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

Katia Giacomino, Roger Hilfiker, Tina Magnin, Lara Allet

1School of Health Sciences, HES-SO Valais-Wallis, Leukerbad, Valais-Wallis, 3954, Switzerland
2Department of Physiotherapy, Bern University of Applied Sciences, Bern, 3008, Switzerland
3Department of Medicine, University of Geneva, Genève, 1205, Switzerland

Abstract

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

Methods: We followed the PRISMA statement for systematic reviews. We explored the effects of high frequency wall compression and intrapulmonary percussive ventilation, compared to a control intervention, on the lung volume and capacity, and quality of life in patients with neuromuscular disease. We further assessed the effects of these two interventions on clinical value, complications, and survival. The literature search was performed on 30/06/2020 in Embase, MEDLINE, CENTRAL, PEDro and CINAHL on 6/07/2020. Inclusion criteria: patients with neuromuscular disease; interventions of interest mentioned above; randomised controlled trials comparing these interventions with a control intervention.

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]).

The assessment with the risk of bias tool 2.0 showed a high risk of bias for all outcomes. Moreover, the evidence is of very low-quality for all outcomes.

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 conclusions.

Registration: PROSPERO ID: CRD42017064703.

Keywords
Neuromuscular diseases, chest wall oscillation, intra-pulmonary percussive ventilation, lung function measurements, quality of life
**Amendments from Version 1**

In our second version of this article, we have made clarifications in the abstract and the method.

We have also updated our article on the basis of the recommendations of the latest PRISMA guideline and updated especially the flowchart, checklist, and added the differences with the protocol in the discussion.

Concerning the results, we have made clarifications according to the minimal clinically important difference of the outcomes when these were available. In addition, we have specified in the text for each outcome what the quality of evidence was.

Any further responses from the reviewers can be found at the end of the article.

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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 3-4. Maintaining clear airways is crucial in patients with NMD, because respiratory insufficiency is one of the main causes of death 5.

For secretion clearance, secretion mobilisation techniques and assisted coughing techniques are recommended 6. 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 7-8, and these patients are generally unable to generate sufficient expiratory flow 9. These techniques are also difficult to apply in cases of chest wall or spinal deformities, as well as osteoporotic ribs 9. 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) 10. 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 impairment 11.

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 flow 12.

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 review 13, 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 Criteria 14. It is thus of clinical relevance to make an up to date synthesis of the available evidence regarding the use of IPV and HFCWC 15.

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 updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 16. The protocol of this review was not published in a peer-review journal but it is available on PROSPERO, the registration number is CRD42017064703.

**Searches**

The research strategy was performed by KG on the following databases: Embase, MEDLINE (through PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), PEDro on 30 June 2020 and on CINAHL on 6 July 2020. No language restriction was set. We used the filters 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 Registry 17. 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 (FEV\(_1\)), peak expiratory flow, peak cough expiratory flow and the Tiffeneau-Pinelli index (FEV\(_1\)/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 fourth 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.

Regarding the missing data, authors were contacted to ask for precisions. In case of non-response one reminder was sent. Among the seven authors, four answered but had not longer access to the requested data and three out of seven authors did not answer.

**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.

**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 calculated the treatment effects of the RXO with the between-session differences of the mean end values and calculated the 95% confidence intervals (95% CIs) if data were available.

Given that a meta-analysis was not feasible, each outcome was presented in a table separated by intervention. We used the Review Manager 5.3\(^{17}\) for the calculations.

**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) guidelines\(^{17}\).

**Results**

The electronic search identified 1588 records. After removing 398 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\(^{17}\) in Figure 1). Five studies were included according to the eligibility criteria\(^{18–22}\). Three RCTs\(^{18,21,22}\) studied HFCWC and one RCT\(^{20}\) and one RXO\(^{23}\) investigated IPV.

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 limited number of studies per outcome assessments, missing data and heterogeneity among studies design. For all these reasons, the results are presented narratively.

**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])\(^{22}\).

One RCT\(^{21}\) 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]; \(P = .78\)). HFCWC may not improve predicted FVC compared to the untreated group. Indeed, the minimal clinically important change estimated in people with idiopathic pulmonary fibrosis is between 2% and 6%\(^{31}\).

The peak expiratory flow rate, evaluated in one RCT\(^{21}\), 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], \(P = .18\)).
There was a very low quality of evidence (GRADE) for the three outcome measures mentioned above for HFCWC.

**Lung volume, capacity and IPV.** One RCT 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). The difference of 1% is lower than the minimal clinically important difference estimated in people with idiopathic pulmonary fibrosis between 2% and 6%.

The body of evidence of the five outcomes presented for IPV were rated very low.

**Secondary outcomes**

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

**Dyspnoea and HFCWC.** One study 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). This effect is higher than the minimal clinically important change estimated at 0.8 in patients with chronic obstructive pulmonary disease with acute exacerbation.

**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 study. 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 (RR: 0.20 with a 95% CI [0.01, 3.54]). 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% [0.16, 2.84]), but statistically not significant.

There was very low quality of evidence (GRADE) for the two outcomes dyspnea and complications.
### Table 1. Study characteristics.

<table>
<thead>
<tr>
<th>Authors/Country</th>
<th>Diagnosis</th>
<th>Inclusion Criteria</th>
<th>Age</th>
<th>Male / Female</th>
<th>No.</th>
<th>Intervention</th>
<th>Treatment modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaisson, 2006 (RCT) / USA</td>
<td>Amyotrophic lateral sclerosis</td>
<td>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 NV within 3 months of study enrolment or at time of study visit 1-based upon the following objective criteria: FVC &lt;50% predicted, PaO2 &lt;50mm Hg, PaCO2 &gt;45 mm Hg, nocturnal SpO2 &lt;88% (either sustained for 5 min or 10% of the monitored time)</td>
<td>EG: 64.0 (4.6)* CG: 53.5 (6.2)</td>
<td>EG: 4/1 CG: 3/1</td>
<td>9</td>
<td>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)</td>
<td>Until death 15 min At least twice per day</td>
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</table>

| Lange, 2006 (RCT) / 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) / 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 | 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) / Belgium | Duchenne muscular dystrophy with tracheotomy | Tracheotomy 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 cmH2O) 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) / 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 cmH2O, maximum expiratory pressure less than 100 cmH2O | 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 40cmH2O), 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); NV = 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>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Pre-intervention Mean (SD)</th>
<th>Post-intervention Mean (SD)</th>
<th>Number of events or number of persons</th>
<th>Within group Mean change (SD)</th>
<th>Relative Risk</th>
<th>Mean difference between groups with 95%CI</th>
<th>P-value</th>
<th>Comments</th>
<th>GRADE</th>
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<td><strong>Lung volume, capacity</strong></td>
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<td><strong>FVC</strong></td>
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<td>Chaisson (RCT)²²</td>
<td>EG</td>
<td>1.93 (0.83)</td>
<td>NA</td>
<td></td>
<td>4 (2.5)</td>
<td>0.8 [-2.56, 4.16]</td>
<td>0.64 Decline (mL/day)</td>
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<td>4, 5, 12, 13, 15</td>
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<td></td>
<td>CG</td>
<td>1.70 (0.37)</td>
<td>NA</td>
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<td>3.2 (2.6)</td>
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<td><strong>Predicted FVC%</strong></td>
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<td>Lange (RCT)²³</td>
<td>EG</td>
<td>NA</td>
<td>NA</td>
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<td>-6.3 (12.27)</td>
<td>-1.2 [-9.70, 7.30]</td>
<td>0.78 Decline (%)</td>
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<td>4, 5, 9, 10, 12, 13, 14, 15</td>
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<td></td>
<td>CG</td>
<td>NA</td>
<td>NA</td>
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<td>-5.1 (12.27)</td>
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<td><strong>Peak expiratory flow</strong></td>
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<td>Lange (RCT)²³</td>
<td>EG</td>
<td>253.4</td>
<td>275.2</td>
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<td>21.8 (80.48)</td>
<td>40 [-16.93, 96.93]</td>
<td>0.18 Change L/min; %</td>
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<td>4, 5, 9, 10, 12, 13, 14, 15</td>
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<td></td>
<td>CG</td>
<td>274.2</td>
<td>256</td>
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<td>-18.2 (80.48)</td>
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<td><strong>Clinical value</strong></td>
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<td><strong>Dyspnoea</strong></td>
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<tr>
<td>Lange (RCT)²³</td>
<td>EG</td>
<td>-1.28 (2.58)</td>
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<td>-2.12 [-3.83, -0.41]</td>
<td>0.02 Borg (1-10)</td>
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<td>CG</td>
<td>0.84 (2.58)</td>
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<td>Chaisson (RCT)²²</td>
<td>EG</td>
<td>0</td>
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<td>0 (NM)</td>
<td>NA</td>
<td>No. of days</td>
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<td>2, 4, 7, 8, 12, 13, 14, 15</td>
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<tr>
<td>Yuan (RCT)²⁶</td>
<td>EG</td>
<td>0</td>
<td></td>
<td></td>
<td>0.20 [0.01, 3.54]</td>
<td>0.27 No. of participants requiring hospitalisation/ intravenous antibiotics</td>
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<td><strong>Antibiotic use</strong></td>
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<tr>
<td>Yuan (RCT)²⁶</td>
<td>EG</td>
<td>2</td>
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<td>0.67 [0.16, 2.84]</td>
<td>0.58 No. of participants requiring oral antibiotics</td>
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<td>2, 4, 12, 13, 14, 15</td>
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<td></td>
<td>CG</td>
<td>3</td>
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## Survival

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<th>Post-intervention Mean (SD)</th>
<th>Number of events or number of persons</th>
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<th>Relative Risk</th>
<th>Mean difference between groups with 95%CI</th>
<th>P-value</th>
<th>Comments</th>
<th>GRADE</th>
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<td><strong>Days of survival</strong></td>
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<tr>
<td>Chaisson (RCT)²⁰</td>
<td>EG 5</td>
<td>340 (247)</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>0.26anelysis done with a log-rank test</td>
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<td></td>
<td>Θ◯◯◯ 5, 12, 13, 15</td>
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<tr>
<td></td>
<td>CG 4</td>
<td>470 (241)</td>
<td></td>
<td></td>
<td>-</td>
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## Quality of life

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<tr>
<th>Authors</th>
<th>N</th>
<th>Pre-intervention Mean (SD)</th>
<th>Post-intervention Mean (SD)</th>
<th>Number of events or number of persons</th>
<th>Within group Mean change (SD)</th>
<th>Relative Risk</th>
<th>Mean difference between groups with 95%CI</th>
<th>P-value</th>
<th>Comments</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lange (RCT)²⁰</strong></td>
<td>EG 19</td>
<td>47.40%</td>
<td></td>
<td></td>
<td>9</td>
<td>RR: 1.52 [0.64, 3.61]</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing difficult</td>
<td>CG 16</td>
<td>31.30%</td>
<td></td>
<td></td>
<td>5</td>
<td>RR: 1.47 [0.52, 4.14]</td>
<td>0.45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm use impaired</td>
<td>EG 19</td>
<td>36.80%</td>
<td></td>
<td></td>
<td>7</td>
<td>RR: 0.60 [0.24, 1.53]</td>
<td>0.28 Proportion showing worsening</td>
<td></td>
<td></td>
<td>Θ◯◯◯ 4, 5, 9, 10, 11, 12, 13, 14, 15</td>
</tr>
<tr>
<td></td>
<td>CG 16</td>
<td>25%</td>
<td></td>
<td></td>
<td>4</td>
<td>RR: 0.56 [0.19, 1.65]</td>
<td>0.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficult to eat</td>
<td>EG 19</td>
<td>26.30%</td>
<td></td>
<td></td>
<td>5</td>
<td>RR: 0.74 [0.34, 1.58]</td>
<td>0.43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CG 16</td>
<td>43.70%</td>
<td></td>
<td></td>
<td>7</td>
<td>RR: 1.52 [0.64, 3.61]</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speech hard to understand</td>
<td>EG 19</td>
<td>21.10%</td>
<td></td>
<td></td>
<td>4</td>
<td>RR: 0.56 [0.19, 1.65]</td>
<td>0.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CG 16</td>
<td>37.50%</td>
<td></td>
<td></td>
<td>6</td>
<td>RR: 0.74 [0.34, 1.58]</td>
<td>0.43</td>
<td></td>
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</tr>
<tr>
<td>Hopeless about the future</td>
<td>EG 19</td>
<td>36.80%</td>
<td></td>
<td></td>
<td>7</td>
<td>RR: 0.74 [0.34, 1.58]</td>
<td>0.43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CG 16</td>
<td>50%</td>
<td></td>
<td></td>
<td>8</td>
<td>RR: 1.52 [0.64, 3.61]</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Italicics 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; RKO = 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; 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.

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Pre-intervention Mean (SD) or Median (IQR)</th>
<th>Post-intervention Mean (SD) or Median (IQR)</th>
<th>Within group change (SD) or % of change</th>
<th>Incidence rate ratio</th>
<th>Mean difference between groups with 95% CI</th>
<th>P value</th>
<th>Comments</th>
<th>GRADE</th>
</tr>
</thead>
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<tr>
<td><strong>Lung volume, capacity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Total lung capacity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reardon (RCT)²⁰</td>
<td>EG 9</td>
<td>3.1 (NA)†</td>
<td>3.1 (NA)†</td>
<td>0 (NM)†</td>
<td></td>
<td>-0.5 (NM)†</td>
<td></td>
<td></td>
<td>⊕ ◯◯◯ 2, 4, 12, 14</td>
</tr>
<tr>
<td>CG 9</td>
<td>3.2 (NA)†</td>
<td>2.7 (NA)†</td>
<td>-0.5 (NM)†</td>
<td></td>
<td>Change between groups: P = NA; Between groups Post: P = NS</td>
<td>Negative value = decline in total lung capacity (L)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Predicted FVC %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reardon (RCT)²⁰</td>
<td>EG 9</td>
<td>36 (NA)†</td>
<td>38 (NA)†</td>
<td>2%</td>
<td></td>
<td>2 (NM)†</td>
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<td></td>
<td>⊕ ◯◯◯ 2, 4, 12, 14</td>
</tr>
<tr>
<td>CG 9</td>
<td>35 (NA)†</td>
<td>39 (NA)†</td>
<td>4%</td>
<td></td>
<td>Change between groups: P = NA; Between groups Post: P = NS</td>
<td>%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Predicted FEV₁ %</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Reardon (RCT)²⁰</td>
<td>EG 9</td>
<td>49 (NA)†</td>
<td>42 (NA)†</td>
<td>-7%</td>
<td></td>
<td>-7 (NM)†</td>
<td></td>
<td></td>
<td>⊕ ◯◯◯ 2, 4, 12, 14</td>
</tr>
<tr>
<td>CG 9</td>
<td>-36 (NA)†</td>
<td>-47 (NA)†</td>
<td>-11 (NM)†</td>
<td></td>
<td>Change between groups: P = NA; Between groups Post: P = NS</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Peak expiratory flow</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toussaint (RXO)¹⁹</td>
<td>EG 8</td>
<td>65.1 (22.9)</td>
<td></td>
<td></td>
<td></td>
<td>5.8 [-4.45, 16.05]</td>
<td>0.27</td>
<td>l/min</td>
<td>⊕ ◯◯◯ 2, 4, 9, 10, 12, 13</td>
</tr>
<tr>
<td>CG 8</td>
<td>59.3 (22.4)</td>
<td></td>
<td></td>
<td></td>
<td>Change between groups: P = NA; Between groups Post: P = NS</td>
<td>cmH₂O; Higher value = better performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maximum expiratory pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reardon (RCT)²⁰</td>
<td>EG 9</td>
<td>32 (NA)†</td>
<td>37 (NA)†</td>
<td>5 (NM)†</td>
<td></td>
<td>4 (NM)†</td>
<td></td>
<td></td>
<td>⊕ ◯◯◯ 2, 4, 12, 14</td>
</tr>
<tr>
<td>CG 9</td>
<td>36 (NA)†</td>
<td>45 (NA)†</td>
<td>9 (NM)†</td>
<td></td>
<td>Change between groups: P = NA; Between groups Post: P = NS</td>
<td>cmH₂O; Higher value = better performance</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Maximum inspiratory pressure</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reardon (RCT)²⁰</td>
<td>EG 9</td>
<td>-36 (NA)†</td>
<td>-47 (NA)†</td>
<td>-11 (NM)†</td>
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<td>-23 (NM)†</td>
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<td>⊕ ◯◯◯ 2, 4, 12, 14</td>
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<tr>
<td>CG 9</td>
<td>-12 (NA)†</td>
<td>-46 (NA)†</td>
<td>-34 (NM)†</td>
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<td>Change between groups: P = NA; Between groups Post: P = NS</td>
<td>cmH₂O; More negative result is better performance</td>
<td></td>
<td></td>
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<tr>
<td>Complications</td>
<td>N</td>
<td>Pre-intervention Mean (SD) or Median (IQR)</td>
<td>Post-intervention Mean (SD) or Median (IQR)</td>
<td>Within group change (SD) or % of change</td>
<td>Incidence rate ratio</td>
<td>Mean difference between groups with 95% CI</td>
<td>P value</td>
<td>Comments</td>
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<tr>
<td>Hospitalisation</td>
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<tr>
<td>Reardon (RCT)</td>
<td></td>
<td>EG 9</td>
<td>0/1000</td>
<td>8.5 [1.1-67]</td>
<td>NA</td>
<td></td>
<td></td>
<td>Patient-days ⊕</td>
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<td></td>
<td></td>
<td>CG 9</td>
<td>4.4/1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory infection</td>
<td></td>
<td>EG 9</td>
<td>0/1000</td>
<td>3.9 [0.43-35]</td>
<td>NS</td>
<td></td>
<td></td>
<td>Patient-days ⊕</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>CG 9</td>
<td>1.7/1000</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Antibiotic use</td>
<td></td>
<td>EG 9</td>
<td>0/1000</td>
<td>43 [6-333]</td>
<td>NA</td>
<td></td>
<td></td>
<td>Patient-days ⊕</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>CG 9</td>
<td>24/1000</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Italicics 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 for 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.
Complications and IPV. One RCT\textsuperscript{20} 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= 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])\textsuperscript{20}.

Survival and HFCWC. One RCT with nine patients\textsuperscript{21} 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 QoL\textsuperscript{2,21}. The five sub-categories of QoL assessment showed inconsistent results in terms of relative risk, but none were statistically significant (Table 2).

A very low quality of evidence was considered in the outcome of complications, survival, and quality of life.

Results of the risk of bias
The overall risk of bias was high for each outcome. The detailed results of the individual question of the ROB 2.0 are available in the appendix (Extended data: File 2, Figures 2–8).

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.

Differences from protocol: We added the assessment of peak expiratory flow because we considered it a relevant information. In addition, we did not exclude a study if it did not contain lung function assessment, as we would have lost important articles responding to our secondary outcomes. We also decided to exclude non-randomised controlled trials.

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 imprecision\textsuperscript{22}. 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 trough sputum weight is inappropriate due to day-to day variability, as well as variability during the day and the fact that secretions can be swallowed\textsuperscript{23}. 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 patient with NMD. Many trials have reported that the use of lung function parameters is questionable because of the lack of observed changes\textsuperscript{24}. Jones et al. (2006) suggest that lung function parameters are insensitive in assessing the acute effects of airway clearance techniques\textsuperscript{25}. In addition, van der Schans (2002) reports that lung function measurement does not appear to reflect differences in mucus transport or mucus expectoration\textsuperscript{26}. 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. Reyechler 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 volume\textsuperscript{27}. 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)\textsuperscript{28} 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\textsuperscript{19,20,21}, 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 multi-centre 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.

Support
This review was not supported financially.

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.n8pk0p2j

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.n8pk0p2j

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Acknowledgements
We would like to thank Elodie Glerum for proofreading the article and Martin Sattelmayer for designing the graphs.

References
   PubMed Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text
   PubMed Abstract
   PubMed Abstract | Publisher Full Text
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   PubMed Abstract | Publisher Full Text
   PubMed Abstract
    PubMed Abstract | Publisher Full Text | Free Full Text
11. Stuart B: The NHO Medical Guidelines for Non-Cancer Disease and local medical review policy: hospice access for patients with diseases other than
Open Peer Review

Current Peer Review Status:  

Version 2

Reviewer Report 23 June 2022

https://doi.org/10.5256/f1000research.134111.r141587

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Masahiro Banno
1 Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Japan
2 Department of Psychiatry, Seichiryo Hospital, Nagoya, Japan

The authors revised the manuscript thoroughly. However, I have one comment for the abstract.

They had better describe that they used the Cochrane revised risk of bias tool for the risk of bias assessment, and that they used the Grade of Recommendation, Assessment, Development and Evaluation (GRADE) approach for the certainty of evidence assessment in the Methods of the abstract.

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.

Version 1

Reviewer Report 19 April 2022

https://doi.org/10.5256/f1000research.30778.r134658

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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.
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.

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**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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