of aging on sensitivity of the pharyngeal and supraglottic areas. *Am J Med* 1997;103(5A):74S–76S.
69. Mehta S. Neuromuscular disease causing acute respiratory failure. *Respir Care* 2006;51(9):1016–1021.
70. Benditt JO. The neuromuscular respiratory system: physiology, pathophysiology, and a respiratory care approach to patients. *Respir Care* 2006;51(8):829–837.
71. Brown R, DiMarco AF, Hoit JD, Garshick E. Respiratory dysfunction and management in spinal cord injury. *Respir Care* 2006;51(8):853–868.
72. Lechtzin N. Respiratory effects of amyotrophic lateral sclerosis: problems and solutions. *Respir Care* 2006;51(8):871–881.
73. Hill NS. Neuromuscular disease in respiratory and critical care medicine. *Respir Care* 2006;51(9):1065–1071.
74. De Troyer A, Estenne M. Coordination between rib cage muscles and diaphragm during quiet breathing in humans. *J Appl Physiol* 1984;57(3):899–906.
75. Winslow C, Rozovsky J. Effect of spinal cord injury on the respiratory system. *Am J Phys Med Rehabil* 2003;82(10):803–814.
76. Ludlow CL. Central nervous system control of the laryngeal muscles in humans. *Respir Physiol Neurobiol* 2005;147(2–3):205–222.
77. McCool FD, Rosen MJ. Nonpharmacologic airway clearance therapies: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(1 Suppl):250S–259S.
78. McCrory DC, Lewis SZ. Methodology and grading of the evidence for the diagnosis and management of cough. ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(1 Suppl):28S–32S.
79. Hess DR. The evidence for secretion clearance techniques. *Respir Care* 2001;46(11):1276–1293.
80. Fink JB, Rubin BK. New horizons in respiratory care: airway clearance techniques. *Respir Care* 2002;47(7):759–760.
81. Hess DR. Secretion clearance techniques: absence of proof or proof of absence? (editorial) *Respir Care* 2002;47(7):757–758.
82. Baker S, Davenport P, Sapienza C. Examination of strength training and detraining effects in expiratory muscles. *J Speech Lang Hear Res* 2005;48(6):1325–1333.
83. Tzelepis GE, Vega DL, Cohen ME, Fulambarker AM, Patel KK, McCool FD. Pressure-flow specificity of inspiratory muscle training. *J Appl Physiol* 1994;77(2):795–801.
84. Leith DE, Bradley M. Ventilatory muscle strength and endurance training. *J Appl Physiol* 1976;41(4):508–516.
85. DePalo VA, Parker AL, Al-Bilbeisi F, McCool FD. Respiratory muscle strength training nonrespiratory maneuvers. *J Appl Physiol* 2004;96(2):731–734.
86. Koessler W, Wanke T, Winkler G, Nader A, Toifl K, Kurz H, Zwick H. 2 years' experience with inspiratory muscle training in patients with neuromuscular disorders. *Chest* 2001;120(3):765–769.
87. Sapienza CM, Wheeler K. Respiratory muscle strength training: functional outcomes versus plasticity. *Semin Speech Lang* 2006;27(4):236–244.
88. Winkler G, Zifko U, Nader A, Frank W, Zwick H, Wanke T. Dose-dependent effects of inspiratory muscle training in neuromuscular disorders. *Muscle Nerve* 2000;23(8):1257–1260.
89. Lotters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. *Eur Respir J* 2002;20(3):570–576.
90. Van Houtte S, Vanlandewijck Y, Gosselink R. Respiratory muscle training in persons with spinal cord injury: a systematic review. *Respir Med* 2006;100(11):1886–1895.
91. McCool FD, Tzelepis GE. Inspiratory muscle training in the patient with neuromuscular disease. *Phys Ther* 1995;75(11):1006–1114.
92. Smeltzer SC, Laviates MH, Cook SD. Expiratory training in multiple sclerosis. *Arch Phys Med Rehabil* 1996;77(9):909–912.
93. Gozal D, Thiriet P. Respiratory muscle training in neuromuscular disease: long-term effects on strength and load perception. *Med Sci Sports Exerc* 1999;31(11):1522–1527.
94. Gosselink R, Kovacs L, Ketelaer P, Carton H, Decramer M. Respiratory muscle weakness and respiratory muscle training in severely disabled multiple sclerosis patients. *Arch Phys Med Rehabil* 2000;81(6):747–751.
95. Klefbeck B, Lagerstrand L, Mattsson E. Inspiratory muscle training in patients with prior polio who use part-time assisted ventilation. *Arch Phys Med Rehabil* 2000;81(8):1065–1071.
96. Klefbeck B, Hamrah Nadjad J. Effect of inspiratory muscle training in patients with multiple sclerosis. *Arch Phys Med Rehabil* 2003;84(7):994–999.
97. Fregonezi GA, Resqueti VR, Güell R, Pradas J, Casan P. Effects of 8-week, interval-based inspiratory muscle training and breathing retraining in patients with generalized myasthenia gravis. *Chest* 2005;128(3):1524–1530.
98. Chiara T, Martin AD, Davenport PW, Boslser DC. Expiratory muscle training in persons with multiple sclerosis having mild to moderate disability: effect on maximal expiratory pressure, pulmonary function, and maximal voluntary cough. *Arch Phys Med Rehabil* 2006;87(4):468–473.
99. Kang SW, Bach JR. Maximum insufflation capacity: vital capacity and cough flows in neuromuscular disease. *Am J Phys Med Rehabil* 2000;79(3):222–227.
100. Sivasothy P, Brown L, Smith IE, Shneerson JM. Effects of manually assisted cough and mechanical insufflation on cough flow of normal subjects, patients with chronic obstructive pulmonary disease (COPD), and patients with respiratory muscle weakness. *Thorax* 2001;56(6):438–444.
101. Chatwin M, Ross E, Harf N, Nichol AH, Polkey MI, Simonds AK. Cough augmentation with mechanical insufflation-exsufflation in patients with neuromuscular weakness. *Eur Respir J* 2003;21(3):502–508.
102. Mustafa N, Aiello M, Lyall RA, Nikolettou D, Olivieri D, Leigh PN, et al. Cough augmentation in amyotrophic lateral sclerosis. *Neurology* 2003;61(9):1285–1287.
103. Sancho J, Servera E, Diaz J, Marin J. Efficacy of mechanical insufflation-exsufflation in medically stable patients with amyotrophic lateral sclerosis. *Chest* 2004;125(4):1400–1405.
104. Kang SW, Kang YS, Moon JH, Yoo TW. Assisted cough and pulmonary compliance in patients with Duchenne muscular dystrophy. *Yonsei Med J* 2005;46(2):233–238.

105. Trebbia G, Lacombe M, Fermanian C, Falaize L, Lejaille M, Louis A, et al. Cough determinants in patients with neuromuscular disease. *Respir Physiol Neurobiol* 2005;146(2-3):291-300.
106. Kang SW, Shin JC, Park CI, Moon JH, Rha DW, Cho D. Relationship between inspiratory muscle strength and cough capacity in cervical spinal cord injured patients. *Spinal Cord* 2006;44(4):242-248.
107. Bach JR. Mechanical insufflation-exsufflation: comparison of peak expiratory flows with manually assisted and unassisted coughing techniques. *Chest* 1993;104(5):1553-1562.
108. Bach JR, Smith WH, Michaels J, Saporito L, Alba AS, Dayal R, Pan J. Airway secretion clearance by mechanical exsufflation for post-poliomyelitis ventilator-assisted individuals. *Arch Phys Med Rehabil* 1993;74(2):170-177.
109. Sancho J, Servera E, Vergara P, Marin J. Mechanical insufflation-exsufflation vs tracheal suctioning via tracheostomy tubes for patients with amyotrophic lateral sclerosis. *Am J Phys Med Rehabil* 2003;82(10):750-753.
110. Winck JC, Gonçalves MR, Lourenço C, Viana P, Almeida J, Bach JR. Effects of mechanical insufflation-exsufflation on respiratory parameters for patients with chronic airway secretions encumbrance. *Chest* 2004;126(3):774-780.
111. Vianello A, Corrado A, Arcaro G, Gallan F, Ori C, Minuzzo M, Bevilacqua M. Mechanical insufflation-exsufflation improves outcomes for neuromuscular disease patients with respiratory tract infections. *Am J Phys Med Rehabil* 2005;84(2):83-88.
112. Pillastrini P, Bordini S, Bazzocchi G, Belloni G, Menarini M. Study of the effectiveness of bronchial clearance in subjects with upper spinal cord injuries: examination of a rehabilitation programme involving mechanical insufflation and exsufflation. *Spinal Cord* 2006;44(10):614-616.
113. Pearl J, Ramirez AR, Petruzziello M, Perdue P. Small bowel perforation after quad cough maneuver. *J Trauma* 2001;51(1):162-163.
114. Gómez-Merino E, Sancho J, Marin J, Servera E, Blasco ML, Belda FJ, et al. Mechanical insufflation-exsufflation: pressure, volume, and flow relationships and the adequacy of the manufacturer's guidelines. *Am J Phys Med Rehabil* 2002;81(8):579-583.
115. Sancho J, Severa E, Marin J, Vergara P, Belda FJ, Bach JR. Effect of lung mechanics on mechanically assisted flows and volumes. *Am J Phys Med Rehabil* 2004;83(9):698-703.
116. Beck GJ, Barach AL. Value of mechanical aids in the management of a patient with poliomyelitis. *Ann Int Med* 1954;40(6):1081-1094.
117. Barach AL, Beck GJ. Exsufflation with negative pressure: physiologic and clinical studies in poliomyelitis, bronchial asthma, pulmonary emphysema, and bronchiectasis. *Arch Int Med* 1954;93(6):825-841.
118. Barach AL, Beck GJ, Bickerman HA, Seanor HE. Physical methods simulating mechanisms of the human cough. *J Appl Physiol* 1952;5(2):85-91.
119. Beck GJ, Scarrone LA. Physiological effects of exsufflation with negative pressure (E.W.N.P). *Dis Chest* 1956;29(1):80-95.
120. Dail CW, Affeldt JE. Clinical aspects of glossopharyngeal breathing. *JAMA* 1955;158(6):445-449.
121. Feigelson CI, Dickinson DG, Talner NS, Wilson JL. Glossopharyngeal breathing as an aid to the coughing mechanism in the patient with chronic poliomyelitis in a respirator. *N Engl Med* 1956;254(13):611-613.
122. Bianchi C, Grandi M, Felisari G. Efficacy of glossopharyngeal breathing for a ventilator-dependent, high-level tetraplegic patient after cervical cord trauma resection and tracheostomy. *Am J Phys Med Rehabil* 2004;83(3):216-219.
123. Warren VC. Glossopharyngeal and neck accessory muscle breathing in a young adult with C2 complete tetraplegia resulting in ventilator dependency. *Phys Ther* 2002;82(6):590-600.
124. Bach JR, Bianchi C, Vidigal-Lopes M, Turi S, Felisari G. Lung inflation by glossopharyngeal breathing and "air stacking" in Duchenne muscular dystrophy. *Am J Phys Med Rehabil* 2007;86(4):295-300.
125. Miske LJ, Hickey EM, Kolb SM, Weiner DJ, Panitch HB. Use of the mechanical in-exsufflator in pediatric patients with neuromuscular disease and impaired cough. *Chest* 2004;125(4):1406-1412.
126. Tzeng AC, Bach JR. Prevention of pulmonary mortality for patients with neuromuscular disease. *Chest* 2000;118(5):1390-1396.
127. Gómez-Merino E, Bach JR. Duchenne muscular dystrophy: prolongation of life by noninvasive ventilation and mechanically assisted coughing. *Am J Phys Med Rehabil* 2002;81(6):411-415.
128. Castro C, Bach JR. Mechanical insufflation (letter). *Thorax* 2002;57(3):281.
129. Bach JR. Mechanical insufflation/exsufflation: has it come of age? A commentary. *Eur Respir J* 2003;21(3):385-386.
130. Bach JR. Don't forget the abdominal thrust. *Chest* 2004;126(4):1388-1389.
131. Gonçalves MR, Bach JR. Mechanical insufflation-exsufflation improves outcomes for neuromuscular disease patients with respiratory tract infections. *Am J Phys Med Rehabil* 2005;84(2):89-91.
132. Bach JR. Update and perspectives on noninvasive respiratory muscle aids, part 1: the inspiratory aids. *Chest* 1994;105(4):1230-1240.
133. Bach JR. Update and perspectives on noninvasive respiratory muscle aids, part 2: the expiratory aids. *Chest* 1994;105(5):1538-1544.
134. Bach JR. Amyotrophic lateral sclerosis: predictors for prolongation of life by noninvasive respiratory aids. *Arch Phys Med Rehabil* 1995;76(9):826-832.
135. Zidulka A, Gross D, Minami H, Vartian V, Chang HK. Ventilation by high-frequency chest wall compression in dog with normal lungs. *Am Rev Respir Dis* 1983;127(6):709-703.
136. King M, Phillips DM, Gross D, Vartian V, Chang HK, Zidulka A. Enhanced tracheal mucus clearance with high frequency chest wall compression. *Am Rev Respir Dis* 1983;128(3):511-515.
137. King M, Phillips DM, Zidulka A, Chang HK. Tracheal mucus clearance in high-frequency oscillation II: chest wall versus mouth oscillation. *Am Rev Respir Dis* 1984;130(5):703-706.
138. Tomkiewicz RP, Biviji A, King M. Effects of oscillating air flow on the rheological properties and clearability of mucous gel stimulants. *Biorheology* 1994;31(5):511-520.
139. King M, Zidulka A, Phillips DM, Wright D, Gross D, Chang HK. Tracheal mucus clearance in high-frequency oscillation: effect of peak flow rate bias. *Eur Respir J* 1990;3(1):6-13.
140. Chang HK, Weber ME, King M. Mucus transport by high-frequency nonsymmetrical oscillatory airflow. *J Appl Physiol* 1988;65(3):1203-1209.
141. Warwick WJ, Marzotto A. Airway clearance by high frequency chest compression. *Pediatr Pulmonol* 1992;(Suppl 8):138-139.
142. Perry RJ, Man GCW, Jones RL. Effects of positive end-expiratory pressure on oscillated flow rate during high-frequency chest compression. *Chest* 1998;113(4):1028-1033.
143. Darbee JC, Kanga JF, Ohtake PJ. Physiologic evidence for high-frequency chest wall oscillation and positive expiratory pressure breathing in hospitalized subjects with cystic fibrosis. *Phys Ther* 2005;85(12):1278-1289.
144. Arens R, Gozal D, Omlin KJ, Vega J, Boyd KP, Keens T, Woo MS. Comparison of high-frequency chest compression and conventional chest physiotherapy in hospitalized patients with cystic fibrosis. *Am J Respir Crit Care Med* 1994;150(4):1154-1157.
145. Scherer TA, Barandun J, Martinez E, Wanner A, Rubin EM. Effect of high-frequency oral airway and chest wall oscillation and conventional chest physical therapy on expectoration in patients with stable cystic fibrosis. *Chest* 1998;113(4):1019-1027.
146. Varekojis SM, Douce FH, Flucke RL, Filbrum DA, Tice JS, McCoy KS, Castile RG. A comparison of the therapeutic effectiveness of and

- preference for postural drainage and percussion, intrapulmonary percussive ventilation, and high-frequency chest wall compression in hospitalized cystic fibrosis patients. *Respir Care* 2003;48(1):24–28.
147. Stites SW, Perry GV, Peddicord T, Cox G, McMillan C, Becker B. Effect of high-frequency chest wall oscillation on the ventral and peripheral distribution of aerosolized diethylene triamine pentaacetic acid as compared to standard chest physiotherapy in cystic fibrosis. *Chest* 2006;129(3):712–717.
 148. Plioplys AV, Lewis S, Kasnicka I. Pulmonary vest therapy in pediatric long-term care. *J Am Med Dir Assoc* 2002;3(5):318–321.
 149. Giarrappa P, Berger KI, Chaiken AA, Axelrod FB, Davey C, Becker B. Assessing efficacy of high-frequency chest wall oscillation in patients with familial dysautonomia. *Chest* 2005;128(5):3377–3381.
 150. Lange DJ, Lechtzin N, Davey C, David W, Heimann-Patterson T, Gelinas D, et al. High-frequency chest wall oscillation in ALS: an exploratory randomized, controlled trial. *Neurology* 2006;67(6):991–997.
 151. Chaisson KM, Walsh S, Simmons Z, Vender RL. A clinical pilot study: high frequency chest wall oscillation airway clearance in patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2006;7(2):107–111.
 152. Cioffi WG, Graves TA, McManus WF, Priuitt BA. High-frequency percussive ventilation in patients with inhalation injury. *J Trauma* 1989;29(3):350–354.
 153. Birnkrant DJ, Pope JF, Lewarski J, Stegmaier J, Besunder JB. Persistent pulmonary consolidation treated with intrapulmonary percussive ventilation: a preliminary report. *Pediatr Pulmonol* 1996;21(4):246–249.
 154. Toussaint M, De Win H, Steens M, Soudon P. Effects of intrapulmonary percussive ventilation on mucus clearance in Duchenne muscular dystrophy patients: a preliminary report. *Respir Care* 2003;48(10):940–947.
 155. Reardon CC, Christiansen D, Barnett ED, Cabral HJ. Intrapulmonary percussive ventilation vs incentive spirometry for children with neuromuscular disease. *Arch Pediatr Adolesc Med* 2005;159(6):526–531.
 156. Price JD, Grimley Evans J. N-of-1 randomized controlled trials: singularly useful in geriatric medicine. *Age Ageing* 2002;31(4):227–232.
 157. Böllert FG, Paton JY, Marshall TG, Calvert J, Greening AP, Innes JA. Recombinant DNase in cystic fibrosis: a protocol for targeted introduction through n-of-1 trials. *Eur Respir J* 1999;13(1):107–113.
 158. Nikles CJ, Clavarino AM, Del Mar CB. Using n-of-1 trials as a clinical tool to improve prescribing. *Br J Gen Pract* 2005;55(512):175–180.
 159. Ottenbacher KJ, Hinderer SR. Evidence-based practice: methods to evaluate individual patient improvement. *Am J Phys Med Rehabil* 2001;80(10):786–796.
 160. Guyatt GH, Juniper EF, Walter SD, Griffiths LE, Goldstein RS. Interpreting treatment effects in randomized trials. *BMJ* 1998;316(7132):690–693.

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 difficult 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 reflux, 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.^{1,2} 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.

1. Bach JR. Continuous noninvasive ventilation for patients with neuromuscular disease and spinal cord injury. *Semin Respir Crit Care Med* 2002;23(3):283–292.

2. Hanayama K, Ishikawa Y, Bach JR. Amyotrophic lateral sclerosis. Successful treatment of mucous plugging by mechanical insufflation-exsufflation. *Am J Phys Med Rehabil* 1997;76(4):338–339.

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 technique 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.

Hornick: 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.