Management of cough ineffectiveness in neuromuscular disorders

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Summary

Cough is a vital function for eliminating excess secretions and foreign particles from the airways. An ineffective cough becomes clinically important in patients with disorders of the airways and/or weakness of respiratory muscles, significantly increasing the risk of acute respiratory failure due to mucus accumulation. The choice of the most appropriate treatment for clearing secretions must be carefully evaluated since some techniques target mainly the peripheral, while others the central airways. In patients suffering from muscular weakness, the latter techniques are preferred because they enhance elastic recoil of the thoracic wall and increase expiratory (cough) flow. In normal subjects, the peak cough flow (PCF) varies from 360 to 1200 L/min. A PCF of at least 270 L/min is necessary to effectively expel secretions; below 160 L/min, the cough is very ineffective. Mechanically assisted coughing (MAC) can become vital to avert acute respiratory failure (ARF).
The history of mechanical insufflation-exsufflation (MI-E) goes back to 1951 with Dr. Alvin Barach adapting a device to provide MI-E via an iron lung valve to create sudden intratank positive pressure after maximum negative intratank pressure to cause a forced lung exsufflation. In 1952 the MI-E was first applied via an oronasal interface. Initially called a Cof-flator (OEM Company, Norwalk, Connecticut) these devices that provide MI-E went off the marked in the late 1960s but came available again in February of 1992 as clinicians turned away from invasive to more noninvasive respiratory management. Mechanically assisted coughing using this device can in conjunction with an exsufflation-timed abdominal thrust can prevent respiratory insufficiency caused by bronchial mucus retention in neuromuscular disease, reduce the time required to wean from invasive mechanical ventilation, and allows for decannulation of patients with tracheostomy tubes. At present, guidelines for managing neuromuscular disorders include MAC with specific indications for both adult and paediatric patients.

KEY WORDS: neuromuscular disease; cough; respiratory insufficiency; mechanical airways clearance; cough machine; in-exsufflator technique.

Introduction

Reflex cough is complex. It begins with stimulation of many mechanical and chemical receptors whose greatest density is found on the posterior tracheal wall, carina, and mainstem bronchi, with lesser density in the more distal airways. There are none in the respiratory bronchioles (1-3). The vagal afferents seem to play the most important role in transmitting the stimulation from the airways to the cough centre, which occupies a broad region of the medulla oblongata (2). The reflex loop is completed by efferents that originate in the ventral respiratory apparatus and send stimuli to the inspiratory and expiratory muscles, the larynx, and the bronchial tree (3). The phrenic nerve and the spinal motor nerves transmit efferent impulses to the respiratory muscles, as do the recurrent laryngeal branches of the vagus nerve to the larynx. Interruptions in this reflex loop or dysfunction of the muscles required for coughing, whether congenital or acquired, can cause an ineffective cough.

Coughing effectiveness depends not only on a normal functioning of the nervous system and the respiratory muscles, but also on the health of the airways.

Coughing effectiveness depends not only on normal functioning of the nervous system and the respiratory muscles, but also on the health of the airways. i.e., on quantity and rheology of mucus, on the condition of the respiratory epithelium and on adequate airway patency. For patients with respiratory muscle weakness or with deformities of the rib cage, pulmonary restriction can result in inadequate volumes (less than 2.3 liters) (4) for effective peak cough flows (PCFs). These patients are in particular danger of developing pneumonia and ARF when airway secretions are abundant as dur-

ing intercurrent respiratory tract infections (5). Infections of the airways can further decrease PCFs in patients with neuromuscular disease, thus creating a vicious cycle (4, 5).

Pathophysiology and measurement of cough effectiveness

To assess cough effectiveness, it is important to evaluate MIP and MEP, PEF, PCF, VC, and MIC.

Cough is generated through four distinct phases: an irritation phase in which a stimulus triggers a reflex arc; an inspiration phase in which air fills the lungs to 85-90% of total lung capacity; rapid closure of the glottis for approximately 0.2 seconds and simultaneous contraction of the abdominal and intercostal muscles (auxiliary respiratory muscles) which raises intrapleural pressure up to 190 cmH_2O; and finally, a sudden opening of the vocal cords which normally results in PCF of 360-1200 L/min (6).

In neuromuscular patients, an ineffective cough can be caused by a deficiency in each of the three phases which follow the irritating stimulus:

1) Inspiratory phase: weakness of inspiratory muscles results in reduced thoracic expansion with consequent suboptimal chest wall recoil (7).

2) Closure of the glottis: the inability of the vocal cords to close tightly causes an insufficient increase in the intrathoracic pressure generated by simultaneous contraction of abdominal and internal intercostal muscles.

3) Expiratory phase: the reduced strength of the abdominal and auxiliary expiratory muscles results in insufficient positive intrathoracic pressure, thus reducing expiratory flow (7).

To assess cough effectiveness, it is thus important to evaluate flow, volumes and pressures generated during the inspiratory and expiratory phases with measurements such as the maximum inspiratory and expiratory pressures (MIP and MEP), the peak expiratory flow (PEF), the peak cough flow (PCF), the vital capacity (VC), and the maximum inspiratory capacity (MIC) (8).

The MIP is related to the force produced by the glottis, and its reduction implies inability to hold an effective pretussive volume. The MEP, on the other hand, assesses the thoracic compression phase and reflects the ability of the expiratory muscles to generate enough force to achieve an effective expiratory flow (8).

The PEF is the maximum flow obtained during forced expiration, starting from total lung capacity (normal range: 360-1200 L/min, average value: 580 L/min). This value indicates the extent to which a patient succeeds in achieving maximum forced expiration independent of glottis function whereas the PCF, on the other hand, is the expiratory flow after the compression phase with a closed glottis. According to some Authors (9), cough assistance is required if unassisted PCF<160 L/min; according to others (10), if PCF<180 L/min. Actually, there is a difference between spontaneous unassisted PCF and PCF assisted by air stacking and an abdominal thrust. When patients are acutely ill it is the assisted cough that is most often used to clear airway secretions so if a patient cannot generate PCF greater than 270 to 300 L/m with or without assistance, MAC is needed to prevent respiratory tract infections from turning into pneumonias and ARF (5).

It has been shown that a PCF>160 L/min is associated with successful extubation or decannulation of patients with neuromuscular diseases (11). For this reason, in the 2009 *ACCP (American College of Chest Physicians)* guidelines for patients with Duchenne muscular dystrophy who must be sedated or given anaesthesia for surgery indicate that MAC is required when PCF < 270 L/min or MEP < 60 cm H_2O (12).

The MIC is the maximum volume of air that can be held with a closed glottis. If the MIC is less than 1500 mL, supplementary passive lung insufflation may be required to augment PCFs (13). Thus, VC, maximum inspiratory pressure measured at the mouth (MIP), maximum expiratory pressure measured at the mouth (MEP), MIC, and total lung capacity (TLC) correlate with PCFs (14).

Standard techniques of bronchial clearance

In the neuromuscular disorders, alterations of the rib cage prevent the patient from maintaining positions for effective postural drainage and can hamper the application of supplementary vibration and percussion manoeuvres.

The prevalent site of airway secretion accumulation, peripheral or proximal, must be determined when choosing the most appropriate method for bronchial clearance.

Clearance of the peripheral airways

Patients with neuromuscular diseases typically have normal airways and airway clearance mechanisms. However, when the peripheral airways are overwhelmed by mucus accumulation during intercurrent respiratory infections, techniques that address this may be beneficial. Although postural drainage is one of the most widely used techniques, there is no evidence to date that this more or less effective than chest percussion, vibration, or oscillation (10). Furthermore, in neuromuscular disorders, alterations of the rib cage often prevent the patient from maintaining positions for effective postural drainage and can hamper the application of supplementary vibration and percussion manoeuvres (8, 10). “Slow total expiration with open glottis in a lateral posture,” is a technique introduced by G. Postiaux in 1987 that may be helpful for the patient with a relatively intact VC and glottic competence (15).

Clearance of the central airways

Air stacking is used as long as glottis function is preserved (MIC-VC>0), and is especially important when the MIC is less than 1500 Ml.

Manoeuvres to clear the central airways are the most important for the neuromuscular patient. These methods are supplementary to or substitute for a dysfunctional cough mechanism. The most important manoeuvres are: 1) manual or mechanical hyperinflation to augment

the inspiratory phase for coughing; 2) manual thrust carried out in the expulsion phase; 3) and nasal/orotracheal aspiration (10).

1. *Manual or mechanical hyperinflation* techniques improve augment cough flows by increasing pretussive volume. Air stacking is used as long as glottis function is preserved (MIC-VC>0),(13) and is especially important when the MIC is less than 1500 mL (13). Air stacking is achieved by using a manual resuscitator (Ambu bag) or volume cycling ventilator to deliver boluses of air to the lungs that are held to a maximum volume by glottis closure. Air stacking can also be done very often by glossopharyngeal Breathing (GPB). Glossopharyngeal breathing consists of the pistoning of small boluses of air (gulps) into the lungs by using the posterior aspect of the tongue to project them through the glottis. When glottis closure is not possible, passive lung insufflations is used. The insufflation phase of MI-E is passive lung insufflation.
2. *Manually Assisted cough* is a technique that increases cough flow by applying an abdominal thrust to the abdomen and/or rib cage after deep lung insufflations by air stacking or passive lung insufflation. The compression is synchronised with the patient's spontaneous cough (glottis opening). The manoeuvre can be less effective if the rib cage is severely deformed. The data from the scientific literature are conflicting. Several studies report PCF increases (9, 16-18), while others do not show any differences in PCF using manually assisted coughing when scoliosis is severe (10). It should be noted that different techniques were used in these studies (hyperinsufflation with Ambu, and a semi-reclining position).
3. *MAC if available or Mechanical aspiration* is performed by introducing a suction catheter into the airways when the manoeuvres described above are inadequate.

The Rationale of in-exsufflation methods

Mechanical insufflation-exsufflation (MI-E) involves the use of a device that deeply insufflates into and then maximally exsufflates air out of the lungs using rapidly repeated cycles of positive and negative pressures. These cycles augment the patient's inspiratory and expiratory phases, respectively. The MI-E devices can be applied to the patient using an oronasal mask, a mouthpiece, or even a tracheal or translaryngeal tube. Utilized mainly in the United States, the technique has been gaining in popularity in Europe since the late 1980s and has been incorporated into the standard treatment for neuromuscular diseases, as specified by various guidelines (19-21).

In the early 1950s it was shown that MI-E was effective in removing radio-opaque material from the airways of anesthetised dogs (22, 23). Subsequently, clinical studies and case reports of patients with polio, asthma, emphysema, and bronchiectasis reported effectiveness in treating atelectasis, hypoxemia and dyspnoea (24-26). However, MI-E was never apparently used via tracheostomy tubes and its use diminished in the 1960s as tracheostomy tubes became the standard of care. The technique is now experiencing a resurgence in combination with noninvasive ventilation (27).

The operating principle of the in-exsufflator

The MAC is the delivery of positive pressure (insufflation phase) followed – in rapid sequence – by negative pressure (exsufflation phase), thereby providing assistance during both the pretussive and expulsive phases of coughing. An abdominal thrust should usually be applied in conjunction with glottis opening to maximize cough flows. From a physiological point of view, the performance of the in-exsufflator can be attributed to the generation of an exsufflation flow exceeding 2.7 L/sec (28). Insufflation should be performed at sufficient pressure (>35 cm H_2O) to full clinical chest expansion then exsufflation performed along with the abdominal thrust until the chest is clinically maximally emptied of air. Dynamic airway collapse is minimized by the abdominal thrust. In a study by Sancho on an artificial lung varying compliance and resistance, it was found that the application of usual pressures (such as ±40 cmH_2O) sometimes does not enable the minimum threshold of expiratory flow (2.7 L/sec) to be reached. For this reason, the authors recommend increasing the pressure up to 60 cmH_2O in cases of obesity or severe deformity of the rib cage (29).

Functional effects

a) Peak Cough Flow

The use of MAC can provide effective cough flows. In a series of 46 patients with different neuromuscular disorders, Bach (9) found that PCFs obtained by MAC are greater than those derived by manual cough assistance alone following "air stacking" or after glossopharyngeal breathing. Similar results were reported for a group of post-polio patients (30). In a study by Chatwin et al. (18), all patients reported a subjective increase in cough effectiveness using MI-E, but the increase in PCF was lower than that obtained by Bach (9) and Sivasothy (17) because lower MI-E pressures were used and abdominal thrusts avoided. Mustfa (16) assessed the effectiveness of various cough assistance manoeuvres for 47 patients with amyotrophic lateral sclerosis (ALS), differentiating between bulbar and non-bulbar ALS. The author concluded that in persons with non-bulbar ALS whose VC is lower than 50% of predicted normal, PCF increased by 14%, and that statistical significance was even reached when insufflation was alone was used.

b) Pulmonary flows and volumes:

Bach et al. found a statistically significant increase in forced (F)VC and an increase in PEF (9) immediately following MAC. The authors emphasized that the most significant increase in these spirometric indexes occurred in subjects with acute respiratory distress. He found a 29% increase in FVC, a 9% increase of PEF, and a 19% increase of 25-75% FEF. The same results were observed in patients with post-polio syndrome (30). The recruitment of underventilated areas of the lungs led to an increase in respiratory volume and consequent increase in oxyhaemoglobin saturation (31). Other authors reported that for high level spinal cord

injury (C1-C7) patients MI-E use significantly increased FVC, FEV_1 and PEF (32). Fauroux, too, has reported a direct correlation between a MI-E operating pressures up to 40 cm H2O and increases in expired volumes and cough flows (33). The lower thoracic compartments were the areas expanded by the insufflation phase (34).

Methods of application - Indications

Without question, MAC needs to be used when patients need to cough. The goal of therapy is to expel secretions, allay secretion-associated dyspnea, and increase pulmonary parameters and oxyhemoglobin saturation.

For patients with tracheostomy tubes, the tube cuff, if present, should be inflated for greatest efficacy or the mouth and nose must be closed or covered if the tube is cuffless. Automatic or manual mode must be chosen. In the automatic mode, the pressures, inspiratory/expiratory times, pause time, and flows are set. In the manual mode, only the pressures and flows must be set. For paediatric patients the parameters are essentially the same as for adults (35). A standard treatment consists of 4-6 cycles of in-exsufflation followed by a pause to avoid hyperventilation. The pressures and times of use differ from study to study, and not all authors provide specific reasons for their parameter settings. In one study that compared the effectiveness of various insufflation and exsufflation pressures (20, 30, 40 cm H_2O), it was noted that the PCFs of patients with ALS and COPD increased only when pressures ≥ +40 / ≤ -40 cm H_2O were used (34). Chatwin et al. (11) used absolute pressures of only about 15 cm H_2O. However, their increase in PCFs, although significant, were less than those obtained by Bach et al. (9) who employed higher pressures. Using pressures ±20 cm H_2O, Sivasothy observed a significant reduction in PCF in cases of COPD and a significant increase in PCF in neuromuscular disease without scoliosis ($p<0.01$) (17). Without question, MAC needs to be used when patients need to cough. This can be as much as every 20 minutes or not at all (36-39). The goal of therapy is to expel secretions, allay secretion-associated dyspnea, and increase pulmonary parameters and oxyhemoglobin saturation. In 2007, the International Standard of Care Committee for Spinal Muscular Atrophy issued a protocol recommending using a pressure of at least 30 cm H_2O and saying that pressures exceeding 40 cm H_2O are ideal. The document suggests the use of bronchial drainage manoeuvres alternated with MI-E treatments (40).

Patient cooperation is important for use of automatic mode MI-E. To enhance patient synchrony some machines have introduced an inspiratory trigger.

Another technique that can be associated with MI-E is intrapulmonary percussive ventilation (IPV) used both before and after sessions (41). At present, several machines (Pulsar SIARE, Pegaso DIMA, Nippy Clearway) offer percussive ventilation together with in-exsufflation, but there are no studies to date confirming greater effectiveness of this combination. Training of caregivers is crucial for MAC and IPV and has a significant effect on both the number and duration of hospital admissions (41, 42, 13), on survival (43), and on the timing of tracheotomy which eventually becomes necessary for ALS patients and few others (44). MAC is used along with oximetry as feedback to maintain normal saturation in ambient air. Bronchodilator medication may also be helpful during intercurrent respiratory infections. Caregivers can usually be trained in the outpatient setting or during the pre-discharge phase from the hospital to ensure continuity of care in the home. A recent study has shown that the use of the MI-E guided by telemonitoring of oxyhaemoglobin saturation and by evaluation of symptoms with an online questionnaire can reduce admissions to emergency rooms and decrease hospitalizations (45).

Indications/Contraindications

The use of MI-E is indicated for all conditions accompanied by ineffective cough (PCF<270 L/min) associated with muscular weakness or rib cage deformity.

The use of MI-E is indicated for all conditions accompanied by ineffective cough (PCF < 270 L/min) (Tables 1 and 2) associated with muscular weakness or rib cage deformity (13). Relative contraindications are previous volutrauma and barotrauma (46), and cardiovascular instability. Any airway collapse that occurs during the expiratory phase is rapidly and spontaneously reversed (47) and minimized by using an exsufflation-timed abdominal thrust. Genioglossus muscle contraction also stabilizes and increases upper airway patency to limit any collapse (48, 49).

Side effects

1) Cardiovascular system: an increase in heart rate, blood pressure (both systolic and diastolic) and cardiac output have all been observed (36). Bradycardia has been observed in cases of spinal cord lesion with spinal shock, and in several paediatric subjects with SMA. In such cases, it is important to increase pressures gradually; premedication with anticholinergics might be indicated.
2) Thoracic pain due to musculoskeletal stretching in patients with severe thoracic deformity and/or very low VC who do not routinely receive maximal insufflation. This can be avoided by increasing pressures gradually and introducing air stacking and GPB.
3) Gastric and abdominal distension, nausea and vomiting: gastric distension generally improves by reducing the operating pressures. In some cases, gastric pressure was observed to increase due to the simultaneous use of abdominal thrusts (16). Abdominal thrusts may need to be gingerly applied for patients with gastroesophageal reflux (39).
4) Two cases of pneumothorax associated with continuous ventilator support and the daily use of MI-E were reported, one in a C4 tetraplegic patient and one for a patient with Duchenne dystrophy (46). Barach and Beck did not observe any barotrauma in over 2000 applications of MI-E on 103 patients (22).

Table 1 - Indications and contraindications for the use of the in-exsufflator.

- Weakness in respiratory muscles, with ineffective cough (PCF < 270 L/min) (16)
- Patients whose bulbar muscles can maintain an adequate stability of the upper airways, but are insufficient for permitting effective manually assisted coughing by air stacking and abdominal thrusts. Examples include patients with Duchenne muscular dystrophy or spinal amyotrophy (17)
- Patients with severe scoliosis: however, in this case, thoracic deformity and asymmetry of the diaphragm make it difficult to position the hands for performing an effective abdominal thrust

The relative contraindications:

- Recent barotrauma
- Pneumothorax
- Bullous emphysema
- Haemodynamic instability
- Facial trauma
- Pneumomediastinum

Table 2 - Neuromuscular disorders in which MI-E is most frequently used.

MYOPATHIES
Dystrophinopathies (Becker's Muscular Dystrophy, Duchenne's Muscular Dystrophy)
Other muscular dystrophies (congenital facial scapulo humeral dystrophy, myotonic dystrophy, Emery-Dreifuss muscular dystrophy)
Other myopathies: acid maltase deficiency, alpha-glucosidase deficiency, mucopolysaccharidosis, mitochondrial myopathies
Inflammatory myopathies: polymyositis
Illnesses of the joints (myasthenia gravis, etc.)
Systemic myopathies
Neurological disorders
Spinal muscular atrophy (I, II, III)
Motor neuron diseases (ALS, PLS, PMA)
Polio
Charcot-Marie-Tooth disease
NEUROPATHIES
Charcot-Marie-Tooth disease
Phrenic nerve paralysis
Guillain-Barré syndrome
OTHERS
Multiple sclerosis
Upper spinal cord lesion
Spina Bifida
Cerebral palsy
Encephalopathies

5) Initial and transient desaturation has been reported due to transient airway collapse and perhaps mobilization of mucus to more central airways (35).
6) Streaks of blood can be observed in the expectorate when inspissated secretions are expulsed that had firmly adhered to the bronchial walls.

Clinical effects during the stable and acute phases

There is a great deal of literature but few randomised, controlled studies on MI-E. A study by Sancho et al. on tracheotomised patients with ALS MI-E was significantly more effective in promoting oxygenation, in decreasing airway resistance, and in secretion expulsion than in controls (50). The use of noninvasive mechanical ventilation combined with MI-E during exacerbations also significantly reduces the risk and duration of hospitalizations (38). Miske reported that MI-E effectively resolves atelectasis and reit-

The routine daily use of MI-E is recommended for maintaining the caregiver's and patients' skills, and the pulmonary compliance with reduction of lung atelectasis.

erated its importance for critical care (35). The other side of the coin is that patients treated only during exacerbation may not use it effectively initially. The routine daily use of MI-E even without excess secretions can help in maintaining the caregiver's and patients' skills as well as provide deep insufflation to maintain pulmonary compliance and diminish atelectasis and is therefore recommended (13).

In conclusion, in view of the great deal of scientific evidence and in accordance with current guidelines MAC is crucial in both the long-term and acute care settings. Positive results have been reported in terms of survival, quality of life and appropriate utilization of health care resources. Unfortunately, in the Italian health care system, very few centres currently offer neuromuscular patients physical medicine and rehabilitation programs that include MAC and noninvasive ventilation alternatives to ARF and tracheostomy despite heightened awareness of their effacity within the pulmonary community worldwide (51).

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