SYSTEMATIC REVIEW

A systematic review on the effects of high frequency chest wall compression and intrapulmonary percussive ventilation in patients with neuromuscular disease [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Respiratory insufficiency is the most common cause of mortality among patients with a neuromuscular disease.

Methods: We explored the effects of high frequency wall compression and intrapulmonary percussive ventilation, compared with standard care or no treatment, on the lung volume and capacity, and quality of life in patients with neuromuscular disease during respiratory infections or in stable periods. We further assessed the effects of these two interventions on clinical value, complications, and survival. The literature search was performed on Embase, MEDLINE, CINAHL, CENTRAL and PEDro. Randomised controlled trials and cross-over studies were eligible.

Results: Five studies were included, and results were presented narratively. High frequency wall compression was not shown to be superior to standard care in terms of lung volume and capacity, quality of life, complications, and survival rate. Compared with standard care, intrapulmonary percussive ventilation showed non-significant differences in terms of lung volume and capacity, and the risk of respiratory infection. Standard care was nevertheless associated with a significantly higher risk of days of hospitalisation (Incidence Rate Ratio 8.5 [1.1-67]) and of antibiotic use than intrapulmonary percussive ventilation (Incidence Rate Ratio 43 [6-333]).

Conclusions: Due to large variety of reported outcomes, missing data and limited number of studies, no meta-analysis could be conducted. The results should be interpreted with caution as the results have a very low certainty of evidence and reported outcomes have a high risk of bias. The evidence for high frequency wall compression and intrapulmonary percussive ventilation is still insufficient to draw final

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Any reports and responses or comments on the article can be found at the end of the article.

conclusions.

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Keywords

Neuromuscular diseases, chest wall oscillation, intra-pulmonary percussive ventilation, lung function measurements, quality of life

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Abbreviations

95% CI, Confidence interval; cmH₂O, Centimetre of water; FEV₁, Forced expiratory volume in 1 second; FVC, Forced vital capacity; GRADE, Grading of recommendations assessment development and evaluation; HFCWC, High frequency chest wall compression; IPV, Intrapulmonary percussive ventilation; IRR, Incidence rate ratio; MD, Mean difference; NMD, Neuromuscular disease; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; QoL, Quality of life; RCT, Randomised controlled trial; RXO, Randomised cross-over study

Introduction

Ineffective cough mechanisms can occur in patients with neuromuscular disease (NMD) as a result of inspiratory and expiratory muscle weakness, as well as impaired glottic function^{1,2}. In the long term, secretion retention leads to airway obstruction, inflammation, breathing difficulty, repeated acute respiratory tract infection, and consequently chronic lung disease and a predisposition to ventilatory failure^{3–6}. Maintaining clear airways is crucial in patients with NMD, because respiratory insufficiency is one of the main causes of death⁴.

For secretion clearance, secretion mobilisation techniques and assisted coughing techniques are recommended⁷. However, the standard secretion mobilisation techniques, such as postural drainage techniques, chest wall strapping, positive expiratory pressure and oscillatory positive expiratory pressure, are ineffective in very weak patients because they are effort-dependent^{2,8}, and these patients are generally unable to generate sufficient expiratory flow³. These techniques are also difficult to apply in cases of chest wall or spinal deformities, as well as osteoporotic ribs⁹. In these specific cases, other techniques are favoured, such as high frequency chest wall oscillations (HFCWO), high frequency chest wall compression (HFCWC) or intrapulmonary percussive ventilation (IPV)⁹. These methods have the benefit of working without the patient's active participation, especially in patients with tracheostomy and/or bulbar failure, and/or intellectual impairment³.

Arcuri *et al.* conducted a systematic review of airway clearance and analysed patients with NMD. They reported that HFCWC does not improve the survival rate or the loss of FVC. In addition, HFCWC does not decrease the frequency of respiratory infections, and IPV is unsuccessful in enhancing peak expiratory flow¹⁰.

Even if there is a growing interest in the use of IPV and HFCWC, Arcuri *et al.* did not include every existing publication in their recent review¹⁰, probably because they included studies with a majority of adults and the severity of the chronic disease had to be identified with the National Hospice Organisation Criteria¹¹. It is thus of clinical relevance to make an up to date synthesis of the available evidence regarding the use of IPV and HFCWC¹².

We hypothesised that IPV and HFCWC might mobilise secretions, recruit obstructed areas of the lungs and prevent the

negative consequences of muscle weakness related to neuromuscular disease. Hence, our main objective was to explore the effects of HFCWC and IPV, as compared with standard care or no treatment, on lung volume and capacity (as a result of secretions mobilisation), as well as quality of life (QoL) in patients with neuromuscular disease in acute or stable condition. We further assessed the effects of IPV and HFCWC on clinical value (arterial blood gases and the patient's subjective respiratory perception of dyspnoea), complications and survival.

Methods

This systematic review followed the recommendations of the Cochrane Guidelines for systematic review of interventions as well as the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement¹³. The registration number of PROSPERO is [CRD42017064703](https://www.crd42017064703).

Searches

On 30 June 2020, reviewer KG performed the search on the following databases: Embase, MEDLINE (through PubMed), CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and PEDro. No language restriction was set. We used the filter for RCTs in PubMed and Embase recommended by Cochrane. We also searched the grey literature in the reference lists of articles, Google Scholar and registered trials in the US National Institutes for Health Clinical Trials Registry¹⁴. The research strategy was composed of two parts that were combined with "AND" (see *Extended data*: File 1 for full search strategies). The first part was composed of relevant terms to identify the population. The second part included terms related to the studied interventions. In both parts, MeSH terms were used when available.

Selection criteria

Study type. Randomised controlled trials (RCTs) and randomised cross-over studies (RXOs) were eligible.

Participants. We included adults and children with NMD with or without tracheotomy.

Interventions. The interventions of interest were HFCWC or HFCWO and IPV.

Comparator. The intervention was compared to either standard care or no treatment. We considered as standard care to comprise active cycles of breathing techniques and chest physiotherapy, such as postural drainage therapy.

Outcomes. The primary outcomes were lung volume and capacity, as measured with lung function tests, including forced vital capacity (FVC), total lung capacity, functional capacity, vital capacity, predicted FVC%, forced expiratory volume in the first second (FEV₁), peak expiratory flow, peak cough expiratory flow and the Tiffeneau-Pinelli index (FEV₁/FVC). The respiratory muscle strength was assessed with the maximal inspiratory pressure and maximal expiratory pressure. The additional outcomes were a) clinical values comprising arterial blood gases and the patient's subjective respiratory perception

of dyspnoea, b) complications (e.g., the number of days of hospitalisation, respiratory tract infection rate, death rate and antibiotic use), c) survival rate, and d) patient QoL.

Study selection and data extraction

Three reviewers (TC, KG, and RH) independently screened the titles and the abstracts and read the full texts. At each step, the results were compared, and disagreements were discussed until a consensus was reached. If disagreement persisted, a third person (LA) made the final decision. Articles in languages other than English, French, German and Italian were excluded if no translator could be found and if articles did not report separate results for patients with NMD. Reviewers KG and TC extracted the data regarding the study characteristics (country, diagnosis, inclusion and exclusion criteria, age, sex and number randomised patients), the interventions (type of interventions, frequency, duration and intensity), and the outcome measures (lung function, blood gas analysis, hospitalisations or antibiotic use, survival rate, mortality rate, respiratory tract infection rate and QoL). Disagreements were discussed, and a consensus was reached. Then, reviewer KG integrated the data into Review Manager 5.3.

Assessment of the risk of bias

Reviewers KG and TC independently evaluated the risk of bias of the RCTs and the RXO with the Cochrane revised risk of bias tool (RoB 2.0 tool; 9 October 2018 version)¹⁵. The results were compared, and differences in the evaluation were discussed until a consensus was reached. If the two reviewers still disagreed, the third reviewer, LA, was contacted to make the final decision. Risk of bias plots are available in the appendix (*Extended data*: File 2, Figures 2–8).

Data synthesis and analysis

We extracted or calculated the treatment effects of the RCTs with the between-group differences of the mean change values and calculated the 95% confidence intervals (95% CIs) if data were available. The relative risk (risk ratio, RR) with a 95% CI was extracted or calculated for dichotomous data. We extracted the incidence rate ratio (IRR) for person-time data. The outcomes were collected after the end of the intervention. We used the Review Manager 5.3 for the analysis.

Certainty of evidence

One reviewer (KG) assessed the certainty of evidence by using the Grade of Recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) guidelines¹⁶.

Results

The electronic search identified 1588 records. After removing 406 duplicates, we screened 1182 titles and abstracts and 1058 records were excluded. In total, 124 full texts were screened, and 119 were excluded for the following reasons: wrong design 13, wrong intervention 4, wrong population 101, study in Hebrew 1. (PRISMA flow diagram in [Figure 1](#)). Five studies were included according to the eligibility criteria^{17–21}.

The characteristics of the included studies are described in [Table 1](#). We could not perform a meta-analysis due to the

diversity of the reported outcomes, the small number of studies, missing data and heterogeneity among studies.

Primary outcomes

The results of the studies are displayed in [Table 2](#) and [Table 3](#).

Lung volume, capacity and HFCWC. For the FVC (1 RCT), we were unable to find evidence against the Null-Hypothesis that HFCWC is equal to the standard care in the rate of decline (mean difference (MD) of 0.8 ml/day in favour of standard care with a 95% CI [-2.56, 4.16])¹⁷.

One RCT¹⁸ assessed the predicted FVC (%) and we failed to find evidence against the Null-Hypothesis that HFCWC is equal to the untreated group in the rate of decline (MD: -1.2% in favour of HFCWC with a 95% CI [-9.70, 7.30]; $P = .78$).

The peak expiratory flow rate, evaluated in one RCT¹⁸, showed no statistically significant difference between the HFCWC group and the untreated group (MD: 40 L/min in favour of HFCWC with a 95% CI [-16.93, 96.93], $P = .18$).

Lung volume, capacity and IPV. One RCT¹⁹ assessed the total lung capacity and the difference between IPV and incentive spirometry post-intervention (0.5L in favour of IPV) was not statistically significant.

In the predicted FVC (%), they were unable to find evidence against the Null-Hypothesis that IPV is equal to incentive spirometry post-intervention (1% in favour of standard care)¹⁹.

The difference between IPV and standard care post-intervention for the predicted FEV₁(%) (0%) was not statistically significant¹⁹.

The peak expiratory flow rate was examined in one RXO study²⁰. We were unable to find evidence against the Null-Hypothesis that the treatment sequence with IPV is equal to without IPV (5.8L/min with a 95% CI [-4.45, 16.05], $P = .27$).

The difference between IPV and standard care in the maximum expiratory pressure post-intervention (8 cmH₂O in favour of standard care), and the maximum inspiratory pressure (-1 cmH₂O in favour of standard care) were not statistically significant¹⁹.

Secondary outcomes

Clinical value and HFCWC. The data on arterial blood gases and mortality rate were not available.

Dyspnoea and HFCWC. One study¹⁸ assessed dyspnoea, and we found evidence against the Null-Hypothesis that HFCWC is not equal to the untreated groups (MD: -2.12 in favour of HFCWC with a 95% CI [-3.83, -0.41]; $P = .02$).

Complications and HFCWC. There was no difference in the number of hospitalisation days between the HFCWC and the usual care groups (0 events in both groups) in one study¹⁷. The difference in the relative risk of requiring hospitalisation and intravenous antibiotics was 80% lower in the HFCWC group than the standard care group, but statistically not significant

Figure 1. Flow diagram illustrating the selection of articles.

(RR: 0.20 with a 95% CI [0.01, 3.54])²¹. The relative risk of requiring oral antibiotics was 33% lower in the HFCWC group than in the standard care group (RR: 0.67 with a 95% CI [0.16, 2.84]), but statistically not significant²¹.

Complications and IPV. One RCT¹⁹ assessed hospitalisation and observed more days of hospitalisation for respiratory reasons in the standard care group than the IPV group, although the lower limit of the CI was close to 1 (IRR: 8.5 with a 95% CI [1.1-67]).

Three events of pulmonary infection (pneumonias or bacterial bronchitis) were observed in the standard care group, whereas the IPV group had no events (IRR: 3.9 with a 95% CI [0.43-35],

$P = \text{NS}$). The number of days of using antibiotics was significantly higher in the standard care groups than the IPV group (IRR: 43 with a 95% CI [6-333])¹⁹.

Survival and HFCWC. One RCT with nine patients¹⁷ found 340 ± 247 days of survival for the HFCWC group and 470 ± 241 days of survival for the standard care. This difference was not statistically significant ($P = .26$) and there were only five patients in the HFCWC group and four in the standard care group.

Quality of life and HFCWC. Lange *et al.* (2006) studied the proportion of worsened QoL¹⁸. The five sub-categories of QoL assessment showed inconsistent results in terms of relative risk, but none were statistically significant (Table 2).

Table 1. Study characteristics.

Authors/ Country	Diagnosis	Inclusion Criteria	Age	Male / Female	No.	Intervention	Duration of intervention	Single session duration	Frequency
Chaisson, 2006 (RCT)¹⁷ USA	Amyotrophic lateral sclerosis	Adults, 18 years of age or older, diagnosis of ALS or probable ALS, mental capacity to provide informed consent, life expectancy greater than 3 months, institution of NIV within 3 months of study enrolment or at time of study visit 1-based upon the following objective criteria: FVC <50% predicted, PaO ₂ <50mm Hg, PaCO ₂ >45 mm Hg, nocturnal SpO ₂ <88% (either sustained for 5 min or 10% of the monitored time)	EG: 64.0 (4.6) [*] CG: 53.5 (6.2)	EG: 4/1 CG: 3/1	9	EG: Standard care + HFCWC (frequencies beginning at 5 Hz to a maximum of 20 Hz as tolerated) CG: Standard care (bi-level positive airway pressure)	Until death	15 min	At least twice per day
Lange, 2006 (RCT)¹⁸ USA	Amyotrophic lateral sclerosis	Probable or definite ALS with respiratory symptoms, lateral sclerosis functional rating scale respiratory subscale ≤11	58.9 (9.7)	EG: 11/11 CG: 10/14	46	EG: HFCWO, pressure between 1–4 and frequency between 10–12 Hz CG: Untreated.	3 mos.	EG: 10–15 min	Twice per day
Yuan, 2010 (RCT)²¹ USA	Cerebral palsy, Duchenne muscular dystrophy, unknown mitochondrial myopathy, unknown myopathy, congenital muscular dystrophy, mitochondrial thymidine kinase 2 deficiency, spinal muscular atrophy type 2, muscle-eye-brain disease, giant axonal neuropathy	>2 years of age, diagnosis of NMD by genotype or muscle biopsy, no acute respiratory distress	EG: 13.4 (3.5) CG: 13.4 (4.4)	EG: 5/2 CG: 4/3	23 ^{**}	EG: HFCWO frequency setting of 12 Hz and machine pressure setting of 4. CG: 2 min each of 6 positions of chest physiotherapy.	5 mos.	12 min	3 times per day
Toussaint, 2003 (RXO)²⁰ Belgium	Duchenne muscular dystrophy with tracheotomy	Tracheotomised Duchenne muscular dystrophy patient with long-term ventilation (at least 18 out of 24 hr per day)	22.2 (3.7)	NA	8	T0: Assisted mucus clearance technique using forced expiratory technique and manual assisted cough, with endotracheal suctioning, followed by nebuliser administration of 5 ml of 0.9% sodium chloride solution for 5 min. IPV + sequence were administered during the T0 (percussion frequency at 120 cycles/min, maximum proximal airway pressure 40 cmH ₂ O) during aerosol administration or IPV-nebuliser administration without IPV; T1: after the T0 treatment, a second session; T2: 45 min after the end of T1, a third session.	5 days		3 sequences/day with 4 hr intervals
Reardon, 2005 (RCT)¹⁹ USA	Duchenne muscular dystrophy, spinal muscular dystrophy, spinal cord injury, mitochondrial, osteogenesis imperfecta	Patient with NMD impaired pulmonary function (defined by restrictive physiology with vital capacity < 60% predicted), maximum inspiratory pressure <90 cmH ₂ O, maximum expiratory pressure less than 100 cmH ₂ O	EG: 17 (11–19) ^{***} CG: 17 (14–19) ^{***}	EG: 6/3 CG: 8/1	18	EG: IPV with normal saline solution and percussion frequency of 120 cycles/min, driving pressure set individually at the minimum pressure that induced visible chest oscillations (range: 20 to 40cmH ₂ O). CG: incentive spirometry.	7 mos.	EG: 10–15 min CG: 5–10 min	Twice per day

^{*}Statistically significant differences; ^{**}Randomisation included cerebral palsy and NMD patients; in the table only the results of the sub-group of NMD are reported; ^{***}median (25th–75th percentile); NIV = non-invasive ventilation; CG = control group; EG = experimental group; HFCWC = high frequency chest wall compression; HFCWO = high frequency chest wall oscillation; hr = hour; Hz = hertz; IPV = intrapulmonary percussive ventilation; ml = millilitre; min = minutes; mo. (plural mos) = month-s; NA = not available; NMD = neuromuscular disease; No. = number; RCR = retrospective chart review; RCT = randomised controlled trial; RXO = randomised cross-over study; USA = United States of America.

Table 2. Results for high frequency chest wall compression.

Authors	N	Pre-intervention Mean (SD)	Post-intervention Mean (SD)	Number of events or number of persons	Within group Mean change (SD)	Relative Risk	Mean difference between groups with 95%CI	P-value	Comments	GRADE
Lung volume, capacity										
FVC										
Chaisson (RCT) ¹⁷	EG 5	1.93 (0.83)	NA		4 (2.5)		0.8 [-2.56, 4.16]	0.64	Decline (ml/day)	⊕○○○ 4, 5, 12, 13, 15
	CG 4	1.70 (0.37)	NA		3.2 (2.6)					
Predicted FVC%										
Lange (RCT) ¹⁸	EG 16	NA	NA		-6.3 (12.27)		-1.2 [-9.70, 7.30]	0.78	Decline (%)	⊕○○○ 4, 5, 9, 10, 12, 13, 14, 15
	CG 16				-5.1 (12.27)					
Peak expiratory flow										
Lange (RCT) ¹⁸	EG 17	253.4	275.2		21.8 (80.48)		40 [-16.93, 96.93]	0.18	Change L/min; %	⊕○○○ 4, 5, 9, 10, 12, 13, 14, 15
	CG 14	274.2	256		-18.2 (80.48)					
Clinical value										
Dyspnoea										
Lange (RCT) ¹⁸	EG 19				-1.28 (2.58)		-2.12 [-3.83, -0.41]	0.02	Borg (1-10)	⊕○○○ 4, 5, 9, 10, 12, 13, 14, 15
	CG 16				0.84 (2.58)					
Complications										
Hospitalisation										
Chaisson (RCT) ¹⁷	EG 5			0		0 (NM)		NA	No. of days	⊕○○○ 2, 4, 7, 8, 12, 13, 14, 15
	CG 4			0						
Yuan (RCT) ²¹	EG 7			0		0.20 [0.01, 3.54]		0.27	No. of participants requiring hospitalisation/ intravenous antibiotics	
	CG 7			2						
Antibiotic use										
Yuan (RCT) ²¹	EG 7			2		0.67 [0.16, 2.84]		0.58	No. of participants requiring oral antibiotics	⊕○○○ 2, 4, 12, 13, 14, 15
	CG 7			3						

Authors	N	Pre-intervention Mean (SD)	Post-intervention Mean (SD)	Number of events or number of persons	Within group Mean change (SD)	Relative Risk	Mean difference between groups with 95%CI	P-value	Comments	GRADE
Survival										
Days of survival										
Chaisson (RCT)¹⁷	EG	5								
	CG	4		340 (247)		-	-	0.26	Analysis done with a log-rank test	⊕○○○ 5, 12, 13, 15
Quality of life										
Lange (RCT)¹⁸	EG	19	47.40%			RR: 1.52 [0.64, 3.61]		0.33		
	CG	16	31.30%	5						
Arm use impaired	EG	19	36.80%	7		RR: 1.47 [0.52, 4.14]		0.45		
	CG	16	25%	4						
Difficult to eat	EG	19	26.30%	5		RR: 0.60 [0.24, 1.53]		0.28	Proportion showing worsening	⊕○○○ 4, 5, 9, 10, 11, 12, 13, 14, 15
	CG	16	43.70%	7						
Speech hard to understand	EG	19	21.10%	4		RR: 0.56 [0.19, 1.65]		0.28		
	CG	16	37.50%	6						
Hopeless about the future	EG	19	36.80%	7		RR: 0.74 [0.34, 1.58]		0.43		
	CG	16	50%	8						

Italics stand for calculated value; *Result expressed in median (25th-75th percentile); 95% CI = 95% confidence interval; CG = control group; EG = experimental group; GRADE = grading of recommendations assessment development and evaluation; IQR = interquartile range; L = litre; min = minutes; ml = millilitre; NA = not available; NM = not measurable; No. = number; NS = not significant; P = P-value; Post = post-intervention; Pre = pre-intervention; QoL = quality of life; RCR = retrospective chart review; RCT = randomised controlled trial; RR = relative risk; RYO = randomised cross-over study; SD = standard deviation; 1 = Studies are retrospective and do not have a control group, so no randomisation and no concealment; 2 = Randomisation was not or probably not concealed; 3 = The study did not analyse the results in the intention-to-treat; 4 = Assessors, care givers or patients were not blinded; 5 = An important proportion of patients were lost to follow up; 6 = Difference in the effect size can be due to inconsistency in the method; 7 = Difference in the effect size can be due to inconsistency in age between groups; 8 = Difference in the effect size can be due to inconsistency in the indirectness of the quality of life; 9 = Indirect because of inadequate comparison or no comparison group; 10 = Indirectness in the intervention, short duration of the treatment; 11 = Indirectness due to indirect outcome of interest for the quality of life; 12 = The studies are composed of small sample size (between 9 and 46 participants) or small number of events; 13 = The confidence interval is wide; 14 = Results are not fully reported; 15 = Conflict of interest exists due to material donation from an industry, sponsoring by an industry or the fact that an author is employed by an industry.

GRADE level of certainty of the evidence: ⊕⊕⊕⊕ = high certainty of the evidence, ⊕⊕⊕○ = moderate certainty of the evidence, ⊕⊕○○ = low certainty of the evidence, ⊕○○○ = very low certainty of the evidence.

Table 3. Results for intrapulmonary percussive ventilation.

Authors	N	Pre-intervention Mean (SD) or Median (IQR)	Post-intervention Mean (SD) or Median (IQR)	Within group change (SD) or % of change	Incidence rate ratio	Mean difference between groups with 95% CI	P value	Comments	GRADE
Lung volume, capacity									
Total lung capacity									
Reardon (RCT) ¹⁹	EG 9	3.1 (NA) [*]	3.1 (NA) [*]	0 (NM) [*]		-0.5 (NM) [*]	Change between groups: P = NA; Between groups Post: P = NS	Negative value = decline in total lung capacity (L)	⊕○○○ 2, 4, 12, 14
	CG 9	3.2 (NA) [*]	2.7 (NA) [*]	-0.5 (NM) [*]					
Predicted FVC %									
Reardon (RCT) ¹⁹	EG 9	36 (NA) [*]	38 (NA) [*]	2%		2 (NM) [*]	Change between groups: P = NA; Between groups Post: P = NS	%	⊕○○○ 2, 4, 12, 14
	CG 9	35 (NA) [*]	39 (NA) [*]	4%					
Predicted FEV ₁ %									
Reardon (RCT) ¹⁹	EG 9	49 (NA) [*]	42 (NA) [*]	-7%		-7 (NM) [*]	Change between groups: P = NA; Between groups Post: P = NS	%	⊕○○○ 2, 4, 12, 14
	CG 9	42 (NA) [*]	42 (NA) [*]	0%					
Peak expiratory flow									
Toussaint (RXO) ²⁰	EG 8		65.1 (22.9)			5.8 [-4.45, 16.05]	0.27	L/min	⊕○○○ 2, 4, 9, 10, 12, 13
	CG 8		59.3 (22.4)						
Maximum expiratory pressure									
Reardon (RCT) ¹⁹	EG 9	32 (NA) [*]	37 (NA) [*]	5 (NM) [*]		4 (NM) [*]	Change between groups: P = NA; Between groups Post: P = NS	cmH ₂ O; Higher value = better performance	⊕○○○ 2, 4, 12, 14
	CG 9	36 (NA) [*]	45 (NA) [*]	9 (NM) [*]					
Maximum inspiratory pressure									
Reardon (RCT) ¹⁹	EG 9	-36 (NA) [*]	-47 (NA) [*]	-11 (NM) [*]		-23 (NM) [*]	Change between groups: P = NA; Between groups Post: P = NS	cmH ₂ O; More negative result is better performance	⊕○○○ 2, 4, 12, 14
	CG 9	-12 (NA) [*]	-46 (NA) [*]	-34 (NM) [*]					

Authors	N	Pre-intervention Mean (SD) or Median (IQR)	Post-intervention Mean (SD) or Median (IQR)	Within group change (SD) or % of change	Incidence rate ratio	Mean difference between groups with 95% CI	P value	Comments	GRADE
Complications									
Hospitalisation									
Reardon (RCT)¹⁹	EG	9	0/1000		8.5 [1.1-67]		NA	Patient-days	⊕○○○ 2, 4, 12, 13, 14
	CG	9	4.4/1000						
Respiratory infection									
Reardon (RCT)¹⁹	EG	9	0/1000		3.9 [0.43-35]		NS	Patient-days	⊕○○○ 2, 4, 12, 13, 14
	CG	9	1.7/1000						
Antibiotic use									
Reardon (RCT)¹⁹	EG	9	0/1000		43 [6-333]		NA	Patient-days	⊕○○○ 2, 4, 12, 13, 14
	CG	9	24/1000						

Italics stand for calculated value; *Result expressed in median (25th-75th percentile), 95% CI = 95% confidence interval; CG = control group; EG = experimental group; GRADE = grading of recommendations assessment development and evaluation; IQR = interquartile range; L = litre; NA = not available; NM = not measurable; NS = not significant; P = P-value; Post = post-intervention; Pre = pre-intervention; RCT = randomised controlled trial; RXO = randomised cross-over study; SD = standard deviation; 1 = Studies are retrospective and do not have a control group, so no randomisation and no concealment; 2 = Randomisation was not or probably not concealed; 3 = The study did not analyse the results in the intention-to-treat; 4 = Assessors, care givers or patients were not blinded; 5 = An important proportion of patients were lost to follow up; 6 = Difference in the effect size can be due to inconsistency in the method; 7 = Difference in the effect size can be due to inconsistency in age between groups; 8 = Difference in the effect size can be due to inconsistency in the difference of treatment intensity; 9 = Indirect because of inadequate comparison or no comparison group; 10 = Indirectness in the intervention; short duration of the treatment; 11 = Indirectness due to indirect outcome of interest for the quality of life; 12 = The studies are composed of small sample size (between 9 and 46 participants) or small number of events; 13 = The confidence interval is wide; 14 = Results are not fully reported; 15 = Conflict of interest exists due to material donation from an industry, sponsoring by an industry or the fact that an author is employed by an industry.GRADE level of certainty of the evidence: ⊕⊕⊕⊕ = high certainty of the evidence, ⊕⊕⊕⊕ = moderate certainty of the evidence, ⊕⊕○○ = low certainty of the evidence, ⊕○○○ = very low certainty of the evidence.

Discussion

Based on this systematic review, 104 patients in five randomised studies, including the diagnoses amyotrophic lateral sclerosis (two studies) or Duchenne muscular dystrophy (three studies, two of them with a mix of other neuromuscular diagnoses), we can report the following main findings: there is very low certainty of evidence that A) HFCWC is not superior to standard care for lung capacity, lung volume, antibiotic use, quality of life, and survival rate, B) HFCWC is superior to standard care for perception of dyspnoea, C) IPV is not superior to standard care for lung capacity, lung volume, and the risk of respiratory infection, and D) IPV is superior to standard care for the reduction of hospitalisation rate and number of days of antibiotic use.

This review has some limitations. First, it is possible that we missed unpublished studies, or studies that were only published in languages other than English and in journals not listed in the searched databases or the clinical trial registries. Because of the low number of studies, we were not able to evaluate the risk of a small study effect or a publication bias. Second, it is known that the reliability of the risk of bias tool is not very high and other authors might come to different conclusions regarding risk of bias of the included studies.

There are limitations regarding the included studies. First, the included studies were very small, had a high risk of bias, and it was not possible to perform a meta-analysis. Therefore, we only have very low confidence in our results, given the downgrading in the GRADE rating because of very serious risk of bias, serious inconsistency and very serious statistical imprecision²². Second, our research question was the effects of HFCWC and IPV on lung volume and capacity as a result of secretions mobilisation. Airway clearance measurement through sputum weight is inappropriate due to day-to-day variability, as well as variability during the day and the fact that secretions can be swallowed²³. Therefore, our primary outcomes were lung volume and capacity as it is often used in the literature as an outcome for airway clearance and to assess the progression of the disease in patients with NMD. Many trials have reported that the use of lung function parameters is questionable because of the lack of observed changes⁸. Jones *et al.* (2006) suggest that lung function parameters are insensitive in assessing the acute effects of airway clearance techniques²⁴. In addition, van der Schans (2002) reports that lung function measurement does not appear to reflect differences in mucus transport or mucus expectoration²⁵. Thus, the ineffectiveness of the two interventions might be influenced by the inefficacy of lung function to assess airway clearance. The lack of significant results could be influenced by the inefficiency of lung function to assess airway clearance.

The results of studies using IPV and HFCWC for other pathologies show similarities and differences as compared with our results. Reychler *et al.* (2018) have performed a systematic review and compared IPV with other airway clearance techniques. They found a reduction in the duration of hospitalisation and have observed an improvement in gas exchange only during the exacerbation phase in patients with chronic obstructive

airway disease. In patients with cystic fibrosis, no difference was observed in the static and dynamic lung volume²⁶. Cough is usually not impaired in patients with chronic obstructive airway disease and cystic fibrosis, thus potentially explaining the contrasting results.

In a recent publication, Chatwin *et al.* (2018)³ highlight that airway clearance such as IPV and HFCWC depend on a normal cough to clear proximal airway. In patients with NMD, these interventions may be ineffective if not combined with cough augmentation technique or device. To our knowledge, no studies investigated the combination of a secretion mobilisation device such as IPV and HFCWC with cough augmentation technique or device.

Our review differs from previous ones in that we included only patients with NMD treated either with HFCWC or IPV. We could include additional studies^{18,19,21}, but we still can only report very low certainty of evidence for or against the use of HFCWC or IPV for airway clearance. In one study, patients in the HFCWC groups showed substantial but statistically not significant fewer survival days compared to the standard care, which was in this case bilevel positive airway pressure. There are no other studies in any type of patients, to our knowledge, that reported increased mortality for patients treated with HFCWC. Therefore, we strongly believe that this decreased survival time in the mentioned study should not be overrated, but future studies should monitor mortality under HFCWC.

Future studies should include larger sample sizes in multicentre trials involving international collaborations and should avoid risk of bias. The comparison treatment should avoid using a 'no treatment' group, and the intervention should be described precisely to facilitate comparison with other studies. We invite researchers to focus on the effects of combined treatments, such as secretion mobilisation interventions with cough augmentation technique, manual cough techniques or mechanical insufflation-exsufflation. We further encourage researchers to investigate more reliable, sensitive and patient-relevant outcome measures to assess the effects of airway clearance techniques.

Conclusions

In this systematic review we explored the effects of IPV and HFCWC, compared with standard care, and found no effects on lung volume and capacity, and QoL. HFCWC might decrease the perception of dyspnoea but shows no difference in the development of complications and survival. Treatment with IPV, compared with control treatment, appears to reduce the number of hospitalisation days and to lessen the need for antibiotics, but no difference was observed regarding the respiratory infection rate.

The certainty of evidence of these results is very low, and all studies presented high risk of bias. The implementation of these interventions in clinical practice should be further evaluated in clinical trials. We invite future studies to improve on these aspects, to explore the effects of combined treatments and to investigate more reliable, sensitive, and patient-relevant outcome measure.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Dryad: A systematic review on the effects of high frequency chest wall compression and intrapulmonary percussive ventilation in patients with neuromuscular disease, <https://doi.org/10.5061/dryad.n8pk0p2tj>²⁷

This project contains the following extended data:

- File 1: Search strategy for all databases used
- File 2: Risk of bias analysis

Reporting guidelines

Dryad: PRISMA checklist for 'A systematic review on the effects of high frequency chest wall compression and intrapulmonary percussive ventilation in patients with neuromuscular disease', <https://doi.org/10.5061/dryad.n8pk0p2tj>²⁷

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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Masahiro Banno

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This study aimed to provide an overview of the effects of HFCWC and IPV, as compared with standard care or no treatment, on lung volume and capacity. The strength of this study was to conduct analysis using a rigorous method of systematic reviews. However, there were some concerns in this study.

First, the authors had better describe the inclusion criteria and exclusion criteria of the included studies, the search date for each database, the Cochrane revised risk of bias tool, GRADE, and the summary of the risk of bias in the abstract.

Second, they had better follow the recommendations of the PRISMA 2020, not the previous version they cited.

Third, it would be better to add the PRISMA 2020 checklist, not the PRISMA 2009 checklist they clarified, as a supplemental file with the page numbers of the manuscript for each item in the PRISMA 2020 checklist.

Fourth, they had better revise the manuscript, or add new limitations in the discussion if any important items in the PRISMA 2020 checklist were not met.

Fifth, they had better clarify PRISMA 2020 flow diagram in Figure 1. The present Figure 1 was the PRISMA flow diagram in the previous version, not PRISMA 2020 flow diagram.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: clinical epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 May 2022

Katia Giacomino, HES-SO Valais-Wallis, Leukerbad, Switzerland

Dear Doctor Masahiro Banno, we would like to thank you for your comments and suggestions for improvement. We have responded to each of your comments below.

Your first comment:

First, the authors had better describe the inclusion criteria and exclusion criteria of the included studies, the search date for each database, the Cochrane revised risk of bias tool, GRADE, and the summary of the risk of bias in the abstract.

Our response:

Thank you for your relevant suggestion. We now specified the in and exclusion criteria, the search date, the risk of bias and the GRADE in the abstract.

Your second comment:

Second, they had better follow the recommendations of the PRISMA 2020, not the previous version they cited.

Our response:

Thank you for having noticed that we used the old version of the PRISMA guideline, we now corrected with the last version.

Your third comment:

Third, it would be better to add the PRISMA 2020 checklist, not the PRISMA 2009 checklist they clarified, as a supplemental file with the page numbers of the manuscript for each item in the PRISMA 2020 checklist.

Our response:

We thank you for your remark, we now used the new version of the checklist of the PRISMA guideline and made the necessary changes. We will also precise the page number of each

item.

Your fourth comment:

Fourth, they had better revise the manuscript, or add new limitations in the discussion if any important items in the PRISMA 2020 checklist were not met.

Our response:

Thank you for this important remark, we changed the checklist for the new version and made the necessary changes in the manuscript.

Your fifth comment:

Fifth, they had better clarify PRISMA 2020 flow diagram in Figure 1. The present Figure 1 was the PRISMA flow diagram in the previous version, not PRISMA 2020 flow diagram.

Our response:

The last version of the flow diagram is now available.

Competing Interests: None of the authors reports any conflict of interest.

Reviewer Report 05 April 2022

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Ivanizia S. Silva

Department of Physical Therapy, Federal University of Rio Grande do Norte, Natal, Brazil

The review is well done overall but I would ask the authors to make some revisions.

Methods:

- In the 'Study selection and data extraction' section: if disagreement persisted, a **fourth** person (LA) made the final decision.
- How were missing data and heterogeneity handled?
- Describe the methods of analysis for crossover trials.

Results:

- Include the results of risk of bias.
- The results needs some revision. It is important not to rely on statistical significance. If the

minimal important difference for an instrument is known, describing the probability of individuals achieving this difference may be more intuitive. Review authors should always seriously consider this option.

- I suggest that the authors integrate GRADE assessments into the review so that there is a consistent message between results and summaries (conclusions, abstract and plain language summary) on the size of any effect and the quality of the evidence.

Discussion:

- As with any study, if the methods proposed in the protocol are changed during the course of conducting the review, these changes should be documented and reported.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Systematic review and Respiratory physiotherapy

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 May 2022

Katia Giacomino, HES-SO Valais-Wallis, Leukerbad, Switzerland

Dear Doctor Ivanizia S. Silva, we would like to thank you for your comments and suggestions for improvement. We have responded to each of your comments below.

Your comment in the method:

In the 'Study selection and data extraction' section: if disagreement persisted, a **fourth** person (LA) made the final decision.

Our response:

We thank for noticing this typing mistake, the corrections were done.

Your comment in the method:

How were missing data and heterogeneity handled?

Our response:

We now specified the section "Study selection and data extraction".
We also specified the paragraph about "heterogeneity" in the results section.

Your comment in the method:
Describe the methods of analysis for crossover trials.

Our response:

In the chapter "Data synthesis and analysis", we specified how we performed the analysis of the cross-sectional study.

Your comment in the results :
Include the results of risk of bias.

Our response:

Thank you for this comment. We now added a section with results of the risk of bias in the chapter of the results.

Your comment in the results :
The results needs some revision. It is important not to rely on statistical significance. If the minimal important difference for an instrument is known, describing the probability of individuals achieving this difference may be more intuitive. Review authors should always seriously consider this option.

Our response:

Thank you for this relevant remark. We now added in the result section the minimal clinically important difference when this value was known.

Your comment in the results :
I suggest that the authors integrate GRADE assessments into the review so that there is a consistent message between results and summaries (conclusions, abstract and plain language summary) on the size of any effect and the quality of the evidence.

Our response:

Thanks for this relevant suggestion. We added in every outcome category the rating of the quality of evidence in the result section.

Your comment in the discussion:
As with any study, if the methods proposed in the protocol are changed during the course of conducting the review, these changes should be documented and reported.

Our response:

We now specified this change in the discussion section and added a paragraph reporting the changes between the protocol and our study.

Competing Interests: No competing interests were disclosed.

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