Effects Of Mechanical In-Exsufflation On Mucus Clearance In Critically Ill Patients On Invasive Mechanical Ventilation

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Research

Keywords: mechanical ventilation, mucus clearance, physiotherapy, mechanical in-exsufflation

Posted Date: August 5th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-52429/v1

Abstract

Background: Mechanical insufflation-exsufflation (MI-E) is a non-invasive technique performed through the CoughAssist In-Exsufflator to simulate cough and remove mucus from proximal airways. To date, the effects of MI-E on critically ill patients on invasive mechanical ventilation (MV) are not fully elucidated. The purpose of this study was to compare the efficacy and safety of MI-E combined or not to manual chest physiotherapy (CPT) in these patients.

Methods: This cross-over clinical study enrolled consecutive patients who were sedated, intubated and on MV > 48h with expected maintenance of these criteria > 24h. Over a 24-hour period, patients randomly performed two sessions of manual CPT with or without additional MI-E before tracheal suctioning. Following each procedure, volume of retrieved mucus (ml) was assessed to evaluate efficacy. We evaluated respiratory flows, pulmonary mechanics and hemodynamics before, during, and after treatment. In addition, safety of MI-E was also appraised.

Results: 26 patients were included. In comparison to CPT, mucus volume retrieved was significantly higher during CPT+MI-E (0.42 [0; 1.39] ml vs 2.29 [1; 4.67] ml; $p < 0.001$). The respiratory system compliance immediately improved from pre and post Crs values in CPT+MI-E group (55.7 ml/cmH_2O [38.3; 67.4] vs. 68.6ml/cmH_2O [47.8;94.9]; $p<0.001$). Although, such increase was not significantly different between CPT and CPT+MI-E group ($p=0.057$). Heart rate significantly increased in both groups ($p < 0.005$) immediately after each intervention. Additionally, a significant impact on oxygenation was observed in the CPT+MI-E group when comparing the baseline values with the values one-hour post-intervention ($p<0.05$). Finally, several transitory hemodynamic variations occurred during both interventions, but these were non-significant and considered clinically irrelevant.

Conclusion: In mechanically ventilated patients, MI-E increases the amount of secretions that can be retrieved post-CPT, without causing clinically significant adverse events.

Clinical Trials Registration Number: NCT03316079 (24/11/2015; retrospectively registered)

Background

Retention of airway secretions is a frequent complication in critically ill patients on invasive mechanical ventilation (MV) (1). The main culprit is the endotracheal tube (ETT), which decreases mucociliary clearance (2) and hinders the ability to generate adequate peak expiratory flows (PEF), upon coughing (3). Inspiratory flow bias during MV (4), patient positioning (5), or suboptimal humidification of respiratory gases (6) further impair mucus clearance. Retention of airway secretions is a risk factor for respiratory infections (1) and hinders the recovery after acute conditions (7,8). Therefore, interventions aimed to improve clearance of secretions are pivotal in decreasing morbidity of intubated patients.

During MV, tracheal suctioning (TS) is routinely applied to remove retained secretions. Suction catheters are often advanced up to the carina, but in several instances marginal removal of peripheral secretions is

achieved (9). Consequently, providers increase TS frequency, leading to an increased risk of associated complications, e.g. alveolar collapse, tracheal mucosa injury and respiratory and/or hemodynamic impairment (10,11).

Manual chest physiotherapy (CPT) techniques are commonly performed before TS to enhance cough airflows and outward clearance of peripheral secretions (12,13). However, although a small body of existing evidence supports the potential use of CPT in the ICU, applied and methods are highly inconsistent across studies complicating extrapolation of the results.

The mechanical insufflation-exsufflation (MI-E) is a non-invasive technique, performed through the CoughAssist In-Exsufflator to reproduce the act of coughing to clear mucus from proximal airways. During this procedure, MI-E first hyperinflates the lungs by applying positive inspiratory pressure (PIP), then the device rapidly shifts to a negative expiratory pressure (NEP) to generate high PEF (14). Theoretically, the high PEF and NEP work alongside to drive mucus outward. To date, only a few studies have evaluated the efficacy and safety of MI-E in ventilated critically ill patients, reporting promising figures on the removal of airway secretions (15–18), and safety (16–18). Encouraging results have also been reported in spontaneously-breathing patients with neuromuscular diseases, unable to produce an efficient cough (19). Interestingly, a PIP/NEP combination of + 40/-40 cm H_2O appeared to be the most comfortable and effective setting (14). However, extrapolation of aforementioned results is challenging due to limitations in study designs, chosen efficacy measures and various methodological biases.

Based on above assumptions and previous studies, we performed a study in sedated critically ill patients on MV > 48 h to evaluate potential adjuvant effects of MI-E in clearing secretions, after CPT. In addition, we comprehensively evaluated resulting airflows and potential adverse events.

Methods

Study design:

We conducted a prospective, cross-over, randomized, single-blind study in a medical and surgical ICU, at Bordeaux University Hospital (France). The study was approved by the institution's ethics boards (*comité de protections des personnes sud-ouest et outre mer III*; DC 2015/02). Clinicaltrials.gov identifier: NCT03316079 (24/11/2015; retrospectively registered).

Population:

Adult patients (>18 years of age) on MV for>48 hours, with Richmond Agitation and Sedation Score (RASS) from -3 to -5, and tracheally intubated (ETT internal diameter of 7.0-8.0), were evaluated daily for inclusion. We excluded patients with lungs trauma and/or with pulmonary emphysema, pneumothorax, MV-associated barotrauma, mean arterial pressure<65mmHg, irrespective of vasoactive support. Patients who met inclusion and exclusion criteria were included fafter the next of kin provided consent. We used a web-based, computer-generated, single-block randomization system to randomly implement, on the same

day, two CPT sessions with or without MI-E. Following each intervention, TS was employed. A wash-out period of four hours was followed between interventions to avoid carry-over effects.

Interventions:

Experienced respiratory physiotherapists performed the CPT session. First, the internal ETT cuff pressure was adjusted to 30 cmH_2O, then semi-recumbent position was confirmed or the head of the bed adjusted to achieve 30º. Based on the probable location of retained secretions, as appraised by chest auscultation, soft/prolonged or hard/prompt manual ribcage compressions were applied to dislodge mucus from either the distal or proximal airways, respectively (20,21). Following CPT, MI-E was delivered with a Cough Assist E-70 Respironics (Philips North America Corporation, MA, USA). The MI-E was set to automatic mode with +/-40 cmH_2O insufflation-exsufflation pressure, middle flow, and an inspiratory-expiratory time of 3 and 2 seconds, respectively, with a one-second pause (22). We performed 4 series of 5 cycles insufflation-exsufflation cycles, with a one-minute pause between series to allow MV and avoid potential oxygen desaturation and/or derecruitment. (Figure 1)

Measurements:

Primary outcome was quantification of wet volume of sputum (ml). Once each procedure was completed, the secretions were suctioned and collected by a 12-Fr catheter (Biçakcilar, Istanbul, TUR) connected to a sterile collector container (Vygon, Ecouen, FR). The TS procedure was performed as recommended by international guidelines (23). As needed, five mL of saline solution was instilled through the suction catheter to clear secretions adherent to the internal lumen. This amount was ultimately subtracted from the overall volume of secretions.

Tidal volumes, airflow rates, and airway pressures were measured before interventions, after TS, and one-hour thereafter through the Fluxmed GrH monitor (MBMED, Buenos Aires, ARG) (24). All data were recorded and analyzed with the dedicated software FluxReview (MBMED, Buenos Aires, ARG). Aforementioned parameters were continuously recorded during MI-E procedure. Of note, prior to MI-E intervention, flow-pressure transducer was connected between the Y-piece of the ventilatory circuit and the ETT, while during MI-E it was moved between the ETT and MI-E circuit. Air flow and pressure rates of five respiratory cycles were averaged and compared. Respiratory system compliance (Crs), airway resistance (Raw), and lung tissue resistance (Rti) were calculated, using standard formulae (4). During MI-E operation, peak inspiratory flow (PIF) and peak expiratory flow (PEF) were recorded and averaged for each in-exsufflation; we also calculated the PEF-PIF difference and PEF:PIF ratio. Heart rate (HR), systolic and diastolic arterial pressure (SAP and DAP), arterial gas exchange (PaO_2 and $PaCO_2$) and oxygen saturation (SaO2) were obtained before during and after the intervention.

MI-E was ceased if pneumothorax occurred or SaO_2 consistently decreased to < 85% or > 10% from baseline, HR increased/decreased >20% from baseline, SAP and/or DAP increased/decreased > 20% from baseline.

Statistical analysis:

We assumed that the difference in volume of retrieved mucus between the two interventions would be 1.5 mL. Thus, for an assumed effect size of 1.33 of the paired t-test, a desired statistical power of 90% and type 1 bias of 5%, we calculated that a total sample size of twenty-six patients was needed, six of whom would potentially be lost during enrollment.

We report the mean (standard deviation) or the median [interquartile range] for continuous variables, while categorical variables are presented as the number and percentage of patients. The Wilcoxon test was used to compare two paired groups. The Friedman test was used to compare more than two paired groups. Linear regression analysis was performed to examine the correlation between continuous variables. As sensitivity analyses, we performed an analysis of variance (ANOVA) model for cross-over designs (25,26) to examine differences in the primary outcome between the two groups, and analysis of covariance (ANCOVA) models for cross-over designs in the rest of the outcomes, to provide supportive information (e-appendix 1). All statistical comparisons were two-sided hypothesis tests, and the significance level was set at 0.05. All confidence intervals (CIs) were two-sided at 95% confidence level. The IBM SPSS Statistics version 25.0 (Armonk, New York, USA) was the statistical software used to analyze the data sets.

Results

A total of 100 consecutive patients were screened from March 2015 to June 2017, and 26 patients met the inclusion criteria (Figure 2). Baseline characteristics of the study population are presented in Table 1. Three patients did not complete the study because they awakened before completion of the protocol. In two patients (one control and one intervention), pulmonary mechanics and gas exchange were not measured following the intervention and one-hour thereafter for technical reasons (Fig. 2). Moreover, respiratory secretions were not registered in one patient (intervention group) due to malfunctioning of the vacuum system.

We recorded a total of 430 MI-E cycles, on average 16.5 (3.7) administered cycles per patient. During MI-E, all volumes, pressures, and flow rates were consistent within the series (e-Table 1). Irrespective of the pre-set in-expiratory pressure (+40/-40 cmH_2O), the device was able to generate an adequate PIP of 41.3 (2.3) cmH_2O, but only 88.6% of the prefixed NEP, (26.3 (9.9) cmH_2O; p = 0.02). MI-E produced PEF and PIF rates of 96.9 (20.6) l/min and 66.7 (11.7) l/min, respectively, resulting in a PEF-PIF difference of 30.6 (12.6) l/min and PIF:PEF ratio of 1.47 (0.20).

Efficacy of mechanical in-exsufflation:

The median (interquartile range) mucus volume retrieved during CPT and MI-E was significantly higher in comparison with only CPT (2.29 [1; 4.67] ml vs 0.42 [0; 1.39] ml; p < 0.001) (Fig. 3). Adjusted mean mucus volume value was higher for CPT+MI-E group compared to CPT group (3.02 ml for CPT+MI-E and 0.84 ml for CPT; p < 0.001; difference between groups, 2.18 ml [95% CI, 1.24 to 3.12]) (Table 3).

Inverse correlation was found between the volume of retrieved mucus and PEF generated during MI-E, but with weak goodness-of-fit (adjusted r-square = 0.17; p = 0.038) (Fig. 4). Whereas, a lack of correlation was observed between the PIF (adjusted r-square = 0.10, p = 0.11), the PEF-PIF difference (adjusted r-square = 0.16, p = 0.059), the PEF:PIF ratio (adjusted r-square = 0.03, p = 0.25) and the volume of mucus retrieved.

Overall, no significant differences in Crs, Raw and Rti were observed when comparing the interventions or evaluation periods (Table 2). Yet, in the CPT+MI-E group, pre and post Crs values significantly differed (55.7 ml/cmH_2O [38.3; 67.4] vs. 68.6ml/cmH_2O [47.8; 94.9]; p<0.001) but the beneficial effect tapered off one-hour post intervention. ANCOVA analyses revealed similar results (Table 3).

Safety of mechanical in-exsufflation:

As shown in Table 2, HR significantly increased following both CPT and CPT+ MI-E group (p<0.05), but the increase was wider in the CPT group and differed consistently even one hour after the intervention in comparison with CPT+MI-E (p<0.05). These differences were not corroborated in ANCOVA analyses (Table 3). All remaining hemodynamic parameters marginally varied throughout the interventions. A significant increase in SaO_2 was found 1-hour post-intervention in the CPT+MI-E group vs. CPT group (p < 0.05) and PaO_2 in the CPT+MI-E group after intervention (p < 0.05) (Table 2). Similarly, ANCOVA analysis showed a statistical improvement in SaO_2 1-hour after intervention of CPT+MI-E group in comparison to CPT group (p = 0.008; Table 3). Despite, this positive results in CPT+MI-E is not correlated with mucus improvement (adjusted r-square = 0.004, p = 0.76). A total of twenty-one episodes of brief desaturations or hemodynamic variations were documented, ten during CPT+MI-E and eleven during single CPT treatments, with no significant difference between interventions (e-Table 2). Importantly, protocol interruption was never required, due to marginal clinical severity and brief duration of the adverse events.

Interestingly, during CPT+MI-E, ETT cuff pressure decreased from 30 cmH_2O to 22.9 (4.90) cmH_2O, while during CPT alone to 24.32 (3.61) cmH_2O (p = 0.20). ANCOVA analysis also showed that adjusted mean cuff pressure value did not differ between groups (23.11 cmH_2O for CPT+MI-E and 24.38 cmH_2O for CPT; p = 0.13; difference between groups, -1.27 cmH_2O [95% CI, -2.96 to 0.43])

Discussion

This is the first clinical trial evaluating the efficacy and safety of mechanical in-exsufflation in combination with manual chest physiotherapy and endotracheal suctioning in a cohort of sedated critically ill patients on MV. The combination of CPT and MI-E was associated with a significant increase in the amount of retrieved pulmonary secretions when compared with CPT alone. Additionally, MI-E was safe and resulted in a short-term improvement in respiratory system compliance.

In a mixed population of 180 intubated and critically ill patients, Ferreira De Camillis et al. found a significant improvement in the weight of suctioned mucus using MI-E rather than CPT (17). In this previous study, CPT included manual chest compressions, applied upon left and right lateral decubitus,

followed by manual hyperinflation. Unfortunately, manual chest compression was poorly described, challenging extrapolation on the benefits of MI-E or inefficacy of the applied CPT techniques. Conversely, in a cross-over study in 43 invasively ventilated ICU patients, Coutinho et al. found negligible effects of MI-E performed prior to TS (16). Coutinho's study presented some incongruencies between planned primary outcome (volume of secretions) and assessed outcome (weight of secretions), questioning whether the study was adequately powered to achieve pre-planned aims. To the best of our knowledge, our study is the first to comprehensively assess the effects of MI-E and CPT, while avoiding potential biases. We found that when MI-E was used in conjunction with CPT, mucus clearance improved. A potential explanation for our positive results is the resulting PEF during MI-E (i.e. 96.9 [20.6] l/min). Previous studies in intubated and ventilated patients have implied that PEF higher than 160 l/min is required to mobilize secretions (27). Yet, a more recent review concluded that a cut-off point between 64–126 l/min could promote benefits in efficient clearance and successful weaning (28). Mechanistic *in-vitro* studies by Guerin et al. concluded that MI-E pressures should be increased up to 50 cmH_2O to achieve the aforementioned PEF values (29) when endotracheal or tracheostomy tubes are used. In our study, patients were fully sedated, hence unable to perform expiratory efforts, while the resistance imposed by the ETT decreased the expiratory pressure by 34%; irrespective, we achieved efficient PEF figures as reported above.

In our settings, the MI-E device was set at + 40/-40 cmH_2O pressure with middle inspiratory flow. We used these pressures because in previous clinical studies (14,19), patients better tolerated the inspiratory and expiratory efforts. Moreover, as recently demonstrated in a bench study (30), a reduction in flow rate during MI-E inspiratory phase augments the expiratory flow bias and enhance mucus displacement. Indeed, Volpe et al. achieved a higher PEF:PIF ratio, by setting MI-E to low inspiratory flow with an expiratory pressure higher than inspiratory pressure (i.e.: +40/-60). Conversely, in our settings the inspiratory and expiratory pressures were equivalent and we decided for middle flow, which may explain our slight inverse relationship between mucus clearance and PEF, while we failed to find an association with PEF:PIF ratio.

Ferreira de Camillis et al. observed short-term improvement of lung compliance following application of MI-E, in comparison with CPT (17), but long-term follow up was overlooked. Recently, Nunes et al. investigated in 16 intubated patients the effects of different MI-E pressure combinations vs. standard TS (18). In this randomized cross-over trial, when inspiratory/expiratory pressures of 50 cmH_2O were applied, lung compliance improved immediately after the intervention, and 10 minutes thereafter. Despite these encouraging previous results, other publications have consistently failed to find benefits (15,16,18). In our study, compliance of the respiratory system increased immediately after CPT + MI-E intervention. Potentially, these positive variations in compliance are related to a higher number of performed MI-E cycles (30 and 20, respectively) in comparison with other negative studies that used lower number of cycles. Nevertheless, we found that the improvement in lung compliance was not sustained one-hour post-intervention and was not significant between groups. One possible explanation for this short effect

is that MI-E acts as a recruitment maneuver, but if positive end-expiratory pressure is not adjusted following MI-E, derecruitment can still occur in the follow-up period.

Nunes et al. observed an improvement in SpO_2 after either endotracheal suctioning or MI-E (18), while other publications failed to corroborate these results (15,16). Sanchez-Garcia et al. demonstrated an improvement in PaO_2 following MI-E (15). Yet, it should be emphasized that in the study by Sanchez-Garcia continuous flow of oxygen at 8 l/min was administered at the filter port, adjacent to the MI-E device. Conversely, in our study, supplementary oxygen was not administered, but still an improvement in PaO_2 and SaO_2 was observed. In this context, it should also be taken into account the effects of MI-E on pulmonary perfusion. Indeed, during insufflation, MI-E creates a high transpulmonary pressure, which may displace blood toward collapsed alveolar regions, resulting in increased shunt and worse saturation (31).

In our study, a few episodes of respiratory and hemodynamic changes occurred during MI-E. However, these events did not differ significantly from the control group, lasted for a very brief period, and early protocol interruption was never necessary by attending clinicians. Indeed, both the MI-E and control group mainly experienced a slight increase in blood pressure and heart rate during interventions. Importantly, occurrence of these events was registered at the end of each intervention. This highlights that MI-E, CPT and TS all affects hemodynamic parameters, which should be taken into account in patients at risk of cardiac complications. In addition, as previously reported MI-E at times has been associated with hypoxemia, derecruitment, and pneumothorax (14,32); thus indication in patients with underlying acute or chronic pulmonary diseases should be carefully pondered. Finally, during both procedures cuff pressure decreased substantially to 22.9 (4.90) cmH_2O in CPT + MI-E group and 24.32 (3.61) cmH_2O during CPT alone. Main complication of this deflation may be ventilator acquired pneumonia (33, 34) which is directly related with an increase of burden during recovery (8). Despite these results, clinical guidelines recommend to maintain cuff pressure between 20 to 30 cmH_2O to avoid microleaks and ventilator acquired pneumonia (35), being in consonance with our results.

Some limitations in this study merit consideration. First, volume of secretions was applied as a surrogate endpoint of mucus clearance, which could ultimately decrease accuracy of our results. However, the crossover design was chosen specifically to offset these limitations and prevent significant differences among patients. Second, respiratory physiotherapists could not be blinded to treatments allocation. Finally, the small sample size should be acknowledged. Yet, we carried out a comprehensive sample size analysis, based on a previous pilot study including 15 patients and in line with previous studies in this field of investigation.

Conclusion

In tracheally intubated patients, we found that a combination of CPT and MI-E before TS improved mucus clearance, in comparison to CPT alone. PEF values achieved during MI-E were lower than those reported in previous literature, yet appeared efficient in our settings. MI-E resulted in a short-term

improvement in respiratory compliance, and induced marginal hemodynamic variations. These findings call for larger clinical trials to evaluate major clinical outcomes and corroborate indication for the use of MI-E in intubated and mechanically ventilated patients.

Abbreviations List

CPT: Chest physiotherapy techniques

Crs: Respiratory system compliance

DAP: Diastolic arterial pressure

ETT: endotracheal tube

HR: Heart rate

ICU: Intensive care unit

MI-E: Mechanical in-exsufflation

MV: Invasive mechanical ventilation

NEP: Negative expiratory pressure

PaCO2: Partial pressure of arterial carbon dioxid

PaO2: Partial pressure of arterial oxygen

PEF: Peak expiratory flow

pH: acidic-basic balance

PIF: Peak inspiratory flow

PIP: Positive inspiratory pressure

RASS: Richmond Agitation and Sedation Score

Raw: airway resistance

Rti: lung tissue resistance

SaO2: Arterial oxygen saturation

SAP: Systolic arterial pressure

TS: Tracheal suctioning

Declarations

Ethics approval and consent to participate: This study was performed in accordance with the declaration of Helsinki and was approved by the correspondent ethics committee (*comité de protections des personnes sud-ouest et outre mer III*; DC 2015/02).

Constent for publication: Not applicable

Availability of data and materials: Roberto Martínez-Alejos and Joan-Daniel Martí had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests: No conflict of interest related to the article aforementioned exist for all the authors involved in this study.

Funding: Support was provided by the Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Research fund 077/2016.

Authors' contributions: *Study concept and design:* RMA, JDM, GLB; *Acquisition of data:* RMA, DGA, XPD, TR, PW; *Analysis and interpretation of data:* RMA, JDM; *Statistical analysis:* AG; *Drafting of the manuscript:* RMA, JDM, GLB; *Critical revision of the manuscript for important intellectual content: AQ,* AT.

Acknowledgements: Not applicable

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Tables

Due to technical limitations the Tables are available as a download in the Supplemental Files.

Figures

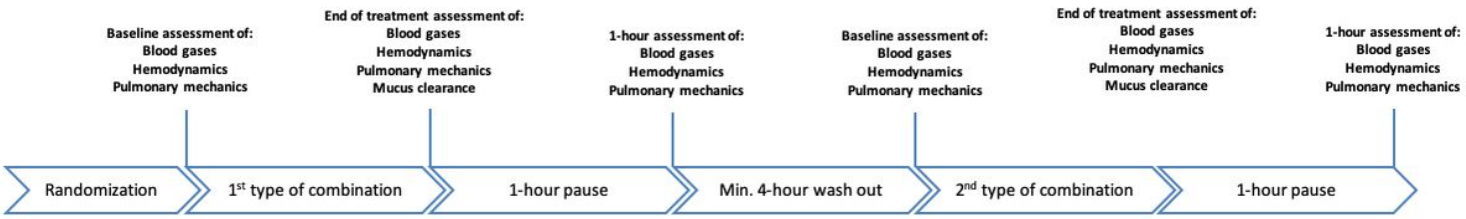

Figure 1

Study protocol. Experienced respiratory physiotherapists randomly and consecutively applied two types of combinations: chest physiotherapy plus tracheal suctioning (control group) and chest physiotherapy plus mechanical in-exsufflation plus tracheal suctioning (intervention group).

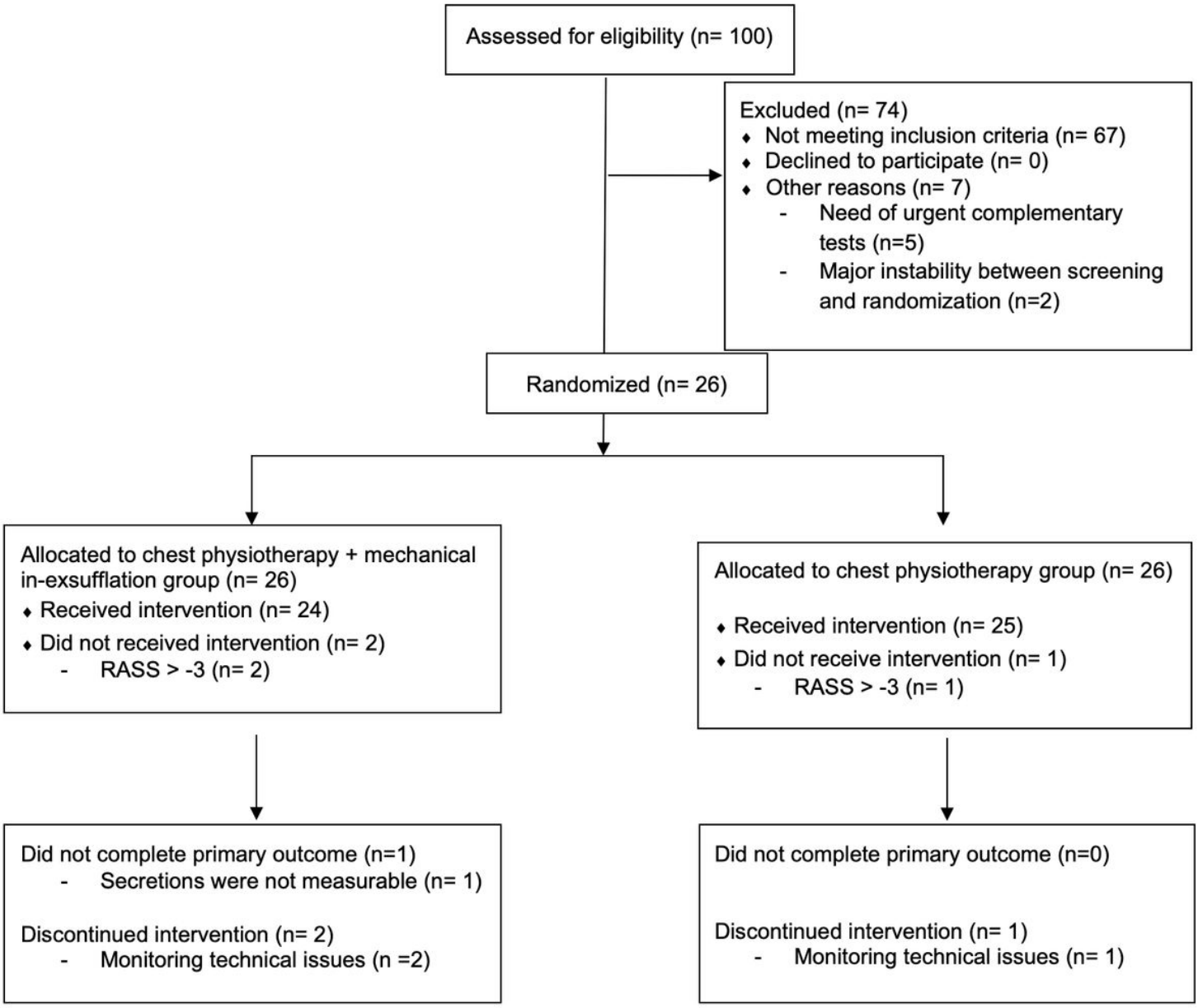

Figure 2

Study flow chart. RASS, Richmond agitation and sedation scale

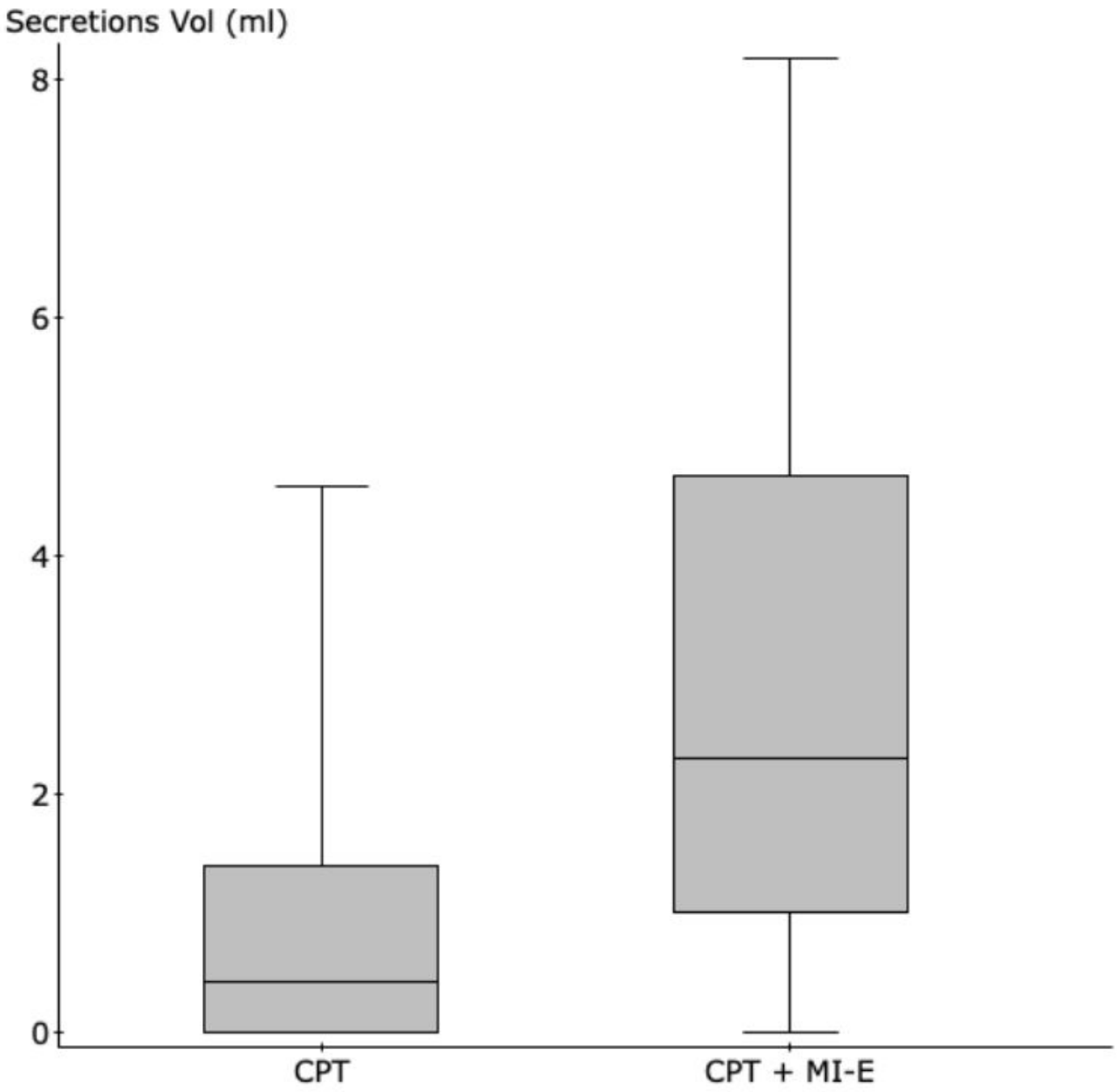

Figure 3

Mucus retrieved during chest physiotherapy compared to chest physiotherapy + mechanical in-exsufflation. CPT+MI-E, chest physiotherapy combined with mechanical in-exsufflation group; CPT, chest physiotherapy group.

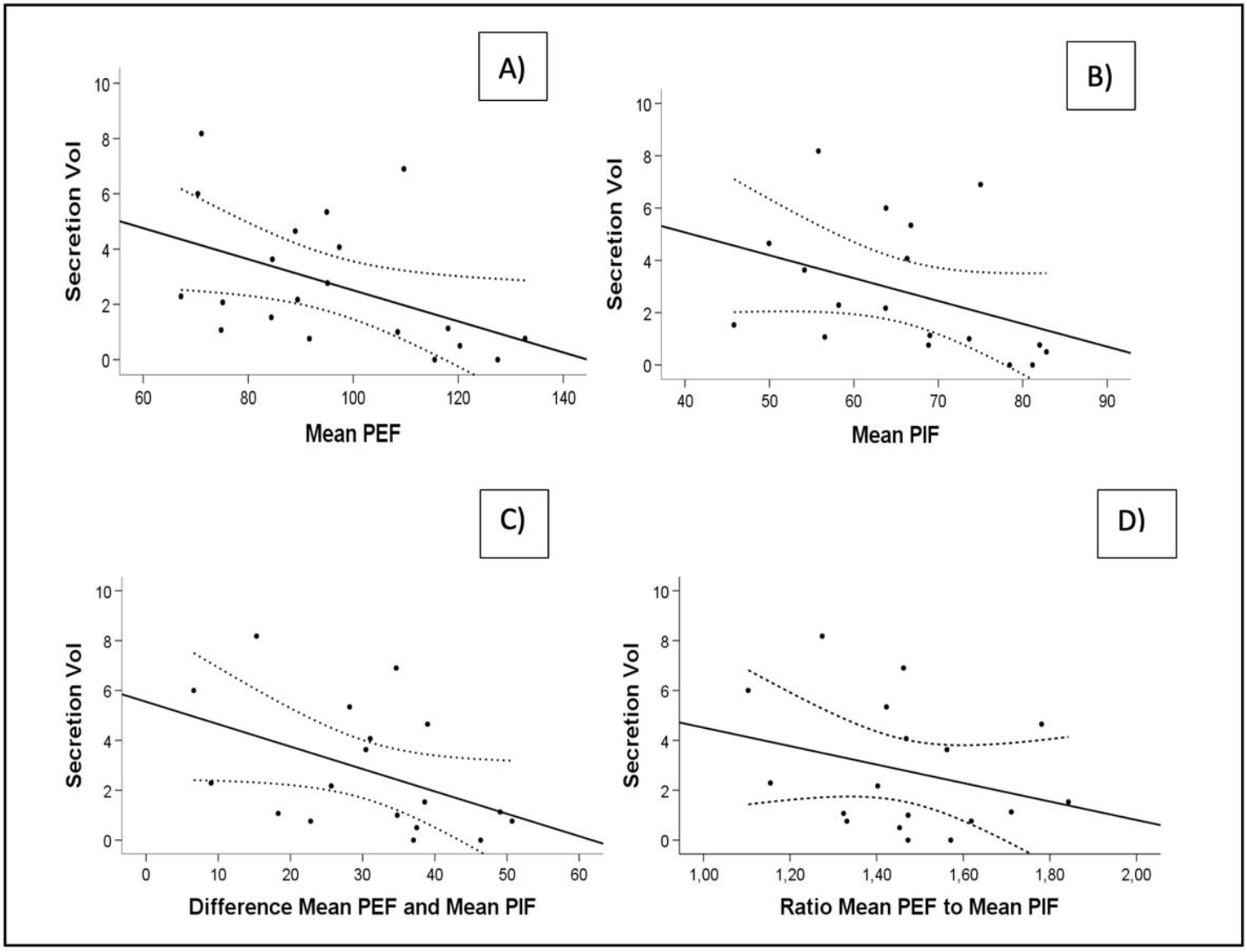

Figure 4

Linear regressions between mucus and flows generated during mechanical in-exsufflation. Relationship between volume of mucus retrieved during chest physiotherapy combined with mechanical in-exsufflation and flows generated during MI-E. A) Linear regression of association between mean peak expiratory flow (PEF) and volume of secretions retrieved. n= 20, r2=0.17; y = -3.37x+8.13; p=0.04 B) Linear regression of association between mean peak inspiratory flow (PIF) and volume of secretions retrieved; n=18, r2=0.1; y = -5.24x+8.57; p=0.11 C) Linear regression of association between PEF-PIF difference and volume of secretions retrieved. n=18, r2=0.16; y = -5.39x+5.55; p=0.06 D) Linear regression of association between mean PEF:PIF ratio and volume of secretions retrieved. n=18, r2=0.03; y = -3.7x+8.22; p=0.25

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.pdf

- SupplementaryTables.pdf