Conference Summary

Airway Clearance: Physiology, Pharmacology, Techniques, and Practice

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Clinicians and their patients are troubled by respiratory secretions, and standard practice calls for efforts to clear secretions from the lungs. On one hand, mucus production and cough are important for airway defense and protection of the lower respiratory tract against inhaled irritations. On the other hand, excessive mucus obstructs airways and excessive cough has been associated with a number of complications. The objective of this conference was to review the scientific basis and clinical evidence for the use of airway clearance therapy to guide the most appropriate approach to airway clearance. An international group of clinicians and scientists addressed the physiology of mucus production and cough, pharmacologic approaches to airway clearance, and the variety of techniques available for airway clearance. Specific issues related to airway clearance in critically ill patients, children, and the elderly were discussed. Outcome measures related to evaluating mucus clearance therapy were also presented. One of the themes repeated consistently throughout this conference was the dearth of high-level evidence related to airway clearance techniques. Appropriately powered and methodologically sound research is desperately needed in this area. *Key words: airway clearance, chest physiotherapy, cough, mucus clearance therapy*. [Respir Care 2007; 52(10):1392–1396. © 2007 Daedalus Enterprises]

Introduction

Many acute and chronic respiratory diseases are associated with retained airway secretions due to increased mucus production, impaired mucociliary transport, or a weak cough. There is a relative lack of evidence describing the effect of increased respiratory tract secretions on the progression of disease, and there is even less evidence that secretion clearance techniques improve the course of disease. Despite this lack of evidence, clinicians and patients are troubled by respiratory secretions, and standard practice calls for efforts to clear secretions from the lungs. Indeed, an important proportion of respiratory therapists' time is spent in efforts to evacuate secretions from the lower respiratory tract. In the home this can constitute a lot of time for the patient and caregiver. In recent years a

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variety of equipment (of varying cost) has become available to assist with this.

Why do we want to clear mucus from the lungs? Airflow obstruction secondary to retained secretions increases the work of breathing, produces ventilation-perfusion mismatch, and can result in gas exchange abnormalities. Retained secretions can serve as a source of infection and inflammation. Coughing and clearing secretions is aesthetically unpleasant. Airway clearance may be the most commonly prescribed therapy in patients with cystic fibrosis (CF), and chest physical therapy (CPT) may be the most frequently omitted treatment outside the hospital in this patient population.

The objective of this RESPIRATORY CARE journal conference was to review the scientific basis and clinical evidence for the use of airway clearance therapy to guide the most appropriate approach to airway clearance. An impressive international group of clinicians and scientists was brought together to highlight the state of the art for what is known, as well as new directions and opportunities for the study of mucus and sputum.

Physiology

The physiology of mucus secretion was addressed by Duncan Rogers. He pointed out the physiologic importance of "getting airway secretions right"—not too runny, not too thick; not too wet, not too dry. He described human bronchial glands that consist of mucous cells (secrete mucins), serous cells (secrete antibacterials), and water secretion. Normally, < 10 mL/d of mucus is produced, and this serves as first-line defense and is protective of the lower respiratory tract. With airway mucus hypersecretion, the amount of mucus produced is abnormal, and this is pathologic and no longer protective. In the case of mucus hypersecretion, there is submucosal gland hypertrophy, goblet cell hyperplasia, and increased mucin synthesis. There is also plasma exudation, decreased mucociliary transport, mucostasis, and mucus plugs. Inducers of airway mucus secretion/hypersecretion include inflammatory mediators, cellular derived mediators, plasma-derived mediators, neural mechanisms, proteinases, bacterial products, irritant gases, reactive gas species, mechanical strain, pH, and ovalbumin sensitization.

Cees van der Schans addressed the physiology of cough and airway clearance. He showed us that cough can be simulated in the laboratory. With simulated cough, it can be shown that airway constriction improves airway clearance, provided that a choke point does not occur. This is from work conducted with a cough machine that Bruce Rubin developed with Malcolm King about 15 years ago. There is an important balance between compression and collapse of airways; with collapse of the airway, clearance is obviously inhibited. With simulated cough it can also be shown that a rapid series of coughing improves airway clearance. The important roles of mucus production, mucociliary transport, and flow transport on airway clearance was also described.

From these presentations it became clear that there is a "yin and yang" related to mucus and cough. On one hand, mucus production and cough are important for airway defense and protection of the lower respiratory tract against inhaled irritations (yang). On the other hand, excessive mucus obstructs airways, and excessive cough has been associated with a number of complications (yin).

Pharmacology

Ruben Restrepo described the roles of sympathomimetics and anticholinergics related to mucociliary clearance. For sympathomimetics, improved mucociliary clearance has been shown in several species, several diseases, and with several formulations (but not in all studies). Increased mucociliary clearance may require greater doses than those used for bronchodilation. Albuterol may improve mucociliary clearance and cough clearance after lung transplantation, which may be important in this patient population. Overall, the clinical importance of sympathomimetics on airway clearance is unclear. Moreover, sympathomimetics may also be counterproductive in some conditions, such as tracheomalacia. The effects of anticholinergics on mucociliary clearance has also been studied in several species, several diseases, and with several formulations. Commonly used inhaled anticholinergics do not retard mucus clearance in a clinically important manner.

The roles of mucolytics and mucokinetics were addressed by Duncan Rogers. He helped us distinguish between expectorants (which increase volume and/or hydration of secretions, and may induce cough), mucolytics (which reduce viscosity of mucus), mucokinetics (which increase kinesis of mucus by cough), and mucoregulators (which reduce the process of chronic mucus hypersecretion). It was pointed out that there are competing effects of mucoactive agents related to mucociliary clearance and cough. A thin mucus layer, ideal sol depth, increased elasticity, and decreased viscosity favors mucociliary clearance. A thick mucus layer, excess sol, lower elasticity, and higher viscosity favors cough. The results of a Cochrane review suggest that mucolytics may be of benefit in COPD.[1] However, it is unclear whether the mechanism was indeed airway clearance or some other effect, such as antioxidant effects. Although affecting mucus would seem a reasonable goal, the usefulness of mucolytics is essentially unproven. This continues to be an area of active scientific inquiry, and new agents are being explored.

Techniques

Conventional CPT is the traditional technique used to enhance airway clearance. This therapy was addressed by Cees van der Schans, who defined CPT as any combination of postural drainage, percussion, chest shaking, huffing, and directed coughing; it does not include the use of exercise, forced expiration technique, positive expiratory pressure (PEP), or other mechanical devices. CPT was compared to no CPT for CF in a Cochrane review.[2] The authors of that review concluded that there is currently *no robust scientific evidence* to support the hypothesis that CPT for the purpose of clearing airway secretions has a beneficial effect in patients with CF. The benefit of manual chest percussion is controversial, but this may be the result of suboptimal frequency of manual percussion. The authors of one meta-analysis concluded that, in CF, cough may be as effective as therapist-administered CPT in removing pulmonary secretions.[3]

Jim Fink addressed forced expiration technique, directed cough, and autogenic drainage. This includes techniques such as directed cough, breathing maneuvers, and positive airway pressure. He stated that high-frequency oscillation of the airway and chest wall more directly support normal mucus transport mechanisms than does postural drainage. This is supported by the observations that gravity is not a major mechanism for airway clearance in health, and the viscosity of normal mucus resists flow into gravity-dependent terminal bronchioles. The definitions for directed cough, active cycle of breathing, and autogenic drainage were appropriately clarified, as these are often confused in clinical usage. It was pointed out that a meta-analysis showed that, although standard CPT resulted in a significantly greater sputum expectoration than no treatment, there were no differences between conventional CPT, PEP, forced expiration technique, and autogenic drainage.[4] In the context of techniques for airway clearance, it was provocatively stated that the question appears to be less one of "will it work?" than "will the patient use it?"

Intrapulmonary and high-frequency chest wall oscillation techniques were presented by Rob Chatburn. The available technologies in this category include intrapulmonary percussive ventilation, high-frequency chest wall compression, and high-frequency chest wall oscillation. A distinction was made between these assisted techniques versus unassisted airway clearance techniques such as CPT. The potential mechanisms of action for intrapulmonary and high-frequency chest wall oscillation techniques include air-liquid shear forces (multiple "mini coughs"), Scherer model, radial displacement of the airway, mechanical rheological effects, and possibly increase in ciliary beating. Evidence-based conclusions were that intrapulmonary percussive ventilation is probably better than standard CPT for atelectasis and secretion clearance; high-frequency chest wall compression is probably better than CPT for secretion clearance; and high-frequency chest wall oscillation is perhaps a better ventilation technique than an airway clearance technique. Guidelines from the American College of Chest Physicians, although not strictly evidence-based, state, "In patients with CF, devices designed to oscillate gas in the airway, either directly or by compressing the chest wall, can be considered as an alternative to CPT."[5]

A relatively recent addition to the armamentarium of airway clearance devices is the mechanical insufflator-exsufflator (CoughAssist In-Exsufflator, JH Emerson, Cambridge, Massachusetts), which was reviewed by Douglas Homnick. The device's objective is to maximize peak cough flow to attain sufficient airflow velocity for airway mucus shear and to promote cephalad flow of secretions; in other words, *to simulate cough.* An earlier version of the device, the Cof-Flator, was available in 1952, but this technique did not really catch on until the Emerson CoughAssist In-Exsufflator was introduced in 1993. The in-exsufflator can be used with or without an abdominal thrust. It is commonly used in patients with neuromuscular disease, although high-level evidence is lacking. The role of the in-exsufflator in diseases other than neuromuscular diseases, such as obstructive lung disease, is unclear.

Tim Myers reviewed PEP and oscillatory PEP techniques. PEP was first developed as an airway clearance technique in Denmark in the 1970s. PEP devices can be categorized as low-pressure devices (5–20 cm H_2O at mid-exhalation) and high-pressure devices (26–102 cm H_2O via forced expiratory maneuvers after maximal inspiration). Oscillatory PEP was first developed in Switzerland as the Flutter device, but there are now similar devices from other manufacturers, such as Acapella and Quake. Proposed mechanisms of action of these devices include a decrease in the viscoelastic properties of mucus, and the creation of short bursts of increased expiratory flow acceleration that assist mucus clearance. It was pointed out that a Cochrane review[4] reported that, in patients with CF, there is no advantage of conventional CPT over other airway clearance techniques in terms of respiratory function. Moreover, there was a trend reported for participants to prefer self-administered airway clearance techniques. In relation to PEP for airway clearance in people with CF, another Cochrane Review[6] reported no clear evidence that PEP was a more or less effective intervention overall than other forms of CPT. There was limited evidence that PEP was preferred by participants, compared to other techniques.

Practice

Airway clearance is an essential part of the care of patients receiving mechanical ventilation. This was addressed by Richard Branson. He discussed the importance of adequate airway humidification in intubated patients

and reminded us that inadequate humidity can partially or completely occlude the artificial airway with dried secretions. Generally, heated humidity is superior to passive humidity, such as that from a heat-and-moisture exchanger. Recent innovations intended to decrease mucus adherence to the inside of the endotracheal tube include the Mucus Slurper, Mucus Shaver, and silver-impregnated endotracheal tubes. However, the utility of these devices in usual practice is yet to be determined. Suctioning should be done as needed, not routinely, with caution for complications. Evidence does not support manual hyperinflation as an airway clearance technique or the use of saline instillation. From the perspective of secretion removal, open suctioning may be superior to closed suctioning, because disconnection stimulates a cough, and it prevents the inspired gas flow from moving secretions away from the distal suction catheter. Continuous lateral rotation and kinetic therapy may improve resolution of atelectasis, but studies on secretion removal are scant. If percussion and postural drainage are used in the mechanically ventilated patient, care must be taken to avoid adverse effects.

Carl Haas addressed airway clearance in the elderly and patients with neurologic or neuromuscular compromise. It was pointed out that age-related structural and functional changes in the elderly may impact cough ability. Functional reserve is compromised in the elderly. Stressors, such as exacerbation of comorbid condition, pneumonia, surgery, and medication combinations, can result in decreased airway clearance. The elderly are at increased risk for aspiration and pneumonia. No specific airway clearance technique has been shown to be particularly useful in the elderly. A number of approaches to airway clearance in the patient with neuromuscular disease have been described. These include respiratory muscle training, manually assisted cough (quad-cough), mechanical cough assist, high-frequency chest wall compression/oscillation, and intrapulmonary percussive ventilation. Each of these may be helpful and appear not to be harmful in the patient with neuromuscular disease, but this is not based on strong evidence. For elderly patients and those with neuromuscular disease, most clinicians are not as aware as they should be of the concepts, procedures, and devices for airway clearance.

Applications in infants and children were covered by Michael Schechter. Most of the important airway diseases of childhood are associated with mucus hypersecretion; the classic example is CF. Airway collapse and/or obstruction are more likely in young children. Compared to adults, children have decreased stiffness of airway walls, decreased functional residual capacity and relative lung volumes, decreased airway diameter, and decreased alveolar collateral channels. Although somewhat controversial, it is generally accepted that gastroesophageal reflux can be problematic in children with airways disease. This may be important in relation to some airway clearance techniques, such as postural drainage. An important consideration is the lack of interaction and cooperation from the child, which can be problematic in the context of airway clearance therapy. It was concluded that airway clearance techniques appear to be of (1) *proven* benefit in routine care of CF (specific technique is probably less important than adherence); (2) *likely* benefit in routine care of neuromuscular disease, cerebral palsy, and the ventilated child with atelectasis; (3) *possible* benefit in routine care of the neonate immediately post-extubation; and (4) *minimal* benefit in routine care of acute asthma (without atelectasis), bronchiolitis, the intubated infant with respiratory distress syndrome, the intubated child with respiratory failure, and the postoperative child.

Bruce Rubin discussed outcome measures for evaluating mucus clearance therapy. He described a variety of in vitro studies that can be performed on sputum. Sputum analysis can tell us potential mechanism of action, onset of action, effective dose, and possible drug interactions. Animal models can be used to study mucus secretion rate, mucus transport rate, radioaerosol deposition and clearance, bioavailability of a medication, safety and toxicity of a medication, airway physiology, and histological assessment of epithelium. However, there are no truly relevant animal models of human airway disease. A number of questions need to be answered when designing a clinical study of airway clearance. These are similar to questions that should be asked when designing any clinical study, such as (1) How will the disease be defined? (2) How will the medication (or technique) be delivered? (3) What is an appropriate control group? (4) Should the design be a parallel group or crossover study? (5) How will the study be blinded? (6) How will adherence to therapy be monitored? (7) When will the subjects be studied? It is also important to choose an appropriate outcome measure. Some traditional measures, such as volume and texture of sputum, may be meaningless. Sputum color can suggest inflammation but not therapeutic response. Other outcome measures that can be used include pulmonary function testing, imaging, days in the hospital and/or days of additional therapy, and frequency of exacerbations. Increasingly, quality of life is the outcome measure of interest.

What to Do?

One of the themes repeated consistently throughout this conference was the dearth of high-level evidence related to airway clearance techniques. Studies in this field are plagued by small sample sizes, crossover designs, assessment of a single treatment session, less than careful attention to technique, surrogate outcome measures, lack of blinding, and statistical concerns (for example, a study reports no difference between techniques but was not designed as an equivalence study). The volume of sputum

expectoration and the comparison between techniques have been done only in short-term studies. Long-term studies showing true efficacy have not been published. It is not clear if, over the long-term, increased volume of sputum is a good thing or a bad thing.

As clinicians we often feel that, if the patient has phlegm, we need to do something about that. As stated by Eid et al[7] more that 15 years ago, "The perception is, if CPT doesn't help, it won't hurt. This lack of knowledge about the effectiveness of CPT in various diseases may lead to the wasting of time on inappropriate orders and, sometimes, to inadvertent medical and surgical complications." Some therapies for airway clearance are not benign. Reported complications of conventional CPT include hypoxemia, increased oxygen consumption, gastroesophageal reflux in infants, increased intracranial pressure, grade III/IV intracranial hemorrhage in preterm infants, brain injury similar to that from nonaccidental shaking injury in low-birthweight infants, and rib fractures.[8]

Does the lack of evidence mean lack of benefit? Is the lack of evidence due to study methodology or is there really no benefit from these techniques? Given the lack of evidence, I suggest the following hierarchy of questions that might be asked when considering secretion clearance therapy for a patient.[8,9]

1. Is there a pathophysiologic rationale for use of the therapy? Is the patient experiencing difficulty clearing secretions? Are retained secretions affecting lung function in an important way, such as gas exchange or lung mechanics? Note that the production of large amounts of sputum does not necessarily mean that the patient is experiencing difficulty clearing sputum.

2. What is the potential for adverse effects from the therapy? Which therapy is likely to provide the greatest benefit with the least harm?

3. What is the cost of the equipment for this therapy? The cost of the device may not be covered by third-party insurers, resulting in considerable out-of-pocket expense for the patient or the hospital.

4. What are the preferences of the patient? Lacking evidence that any technique is superior to another, patient preference is an important consideration.

When a clinical decision is made to try a secretion clearance technique, a simple clinical trial can be conducted (*n*-of-1 trial). Imagine that a decision is made to try oscillatory PEP therapy for a patient with chronic obstructive pulmonary disease. The clinician and patient agree that a clinically useful outcome measure is fewer symptoms related to chest congestion and coughing up phlegm. A randomized controlled trial is designed. Oscillatory PEP is used for 2 weeks, a sham device is used for 2 weeks, and this is repeated 3 times. The patient, who is naive to the therapy, does not know which device is potentially therapeutic. The order of treatments is randomized (the patient flips a coin) and the sequence is repeated 4 times. Each day, the sputum produced during the therapy session is weighed. A diary is also kept, in which events such as chest infections and other symptoms are logged. At the end of 12 weeks, the results are analyzed (which may include statistical analysis), reviewed together by the clinician and patient, and a collaborative decision is made regarding the benefit of the therapy. In this manner, an objective decision is made regarding the benefits of this therapy for this individual patient.

Summary

Despite the clinical observation that retained secretions are detrimental to respiratory function, and despite anecdotal associations between airway clearance and improvements in respiratory function, there is a dearth of high-level evidence to support any airway clearance technique. This is problematic, given that an important aspect of respiratory care practice is related to airway clearance. Although lack of evidence does not mean lack of benefit, it is desirable to have better evidence to support this practice. Appropriately powered and methodologically sound research is desperately needed in this area.

> If the patient suffers from hissing cough, if his windpipe is full of murmurs, if he coughs, if he has coughing fits, if he has phlegm: bray together roses and mustard in purified oil, drop it on his tongue, fill, moreover, a tube with it and blow it into his nostrils. Thereafter, he shall drink several times beer of the finest quality. Thus he will recover. — From an Assyrian tablet.
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> Sigerist, *History of Medicine*
> Oxford University Press, 1951

REFERENCES

1. Poole PJ, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006;(3):CD001287.
2. van der Schans C, Prasad A, Main E. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. Cochrane Database Syst Rev 2000;(2):CD001401.
3. Thomas J, Cook DJ, Brooks D. Chest physical therapy management of patients with cystic fibrosis: a meta-analysis. Am J Respir Crit Care Med 1995;151(3 Pt 1):846–850.
4. Main E, Prasad A, Schans C. Conventional chest physiotherapy compared to other airway clearance techniques for cystic fibrosis. Cochrane Database Syst Rev 2005;(1):CD002011.
5. McCool FD, Rosen MJ. Nonpharmacologic airway clearance therapies: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(1 Suppl):250S–259S.
6. Elkins MR, Jones A, van der Schans C. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. Cochrane Database Syst Rev 2006;(2):CD003147.
7. Eid N, Buchheit J, Neuling M, Phelps H. Chest physiotherapy in review. Respir Care 1991;36(4):270–282.
8. Hess DR. The evidence for secretion clearance techniques. Respir Care 2001;46(11):1276–1293.
9. Hess DR. Secretion clearance techniques: absence of proof or proof of absence? Respir Care 2002;47(7):757–758.