Mechanically assisted cough strategies: user perspectives and cough flows in children with neurodisability

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Shareable abstract (@ERSpublications)
Various MI-E setting strategies may be used depending on whether the focus is comfort or maximal flow. All tested strategies generated cough flows above therapeutic thresholds and were rated as slightly to moderately uncomfortable. https://bit.ly/47u9t90

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Abstract

Background Mechanical insufflation–exsufflation (MI-E) is used to augment cough in children with neurodisability. We aimed to determine the user comfort and cough flows during three MI-E strategies, and to predict factors associated with improved comfort and cough flows.

Methods This multicentre, crossover trial was done at four regional hospitals in Norway. Children with neurodisability using MI-E long term *via* mask were enrolled. In randomised order, they tested three MI-E setting strategies (in-/exsufflation pressure (cmH_2O)/in (In)- *versus* exsufflation (Ex) time): 1) "A-symmetric" (±50/In=Ex); 2) "B-asymmetric" (+25– +30)/−40, In>Ex); and 3) "C-personalised", as set by their therapist. The primary outcomes were user-reported comfort on a visual analogue scale (VAS) (0=maximum comfort) and peak cough flows (PCF) ($L \cdot min^{-1}$) measured by a pneumotachograph in the MI-E circuit.

Results We recruited 74 children median (IQR) age 8.1 (4.4–13.8) years, range 0.6–17.9, and analysed 218 MI-E sequences. The mean±SD VAS comfort scores were 4.7±2.96, 2.9±2.44 and 3.2±2.46 for strategies A, B and C, respectively (A *versus* B and C, p<0.001). The mean±SD PCF registered during strategies A, B and C were 203±46.87, 166±46.05 and 171±49.74 $L \cdot min^{-1}$, respectively (A *versus* B and C, p<0.001). Using low inspiratory flow predicted improved comfort. Age and unassisted cough flows increased exsufflation flows.

Conclusions An asymmetric or personalised MI-E strategy resulted in better comfort scores, but lower PCF than a symmetric approach utilising high pressures. All three strategies generated cough flows above therapeutic thresholds and were rated as slightly to moderately uncomfortable.

Introduction

Children with neurodisability may have an ineffective cough that predisposes them to respiratory tract infections (RTIs) and secondary respiratory failure [1, 2]. Mechanical insufflation–exsufflation (MI-E), a treatment option to assist expiratory cough flows [3–9] and airway secretion clearance, may be used to treat and prevent RTIs to avoid hospitalisations and improve longevity and well-being [10, 11].

MI-E users have reported the treatment to ease breathing [7] but also as tiring [12]. The optimal MI-E setting in paediatrics is unknown [13], and clinical settings vary greatly [5, 14]. Effective MI-E treatment

is assumed to be achieved by an appropriate set-up of insufflation and exsufflation timings and pressures. Various combinations may be applied to deliver alternating positive and negative pressures to the airways. In 2003, Bach and Bianchi [15, 16] suggested a protocolised approach with symmetric high pressures applied at equal durations. In contrast, an asymmetric setting approach, using lower positive than negative pressures favouring insufflation times, developed in Europe [6, 14]. Independent of strategies, the effectiveness of MI-E treatment was consistently judged by improvements in peak cough flow (PCF), with less consideration of the user's opinion [6, 13, 17]. An optional strategy with individualisation of MI-E settings according to subjective factors, such as a visual chest-wall rise during insufflation, increased cough sounds and user feedback, is suggested [5].

A barrier to MI-E use is child resistance [18]. Thus, comfort during MI-E treatment may impact MI-E treatment adherence, as in noninvasive ventilation [19, 20]. However, we are unaware of studies comparing PCF and comfort ratings of MI-E using symmetric, asymmetric or personalised settings.

In this study in children with neurodisability, we aimed to determine the user-rated comfort and PCF during three suggested MI-E treatment strategies: the symmetric, the asymmetric or the personalised approach. Secondly, we aimed to assess the impact of MI-E settings, the MI-E routine and child characteristics on comfort and PCF.

Method

A Norwegian, multicentre, within-subject, crossover, double-blinded randomised clinical trial was conducted at four hospitals (details in supplementary e-table 1).

Participants

Children with neurodisability, defined as dysfunction or injury in the central nervous system (CNS) or with neuromuscular disorders (NMD), resulting in neurological impairments and functional limitations, including difficulties with movement, cognition, hearing and vision, communication, emotion and behaviour [21], aged 6 months to 18 years using MI-E therapy long term (>3 months) were eligible for enrolment. Children with tracheostomy or using MI-E *via* mouthpiece, children with an obstructive lung disease expressed as radiological indicated emphysema or hyperinflation and children with PCF ⩾5th percentile [22] if 4–12 years and >270 $L \cdot min^{-1}$ if older were excluded. Health professionals specialised in respiratory care enrolled eligible children. The main hospital invited all eligible children, the other three hospitals invited a convenience sample.

Intervention

Each participant was their own control and tested three setting strategies: "A-Symmetric", "B-Asymmetric" and "C-Personalised", in randomised order. All strategies were tested in a minimum of three cycles using Cough Assist E70 (Respironics, Murrysville, PA, USA), with at least a 3-min pause between each sequence. The familiar caregiver performed the intervention without additional manual thrust. The study process and MI-E settings are shown in figure 1. Data were collected at in- or outpatient clinics between 1 February 2019 and 1 February 2021.

Outcome measures

The study had two primary outcome measures:

1) The user-rated comfort ($VAS_{comfort}$) of each MI-E strategy was measured utilising a visual analogue scale (VAS) [23] asking "How comfortable was this setting?". The child, with practical and psychological parental support as needed, rated their opinion by placing a movable line on a step-less 100 mm scale between faces labelled "very comfortable" and "very uncomfortable" at the extremes. On the ruler's backside, the line indicated values ranging from 0 to 10, representing the most and least comfortable strategy. Used cut-off points were 0–3 not/slightly, 4–6 moderately and 7–10 very uncomfortable [24].

2) The MI-E-assisted peak expiratory flow (PCF_{MI-E}), measured using a pneumotachograph in the MI-E-circuit, was accessible *via* the Flow-lab software (Citrix H4; IMT Medical, Buchs, Switzerland) (supplementary e-figure 1, Appendix S1 Method).

In preschoolers and children with cognitive impairment unable to indicate their perception, a blinded evaluator performed supplementary ratings using the "Face, Legs, Activity, Cry, Consolability scale" (FLACC) [25]. The FLACC classification is 0 ("relaxed/comfortable"), 1–3 (mild discomfort), 4–6 (moderate pain) and 7–10 (strong discomfort/pain) [26].

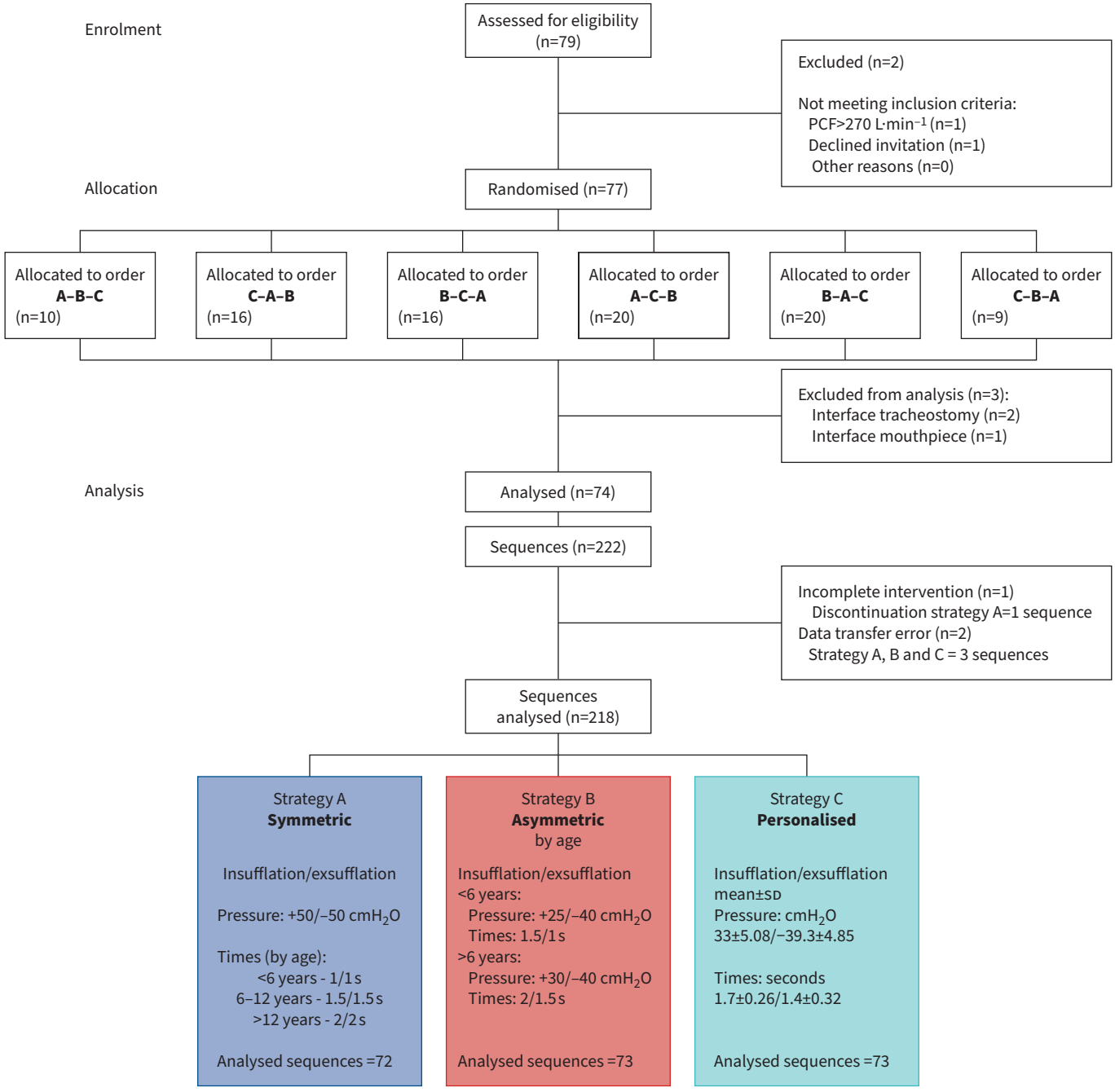

FIGURE 1 Study profile. PCF: peak cough flow.

Another VAS ruler scored user-rated efficacy ($VAS_{efficacy}$) asking "How effective was this setting?" (0=most, 10=least effective). The $VAS_{efficacy}$ ruler further characteristics was equivalent to the $VAS_{comfort.}$ruler.

The gaseous exchange was recorded continuously (SenTec Digital Monitor, SenTec AG, Thervil, Switzerland). Automatically drift-corrected changes in oxygen saturation (S_{pO_2}) >5 percentage points and transcutaneous carbon dioxide pressure (TcP_{CO_2}) >10 mmHg, according to the American Association for Sleep Medicine criterion, were considered as significant changes between pre- and post-values [27]. Signs of respiratory distress, *e.g.* reflux, vomiting, substantial mask leak and child/parent-driven termination of the MI-E sequence, were noted. Routines and equipment to describe clinical characteristics are given in supplementary Appendix S1 Method.

The three MI-E strategies were tested in one of six possible randomly assigned orders, using Latin-square randomisation. An independent, unblinded staff member performed randomisation, titrated the MI-E devices and enclosed the test order in opaque sealed envelopes marked with inclusion numbers. One person, blinded at all times, performed the data sampling at all locations. The unblinding was performed after the completion of all data sampling.

The study was approved by the regional ethical board and registered in ClinicalTrials.gov (NCT04081116). Children/parents signed informed consent for participation and publishing of results. The Consort statement [28] guided the reporting.

We based the power analysis on PCF and estimated a difference of 14 $L \cdot min^{-1}$ as clinically important. To detect a difference of 14 $L \cdot min^{-1}$, assuming a standard deviation of the difference of 34.8 [29], 50 children had to be included to obtain a statistical power of 80% and a two-sided significance threshold of 5%.

Statistical analysis

Categorical data are presented as counts (%); continuous data as means±SD or median (interquartile range), depending on the distribution. Paired sample t-tests were conducted to determine any difference in $VAS_{comfort}$, PCF_{MI-E} and $VAS_{efficacy}$ between strategies A and B, A and C, and B and C. To account for age-related differences, the children were stratified in two groups; preschool (0–6 years) and school-age (7 to <18 years).

Linear mixed-effects models were conducted to predict how the MI-E settings (insufflation flow (low–medium–high), In- and exsufflation duration and pressures), the MI-E routine (MI-E user years and frequency) and the child's clinical characteristics (age, sex, diagnosis group, unassisted cough flows (PCF), ventilator dependency and the presence of percutaneous feeding tube (PEG)) were associated with $VAS_{comfort}$ and PCF_{MI-E}. To account for repeated measures, we defined the three strategies "A-Symmetric", "B-Asymmetric" and "C-Personalised" as repeated factors. Possible multicollinearity of factors was explored using Pearson or Spearman correlation coefficient >0.7 as the cut-off. To reach a final adjusted model, we conducted a manual backward elimination procedure removing non-significant factors one by one, until all remaining factors were significant. With two primary outcome measures, we applied an α level of $p < 0.025$ to account for multiplicity. All analyses were performed using STATA SE software, version 17.0 (StataCorp LLC, College Station, TX, USA).

Results

Overall, 74 children aged 7 months to 17.9 years, 54 with NMD and 20 with CNS conditions, performed 218 MI-E sequences. Four sequences were missing due to discontinuation (one) and data transfer errors (three). Enrolment details are given in figure 1, clinical characteristics in table 1 and diagnosis details in supplementary Appendix S2 Results.

The mean±SD settings for "C-personalised" were insufflation/exsufflation pressures of 33±5.08/−39.3±4.85 cmH_2O and timings of 1.7±0.26/1.4±0.32 seconds. Further strategy details by age are shown in supplementary e-figure 2.

Comfort and PCF

The mean±SD $VAS_{comfort}$ scores were 4.7±2.96, 2.9±2.44 and 3.2±2.46 for strategies A, B and C, respectively (A *versus* B and C, p<0.001) (figure 2a). Strategy A received the highest score (lowest comfort) in preschool and school-aged children.

The mean±SD PCF_{MI-E} registered during strategies A, B and C were 203±46.87, 166±46.05 and 171 ±49.74 $L \cdot min^{-1}$ (A *versus* B and C, p<0.001). The results were similar in preschool and school-aged children (figure 2b).

Secondary outcomes

The user-perceived effectiveness ($VAS_{efficacy}$) during the three strategies was rated similarly (figure 3). The FLACC score (n=33) supplementing the $VAS_{comfort}$ scores increased by 1 point pre- and post-treatment at "strategy A", whereas there was no difference pre-post at "strategies B and C" (figure 4). The S_{pO_2} and TcP_{CO_2} measurements pre- and post-MI-E sequences were unchanged within defined limits. Signs of gastro-oesophageal reflux (n=2) and intense discomfort resulting in discontinuing the MI-E sequence (n=5) were observed at "Strategy A". Complaints of abdominal bloating (n=1) and discontinuation due to discomfort (n=1) were reported following "Strategy B", while no discomfort comment was reported at

TABLE 1 Clinical characteristics and treatment details by age group

Characteristics	n	Overall	n	0–6 years	n	7–18 years
Participants n		74		29		45
Age years	74	8.1 (4.4–13.8)	29	3.8 (2.6–5.3)	45	13.2 (10.4–15.9)
Gender						
Male		45 (61)		18 (62)		27 (60)
Female		29 (39)		11 (38)		18 (40)
Diagnosis						
Neuromuscular disorder		54 (73)		22 (76)		32 (71)
Condition with CNS origin[#]		20 (27)		7 (24)		13 (29)
Lung and cough function						
FVC L	42	0.81 (0.51–1.07)	10	0.65 (0.36–0.86)	32	0.87 (0.55–1.19)
FVC % pred	42	40.5 (11–60)	10	57 (43–65)	32	30 (19–53)
PCF L·min^{-1}	42	120 (106–171)	10	109 (75–115)	32	130 (112–200)
MIP cmH_2O	31	34 (22–46)	2	28 (24–32)	29	36 (22–46)
MEP cmH_2O	31	26 (17–38)	2	35 (25–44)	29	26 (17–38)
Baseline respiratory function						
S_{pO_2} %	63	97 (96–98)	22	96 (95–97)	41	97 (96–98)
TcP_{CO_2} mmHg	60	37.5±6.05	21	35.3±6.28	39	38.6±5.67
Treatment details						
MI-E use years	74	2.5±1.0–5.2	29	1.6±0.5–2.9	45	4.4±2.0–6.3
NIV	74	44 (59)		22 (76)		22 (49)
PEG	74	51 (69)		22 (76)		29 (64)
Assessment details						
FLACC scored[¶]	33/74	33 (45)		24 (83)		9 (20)
Neuromuscular disorder		18 (33)		17 (77)		1 (3)
Condition with CNS origin		15 (75)		7 (100)		8 (62)

Data are presented as n, n (%), mean±SD or median (IQR). IQR: interquartile range; CNS: central nervous system; FVC: forced vital capacity; PCF: peak cough flow; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; S_{pO_2}: peripheral oxygen saturation; TcP_{CO_2}: transcutaneous measured carbon dioxide pressure; MI-E: mechanical insufflation–exsufflation; NIV: non-invasive ventilator support; PEG: percutaneous feeding tube; FLACC: Face, Legs, Activity, Cry, Consolability scale. [#]: conditions with CNS origin include cerebral palsy, degenerative disorders in the CNS and encephalopathy; [¶]: FLACC scorings (% per age and diagnosis group) supplementing child/parent comfort scorings in children, due to age or intellectual disability.

"Strategy C". Mask leakage was reported during strategies A, B and C in five, two and one children, respectively (supplementary appendix S2 Results).

Factors influencing comfort and PCF

When changing the inspiratory flow setting from low to medium, a higher unassisted PCF and a PEG was associated with decreased comfort (higher $VAS_{comfort}$ score) (table 2).

Higher insufflation pressure, increased age and higher unassisted PCF were positively associated with increased PCF_{MI-E} (table 2). Univariate and non-significant results are given in supplementary Appendix S2 Results.

Discussion

In children with neurodisability using MI-E therapy long-term, asymmetric or personalised strategies improved comfort but decreased PCF_{MI-E} compared to a symmetric high-pressure approach. Comfort differences were more apparent in school-aged than preschool children, while PCF_{MI-E} differences were constant. Higher unassisted PCF and PEG use was related to lower comfort. Low inspiratory flow (*i.e.* long rise time) improved comfort. Increased insufflation pressure, higher unassisted cough flows and older age were associated with increased $PCF_{MI-E.}$

The present study's mean comfort scores of the MI-E strategies were below 5 of 10 for all strategies. The children/parents reported the asymmetric and personalised strategies as slightly uncomfortable ($VAS_{comfort}$ 0–3), whereas the symmetric high-pressure strategy was judged moderately uncomfortable ($VAS_{comfort}$ 4–6) [24]. The present findings in children aligns with findings in adults and mixed populations, where MI-E was compared to other cough augmentation techniques *via* breathing comfort scorings [8, 30].

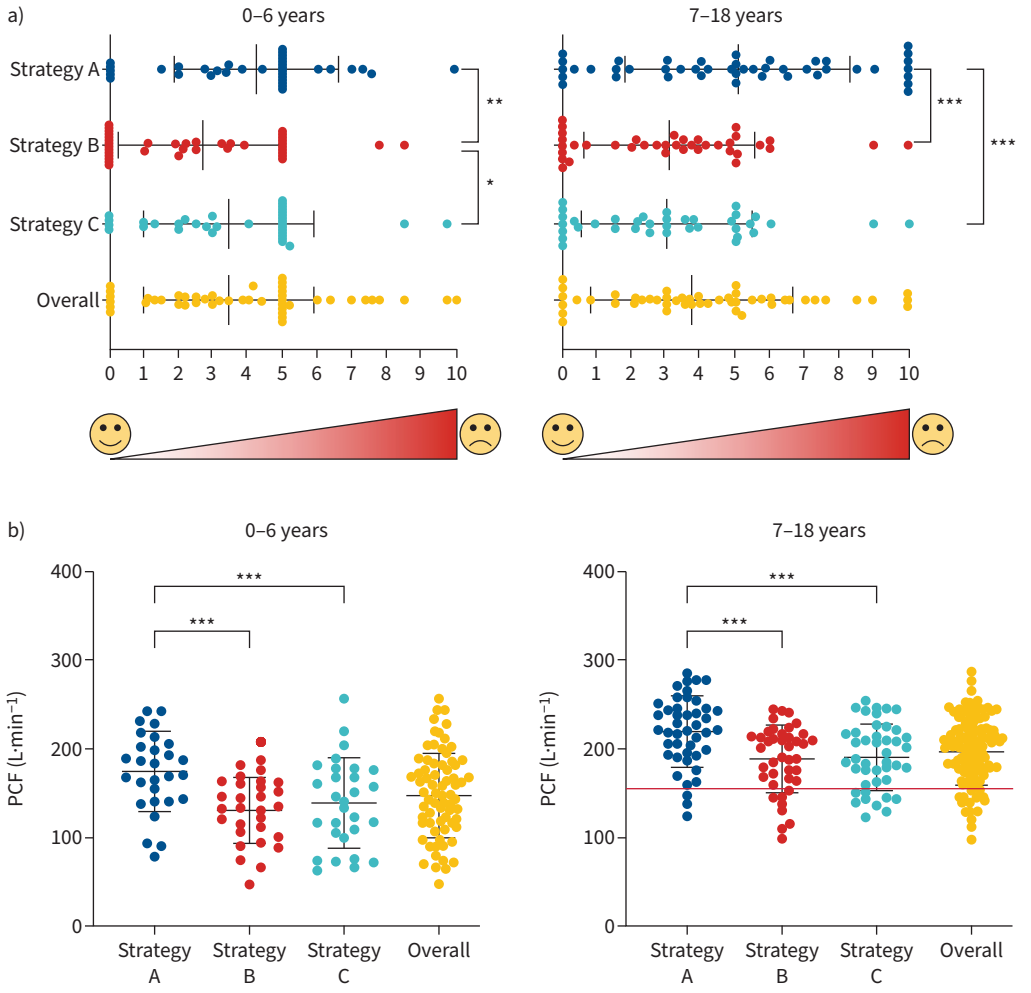

FIGURE 2 The three MI-E strategies and overall mean±SD a) perceived comfort and b) MI-E-assisted PCF in two age groups. Visual analogue scale in a: 0=maximum and 10=minimum comfort. PCF reference line in red: 160 L·min^{-1} in b. Details in supplementary appendix S2 Results. MI-E: mechanical insufflation–exsufflation; PCF: peak cough flow. *p<0.025; **p<0.01; ***p<0.001.

The notion of comfort is subtle and difficult to define [31]. Our study is related to the experience of respiratory comfort, and the comfort scores should be interpreted in the context of the disorder and its treatments. The MI-E treatment may be experienced as tiring and sometimes distressful [12]. However, MI-E therapy can also ease breathing by removing airway secretions [7]. The minimal clinically important difference (MCID) of a $VAS_{comfort}$ score in children is unknown. According to previously reported MCID of a VAS score between 1.0 and 1.2 cm rating comfort/pain [32], the difference between the score of 4.7 using the symmetric, compared to 2.9 and 3.2 using an asymmetric or personalised strategy, respectively, might indicate a clinically meaningful difference.

A known barrier to MI-E use is child resistance [18]. In the present study, five, one and zero children discontinued MI-E sequences due to discomfort during strategies A, B and C, respectively. We found that having a PEG and using a medium instead of low inspiratory flow setting was related to lower comfort. Using a low insufflation flow setting is a known strategy in individuals with bulbar amyotrophic lateral sclerosis [33]. We did not assess laryngeal function. However, assuming that using PEG is due to dysphagia, our findings support testing the low insufflation flow setting in individuals with dysphagia reporting low comfort. Finally, mask leakage, associated with decreased comfort in long-term ventilation support [19], was more frequently reported using strategy "A-Symmetric".

The mechanical principle of MI-E therapy is to augment expiratory flows to improve airway clearance. In the present study, a symmetric high-pressure strategy resulted in higher PCF_{MI-E} than an asymmetric or

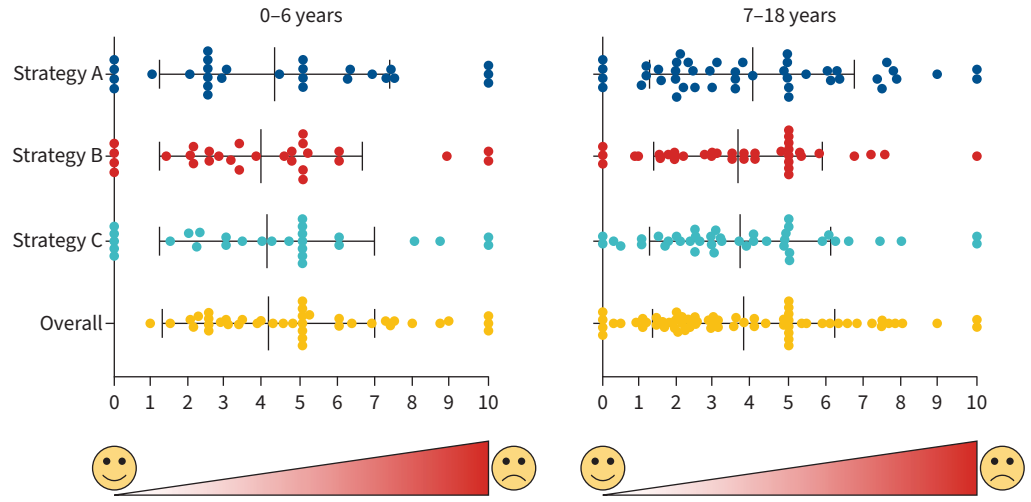

FIGURE 3 The three mechanical insufflation–exsufflation (MI-E) strategies and overall mean±SD perceived efficacy in two age groups. Visual analogue scale: 0=maximum and 10=minimum effective. Details in supplementary Appendix S2 Results.

personalised strategy utilising lower treatment pressures. Accordingly, we report that increasing insufflation pressures predict higher PCF_{MI-E}, confirming the results of a bench study [34]. This finding also aligns with Fauroux *et al*. [7], who reported increasing PCF with increasing pressure. In the present study, we compared very similar exsufflation pressure alternatives, −40 and −50 cmH_2O, and cannot confirm or challenge previous findings where exsufflation pressures were the most important setting alternative to increase PCF [7, 34, 35].

In line with PCF normative values where older children generate higher PCFs [22], we found that PCF_{MI-E} increases with age. In children >12 years, a frequently used therapeutic threshold to determine cough efficacy is PCF >160 $L \cdot min^{-1}$ [1]. In the present study, the mean PCF_{MI-E} in children aged 7–18 years was >160 $L \cdot min^{-1}$ using all strategies. This result indicates that all tested strategies may clear airway secretion in most children. However, applying 160 $L \cdot min^{-1}$ as a threshold should be used cautiously as its justification is based on risk of severe RTI [1] or extubation failure [36], not MI-E efficacy. Evaluation of cough flows in children <12 years still relies on a clinical assessment, guided by normative values in children >4 years [22].

We found no difference between the strategies regarding user-perceived efficacy. The overall score of 4.0 is in line or slightly higher (perceived less effective) than $VAS_{efficacy}$ scores reported in previous studies comparing perceived MI-E efficacy with other cough augment therapies in adult/mixed populations [27, 8, 30].

We noted no severe adverse events requiring medical attention, supporting that complications are rare and that MI-E treatment is generally safe [4, 6]. Safety is important as fear of adverse events may affect adherence [18]. The gas exchange measurements remained stable and returned to baseline after each MI-E sequence, in line with previous findings [7]. In two children, we noted signs of reflux. Available recommendations planning MI-E therapy prior to meals seem appropriate [4, 10].

Limitations

Quantifying children's perceptions using a VAS scale has several limitations. Originally designed to report feelings [23], the VAS scale is commonly used to measure pain and dyspnoea. To report comfort before and after MI-E intervention, the VAS scale is used in both directions, with zero as the most [12] or least favourable value [8, 30]. A modified ruler, featuring faces and text, aided the children's understanding of the scale's extremities. However, formal validation of the VAS ruler is lacking. In some children, rating $VAS_{comfort}$, shyness, age or cognitive impairments necessitated varying degrees of parental support. Consequently, ratings comprise a blend of child and parent input, potentially affecting comfort ratings. Notably, discrepancies in comfort ratings between strategies were significant in NMD but not CNS, possibly due to statistical power (supplementary e-figure 5). In cases where independent rating was unfeasible (n=33), complementary FLACC scores supported less discomfort during the asymmetric than the symmetric approach.

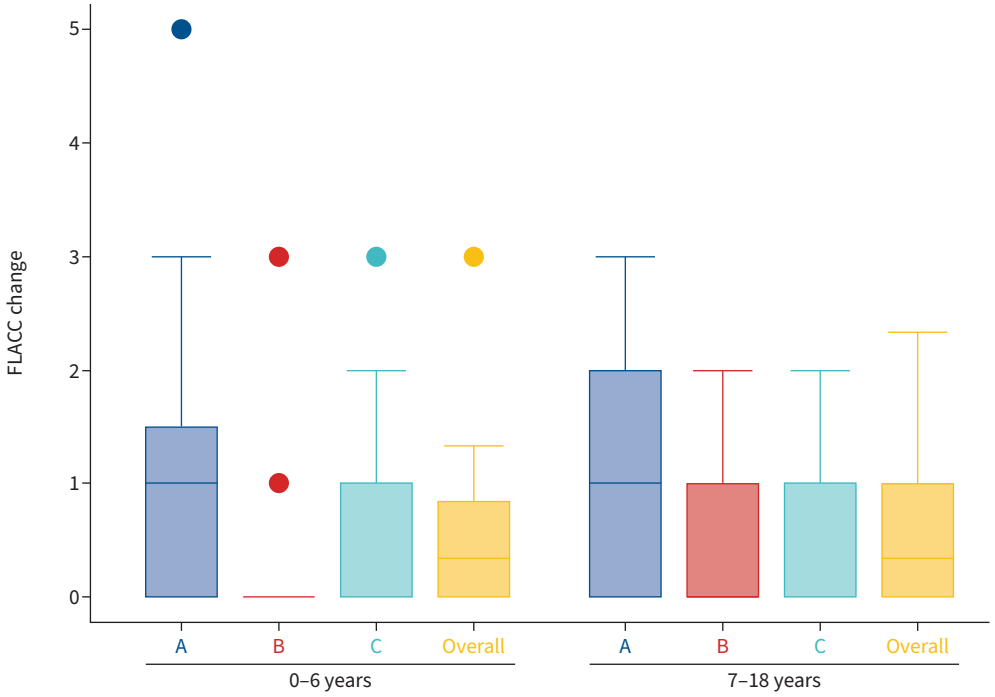

FIGURE 4 Comparison of the FLACC score difference between pre- and post-treatment for the three MI-E strategies: strategy A in blue, strategy B in red, strategy C in green and overall in yellow. Details in supplementary Appendix S2 Results. FLACC: Face, Legs, Activity, Cry, Consolability scale; MI-E: mechanical insufflation–exsufflation.

Recently, limitations of PCF as an outcome measure to evaluate cough have gained attention due to its failure to detect upper airway closure, possibly impacting cough efficacy [37–39]. For future studies, we support analysing air flow curves to reveal and separate peaks from sustained flows when evaluating cough efficacy [39].

TABLE 2 Factors impacting comfort and cough flow (final mixed effect model)

Outcome	$VAS_{comfort}$		PCF_{MI-E}, $L \cdot min^{-1}$	
	β (95% CI)	p-value	β (95% CI)	p-value
MI-E settings				
Inspiratory flow: low–medium	**1.9 (0.42–3.31)**	**0.011**	15.8 (−8.28–39.86)	0.200
Inspiratory flow: medium–high	−0.3 (−3.71–3.12)	0.865	21.8 (−35.16–78.78)	0.453
Insufflation time	0.1 (−2.09–2.36)	0.905	9.6 (−14.63–33.90)	0.436
Exsufflation time	0.5 (−1.67–2.58)	0.674	7.9 (−15.48–31.28)	0.508
Insufflation pressure	0.0 (−0.15–0.14)	0.958	**2.3 (0.65–3.88)**	**0.006**
Exsufflation pressure	0.0 (−0.16–0.09)	0.598	−1.5 (−2.97–−0.07)	0.040
Clinical characteristics				
Age	NS – excluded in model		**5.4 (3.00–7.77)**	**<0.001**
PCF % pred	**6.1 (3.13 9.18)**	**<0.001**	**88.4 (33.31–143.54)**	**0.002**
PEG	**1.3 (0.34–2.37)**	**0.009**	NS – excluded in model	

Data are presented as the regression coefficient; β (95% confidence interval) and p-value for each MI-E setting and the clinical characteristic significant to predict $VAS_{comfort}$ or PCF assisted by MI-E in the final mixed regression models utilizing a manual backward elimination procedure. Repeated factors in the analysis were the three strategies: "A-Symmetric", "B-Asymmetric" and "C-Personalised". Factors tested but not included in table (p>0.025) were: MI-E user years and frequency, sex, diagnosis group and ventilatory dependency. Values with p<0.025 are marked as significant in bold. MI-E: mechanical insufflation–exsufflation; VAS: visual analogue scale; PCF_{MI-E}: MI-E assisted peak cough flow; NS: nonsignificant; PCF % pred: unassisted PCF in % of age-related normal values [22]; PEG: percutaneous feeding tube.

We compared settings proposed from pioneering work on MI-E therapy [15], settings in clinical use in Europe [14] and settings personalised by the children's therapist. The asymmetric and personalised strategies were similar, with the first utilising a 5 cmH_2O lower insufflation pressure as the main distinction. Thus, the children were adapted to strategies B and C and may thus score better comfort than, for most children, the more unfamiliar strategy A. We did not include sham settings and tested only supposed effective setting combinations. The findings may be different during RTIs.

Missing data in spirometry lung function measurements, particularly among children aged 0–6 years, derives from age or cognitive limitations, and are thus not used for analyses. Moreover, children <6 years rarely perform reproducible curves, and those with muscular weakness struggle to sustain expiratory effort as per American Thoracic Society criteria. Consequently, interpretation of lung function measurements requires appropriate consideration.

Generalisability

In the present study we included 74 children with neurodisability from all Norwegian health regions covering ∼69% of the national paediatric population [3] using MI-E long term. Three participating hospitals included children from a convenience sample, a possible threat to the generalisability. Furthermore, the main centre, located in the highest populated health region, invited and enrolled 49 (80%) of the children included. In the second largest population, 94% of the population were included (supplementary e-table 1). Thus, we judge the population to be representative.

We included children adapted to MI-E treatment. Local differences may impact which children are given devices. Children with prescribed MI-E treatment but unsuccessful treatment trials or children who have chosen to quit therapy were not included, possibly falsely skewing our findings toward greater comfort. We cannot generalise the present results to children who could hypothetically benefit from the treatment, as findings may differ in MI-E naïve children.

Clinical advice

We compared three suggested strategies, all considered safe and applicable concerning comfort and efficacy. In clinical practice, rather than looking for maximum cough flow *or* maximum comfort, we suggest titrating the MI-E aiming for sufficient cough flow to move secretions *and* the comfort necessary to tolerate the MI-E therapy long term.

As the use and knowledge of MI-E in children develop, the clinician might move on from standardised settings to include the subjective rating of comfort when titrating treatment. The clinician should make a particular note of comfort in children with PEG and those with high unassisted PCF. The user's opinion may change with age, cough function and as the child familiarises with the treatment. Especially in the developing child, the settings should be reassessed regularly and adjusted when needed. The clinician should continuously confer with the child and parent to optimise the tolerance and efficacy of the MI-E settings for long-term use. The likelihood of successful long-term MI-E therapy may improve by tailoring the MI-E setting to the child's needs in terms of clearing secretions and improved comfort.

The children remained ventilatory stable during all strategies, and no severe adverse events were recorded. Future studies should validate the use of proxy to describe a child's comfort, possibly by triangulating with other outcome measures. Moreover, studies should aim to identify factors influencing comfort and tolerance and identify the cut-off values where the MI-E treatment is judged too uncomfortable to be used and thus challenge adherence. We suggest that comfort should be included as a core outcome measure when evaluating long-term MI-E treatment.

Conclusion

A personalised or asymmetric setting strategy was rated higher regarding user-rated comfort than a protocoled approach utilising symmetric high pressures. In contrast, a strategy using higher symmetric pressures resulted in higher cough flows. The presence of a PEG and a high unassisted PCF may challenge comfort. All strategies resulted in PCF above therapeutic thresholds, and the children rated the comfort during MI-E as slightly to moderately uncomfortable.

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This study is registered at www.clinicaltrials.gov with identifier number NCT04081116. Data may be shared by application upon reasonable request, given that the purpose coincides with existing approvals.

Conflict of interest: T. Andersen has participated on an advisory board for airway clearance (Breas) and received honoraria for lectures (Philips and Breas). All other authors declare no other conflicts of interest.

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