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Respiratory adjuncts to NIV in neuromuscular disease

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Abstract

Muscle weakness is an intrinsic feature of neuromuscular diseases (NMDs). When the respiratory muscles are involved, the ability to take a deep breath is compromised, leading to reduced lung volumes and a restrictive ventilatory impairment. Inspiratory, expiratory and bulbar muscle weakness can also impair cough, which may impede secretion clearance. Non-invasive ventilation (NIV) is an established and indispensable therapy to manage hypoventilation and respiratory failure. The role of other therapies that support respiratory health is less clearly defined and the evidence of efficacy is also harder to summarise as the underlying data are of a lesser quality.

This narrative review appraises the evidence for respiratory therapies in adults with NMD and respiratory system involvement. Techniques that assist lung inflation and augment cough such as lung volume recruitment (LVR) and mechanical insufflation-exsufflation (MI-E) are a particular focus of this review. The evidence suggests that LVR, MI-E and various combinations thereof have clinical utility generally, but important methodological limitations limit the strength of clinical recommendations and hamper the integration of evidence into practice. Future trials should prospectively assess the long-term impact of LVR and cough augmentation on clinical outcomes and burden of care in addition to lung mechanics, as well as determining clear predictors of benefit from these techniques.

Key words

Neuromuscular diseases; respiratory insufficiency; respiratory therapy; mucociliary clearance; insufflation

Short title

Respiratory adjuncts to NIV in NMD

Abbreviations

NMD, neuromuscular disorder

NIV, non-invasive ventilation

ACT, airway clearance technique

IC, inspiratory capacity

RTI, respiratory tract infection

PCF, peak cough flow

DMD, Duchenne muscular dystrophy

ALS/MND, amyotrophic lateral sclerosis / motor neurone disease

LVR, lung volume recruitment

GPB, glossopharyngeal breathing

MI, mechanical insufflation

IPPB, intermittent positive pressure breathing

MI-E, mechanical insufflation-exsufflation

LIC, lung insufflation capacity

MIC, maximal insufflation capacity

RV, residual volume

VC, vital capacity

FVC, forced vital capacity

RCT, randomised controlled trial

MAC, manually assisted cough

1. Introduction

Many neuromuscular diseases (NMDs) affect inspiratory and/or expiratory respiratory muscles, resulting in ventilatory failure and a greater risk of respiratory infection and mortality.[1-4] Respiratory therapy for patients with NMDs has largely focused on ventilatory support, particularly overnight with non-invasive ventilation (NIV). While NIV has clearly improved survival and quality of life for many people living with NMDs,[5,6] less research and practice has focussed on other aspects of respiratory care. Attention to therapies that maintain chest wall mobility and aid in clearing secretions are considered fundamental adjuncts to care both in the hospital and at home.[7,8] This narrative review addresses the evidence in adults for physical therapies that target chest wall mobility and excess secretion clearance when people living with NMD are both heathy and acutely unwell.

There are numerous respiratory therapies that are employed clinically to support the care of people with NMD. A consensus meeting convened by the European Neuromuscular Centre in 2017 discussed the role of these techniques in airway clearance specifically, and classified them in terms of clearing the proximal airways or lung periphery.[8] Proximal clearance or cough augmentation techniques aim to improve pre-cough inspiration, expiratory flow or both. Peripheral airway clearance techniques aim to mobilise secretions

towards the central airways from the periphery such that they are expectorated.[7,8]

In people living with NMD, the ability to clear sputum or secretions from the airways can be compromised for a number of reasons. Typically it is difficulty expectorating, rather than excessive secretion production that results in an imbalance between sputum production and excretion in NMD. Weak inspiratory muscles and a resultant reduced inspiratory capacity (IC) may limit pre-cough inspired volume and contribute to regions of poor ventilation. Over time, breathing at lower lung volumes is hypothesised to stiffen chest wall and lung tissue, as the respiratory system is not expanded through its full range of movement.[9-11] Decreased expiratory muscle strength and impaired glottic and upper airway control can also limit the effectiveness of forced expiratory manoeuvres, especially cough.

Importantly lung parenchyma, respiratory mucosa, ciliary function and mucus rheology are usually not abnormal in NMD, hence sputum amount, viscosity and tenacity are generally unaffected. In contrast, oral secretions may be excessive, pool in the pharynx or be aspirated due to bulbar muscle dysfunction. Strategies for managing excessive oral secretions vary and the evidence base for clinical practice is poor. Clinical options include nebulised normal saline, grape or pineapple juice to break down thick secretions; medications (glycopyrrolate, propantheline, topical hyosine patches, amitriptyline, anxiolytics) or botulinum

toxin injections into the salivary glands for excessive watery secretions; and oropharyngeal suctioning if secretions remain difficult to manage.

There are times in the course of living with a NMD when airway clearance may need to be assisted. During an acute respiratory tract infection (RTI) for example, when sputum load increases and respiratory muscle strength drops further, potentiating lung volume loss.[12,13] It is postulated that an ineffective cough or more severely impaired respiratory function increases risk of developing RTIs, but currently there are no prospective data from adequately sized samples that confirms this clinical belief.[2,14] One prospective study has demonstrated that a peak cough flow (PCF) of 255 L/min when well is a good predictor of an ineffective cough during an acute RTI, however the association between baseline respiratory function and incidence of RTI was not examined.[15] Similarly, there are little data linking cough effectiveness measured by PCF to regional mucociliary clearance. Furthermore, the incidence of RTI in the NMD population is not well established.[2,15]

This narrative review builds on previous reports by considering NMD as a chronic disease with various phases, and appraises the evidence across this continuum. The same respiratory techniques are often used in an individual with NMD, but clinicians may modify dosage and frequency depending on need at any particular time. The literature has thus been grouped into studies during periods of clinical stability and reports during an acute RTI.

1.1. Evidence of efficacy during clinical stability

1.1.1. Techniques to maintain lung volume over time

Spontaneous breathing is a complex interaction between respiratory muscle power and respiratory load, controlled by central respiratory drive. The inspiratory muscles must generate enough power to overcome airway resistance and the elastic recoil of the lungs and chest wall. The increase in thoracic cavity volume during inspiration produces a drop in alveolar pressure and an inflow of air. Progressive loss of power as diseases progress and muscles weaken reduces one side of this equation. Lung and chest wall compliance are decreased in chronic NMD, possibly due to micro-atelectasis, alteration in lung tissue elasticity and musculoskeletal stiffening of the costovertebral joints, tendons and ligaments of the thoracic cage.[9-11] The resultant increase in respiratory load requires greater inspiratory work of breathing, and lung volumes progressively decline over time as weakened muscles struggle against the greater load.

Interventions that counter the reduction in lung and chest wall compliance may restore some of the balance towards the impaired muscles. Augmenting IC beyond the spontaneous unassisted range may recruit alveoli, stretch the lungs and thoracic cage and increase total pulmonary system compliance – akin to "range of movement" exercises for the respiratory system.[16,17] Whilst this thesis has biological plausibility and face validity, unfortunately it also has little

compelling clinical evidence; there are few controlled trials and the quality of the evidence is poor overall. Absence of evidence is not evidence of absence of effect however, and the available literature is used by clinicians to guide practice and has been synthesised into expert opinions and practice statements.[7,8,18-20] The majority of the literature reported is in cohorts of mixed diagnoses, with the exception of studies in Duchenne muscular dystrophy (DMD) or amyotrophic lateral sclerosis / motor neurone disease (ALS/MND).

Therapies for augmenting IC beyond that achievable with spontaneous breathing can be categorised as lung volume recruitment (LVR), glossopharyngeal breathing (GPB) or mechanical insufflation (MI) delivered via non-invasive ventilation (NIV), intermittent positive pressure breathing (IPPB) or the insufflation component of a mechanical insufflation-exsufflation (MI-E) device (Table 1). Regardless of method, the aim of assisted inflation is to achieve a maximal patient-tolerated inspiratory volume; an inspiratory volume that is greater than that which can be achieved by maximal spontaneous inspiration.[7,8] This assisted inspiratory volume has been described in the literature as the Lung Insufflation Capacity (LIC) or the Maximum Insufflation Capacity (MIC).

The LIC is the maximum, tolerable, externally assisted inflation capacity that is independent of glottic control of exhalation,[21,22] whereas the MIC volume remains dependent on effective glottic function.[23-25] Both volumes extend to

residual volume (RV) and are measured on exhalation, similar to a vital capacity manoeuvre (VC). Conceptually, they represent passive IC and have been interpreted as a marker of respiratory system range of movement.[24] A LIC is measured following breath-stacking using a manual resuscitation bag with a one-way value or a single breath inflation using a NIV, IPPB, or MI-E device set to volumes/pressures that exceed spontaneous IC. The MIC is the exhaled volume after insufflation using GPB, a manual resuscitation bag without a one-way valve, or breath-stacking using a NIV (typically volume) device.[7,8]

For assisted inflation techniques to effectively maintain lung voume over time, the LIC or MIC must be greater than spontaneous VC (Figure 1). Techniques that yield LIC are reported as more effective in patients with moderate to severe bulbar dysfunction, although in some cases any insufflation beyond VC may be unachievable.[21]

1.1.1.1.1. Assisted inflation: lung volume recruitment

Lung volume recruitment, performed using a manual resuscitation bag with or without a one-way valve and mouthpiece or mask is a well described method that is commonly known as “breath-stacking”. Breath-stacking methods are characterised by brief plateaus of zero flow between consecutive insufflations. With LVR, compression of the manual resuscitation bag transmits inspiratory pressure to the airways through an airtight oro-nasal mask or mouthpiece (Figure 1b). Exhalation between each insufflation is prevented by either a one-

way valve or the patient controlling their glottis.[23-25] The resultant lung inflation volume is commonly pressure limited by patient tolerance, although a circuit with a pressure-release value may also be used. Once the maximum, tolerated assisted inspiratory capacity is reached, exhalation to functional residual capacity or a spontaneous or assisted forced expiratory manoeuvre (e.g., cough) follows. Breath-stacking can also be performed using GPB or a volume-cycled NIV device. The "NIV method" appears to be as effective as a manual resuscitation bag in increasing MIC, assisted PCF and mastering the technique.[26]

Unfortunately there are no published, comprehensive population registry or other data which describe the effect of LVR in NMD over time. Observational clinical cohorts typically have ascertainment, attrition and other biases and as such, the results must be interpreted with caution. The best described clinical cohort reported slower rates of decline in VC following the initiation of LVR therapy in people with DMD prescribed daily LVR (median follow-up of 3.75 and 6.1 years). The rate of decline in forced vital capacity (FVC) (% predicted) was significantly different within participants pre- and post-LVR initiation (-4.5 per year compared to -0.5 per year). The maximal, LVR-assisted insufflation capacity (LIC) increased slightly during the first 4-5 years of routine therapy and remained unchanged at last measurement compared to at LVR initiation (median [IQR] = 1.6 [1.2-1.8] vs 1.3 [0.8-4.0]). Peak cough flow was also stable over time. The proposed mechanism for plateauing lung function, in the

presence of progressive disease and worsening respiratory muscle strength is maintenance of chest wall range of movement, improved respiratory system compliance and thus relatively lower load for the weakened inspiratory muscles to work against.[16,17]

Results in other NMD support the observations in DMD. Thirty-five people with multiple sclerosis underwent baseline assessment and were prescribed LVR if it augmented PCF. This sub-group had lower baseline FVC and unassisted PCF compared to those that did not demonstrate an immediate improvement. Over a median follow-up period of 13.4 months, the rate of decline in VC was slower and MIC stable in those that were prescribed routine LVR. These data suggest that LVR could modify change in pulmonary function over time and also that there may be responders and non-responders to LVR; with the latter suggested to be those who are less severely restricted.[27]

Retrospective cohort data from 108 patients likewise suggested that routine LVR may be appropriate and beneficial for some but not all people with NMD. Forty-seven people unable to cooperate, with better lung function (VC > 2 litres) or a tracheostomy were excluded. Eighteen of the remaining 61 could not achieve a MIC greater than VC presumably due to bulbar muscle dysfunction preventing glottic closure. Of the remaining 43 people taught daily LVR, 70% demonstrated a beneficial response. Follow-up period was not well described, however MIC and assisted PCF improved over time and was associated with

maintained VC and unassisted PCF in the 70% of the sample who were "responders". The remaining patients had a fall in MIC, VC and assisted PCF over time.[24] All of these cohorts are obviously limited in their findings and generalizability by biases (selection, incomplete follow-up, etc.) and the lack of an appropriate control group, however the pattern of results are broadly consistent across studies.[16,17,21,24,27]

Small, prospective observational studies of 3-6 month duration have reported conflicting outcomes. Forced vital capacity and MIC did not change in 18 patients, but small gains in PCF (257.80 ± 84.31 pre vs 277.90 ± 90.24 L/min post) were observed.[28] Whether this PCF change is clinically significant is unclear, as normal PCF variability is not known. No change in FVC or LIC was found in a group of ALS/MND, post-polio syndrome or myotonic dystrophy patients as a whole, however when only the 50% who were adherent to twice daily LVR were analysed, LIC and the LIC-FVC difference did improve.[22] No change in quality of life was detected over the three-month period, which the authors interpreted as evidence of no additional burden with regular LVR use; alternatively it may indicate a perceived lack of improvement in health. Like the majority of studies in this area, the lack of a control group is a significant limitation.

Although it is beyond the scope of this review to discuss in detail, data in the paediatric, adolescent or young adult population have also shown variable

results. Stehling and colleagues retrospectively analysed records of 21 patients with heterogeneous NMD advised to perform twice daily MI-E incorporating inflations, and found an increase in VC in 86% of patients within the first year.[29] Conversely, a 3-month, matched-pair RCT of inflations in children with DMD found no difference in FVC between those treated with daily IPPB compared to control.[30] Dosage was different between the studies and may explain some of the variability; inflation pressures ranged from 18 to 40 cmH_2O[29] compared to 10 to 18 cmH_2O[30] and treatment time 20[29] versus six[30] minutes per day.

Adherence to long-term therapies is an important consideration when recommending prophylactic intervention in the community. The only randomised controlled trial in this area randomised people with ALS/MND to twice daily LVR or MI-E, at the same time that NIV was initiated. Seventy-one percent used LVR as advised over the 12-month follow-up period. Adherence to MI-E was lower with 47% of the subgroup electing to not perform the technique. The primary outcome measure of chest infection rate was lower than anticipated; a total of 32 respiratory tract infections (0.8/participant/year), hence the power to detect therapeutic efficacy was compromised and no difference between groups was observed. Lung function and PCF over time was not different between the two groups, and no adverse events were reported, providing some data regarding the safety of these interventions.[31]

Short-term studies in people with stable disease may provide insights into the mechanisms of effect.[32-36] A single session of ten LVR manoeuvres increased total respiratory system compliance by 39.5 ± 9.8% immediate post therapy, however this returned to baseline after one hour. The 12 participants all had severe respiratory muscle weakness, restriction and used domiciliary nocturnal NIV. Individual response within the 12 participants varied considerably with some people improving by more than 80%, reiterating that there are likely to be responders and non-responders to the intervention. No change in static lung volumes (IC, functional residual capacity) or unassisted PCF was observed suggesting that the physiological improvement did not translate into functional gains.[32] Improvements in lung compliance were detected in nine out of 14 people with ALS/MND after five minutes of assisted inflation using NIV,[33] but other studies using IPPB have found no effect.[35,36] It is possible that a single 15-20 minute session of assisted inflation in people already severely restricted and unable to reach their predicted total lung capacity is not a high enough dosage to demonstrate change in lung or chest wall compliance, but that more frequent sessions may. Unfortunately there are no well-conducted dose-response studies in the literature.

Together, these longitudinal and short-term studies support the hypothesis that assisted inflations, and specifically LVR, can maintain or increase MIC/LIC. Regular chest wall and lung expansion beyond that able to be generated spontaneously may minimise stiffening, improve compliance, ameliorate

respiratory load and modify the natural history of NMDs. There is no evidence that these techniques alter the progressive decline in respiratory muscle strength, but by reducing the work of breathing, weak muscles could still produce similar changes in lung volume, as evidenced by a slower loss of VC and PCF.

The literature suggests that LVR may not be equally beneficial in all, but the characteristics of responders versus non-responders are uncertain currently. Adherence to therapy has relied largely upon self-report, and in the case of the retrospective trials, in cohorts of patients who self-selected to continue to return to the same centre. Without a comparison group nor knowing how often exercises were actually performed, changes in lung function over time cannot be fully appreciated. Furthermore, considering that only half of the recruited patients elected to use LVR more than twice a day in one study,[22] the question of burden of use versus perceived benefit of regular, long-term therapy emerges as one equally as important as efficacy.

1.1.2. Techniques to augment cough in stable NMD

Assessment of cough in people with NMD has traditionally centred on the measurement of PCF. Prior to reviewing the available literature, it is important to note that there is little evidence linking PCF to clinical outcomes. One recent study in 48 people with ALS/MND and a RTI found a PCF cut-off of 166 L/min the best predictor of an ineffective cough, defined as inability to clear

secretions, but this prospective study is the first of its kind.[37] Data from the COPD population has previously demonstrated that there is no correlation between PCF and radioaerosol clearance of secretions from lung regions.[38] Removal of secretions is dependent on the gas linear velocity being high enough to generate adequate kinetic energy and shearing forces; with velocity dependent on flow and inversely proportional to cross-sectional area of the airways. Flow is therefore but one element that contributes to effective secretion clearance; the influence of cross-sectional area, airway diameter, dynamic airway compression and intrathoracic pressure is often overlooked.[39-41]

Notwithstanding these conceptual limitations, cough effectiveness has been evaluated primarily by using PCF. There is consensus among the many studies that have examined the immediate effect of interventions on PCF in NMD that both inspiratory or expiratory intervention can augment cough compared to a spontaneous, unassisted effort (Table 2).[23,28,42-46] Inspiratory assistance can be provided in the form of breath-stacking using a manual resuscitation bag or volume-cycled ventilator, NIV, IPPB or the insufflation component of MI-E, with the cough following from this elevated IC. One study has demonstrated that the optimal inflation volume for generating the maximal assisted PCF may actually be lower than MIC or LIC, i.e., a submaximal inspiratory capacity.[47] Augmentation of expiratory airflow can be provided by either a thoracic or abdominal manually assisted cough (MAC) or exsufflation using a MI-E device.

The greatest improvement in PCF however is seen when a combination of these elements is used, whether that be assisted inflation followed by MAC, or MI-E.[23,37,42-46,48,49] People with ALS/MND and bulbar symptoms may however be an important exception to this general principle.[50,51] A series of recent studies using direct visualisation of the upper airway during MI-E by flexible laryngoscopy have captured laryngeal adduction during insufflation and hypopharyngeal narrowing during exsufflation in all patients.[52,53] These responses would clearly compromise the effectiveness of MI-E to both inflate the lungs and then subsequently to assist with secretion expectoration. Importantly, the research also demonstrated that careful titration of MI-E settings could minimise these ineffective efforts highlighting the importance of individually customised settings.

The importance of individualisation is not limited to MI-E and applies to cough augmentation more broadly. The studies above revealed that cough augmentation is greater in people with more impaired respiratory function (VC or PCF).[21,42,45,54] Additionally, some individuals have larger improvements in their assisted PCF with one method of assisted inflation over another, or with expiratory rather than inspiratory assistance. This may reflect different patterns of respiratory impairment; for example people with predominant expiratory muscle weakness may benefit from MAC more so than breath-stacking. In the absence of evidence to determine what pattern of weakness is best managed

with which technique, assessing, trialling and titrating various cough augmentation techniques on each individual is recommend and appropriate.

1.1.3. Sputum clearance techniques

Excessive lung secretion production (sputum) isn't typically an issue for people with NMD because the lung parenchyma, respiratory mucosa, mucociliary function and/or mucus rheology are not commonly impaired. Whilst bulbar muscle function can be significantly impaired, resulting in difficulty swallowing, hyper-secretion and pooling of oral secretions, sputum mobilisation per se is unaffected. What is impaired is cough, hence the research focus outlined previously. Research on peripheral airway clearance techniques in adults with NMD is based largely on case reports, small studies or extrapolated from other populations. These studies have been recently reviewed elsewhere.[7,8]

1.1.4. Community respiratory health protocols

Respiratory support therapies used by people with NMD in the community aim to keep people well; to maintain lung function and secretions such that the person does not get an RTI and/or a hospital admission. To this end, protocols have been developed that comprise daily LVR, the addition of MI-E when PCF falls below 270 L/min and the provision of oximeters for spot-checking of oxygen saturation levels.[14,23] These protocols combine the theoretical principles of maximising lung volumes and augmenting cough, and incorporate a

management plan for escalating therapies based on oxygen saturation levels or signs of impending infection.

Retrospective reviews of these protocols, and observational studies comparing patients pre and post protocol or comparing patients managed in pre and post protocol eras have been published.[14,23,55-57] These studies generally suggest benefit, but are all limited methodologically (selective, biased sampling, cross-over of patients between groups and the exclusion of people who were lost-to-follow-up). As such, outcome data is not well established and the efficacy of these protocols is very difficult to assess.

1.2. Evidence of efficacy during acute respiratory tract infection (RTI)

The vast majority of research into respiratory therapies in people with progressive NMD has been conducted during periods of relatively stability. Evaluation of these techniques during acute respiratory illness in people with NMD is confined to prospective cohorts,[37,58] case reports and uncontrolled series of MI-E use [59,60] and three small controlled trials (Table 3).[37,61,62] There are however some data to suggest that MI-E may be superior during an acute RTI. In a recent study of people with ALS/MND presenting with an RTI, MI-E effectively cleared secretions in 83% of patients, compared to 35% using LVR plus MAC.[37] A randomised cross-over trial compared the addition of MI-E to standard respiratory therapy (breathing exercise with NIV in situ, percussion,

cough augmentation with inflation plus MAC) in eight patients. Both interventions improved secretion clearance, oxygen saturation and transcutaneous carbon dioxide. The addition of MI-E shortened session length but patients reported more fatigue.[61] Vianello and colleagues compared the outcomes of 11 admitted patients treated with MI-E and standard respiratory therapy to historical controls managed with standard therapy alone. Treatment failure, defined as need for minitracheostomy or endotracheal intubation was greater in the control group however bronchoscopy rates and hospital length of stay were the same.[62]

These data suggest that MI-E is likely safe and effective during respiratory illness, although superiority over other respiratory adjuncts has not been firmly established. No comparison of respiratory therapy versus no therapy exists and it is unclear whether there is clinical equipoise to perform such a study. Studies performed during the stable phase discussed above however provide the rationale for use during acute episodes. Assisted inflation above spontaneous VC may recruit areas of atelectasis, improve regional ventilation, mucociliary clearance and cough augmentation. Consensus opinion recommends MI-E as the preferred treatment for the weakest patients, when assisted inflations or MAC are not adequate and in ICU to prevent re-intubation.[7]

1.3. Conclusion

Respiratory muscle weakness in NMD is a key cause of morbidity, including RTIs, and mortality despite the increasing use of NIV to manage ventilatory failure. The reduction in IC is also related to progressive impairment in lung mechanics, with reduced compliance and increasing work of breathing. Assisted inflation techniques acutely improve these changes, with observational studies suggesting that regular use of LVR may improve long-term ventilatory function. There is a lack of RCTs and assessment of clinical outcomes such as mortality and RTI upon which to base recommendations for regular long-term use of LVR as a preventative measure in adults, although it is recommended in some guidelines based on the observational studies. Similarly, cough augmentation techniques based on increasing IC often in conjunction with forced expiratory manoeuvres increase PCF in patients with NMD. There is limited evidence that this translates into reduced risk or more rapid resolution of RTIs in comparison to standard chest physiotherapy techniques and it is questionable whether there would be clinical equipoise to conduct a trial in comparison to no sputum clearance techniques. Future trials should prospectively assess the long-term impact of LVR and cough augmentation on clinical outcomes and burden of care in addition to lung mechanics, as well as determining clear predictors of benefit from these techniques.

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Table 1: Summary of respiratory therapies used to maintain or improve chest wall mobility / lung volume during periods of clinical stability.

Assisted inflation techniques	Evidence of efficacy	Considerations and limitations
Lung volume recruitment (manual resuscitation bag or NIV volume-cycled device) Glossopharyngeal breathing NIV (bilevel pressure device) IPPB device Mechanical insufflation component of MI-E device	Assisted inflation techniques may: slow the rate of decline of FVC[16,17,24,27] maintain or improve LIC or MIC over time[16,17,24,27] maintain PCF over time[16,17] improve short-term lung or respiratory system	Limited data, predominantly from retrospective or observational cohort studies Carry-over effect to clinical outcomes (e.g., RTI incidence, time to NIV) is not known Techniques may not benefit all – likely to be responders and non-responders No data regarding dose-response, optimal prescription or when to commence techniques

	compliance[32,33]	Adherence rates suggest barriers to treatment that have not been explored

NIV, non-invasive ventilation; IPPB, intermittent positive pressure breathing; MI-E, mechanical insufflation-exsufflation; FVC, forced vital capacity; LIC, lung insufflation capacity; MIC, maximal insufflation capacity; PCF, peak cough flow; RTI, respiratory tract infection

Table 2: Summary of respiratory therapies that aim to augment cough during periods of clinical stability.

Cough augmentation techniques	Evidence of efficacy	Considerations and limitations
Inspiratory assistance (i.e. assisted inflation techniques) Expiratory assistance (i.e. manually assisted cough, mechanical exsufflation component of MI-E device)	Inspiratory or expiratory assisted PCF is greater than spontaneous, unassisted PCF[23,28,42-46] Combined inspiratory and expiratory assistance likely to result in greatest assisted PCF[23,37,42-46,48,49]	Limited data linking PCF to clinical outcomes[37,38] Individual assessment, trial and evaluation of therapies is paramount: • Optimal inflation volume for generating maximal assisted PCF may be submaximal[47] • Use of MI-E requires individually customised settings, especially in people with ALS/MND or bulbar muscle dysfunction[50-53]

Combined inspiratory and expiratory assistance	Improvements in assisted PCF are greater in people with lower VC or PCF[21,42,45,54]

MI-E, mechanical insufflation-exsufflation; PCF, peak cough flow; ALS/MND, amyotrophic lateral sclerosis/motor neurone disease

Table 3: Recommendations for respiratory therapies during periods of respiratory tract infection.

Techniques studied	Clinical rationale / aim	Evidence of efficacy
Assisted inflation (e.g. lung volume recruitment or breathing exercises with NIV) combined with MAC	Increase alveolar ventilation, recruit areas of atelectasis Improve mucociliary clearance Augment cough	Respiratory therapies may improve secretion clearance and ventilation (oxygen saturation, transcutaneous carbon dioxide)[61] MI-E may be superior in clearing secretions during acute respiratory compromise[37]
MI-E		MI-E can result in shorter therapy sessions but may induce fatigue[61]

NIV, non-invasive ventilation; MAC, manually assisted cough; MI-E, mechanical insufflation-exsufflation

Figure legends

Table 1: Summary of respiratory therapies used to maintain or improve chest wall mobility / lung volume during periods of clinical stability.

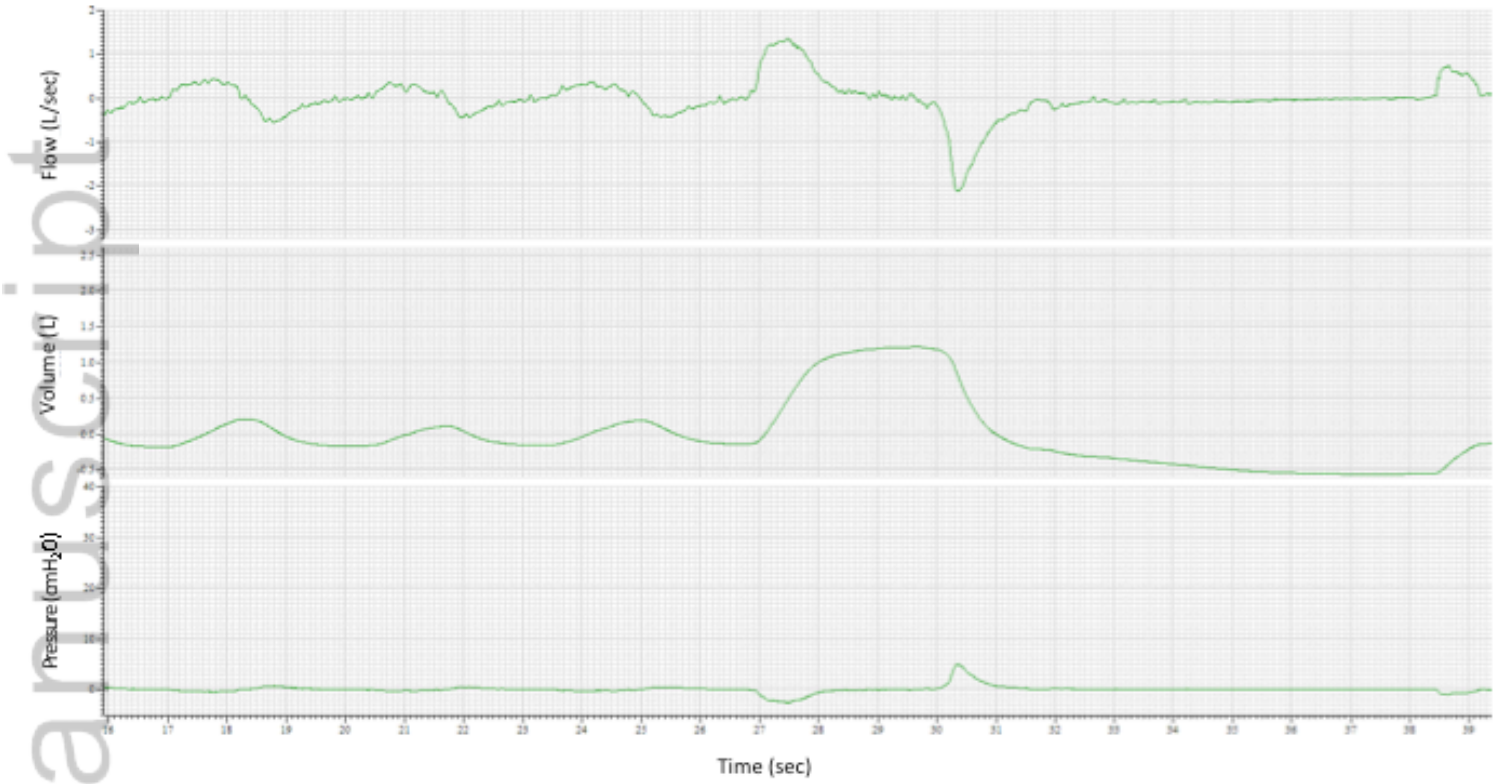
Figure 1: Flow-time (top), volume-time (middle) and pressure-time (bottom) traces, obtained using a pneumotachometer and mouthpiece/noseclip, of a) spontaneous vital capacity (VC)(left) and b) lung insufflation capacity (LIC)(right) in a patient with motor neurone disease.

Units of measurement: Flow (L/sec); volume (L); mouth pressure (cmH_2O); time (sec).

Measured VC = 1.785 L; measured LIC = 2.538 L.

Table 2: Summary of respiratory therapies that aim to augment cough during periods of clinical stability.

Table 3: Recommendations for respiratory therapies during periods of respiratory tract infection.



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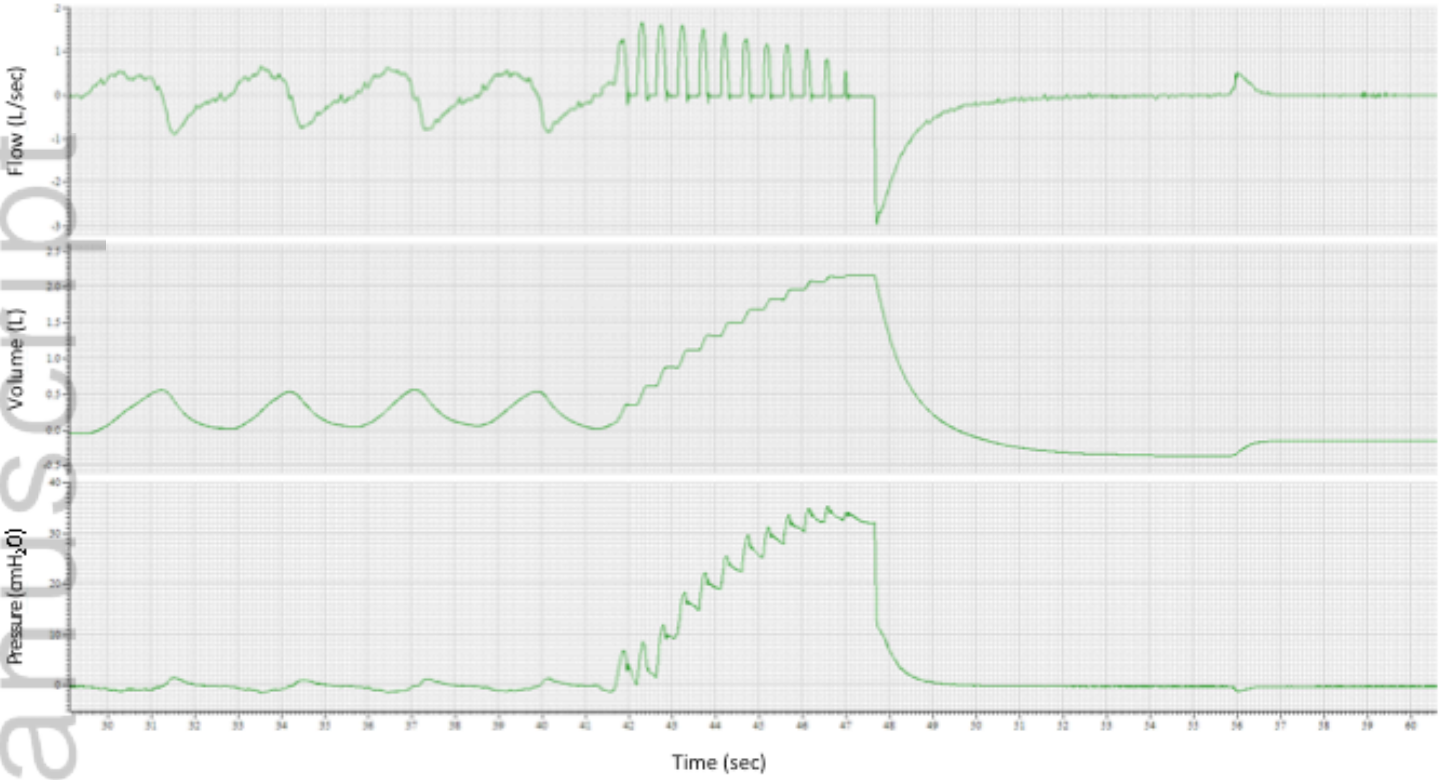

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