Will the Addition of Oscillations in Mechanical Insufflation-Exsufflation Ever Be Beneficial?

Mechanical insufflation-exsufflation (MI-E) devices have been around since the polio epidemic. They have been used in the treatment of other neuromuscular disorders, and they are usually the first option for secretion clearance in patients with amyotrophic lateral sclerosis (ALS) regardless of bulbar function. The technology is constantly evolving as manufacturers aim to improve their devices. As a result, MI-E devices have become smaller and begun to have both external and internal batteries for portability. In 2013, a new MI-E device came to the market and offered clinicians the option to add oscillations to insufflation, to exsufflation, or to both. This device only offered one fixed frequency (4 Hz), which was intended to meet a growing demand in the market for a device that could offer oscillations and ventilatory support in one device and to bridge a gap because, intrapulmonary percussive ventilation devices were no longer widely available in some countries. Subsequent devices have come to market, and oscillation delivery can vary significantly among different manufacturers' devices. Oscillatory therapies have been reported to enhance mucociliary clearance and alter sputum viscosity.[1,2] The hypotheses for the increased mucus clearance included cephalad bias of air flow, reduction of mucus crosslinking, decreased mucus viscosity, and enhanced ciliary beat frequency.[1,3] Chatburn[4] suggested that high-frequency oscillations cause miniature coughs within the airways on the basis of in vitro[5,6] and in vivo[1] studies, resulting in higher expiratory flows compared to inspiratory flows, which favored airway clearance. Soon manufacturers added this feature to their devices and allowed a wider range of frequencies and amplitudes. In some countries, this treatment mode (MI-E with oscillations) has been used in clinical practice despite no evidence base. Sancho et al[7] evaluated the effect of MI-E with oscillations on cough peak flow (CPF) and reported no improvement in cough peak flow with the addition of oscillations in stable ALS subjects.[7] Andersen and co-workers[8] longitudinally evaluated upper airway function in ALS. They reported that, over time, adverse laryngeal events were present prior to the onset of bulbar symptoms, and that the addition of oscillations at 10 Hz to both insufflation and exsufflation created a more stable laryngeal opening in some subjects. Thus it appears sensible to use oscillations to stabilize the airway so that the application of MI-E is more effective and might help prevent or decrease adverse laryngeal movements, possibly because the oscillations reduce mean airway pressure.

SEE THE ORIGINAL STUDY ON PAGE 596

In this issue of the Journal, Sancho et al[9] address the long-term benefit of MI-E with oscillations in a particularly difficult population to study. They report the 12-month follow-up of 56 subjects with ALS, prospectively recruited and randomized to MI-E with the addition of oscillations ($n = 27$) or to MI-E alone ($n = 29$). Although not statistically significant, 41% of the subjects in the MI-E group had a gastrostomy compared to 33% in the MI-E + oscillations group. Despite the differences in the requirement for enteral feeding, there was no difference in their primary outcome measure, which was the need for bronchoscopy or tracheostomy due to ineffective MI-E. There was also no difference between the groups for the secondary outcome measures of hospitalization, respiratory tract infections, or a survival bias at 1 y. The authors also looked at the adjusted risk for long-term noninvasive management failure due to ineffective secretion management and found no difference. However, the mean ± SD number of respiratory episodes was low for both groups (MI-E, 0.58 ± 0.16; MI-E + oscillations, 0.25 ± 0.08, $P = .10$). That said, by the end of the study period, 5 subjects had tracheostomies inserted and 25 had died (failure of secretion management was reported in 4 deaths). These results highlight the poor prognosis in this patient group and difficulties around long-term studies.

The work of Sancho et al[9] sets a precedent as it shows that oscillatory therapy is of no long-term benefit in patients with ALS, despite the report by Andersen and co-workers[8] that MI-E with oscillations have the potential to stabilize the upper airway. Why is it that Sancho et al[9] did not

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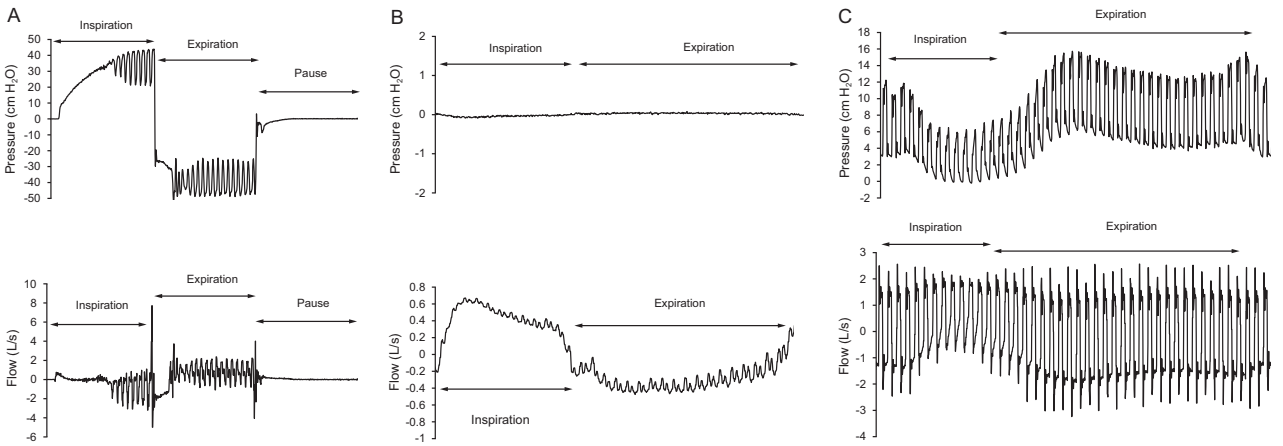

Fig. 1. Flow and pressure traces for 3 oscillatory devices. The inspiratory and expiratory component for each device is highlighted. Flow and pressure signals were recorded via a heated Fleisch no. 2 pneumotachometer (Metabo, Lausanne, Switzerland) placed in line between the different devices and an adult test lung (SmartLung, IMT Medical, Buchs, Switzerland). The characteristics of the lung were set at intermediate compliance (20 mL/cm H_2O) and the lowest resistance (5 cm H_2O/L/s) of the test lung. Recorded data were computed in a data analyzer (MEC, Medical Electronic Construction, Brussels, Belgium). A: CoughAssist E70 mechanical insufflation-exsufflation device (Philips Respironics, Murrysville, Pennsylvania). Insufflation pressure 35 cm H_2O and exsufflation pressure −40 cm H_2O, with insufflation time, exsufflation time, and pause all set at 2 s. Oscillations set on insufflation and exsufflation at frequency of 10 Hz and amplitude of 10 cm H_2O. B: Respin11 vest-type device (RespInnovation, Seillans, France) with a frequency of 7 (14 Hz) and power of 6. C: Impulsator intrapulmonary percussive ventilation (Percussionaire, Sandpoint, Idaho) with a rate of 350 cycles/min (5.8 Hz) and a peak inspiratory pressure of 15 cm H_2O.

observe a reduction of respiratory tract infections and hospitalizations by combining MI-E with oscillatory therapy compared to MI-E alone, when others[10-12] have reported that long-term oscillatory therapies in neuromuscular and neurological disorders decreased hospitalizations and antibiotic usage? One must first think about airway clearance strategies, the patient is assessed, the problem identified, and then treatment is targeted appropriately. Lannefors and colleagues[13] clearly identified 4 stages of airway clearance. Stage 1 involves getting air behind mucus to open up the airways. Stage 2 involves loosening the secretions from the small airways. Stage 3 involves mobilizing the secretions through the small airways to the larger airways. Stage 4 involves clearing the secretions from the central airways. Stages 1–3 target peripheral airway clearance techniques, and stage 4 targets proximal airway clearance techniques. The stage to target and to commence airway clearance techniques depends on the location of secretions. Treatment often moves through all 4 stages and then starts again.

Second, what airway clearance strategy is being used and why? Airway clearance strategies can be categorized into peripheral strategies (eg, secretion mobilizing) and proximal strategies (eg, cough augmentation).[14,15] Therefore, in its "true" form, MI-E is a proximal airway clearance strategy, and oscillatory therapies are peripheral airway clearance strategies.[14,15] MI-E consists of an increase in the inspiratory volume followed by an increase in expiratory air flow that is enhanced by negative pressure, which simulates what occurs during a normal cough and enhances the movement of secretions from the proximal airways toward the mouth. Sancho and co-workers[9] hypothesized that combining MI-E with oscillations essentially combines peripheral and proximal airway clearance strategies and will enhance secretion clearance and therefore improve outcomes. Although this appears to make sense, one must remember that the evidence base for the use of oscillatory therapy comes from different devices, and secretion movement has not been evaluated in MI-E devices with oscillations. It is important to note that the oscillations produced are different and specific to each device (Fig. 1). Furthermore, the oscillations are specific to each therapy and are not delivered in the same fashion. For example, high-frequency chest wall compression and high-frequency chest wall oscillation therapies deliver oscillations around the thorax via an inflatable jacket or a cuirass; the oscillations around the outside of the thorax are transmitted internally within the lungs. On the other hand, intrapulmonary percussive ventilation (IPV) delivers oscillations via the mouth to the lungs. In both therapies, the patient is breathing spontaneously, and the oscillations are superimposed throughout. However, in some cases of IPV the patient lets the device take over and they are ventilated by high-frequency oscillation. MI-E devices have oscillations superimposed on insufflation, on exsufflation pressures, or on both. Therapies have a wide range of frequency settings (eg, high-frequency chest wall compression, 5–20 Hz; IPV, 10–30 Hz; MI-E, 0–20 Hz); high-frequency chest wall compression and IPV oscillations typically are "tuned" to the patient, typically more than one frequency is used for a set period of time, and treatments usually last up to 30 min. IPV can also be set to provide PEEP, thereby

preventing airway collapse, utilizing collateral ventilation, and enhancing secretion movement.[16] Conversely, MI-E with the addition of oscillations has the potential to cause airway closure in the small airways on exsufflation. Small airway collapse is also a concern with high-frequency chest wall compression, but it can be overcome in weak patients with the addition of noninvasive ventilation. We have learned that MI-E should be titrated and individualized to patients.[17,18] Sancho and co-workers[9] used an oronasal mask and individually titrated settings to provide a cough peak flow > 159 L/min. The device used in their study delivered oscillations at 15 Hz and an amplitude of 10 cm H_2O on mean ± SD insufflation pressures of 35.7 ± 3.6 cm H_2O and exsufflation pressures of −40 ± 1.1 cm H_2O for 2 sessions of 6–8 cycles/d. Typically, the 6–8 cycles involved an insufflation-exsufflation sequence followed by a 1-second pause repeated at least 6 times but no more than 8 times. Subjects were told to increase this if there were secretions present. During an acute respiratory infection, the treatment was provided at least twice every 8 h or in the presence of secretions or dyspnea. Subjects did not need to cough with every exsufflation and only did this when the secretions were high enough to clear.[9] This would mean a typical treatment could take only 2–5 min. This would be long enough to clear proximal secretions but is likely not long enough to clear secretions from the peripheral airways. This means, that the length of treatment is likely to be a factor, if the aim of treatment is to target peripheral secretions. However, patients are likely to hyperventilate using MI-E with the addition of oscillations for a long period of time with insufflation and exsufflation pressures optimized for enhanced coughing. Therefore, further evaluation is required to see if MI-E with oscillations at lower pressure will lead to long-term enhanced outcomes. Further research will also reveal whether treatment needs to be targeted, i.e., MI-E with oscillations at lower pressures targeting peripheral airway clearance followed by MI-E being optimized as a proximal airway clearance strategy.

Sancho and co-workers[9] should be congratulated on being the first to evaluate the long-term use of MI-E with the addition of oscillations in a particularly difficult study group. We now know that simply adding oscillations to a patient's current MI-E settings is of no benefit. Questions to be addressed not only include length of treatment and how to manipulate settings to increase the treatment time to allow secretion movement, but also optimal frequency, and whether the frequency should be "tuned." Should we use 10 Hz only if we are using oscillations with MI-E to stabilize the upper airway as Andersen and co-workers found.[8] Does MI-E with oscillations improve cephalad movement of secretions? No studies have evaluated this question. There are certainly bench studies with lung models that might answer this question.[19]

Ultimately the efficacy of MI-E will be limited by the patient's bulbar function in ALS; however, Sancho and co-workers[9] have set a precedent in the evaluation of MI-E with oscillations in subjects with ALS, although using this technique in its current form does not improve outcomes in ALS and should not yet be adopted as routine clinical practice. With individualization and adaption of settings, the effect of MI-E with oscillatory therapy may produce different results.

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