

REVIEW

A Review on Cough Augmentation Techniques: Assisted Inspiration, Assisted Expiration and Their Combination

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Summary

Cough is an important mechanism of airway clearance. In patients who present weak and ineffective cough, augmentation techniques aim to assist or simulate the maneuver. These techniques target different phases of the cough cycle, mainly the inspiratory and expiratory phases, through assisted inspiration, assisted expiration and their combination. They include the manual hyperinflation, ventilator hyperinflation, glossopharyngeal breathing, manually assisted cough and mechanical insufflator-exsufflator, each applied individually or in different combinations. The aim of this review is to investigate the effectiveness and safety of cough augmentation techniques. Findings support that all commonly used techniques can theoretically improve airway clearance, as they generate higher cough peak flows compared to unassisted cough. Still, the studies assessing cough augmentation present considerable limitations and the direct comparison of different techniques is challenging. Current evidence indicate that cough peak flow shows higher increase with the combination of assisted inspiration and expiration, and improvement is greater in patients with lower unassisted values. Associated adverse events are infrequent.

Key words

Cough augmentation • Cough assist • Airway clearance • Manually assisted cough • Hyperinflation • Mechanical insufflator-exsufflator

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Introduction

Cough is the physiological defense system of airway clearance along with the mucociliary escalator (Widdicombe and Fontana 2006). It is also a troublesome symptom that can be frequent and vigorous, and has the potential to serve as a measure of disease (Birring *et al.* 2003, Spinou and Birring 2014, Lee *et al.* 2017, Spinou *et al.* 2017). Still, on the opposite side of this spectrum, cough can be absent, weak and inadequate to clear the airways (Spinou 2018). When it does not generate effective airflows to achieve airway clearance, cough augmentation techniques can support one or more of the cough inspiratory, compressive, and expiratory phases (McCool 2006, Spinou 2018). These techniques are categorized into assisted inspiration, assisted expiration, or a combination of assisted inspiration and expiration, and include the manual hyperinflation, ventilator hyperinflation, glossopharyngeal breathing, manually assisted cough (MAC) and mechanical insufflator-exsufflator (MI-E), each applied individually or in different combinations (Chatwin *et al.* 2018).

Cough augmentation is commonly used in neuromuscular diseases, neurological weakness, spinal cord injury, and critically ill intubated and mechanically ventilated patients (Rose *et al.* 2014, Prevost *et al.* 2015, Hov *et al.* 2018). It is applied in acute and long-term settings and aims to reduce mucus retention and consequently respiratory infections and the risk of respiratory failure. Several studies investigate the cough augmentation techniques. The aim of this narrative review is to investigate the effectiveness and safety of the

main cough augmentation techniques and their combination.

Effects of cough augmentation on cough peak flow

Assisted inspiration

Cough augmentation techniques that target the inspiratory phase of cough include the manual hyperinflation, ventilator hyperinflation and glossopharyngeal breathing (Chatwin *et al.* 2018). Manual hyperinflation, bagging or breath stacking aims to increase the inspiratory volume and ultimately result in higher expiratory airflow at the expulsive phase of cough (Paulus *et al.* 2012, Spinou 2018). Bagging involves delivering an inspiratory volume to the patient during inspiration, usually until maximum insufflation capacity, at a low inspiratory flow, with an inspiratory pause and then quick release to provide a high expiratory flow (Paulus *et al.* 2012). Application of the manual hyperinflation can be via a non-resuscitation bag, a resuscitation bag with one-way valve adjustment, or a resuscitation bag with the patient using glottic closure to retain the air volume in multiple breaths (Denehy 1999, Crowe *et al.* 2006, Toussaint *et al.* 2009). In the ventilator hyperinflation, mechanical means deliver positive pressure through adjusting the mechanical ventilation settings in critically ill patients (Dennis *et al.* 2012). Alternative devices deliver inspiratory positive pressure, such as the intermittent positive pressure breathing (IPPB), non-invasive ventilator (NIV), and insufflation using the MI-E (Trebbia *et al.* 2005, Dohna-Schwake *et al.* 2006, Mellies and Goebel 2014). Glossopharyngeal breathing is a specific way of breathing to increase inspiratory volume, which aims to hyperinflation, increases the maximum insufflation capacity and serves as a safety option for ventilator-dependent patients in events of machine failure (Feigelson *et al.* 1956, Bach *et al.* 1993, Bianchi *et al.* 2004, Nygren-Bonnier *et al.* 2018).

Several studies have shown that assisted inspiration techniques increase the cough peak flow (CPF) alone or in combination with other cough augmentation techniques compared to unassisted cough in patients with neuromuscular disease, Duchenne muscular dystrophy, amyotrophic lateral sclerosis, spinal cord injury and patient using mechanical ventilation due to post-poliomyelitis muscle weakness (Kirby *et al.* 1966, Kang *et al.* 2005, Kang *et al.* 2006, Toussaint *et al.* 2009,

Sarmiento *et al.* 2017, Bach *et al.* 1993). Although the increase is higher to unassisted cough, it is generally lower than the increase from expiration or the combination of inspiration and expiration cough augmentation. Moreover, hyperinflation techniques are more effective in the absence of scoliosis (Marques *et al.* 2014). One study found that air stacking is more effective than the MAC, although the combination of both is more effective than any of these two alone (mean \pm standard deviation (SD) CPF unassisted 138 \pm 70 l/min, MAC 204 \pm 75 l/min, hyperinflation 236 \pm 68 l/min, and hyperinflation with MAC 302 \pm 78 l/min, all $p < 0.0001$) (Ishikawa *et al.* 2011). Assisted inspiration generates higher CPF increase in patients with lower vital capacity (Kang and Bach 2000).

Assisted expiration

Assisted expiration techniques include the MAC and exsufflation using MI-E (Chatwin *et al.* 2018). Their aim is to support the expiratory phase of cough to generate an expiratory flow bias and achieve mucus mobilization based on the two-phase gas-liquid interaction (Spinou 2018). MAC uses external mechanical force or compression applied on the thoracic, abdominal, and thoraco-abdominal areas during expiration (Sivasothy *et al.* 2001, Spinou 2018). The technique is applied by therapists, carers or patients who use self-assistance (Bianchi *et al.* 2014, Kan *et al.* 2018). The exsufflation involves applying the expiratory phase settings of the MI-E during expiration, without using the other MI-E settings (Mustfa *et al.* 2003).

Most studies of assisted expiration have investigated MAC and only a few investigated MI-E exsufflation only (Chatwin *et al.* 2003, Mustfa *et al.* 2003). Studies indicate that MAC increases the CPF in patients with expiratory muscle weakness compared to unassisted cough in neuromuscular disease, amyotrophic lateral sclerosis, Duchenne muscular dystrophy and spinal cord injury (Braun *et al.* 1984, Jaeger *et al.* 1993 Mustfa *et al.* 2003, Trebbia *et al.* 2005, Toussaint *et al.* 2009). This improvement is higher compared to assisted inspiration techniques alone and lower than when the techniques of assisted inspiration and expiration are combined. A study in 28 patients with Duchenne muscular dystrophy showed that CPF (mean \pm SD) is higher with the combination of the MAC with manual hyperinflation using a resuscitation bag (292 \pm 86 l/min), compared to the techniques alone, MAC (231 \pm 81 l/min), hyperinflation (225 \pm 80 l/min), and unassisted cough

(171±67 l/min) (Brito *et al.* 2009). In mechanically ventilated patients, CPF was also higher when MAC was applied with an increased positive end-expiratory pressure and inspiratory time compared to MAC alone (112.3±15.6 l/min versus 95.8±18.3 l/m, $p < 0.05$) (Silva *et al.* 2012). MAC produced higher CPF than unassisted cough and electrically stimulated coughs in 24 patients with spinal cord injury (Jaeger *et al.* 1993). Interestingly, a study with patients with amyotrophic lateral sclerosis (21 bulbar vs. 26 non bulbar) showed that CPF (mean ± SD) was higher compared to unassisted cough (178±61 vs. 217±84 l/min) using MI-E exsufflation only (225±76 vs. 279±87 l/min), vs. MAC (197±63 vs. 244±83 l/min), insufflation (188±64 vs. 226±86 l/min), and MI-E (212±75 vs. 264±73 l/min) (Mustfa *et al.* 2003).

Combination of assisted inspiration and expiration

The combination of assisted inspiration and expiration has various forms and studies have used a variety of means to combine the aforementioned techniques. Assisted cough using a MI-E device is a common method that aims to simulate the cough maneuver by altering the delivery of positive pressure (insufflation) and negative pressure (exsufflation) to the airways, with manual or automatic pausing in between (compression) (Bach 1993, Homnick 2007). Furthermore, at the end of the MI-E treatment there is application of insufflation, which provides inspiration to appropriate functional residual capacity (Hull *et al.* 2012). MI-E can be used with various interfaces on patients who are spontaneously breathing, intubated or tracheotomized (Miske *et al.* 2004, Bach *et al.* 2014).

Effectiveness and individual thresholds of tolerance guide the application of the MI-E pressures. Still, insufflation (inspiratory phase) and exsufflation (expiratory phase) pressures of 40 mmHg have been generally suggested (Fauroux *et al.* 2008). Clinically, patients receive 5-15 mmH₂O lower pressure than it is indicated in the MI-E device settings (Fauroux *et al.* 2008). In the presence of endotracheal tube or tracheostomy, the tube diameter increases the resistance and requires greater pressure to achieve higher expiratory flows, so pressures range from 38 mmHg to 51 mmHg (Guerin *et al.* 2011). Lung models have shown that higher pressures of exsufflation than insufflation and higher times of insufflation than exsufflation can increase expiratory flow (Gomez-Merino *et al.* 2002, Striegl *et al.*

2011). The exsufflation pressures are usually greater than the insufflation pressures in absolute value and also the exsufflation duration is longer than the insufflation (Chatwin and Simonds 2019). Higher pressures may be required in patients with lower unassisted CPF, whilst MI-E application in patients with amyotrophic lateral sclerosis might need lower pressures from other neuromuscular disease patients because there is evidence of upper airway collapse in flexible trans-nasal fibre-optic laryngoscopy (Andersen *et al.* 2017, Chatwin *et al.* 2018). Still in clinical practice, the pressures applied vary amongst patients and a European survey found that age is also a factor that results in differences on the applied pressures, with younger patients using lower pressures than older (Hov *et al.* 2018, Chatwin and Simonds 2019).

Many cross-over studies indicate that the increase of the CPF is higher when MAC is combined with assisted inspiration techniques and the MI-E generates higher PCF compared to unassisted cough and cough augmentation techniques in isolation (Kirby *et al.* 1966, Bach 1993, Bach *et al.* 1993, Morrow *et al.* 2013, Kim *et al.* 2016, Sancho *et al.* 2017). Breath stacking with the addition of MAC and also MI-E produced greater CPF compared to unassisted cough in patients with muscle weakness due to post-poliomyelitis (Bach *et al.* 1993). Breath stacking in combination with MAC generated the higher increase of CPF compared to the stand alone techniques in 179 patients with neuromuscular disease (Toussaint *et al.* 2009). The combination of IPBB with MAC showed a greater increase in CPF than MAC or IPPB alone in 10 patients with neuromuscular disease (Trebba *et al.* 2005).

There was a significant increase in the PCF in bulbar and non-bulbar patients compared to unassisted cough (Mustfa *et al.* 2003), in a randomized cross-over study of MAC, insufflation using MI-E, exsufflation using MI-E and MI-E in 21 bulbar and 26 non bulbar patients with amyotrophic lateral sclerosis. MI-E produced higher CPF than MAC with or without manual hyperinflation or bi-level ventilator hyperinflation in 16 patients with amyotrophic lateral sclerosis, and there was no difference between the bulbar and non-bulbar groups (Senent *et al.* 2011). MI-E also produced higher CPF compared to unassisted cough in 17 children with Duchenne muscular dystrophy, spinal muscular atrophy and other myopathies during a clinically stable stage (192±99 l/min vs. 162±97 l/min) (Fauroux, Guillemot *et al.* 2008). Similar results were shown in 21 patients with muscle weakness and NIV ventilator users, mean ± SD

CPF of unassisted cough 109 ± 62 l/min, air stacking 202 ± 64 l/min, MAC 256 ± 77 l/min and MI-E 448 ± 61 l/min, $p < 0.001$ (Bach 1993).

In a randomized study with an age-matched historical control, 22 patients with neuromuscular weakness generated greater increase in the CPF with MI-E compared to unassisted cough, MAC, assisted cough using NIV, and exsufflation using MI-E ($p < 0.001$) (Chatwin *et al.* 2003). CPF was higher when MI-E was combined with MAC in a study with 40 patients with neuromuscular disease and respiratory muscle dysfunction. The mean \pm SD CPF during MAC with MI-E was 202.4 ± 46.6 l/min compared to the unassisted cough, hyperinflation with MAC, and MI-E, 95.7 ± 40.5 , 155.9 ± 53.1 , 177.2 ± 33.9 , respectively (Kim *et al.* 2016). A study with 12 patients with Duchenne muscular dystrophy found that MI-E with MAC generated higher CPF (240 ± 38 l/min) compared to MAC (113 ± 32 l/min) or MI-E (199 ± 40 l/min) alone, hyperinflation with MAC (224 ± 62 l/min), hyperinflation without MAC (170 ± 30 l/min), and unassisted cough (59 ± 34 l/min), all higher

than unassisted cough, $p < 0.01$ (Kikuchi, Satake *et al.* 2018). Still, patients who reached CPF of 300 l/m using hyperinflation and MI-E did not have a higher CPF by adding MAC, probably because the cough effort from the combination of two exceeds the capacity of the device for pressure (Lacombe *et al.* 2014, Kim, Choi *et al.* 2016).

In contrast to the previous studies, hyperinflation using IPPB with MAC resulted in greater CPF increase than MI-E with or without MAC in 18 patients with neuromuscular disease and severe respiratory muscle dysfunction (Lacombe *et al.* 2014). In a randomized controlled trial with 26 patients with amyotrophic lateral sclerosis with bulbar or nonbulbar dysfunction, CPF of MAC combined with maximum insufflation or with MI-E was lower in the bulbar subgroup of seven patients who had unassisted CPF < 270 l/min compared to the other patients. These authors suggested that MI-E is ineffective in patients with bulbar dysfunction who generate maximum insufflation capacity > 1 l and unassisted PCF < 162 l/min (Sancho, Servera *et al.* 2004).

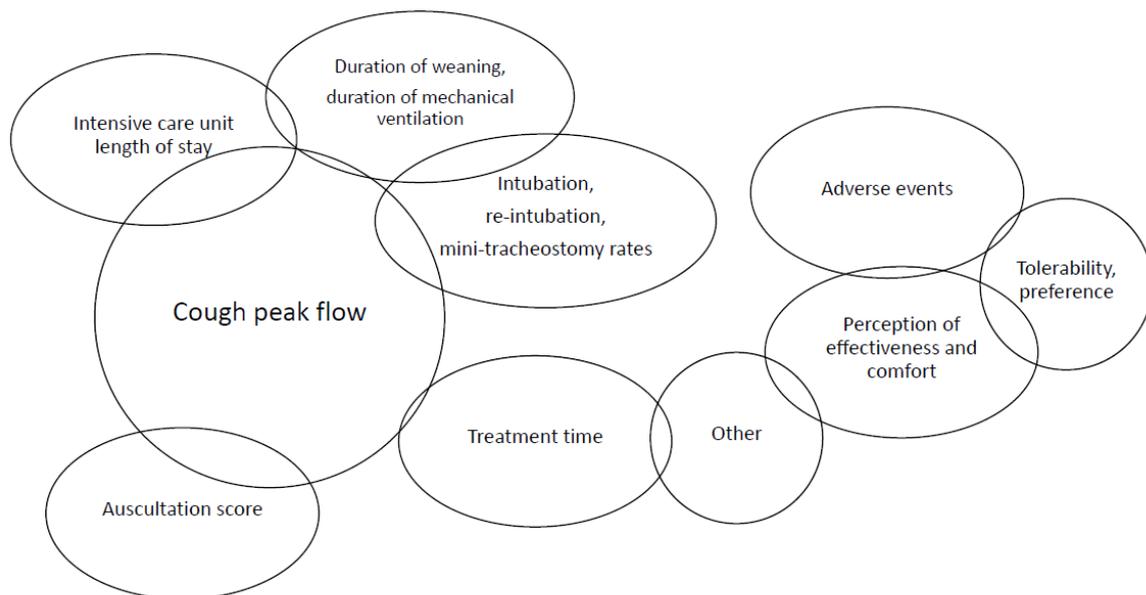


Fig. 1. Outcome measures used to assess the cough augmentation techniques

Patients with chronic obstructive pulmonary disease and individuals with scoliosis

In a small randomized study, cough augmentation using MAC with or without exsufflation, did not significantly change CPF in nine healthy individuals and decreased the CPF and cough expiratory volume in eight patients with chronic obstructive

pulmonary disease (COPD) (Sivasothy *et al.* 2001). Another study that included nine patients with COPD showed that CPF did not change significantly with the use of MI-E, but this one involved a higher risk of bias (Winck, Goncalves *et al.* 2004). Additionally, there was no increase in the CPF in four patients with respiratory muscle weakness with scoliosis, although there was an increase in the patients with respiratory muscle weakness

without scoliosis (Sivasothy *et al.* 2001, Chatwin *et al.* 2003). In contrast, a small study in patients with Duchenne muscular dystrophy did not show a significant difference between the patients who had kyphoscoliosis and those who did not, although this was again a study with higher risk of bias (Brito *et al.* 2009).

Other outcomes of cough augmentation

Most studies assess CPF as their primary outcome for investigating the effectiveness of cough augmentation techniques, but other outcomes have also been reported (Fig. 1). A Cochrane review including three studies in mechanically ventilated critically ill patients found no reports about the effect of MI-E on the duration of weaning (Rose *et al.* 2017). A study with 75 critically ill patients who were receiving mechanical ventilation through endotracheal intubation or tracheostomy, reported higher extubation success (no reintubation within 48 hours) in the group that received MI-E combined with MAC compared to standard care without cough augmentation, 82.9 % vs. 52.5 %, $p < 0.05$, relative risk (95 % CI) 1.58 (1.13, 2.20) (Goncalves *et al.* 2012). In another study, the success rates of extubation (no reintubation during hospitalization) for MI-E were 95 % and 91 % in case series with 157 and 98 patients with neuromuscular disease or weakness presenting vital capacities < 20 % of normal values, respectively (Bach *et al.* 2010, Bach *et al.* 2015). Furthermore, a study found that the MI-E group had higher success rate for mini tracheostomy and endotracheal intubation compared to usual chest physiotherapy without MI-E, 2/10 vs 10/16, $p = 0.047$ (Vianello *et al.* 2005).

Evidence indicate a reduction of mechanical ventilation duration and intensive care unit length of stay, but the corresponding level of evidence is low (Niranjan and Bach 1998, Goncalves *et al.* 2012). There was a reduction in the mechanical ventilation duration for patients who received MI-E, mean difference (95 % CI) - 6.1 days (-8.4, -3.8) (Goncalves *et al.* 2012). Ten patients who underwent tracheostomy and were in the MI-E group, had shorter intensive care unit length of stay than a historical control of patients (3.5 \pm 0.5 days vs. 51.1 \pm 7.8 days, $p < 0.001$) (Niranjan and Bach 1998). Another study found a lower mean intensive care unit length of stay after extubation in the MI-E group when compared with controls (3.1 \pm 2.5 vs. 9.8 \pm 6.7 days, $p < 0.05$), but without significant difference in the total intensive care unit length of stay (Goncalves *et al.* 2012). A small study

investigating air stacking vs. MI-E did not show any differences in respiratory tract infections, days on antibiotics, or hospitalisations (Rafiq *et al.* 2015). On the other hand, MI-E reduced the risk of pneumonia in a retrospective study in 62 children with neuromuscular diseases (Miske *et al.* 2004).

One systematic review of randomized clinical trials compared the ventilator and manual hyperinflation techniques and found no differences between manual and mechanical hyperinflation, in sputum wet weight, pulmonary compliance, oxygenation and cardiovascular stability (Anderson *et al.* 2015). A randomized crossover study with eight patients with spinal muscular atrophy and congenital myopathy during an acute respiratory tract infection found that MI-E with MAC decreases the treatment time, improves the auscultation scores and increases the patient-reported effectiveness on the visual analogue scale (Chatwin and Simonds 2009). In a study assessing patient perception of effectiveness and comfort on a visual analogue scale, effectiveness was statistically higher for MI-E with MAC and comfort was higher for hyperinflation and MAC although this was not statistically significant (Lacombe *et al.* 2014).

Relevant studies do not commonly report mortality, morbidity, quality of life and serious adverse events outcomes (Morrow *et al.* 2013). One trial reported mortality on intensive care unit within the 48 hours following extubation, but had no participants dying in either group of MI-E or a control group of standard care without cough augmentation (Goncalves *et al.* 2012). A retrospective study showed that access to non-invasive respiratory aids including MI-E could improve survival, extubation and decannulation in patients with Duchenne muscular dystrophy (Gomez-Merino and Bach 2002). MAC and MI-E, along with oximetry and home use of NIV decreased hospitalizations and respiratory complications and mortality in patients with amyotrophic lateral sclerosis (Vitacca *et al.* 2010). Long term use of the MI-E can improve vital capacity in neuromuscular disease patients (Stehling *et al.* 2015).

Furthermore, MI-E was well tolerated in patients with amyotrophic lateral sclerosis and neuromuscular diseases (Winck *et al.* 2004). A study that included children showed that MI-E was well tolerated, although the children with spinal muscular atrophy generated the lowest CPF values and reported the lowest comfort rates (Fauroux *et al.* 2008). Patients with spinal cord injury found MI-E more comfortable than suction via endotracheal tube (Sancho *et al.* 2003). However, patients

with neuromuscular diseases who use the MI-E as part of their home management, report its size, weight and the burden to the carer as disadvantages (Mahede *et al.* 2015). The use of MI-E in home care needs to consider social and individual aspects, and health professionals must provide clear instructions, training and confidence to the users, and ensure continuity of care (Moran *et al.* 2015).

Adverse events of cough augmentation techniques

Few studies have reported adverse events from cough augmentation techniques when these are applied appropriately. The application of positive pressure could be associated with barotrauma, but the generated pressures are lower than pressures of the physiological cough and of short duration (Gomez-Merino *et al.* 2002). Pneumothorax is rare, and it was reported when using MI-E and NIV in two patients with neuromuscular disease who had scoliosis (Suri *et al.* 2008). A study combining MAC with either hyperinflation or MI-E, did not have adverse events (Nijland *et al.* 2010). A systematic review on manual hyperinflation in intubated and mechanically ventilated patients in the intensive care unit showed that manual hyperinflation resulted in infrequent and short-term adverse events such as decrease in cardiac output, alteration of heart rate and increase in central venous pressures, based on eight out of 13 included studies (Paulus *et al.* 2012). Although cardiovascular instability risk is low, in glossopharyngeal breathing syncope may occur (Nygren-Bonnier *et al.* 2018). In a retrospective study, five out of 62 patients with neuromuscular disease (Duchenne muscular dystrophy, spinal muscular atrophy, myopathy and other, including tracheostomy users and children), did not continue the MI-E due to safety issues (Miske *et al.* 2004). A small study with 16 consecutive patients in the intensive care unit, who were intubated and mechanically ventilated, did not report adverse events with MAC (Avena *et al.* 2008). The number of patients who required reintubation due to secretions and severe hypoxemia, were nine out of 40 patients (22.5 %) in the control group of standard care without cough augmentation compared to two out of 35 patients (6 %) who received MI-E with MAC, relative risk (95 % CI) 0.25 (0.06, 1.10) (Goncalves *et al.* 2012).

A Cochrane review showed that there were no new-onset arrhythmias, heart rate increase >25 %, or

pneumothorax for those who received cough augmentation vs. the patients receiving standard care. Still, the studies of this review evaluated a combination of cough augmentation techniques rather than one technique in isolation (Rose *et al.* 2017). A study reported that one participant in the breath stacking group had an episode of coughing during suctioning, which elevated the participant's blood pressure for more than 30 minutes (Crowe 2006). In a retrospective study with patients with tracheostomy or spinal muscular atrophy, the use of MI-E contributed to chronic abdominal pain, chest discomfort during its application, short-term abnormal cardiac rhythm, but no episodes of pneumothorax (Miske *et al.* 2004). In one study assessing MI-E in eleven critically ill patients, treatment failed due to repeated episodes of gastroesophageal reflux that resulted in bronchospasm and endotracheal intubation. Also, one patient presented stomach distension but did not discontinue the therapy, whilst another patient developed mild nasal bleeding and discontinued the treatment (Vianello *et al.* 2005).

Discussion

Evidence indicate that cough augmentation techniques increase the CPF compared to unassisted cough in patients who present muscle weakness. The CPF increase is greater for the patients who present lower unassisted CPF compared to those with higher values (Mustfa *et al.* 2003, Ishikawa, Miura *et al.* 2011). Moreover, cough augmentation techniques seem to have a greater impact on CPF when they target the inspiratory and expiratory cough phases. Still, there is high heterogeneity in the studies that assess the cough augmentation techniques. It is hard to assess the effectiveness of individual techniques over others, as studies applied different treatment arms and in different populations. Most of the studies assessing the cough augmentation techniques have small sample sizes, crossover design, and a short duration (Morrow *et al.* 2013). Additionally, only few studies were randomized, and the interventions mainly followed a sequence of applying unassisted cough, assisted inspiration, assisted expiration and then the combination of assisted inspiration and expiration. As a result, there is a high risk of bias, particularly in relation to placebo and learning effects (Fauroux *et al.* 2008). A systematic review with twelve included studies (four randomized controlled trials) showed that there is still poor evidence to guide the

clinical practice about the application of MI-E in patients with neuromuscular disease (Auger *et al.* 2017). This was in line with an earlier Cochrane review that analyzed five studies (Morrow *et al.* 2013).

Researchers and clinicians widely use the CPF values for assessing cough augmentation. Nonetheless, there is a known risk of fixed and proportional bias in assessing CPF with the peak flow meter, which is the outcome that most studies use and a measure that is easy to perform in the clinical setting (Kikuchi *et al.* 2018, Kulnik *et al.* 2019). Clinicians need to be cautious when they use the CPF cut off points to guide their clinical

decision making for cough augmentation techniques (Kikuchi *et al.* 2018, Kulnik *et al.* 2019). They need to assess the evidence about effectiveness, adverse effects, precautions and contraindications of the techniques, alongside patient assessment and ability to perform unsupported coughs. Clinicians, patients and carers also need to consider additional factors such as the tolerance, adherence, treatment burden, knowledge of the technique, confidence, availability of devices, and cost.

Conflict of Interest

There is no conflict of interest.

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