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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The use of respiratory physiotherapy in the Intensive Care Unit

Leenne Broeders
Annick Engelen

Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

PROMOTOR :

De heer Chris BURTIN

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The use of respiratory physiotherapy in the Intensive Care Unit

What is the currently available evidence of the most frequently used techniques of respiratory physiotherapy in the population of critically ill patients hospitalized in the Intensive Care Unit?

Broeders Leenne - 1436791
Engelen Annick - 1436706

“Significant improvements found in the maximal inspiratory pressure, expiratory flow, maximal ventilation volume, peak cough and Tobin index after treatment with threshold spirometry. ”

“Conflicting evidence found on the effectiveness of incentive spirometry.”

“Significant short-term effects of suctioning combined with chest compressions found for the aspirated secretions in mechanically ventilated patients.”

“Intrapulmonary Percussive Ventilation appears to have significantly positive effects on respiratory and hemodynamic parameters, blood gases, and other outcome measures such as length of hospital stay.”

Promotor: Dr. C. Burtin

CONTEXT OF THE MASTER THESIS

This master thesis is part of the master of Rehabilitation Sciences and Physiotherapy at the University of Hasselt. The literature study fits in the Research Department of the Rehabilitation of Internal Disorders. This literature study provides an overview of the several different techniques of respiratory physiotherapy used in the Intensive Care Unit. The available evidence of these techniques in the population of critically ill patients will be looked at in detail.

The master thesis is the start of a new pilot project. The first part of this master thesis is the literature study, executed by two students of the Rehabilitation Sciences and Physiotherapy at the University of Hasselt. The central format was applied. A research question with an appropriate search strategy was formulated by the two students under the supervision and deliberation of the promotor Chris Burtin. The students executed the title and abstract screening independently of each other while quality assessment was done together. The further text screening, writing of the method, results, discussion and conclusion were discussed together and divided between the students.

For the second part of the master thesis, a new protocol was formulated by the master thesis students. This happened under the supervision and deliberation of Chris Burtin (promotor, post doctorate researcher at the University of Hasselt), Dr. Tom Fivez (anesthetist on the ICU of Ziekenhuis Oost-Limburg (ZOL)) and David Schramme (senior physiotherapist on the ICU of ZOL). The primary aim of the second part of the master thesis is to investigate the influence of chest physiotherapy including Intrapulmonary Percussive Ventilation in combination with assisted autogenic drainage on the distribution of ventilation in a heterogenous group of sedated patients. The study will take place at the ICU of Ziekenhuis Oost-Limburg (ZOL), campus Sint-Jan. Approval for this protocol will be obtained from the Medical Ethics Committee of Ziekenhuis Oost-Limburg and the University of Hasselt.

Table of contents

PART ONE – OVERVIEW OF THE LITERATURE

1. Abstract

Background: Respiratory complications occur often in the patient population of the Intensive Care Unit (ICU) due to prolonged bed rest and the need for Mechanical Ventilation (MV). Respiratory physiotherapy aims to prevent and minimize these complications. This review provides an overview of the currently available evidence of the interventions most used in the ICU.

Methods: In January and April of 2018**,** PubMed and Web of Science were used as data sources. All randomized controlled trials, investigating respiratory physiotherapeutic interventions in patients older than 18 years in the ICU, were included. The PEDro scale and an strength-weakness analysis were conducted to investigate the quality of each article.

Results: Out of 1899 hits, twenty-five trials were reviewed. There is conflicting evidence for the application of manual hyperinflation, chest wall vibrations and multimodal chest physiotherapy. Inspiratory muscle training, intrapulmonary percussive ventilation (IPV), chest compression, and positive expiratory pressure devices have generally positive effects on ICU patients.

Discussion and conclusion: There is some evidence for the use of respiratory physiotherapy in the ICU, but more uniform high-quality research needs to be available to draw definitive conclusions.

Aim of the research: Investigate the effect of intrapulmonary percussive ventilation (IPV) in combination with assisted autogenic drainage in a heterogenous group of sedated patients requiring MV.

Operationalization research question: Treatment effects on the distribution of ventilation, dynamic changes of lung ventilation and influence on gas exchange parameters before, after and during is investigated.

Most important key words: *intensive care units, physical therapy modalities, respiratory physical therapy*

2. Introduction

Whether it is a small or large one, every hospital has its own Intensive Care Unit (ICU). The ICU is a ward in the hospital where the most critically ill patients receive all the care they need. A team of specialized doctors, surgeons, anesthetists, radiologists, nurses and other health care providers are available 24 hours a day to monitor the patient's life-threatening situation and provide special care where needed. Physiotherapists are also part of this team. The most common pathologies on the ICU are complications and infections after surgery, intracerebral hemorrhage, multiple trauma, gastro-intestinal complications, neurological complications, sepsis, respiratory and cardiac insufficiency. Some of the patients in the ICU require Mechanical Ventilation (MV) via an endotracheal intubation or tracheostomy. Mechanical ventilation helps to preserve a stable airway, to decrease the patients work of breathing and to maintain a stable gas exchange (Ciesla, 1996; Naue Wda, Forgiarini Junior, Dias, & Vieira, 2014; Templeton & Palazzo, 2007).

The length of stay in the ICU can vary from some days to several weeks or months. However, it is logical that a longer stay in the ICU is related to a more severe pathology which leads to a worse health status for the patients but also to higher hospital costs. The study of Rodriguez Villar and Barrientos Yuste (2014) investigated the effect of the ICU length of stay on the mortality rate. In this study, the mortality rate of patients who stayed more than 20 days in the ICU was nine times higher than of those patients with a shorter length of stay. The mortality rate in patients older than 65 years is even higher. In the study of Moitra, Guerra, Linde-Zwirble, and Wunsch (2016), 57.8 percent of the elderly who stayed more than 21 days in the ICU died one year after their discharge. Furthermore, the critically ill patients who receive MV spend more days in the ICU and have a higher risk of mortality in the ICU and the in-hospital period than the patients who are able to breathe on their own (Loss et al., 2015).

The prolonged bed rest in the ICU results in immobilization of the patients, which leads to a loss of muscle mass and strength. This immobilization, in combination with other aspects such as malnutrition, sepsis and medication like corticosteroids, often leads to a combination of polyneuropathy and myopathy. This is called Intensive Care Unit Acquired Weakness (ICU-AW) (Koukourikos, Tsaloglidou, & Kourkouta, 2014). The weakening of proximal limb muscles results in functional impairments after discharge from the ICU. ICU-AW also affects the respiratory muscles (Hermans & Van den Berghe, 2015).

Respiratory complications occur often in the ICU population. Due to pain and prolonged bed rest, patients breathe more superficial which can result in atelectasis (Makhabah, Martino, & Ambrosino, 2013). MV offers many advantages for the critically ill patients, but the adverse effects cannot be ignored. MV weakens the inspiratory muscles (Tobin, Laghi, & Jubran, 2010) and the cough reflex (Yousefnia-Darzi, Hasavari, Khaleghdoost, Kazemnezhad-Leyli, & Khalili, 2016), which can lead to an impairment of the mucocillairy transport with retained secretions as a result (Branson, 2007). Patients who receive MV have a risk of ventilator-associated pneumonia (Kalanuria, Ziai, & Mirski, 2014).

The role of the physiotherapist within the ICU team is to minimize these complications related to the muscular and respiratory system. Recent systematic reviews provide sufficient evidence of the fact that early mobilization and rehabilitation is safe and feasible in the ICU population (Hashem, Parker, & Needham, 2016; Ntoumenopoulos, 2015; Nydahl et al., 2017; Stiller, 2013). It improves the patients functional outcomes, the gas exchange and muscle strength, but also decreases the duration of mechanical ventilation and the length of stay in the ICU. Respiratory physiotherapy is another important aspect of physiotherapy in the ICU that cannot be forgotten. It is part of the daily care routine, especially in the treatment of patients who receive MV. Respiratory physiotherapy consists of several interventions to prevent and minimize respiratory complications. If complications can be prevented, the length of stay in the ICU will decrease as a result. There is a large range of articles that investigate and discuss the several techniques of respiratory physiotherapy. However, an overarching review that investigates and compares the evidence of these several different techniques, to our knowledge, has not been performed. The aim of this review is to provide an overview of the most frequently used techniques of respiratory physiotherapy in the ICU and the currently available evidence for their application.

3. Methods

3.1 Research question

The aim of this review is to provide an overview of the available evidence on the use of respiratory physiotherapy in the Intensive Care Unit. This research question results in the following PICO:

Patient	Patients (age > 18 years) in the Intensive Care Unit
Intervention	Respiratory physiotherapy
Comparison	Not specified
Outcome	Not specified

3.2 Literature search

In January of 2018, Web of Science and PubMed were searched for relevant articles. The search was repeated on the fifth of April 2018 to obtain a complete and up-to-date set of articles. Our search strategy consisted of two components that were combined with the “AND” operator. Within these components the “OR” operator was used. The first component included terms related to the setting of the studies, those being “Intensive care units”, “Respiratory care units”, “ICU”, and “Intensive care”. The second component comprised the relevant interventions. Used terms are: “Physical therapy modalities”, “breathing exercises”, “respiratory physical therapy”, “respiratory physiotherapy”, “Respiratory rehabilitation”, “Intrapulmonary percussive ventilation”, “incentive spirometry”, “Patient positioning”, “airway clearance”, “manual lung inflation”, “postural drainage”, “chest wall vibration”, “chest wall percussion”, “inspiratory muscle training”, and “chest wall oscillation”. The search was narrowed down by combining the terms “pediatrics”, “pediatric”, “pediatric intensive care units”, “child”, and “infant” with the “NOT” operator. As Web of Science does not use MeSH terms the search strategy for Web of Science differed slightly compared to the strategy used for PubMed. An overview of the search strategy is included in Table 1.

Articles that were not excluded in the initial title screening underwent an abstract screening. Systematic reviews, practice guidelines, articles that were not available in Dutch or English, publications of other text types and articles that did not relate to the research question in any way were excluded. As the text screening still included over 180 articles, the articles were screened once more and only randomized controlled trials (RCT’s) were included, generating a selection of articles of higher quality and level of evidence.

3.3 Selection criteria

To be included in this review, articles had to meet all of the following criteria:

- RCT design
- Patient age > 18 years
- Patients in Intensive Care Units, either mechanically ventilated or breathing independently
- Intervention contains respiratory physiotherapeutic techniques

Articles that met the following criteria were excluded:

- Articles that were not available in English or Dutch

3.4 Quality assessment

Included articles were rated using the PEDro scale for RCT's, which consists of 11 criteria to assess the quality of the articles, considering aspects such as random and concealed allocation, blinding and drop-out.

Furthermore, an additional analysis of strengths and weaknesses was performed on all individual studies, as the PEDro scale alone does not provide sufficient information to assess study quality. In this analysis the following criteria were used:

- Risk of bias: selection, performance detection, attrition, or reporting bias or other biases.
- Level of evidence
- Patients: group size, recruitment strategy, documentation of patient demographics, risk of selective loss-to-follow-up
- Intervention:
    - Clearly described and uniform intervention
    - Are there non respiratory intervention components that were administered to the intervention group but not to the control group?
    - Was treatment universally and consistently administered within the intervention group?
- Control
    - Use of true control group
    - Clearly described and uniform control intervention
    - Use of placebo intervention
- Outcome measures
    - Clearly described outcome measures and used instruments
    - Do used instruments and outcome measures assess the intended variables?
- Results: Are all results clearly reported for all outcome measures?
- Conflict of interests

3.5 Data extraction

The following information was obtained from all included studies: patient demographics and pathology, respiratory status (i.e. mechanical ventilation, supported breathing, independent breathing), study setting, group size, study and control interventions, duration of follow-up, used outcome measures, and results. The included articles were divided into 7 groups based on the used intervention: manual hyperinflation, inspiratory muscle training, chest compression, intrapulmonary percussive ventilation, chest wall vibrations, positive expiratory pressure devices, and multimodal chest physiotherapy that consisted of multiple techniques.

4. Results

4.1 Results study selection

In December the search strategy generated 986 hits in PubMed and 886 in Web of Science. The search in April brought the total amount to 1000 hits in PubMed and 899 hits in Web of Science.

A total of 1253 articles was excluded in the title screening. Of these articles 1141 did not answer any part of the research question and 44 were excluded based on the language criteria. Furthermore 46 systematic reviews, four practice guidelines, eight clinical reviews, five study protocols, one comment, a reply to a letter from the editor and a conference presentation were excluded. The remaining 646 articles underwent an abstract screening. Of the 389 excluded articles there were 303 that did not answer the research question, 10 that were not written in English or Dutch, 27 clinical reviews, one animal study, two laboratory studies, and 16 articles of other text types (e.g. letters, editorials, commentaries). There was no available abstract or full text of six articles. As said articles were published between 1968 and 1972, had broad titles, and were not retrievable in any way, these were also excluded. After the abstract screening 65 duplicates were detected and excluded. Lastly, a text screening was performed on 192 articles. In the first phase of the text screening a total of 98 articles was excluded. Fifteen articles gave an overview of available techniques but did not discuss the effectiveness of the described interventions. Eight articles were excluded because they did not have an ICU setting. Forty-three used only non-respiratory techniques. There were ten clinical reviews, one systematic review and six articles of other text types. Two studies did not pass the language criteria. The remaining 13 articles did not answer the research question or did not conform to the set PICO. There were still 94 eligible articles after this first phase. To attain a selection of high-quality articles, only RCT's were selected for the review, bringing the number of articles down to twenty-five.

An overview of the study selection and of the articles that were excluded in the text screening can be found in Figure 1 and Table 2, respectively.

4.2 Results quality assessment

A full overview of the conducted quality assessment can be found in Table 3 and Table 4 for the PEDro checklist and the strengths-weaknesses analysis, respectively.

PEDro scores ranged from five out of eleven items (Gosselink et al., 2000) up to ten out of eleven items (Patman, Jenkins, & Stiller, 2009). All articles analyzed all patients in their allocated groups, provide both point measures and measures of variability for at least one key outcome and include between-group comparisons in their statistical analysis. Furthermore, only in the study of Kuyrukluyildiz et al. (2016) allocation was neither random nor concealed. In all studies, with the exception of Gosselink et al. (2000), the groups were comparable for the most important variables at baseline. However, the groups in the study of Patman et al. (2009) did differ in gender and BMI. In general, the included articles performed poorly on items related to blinding. Only Patman et al. (2009) reported blinding all of their patients, and only the study of Clini et al. (2006) blinded all the therapists connected to their research.

Eleven articles did not clearly report whether their assessors were blinded, while in four articles they were not (Cader, de Souza Vale, Zamora, Costa, & Dantas, 2012; Cader et al., 2010; Chicayban, Zin, & Guimaraes, 2011; Gosselink et al., 2000). Another frequently occurring weakness is the small sample size. Sample sizes range from only five per group (Barker & Adams, 2002) up to 87 per group (Templeton & Palazzo, 2007), with the average number of patients per group being 30,06. Group averages range from 15 patients per group (group six, containing only one article) and 20,71 patients per group (group one) to 69,5 patients per group (group five). Finally, there is a risk of selection bias in four articles (Barker & Adams, 2002; Gosselink et al., 2000; Kuyrukluyildiz et al., 2016; Postma et al., 2014).

4.3 Results data extraction

The results of the data extraction can be found in Table 6.

4.3.1 Manual hyperinflation

There were three articles that investigated the effect of manual hyperinflation in the intensive care unit. All patients were intubated via endotracheal tube and mechanically ventilated. For comparison of three treatment approaches, Barker and Adams (2002) looked at respiratory parameters, blood gases, and blood oxygenation. All three groups in the study received pre-oxygenation and endotracheal suctioning. In the second group positioning in left and right decubitus position was added to the treatment. Along with these techniques, the third group was administered six manual hyperinflation breaths before suctioning using the Mapleson C system. Paulus et al. (2011) compared patients who underwent manual hyperinflation every six hours and directly before extubation with a control group that only received manual hyperinflation when deemed necessary. This comparison was based on respiratory parameters and chest radiographs. In the third article, Berti et al. (2012) investigated the effect of two sessions of manual percussion and manual hyperinflation daily on APACHE II and Murray scores and on more functional parameters such as weaning success, 30-day mortality and length of ICU stay, by comparing it to standard positioning and suctioning.

Two of the included articles include a measure of blood oxygenation in their analysis. Barker and Adams (2002) found a significantly lower mixed venous oxygenation saturation for the second group in a between-group comparison, with no significant differences in within-group analyses. Paulus et al. (2011) found no between-group differences in PaO2/FiO2 values at any point. Based on these findings, it appears there is no large effect of manual hyperinflation on blood oxygenation. Furthermore, manual hyperinflation appears to improve the Murray score (Berti et al., 2012). This score is used to identify lung injury based on the chest roentgenogram score for alveolar consolidation, PaO2/FiO2, PEEP, and lung compliance, with lower values indicating a better score (Barker & Adams, 2002). Lastly, combining manual percussion and manual hyperinflation significantly reduced the duration of mechanical ventilation and the length of stay in the intensive care unit (Berti et al., 2012).

4.3.2 Inspiratory muscle training

A full overview of the articles in this group can be found in Table 7.

Of the eight articles that employ a form of inspiratory muscle training, five used threshold spirometry in their intervention groups. Cader et al. (2010) investigated the effect of threshold spirometry on maximal inspiratory pressure, the Tobin index, weaning time and duration of mechanical ventilation in elderly patients. This training, that was performed twice daily, was compared to usual care, which consisted of mobilization, chest compression, aspiration and positioning. In 2012 this protocol was repeated in the same patient population, with the inclusion of success of extubation as a new outcome measure (Cader et al., 2012). Postma et al. (2014) used an interval-based, high-intensity protocol for patients with spinal cord injury that were breathing independently to investigate long-term effects of threshold spirometry. For their analysis, they primarily looked at respiratory parameters, but also included more functional measures such as quality of life and perceived limitations and health. Savci et al. (2011) used similar outcome measures, but focused on short-term effects. They used lower intensities in a training that was performed twice daily in a CABG population. The most recent study to be included in this category, Bissett, Leditschke, Neeman, Boots, and Paratz (2016) focused almost entirely on more functional parameters such as time in hospital and in-hospital mortality, quality of life and fatigue. Their intervention group, which consisted of successfully weaned patients in the intensive care unit, performed high-intensity inspiratory muscle training five days per week for two weeks. All articles compared their intervention with usual care only, with Postma et al. (2014) including two educational sessions on respiratory function for both patient groups.

Two articles examined the effect of incentive spirometry after surgery. Sah, Akcil, Tunali, Vehid, and Dilmen (2017) compared changes in the respiratory parameters and blood gases of three groups, with one group performing incentive spirometry, the second group receiving CPAP, and the third group serving as controls that were administered oxygen via an oronasal mask only. These interventions were all executed in the first six hours after elective supratentorial craniotomy, with CPAP and incentive spirometry being performed five minutes per hour. The follow-up period lasted for 24 hours. In the second study, Gosselink et al. (2000) combined breathing exercises and postural drainage with hourly incentive spirometry in a group of patient who underwent elective thoracic surgery for either lung or esophagus resection. To investigate effects of incentive spirometry on respiratory parameters, the incidence of pulmonary complications and length of hospital stay measurements of this group were compared with those of a control group that received breathing exercises and postural drainage alone. Lastly, Tonella et al. (2017) compared electronic inspiratory muscle training to intermittent nebulization in a pilot study with patients who had been tracheostomized and were successfully weaned from the ventilator.

In general, threshold spirometry appears to have a positive effect regarding respiratory parameters. All studies found significant improvements in maximal inspiratory pressure. Savci et al. (2011) found a significant within-group difference for the experimental group. Two articles found a significant within-group improvement in both intervention and control groups (Bissett et al., 2016; Postma et al., 2014). There was also a significant between-group difference in four studies (Bissett et al., 2016; Cader et al.,

2012; Cader et al., 2010; Postma et al., 2014), however Postma et al. (2014) found that this difference was not retained into follow-up. Additionally, threshold spirometry appears to improve expiratory flow, maximal ventilation volume, and peak cough flow (Postma et al., 2014), and the Tobin index, which is calculated by dividing the respiratory rate by the tidal volume in liters (Cader et al., 2012; Cader et al., 2010). There appears to be no effect of threshold spirometry on forced vital capacity, FEV1, or maximal expiratory pressure, as Savci et al. (2011) and Postma et al. (2014) found no significant between-group differences for this parameter. Furthermore, significant improvements were found for weaning time (Cader et al., 2012; Cader et al., 2010); perceived limitations with breathing, talking, coughing, and clearing one's nose, perceived limitations in daily life, perceived health, and incidence of respiratory complications (Postma et al., 2014); time in ICU, functional exercise capacity, and anxiety and depression scales (Savci et al., 2011); and aspects of quality of life. (Bissett et al., 2016; Savci et al., 2011).

There is conflicting evidence on the effectiveness of incentive spirometry. Sah et al. (2017) found significant within-group differences in forced vital capacity (FVC), FEV1, Tiffenau index (FVC/FEV1), and PaCO2. However, Gosselink et al. (2000) found no significant differences in between- or within-group comparisons for any outcome measures, which also included FVC and FEV1.

Finally, Tonella et al. (2017) reported no significant effects of electronic inspiratory muscle training on the Tobin index or the duration of mechanical ventilation. A significant between-group difference was found for weaning time with the intervention group scoring significantly better than the control group. For maximal inspiratory pressure, a significant increase was found in the intervention group in the within-group comparisons.

4.3.3 Chest compression

There were three articles with a crossover design comparing suctioning combined with thoracic squeezing to suctioning alone. All three articles looked at short-term effects and included mechanically ventilated patients with respiratory, cardiac, ischemic, and other pathologies. Yousefnia-Darzi et al. (2016) focused on aspirated secretions with or without thoracic squeezing, therefore there was no follow-up period. Naue Wda et al. (2014) measured respiratory and hemodynamic parameters and amount of secretions one minute after the intervention or aspiration. Outcome measures in a study by Unoki et al. (2005) included sputum weight, blood gases, and respiratory parameters. Measurements were taken 25 minutes after suctioning.

Significantly more secretions were aspirated when performing suctioning combined with chest compressions than with suctioning alone (Naue Wda et al., 2014; Yousefnia-Darzi et al., 2016). Results of Unoki et al. (2005) did not back up this statement. When dividing patients into either a cerebral disease or an internal disease group and checking for potential effects of disease diagnosis on effect of chest compressions, Yousefnia-Darzi et al. (2016) found that between-group differences in sputum weight were only significant in the group of patients with cerebral diseases. Furthermore, Naue Wda et al. (2014) found significant between group differences in expiratory tidal volume and dynamic compliance in favor of the intervention group. This difference in dynamic compliance was again not found in the

study of Unoki et al. (2005), as they did not report any significant differences within or between groups. Lastly, heart rate was significantly raised one minute after chest compression, but this difference was found to be not clinically relevant.

4.6.4 Intrapulmonary Percussive Ventilation

The selection process of this review included three articles that administered intrapulmonary percussive ventilation (IPV) to their intervention groups (Antonaglia et al., 2006; Clini et al., 2006; Vargas et al., 2005). Antonaglia et al. (2006) compared IPV with standard physiotherapeutic treatment including chest clapping, mobilization and postural drainage in COPD patients who received noninvasive positive-pressure ventilation by helmet. Measurements were also compared to those of a third group that received facial mask noninvasive positive-pressure ventilation only. Respiratory and hemodynamic parameters were compared at baseline, immediately after the first physiotherapy session and at discharge. Patients in the study of Vargas et al. (2005) were also hospitalized because of an acute exacerbation of COPD, but were breathing room air at the time of the study. Their control group received standard treatment that did not include physiotherapy. Measurements were taken at baseline, at the end of the first IPV session, and once daily until discharge, and included mostly hemodynamic parameters and more functional outcome measures such as the need for noninvasive ventilation and length of hospital stay. Clini et al. (2006) used a broader patient population that received either IPV or chest physiotherapy. Respiratory parameters and blood gases were taken at baseline and after five, ten, and fifteen days and after one month.

From the data reported in the articles included in this review, IPV appears to have positive effects on respiratory and hemodynamic parameters, blood gases, and other outcome measures such as length of hospital stay. Patients receiving IPV treatment have significantly higher PaO2/FiO2 (Antonaglia et al., 2006) and MEP values (Antonaglia et al., 2006; Clini et al., 2006) than patients receiving other chest physiotherapy. Both significant between-group and within-group differences were found for blood gas values in favor of IPV, with arterial oxygen and carbon dioxide pressure being significantly higher and lower, respectively (Antonaglia et al., 2006; Clini et al., 2006; Vargas et al., 2005). However, Clini et al. (2006) did not find any significant differences for PaCO2. Furthermore, IPV shortens duration of ventilatory assistance and length of ICU and hospital stay (Antonaglia et al., 2006; Vargas et al., 2005) and lowers the incidence of COPD exacerbations, need for noninvasive ventilation and complications (Clini et al., 2006; Vargas et al., 2005), although the study of Antonaglia et al. (2006) does not report significant differences in the incidence of complications. Lastly, Antonaglia et al. (2006) report a significant rise in blood pH levels, while evidence of Vargas et al. (2005) and Clini et al. (2006) did not support this finding.

4.3.5 Multimodal chest physiotherapy

Three articles did not fit into any of the groups because they included several different techniques (Patman et al., 2009; Pattanshetty & Gaude, 2010; Templeton & Palazzo, 2007). All three articles followed patients until their discharge from the ICU or until they died and included outcome measures such as mortality, incidence of VAP and length of ICU stay. Templeton and Palazzo (2007) compared positioning, rib springing, manual hyperinflation, general mobilization, and suctioning with general mobilization and suctioning alone. They included a variety of pathologies, including head trauma, neurological problems, and respiratory insufficiency. Pattanshetty and Gaude (2010) investigated the effects of manual chest wall vibration and positioning by combining these treatments with manual hyperinflation and suctioning and comparing them to hyperinflation and suctioning alone. Patman et al. (2009) included patients with an acute brain injury in their study. All patients received the routine nursing care, with the treatment group receiving manual hyperinflation, suctioning, and positioning.

Templeton and Palazzo (2007) did not find any significant differences, with exception of a significant within-group difference in duration of mechanical ventilation, which was longer in the intervention group. There were no significant differences for any of the outcome measures in the study of Patman et al. (2009). In contrast, Pattanshetty and Gaude (2010) did report significant differences for several outcome measures. According to their results, the combination of chest wall vibrations and positioning lowers the mortality rate, leads to a higher chance of successful weaning, and lowers the incidence of ventilator-associated pneumonia significantly more than manual hyperinflation and endotracheal suction.

4.3.6 Chest wall vibrations

Of all included articles, only one investigated the use of chest wall vibrations in the ICU population. Kuyrukluyildiz et al. (2016) administered high frequency chest wall oscillation to their patients using a vest system. All patients received positioning, chest wall percussion, and aspiration. Measurements were taken at baseline and after 24, 48, and 72 hours.

According to their findings, treatment including chest wall oscillations leads to significant improvements in the lung collapse index, blood lactate levels, and blood oxygen pressure. Furthermore, the amount of aspirated sputum was significantly lower in the treatment group than in the control group after 72 hours (Kuyrukluyildiz et al., 2016).

4.3.7 Positive expiratory pressure (PEP) devices

Three articles employed a form of positive expiratory pressure training (Bellone et al., 2002; Chicayban et al., 2011; Urell et al., 2011). Chicayban et al. (2011) used a crossover design to examine the immediate effects of a flutter intervention on sputum production, respiratory mechanics, hemodynamics, and measures of gas exchange in mechanically ventilated patients that were diagnosed with pulmonary infection and hypersecretion. Patients in the study of Bellone et al. (2002) were hospitalized because of an acute COPD exacerbation and received noninvasive positive pressure ventilation. They performed assisted coughing, with the intervention group additionally completing three sessions of breathing at tidal volume with a PEP mask, each session lasting 30 to 40 minutes. Urell et al. (2011) looked at short-term effects different protocols using a PEP mouthpiece in patients recovering from a CABG or valve surgery. They compared patients who performed 30 deep breaths per hour with patients performing only ten deep breaths per hour by assessing differences in respiratory parameters and blood gases on the second postoperative day.

According to Chicayban et al. (2011), the Flutter intervention is beneficial in mechanically ventilated patients with pulmonary infection and hypersecretion. They found the investigated respiratory and hemodynamic parameters, with exception of resistance and PaCO2 and mean arterial pressure and heart rate, respectively, to be significantly improved in the flutter group. There were both between-group and within-group differences observed in most outcome measures, with only between-group differences in SpO2 and PetCO2. Bellone et al. (2002) report significant differences for sputum aspiration and weaning time, but failed to find an effect of the PEP mask on incidence of need for intubation or mortality. Lastly, evidence of Urell et al. (2011) indicates that a higher training volume generates significantly higher blood oxygen saturations and pressures, but does not influence changes in any of the investigated respiratory parameters or arterial carbon dioxide pressure. Moreover, length of ICU stay did not differ between the two groups.

5. Discussion

The aim of this review is to provide an overview of the available evidence on the use of respiratory physiotherapy in the Intensive Care Unit. There is conflicting evidence of the application of manual hyperinflation, multimodal chest physiotherapy and chest wall vibrations. Significant treatment effects in the ICU population were found after treatment with inspiratory muscle training, intrapulmonary percussive ventilation (IPV), positive expiratory pressure (PEP) devices and chest compression combined with suctioning.

5.1 Reflections on the quality of the included studies

Based on the executed quality assessment, the quality of the included studies ranged from moderate to good. In general, most studies scored poorly on blinding criteria. When investigating the use of respiratory physiotherapeutic therapy, it is rather difficult to blind therapists and patients as there is often no placebo treatment available for these techniques. However, it is possible to blind all assessors, which was either not reported or not performed by 15 of the included studies. Furthermore, many articles used small sample sizes. Although the average sample size was 30 patients per intervention group, calculating the average sample size per treatment group showed that the multimodal chest physiotherapy group had an average of 69,5 patients per group, substantially elevating the overall average. When leaving out this group there was an average of 25 patients per group, which is rather low. As these sample size averages vary considerably between groups, some caution has to be taken when drawing conclusions for the groups with smaller sample sizes. A last noteworthy point is that group six consisted of only one article (Kuyrukluyildiz et al., 2016) that did not use a concealed, randomized allocation. Very few articles of considerable quality were available on this topic. Because the intervention and the control group were comparable at baseline despite the allocation being based on the appropriateness of the treatment apparatus, the decision was made to include the article in this review.

5.2. Reflections on the findings in function of the research questions

5.2.1 Manual hyperinflation

Only three randomized controlled trials that investigated the effect of manual hyperinflation in the intensive care unit were included. Despite the fact that each article used different outcome measures, manual hyperinflation seems to have a positive effect for some outcome measures in mechanically ventilated patients. These differences made it difficult to come to a generalizable conclusion of the results. For example, to find significant changes in the blood oxygenation Barker and Adams (2002) used the mixed venous oxygen saturation while Paulus et al. (2011) looked at the PaO2/FiO2 values. Another aspect that made the comparison of results across the articles more difficult was the difference between demographic characteristics of the patient population. The included group of participants was no homogenous group that all had the same kind of pathology. The article of Berti et al. (2012) included patients with different pathologies while the patients of Barker and Adams (2002) had an acute lung injury, so an influence of pathology on the outcome measures cannot be ruled out.

5.2.2. Inspiratory muscle training

All five articles that used threshold spirometry in the intervention groups found a significant improvement in maximal inspiratory pressure. Only the articles of Cader et al. (2010) and Cader et al. (2012) found a significant difference in the Tobin index. Furthermore, no significant difference was found in the in-hospital mortality in the article of Bissett et al. (2016). However, the p-value for the between-group difference was 0.051. The power in this article was calculated for the outcome measure maximal inspiratory pressure, therefore the sample size might be too small to detect a significant difference in the in-hospital mortality. Due to the fact that the p-value is close to significance, a possible effect of inspiratory muscle training on this outcome measure cannot simply be ruled out.

Of the five articles, only Postma et al. (2014) and Savci et al. (2011) investigated the forced vital, forced expiratory volume in the first second (FEV1) and maximal expiratory pressure. Significant within-group differences were found in the article of Postma et al. (2014), but not in Savci et al. (2011). The differences between the articles can possibly be explained by the fact that the treatment and follow-up period in Savci et al. was only five postoperative days. Postma et al. (2014) had a treatment period of nine weeks with one year follow-up after the intervention.

Postma et al. (2014) did not found any significant difference in the quality of life (QoL) while both the articles Savci et al. (2011) and Bissett et al. (2016) found a significant difference. Each article used a different measurement instrument. The Nottingham Health Program was used in Savci et al. (2011), the SF-36 and the EQ-5D-3L in Bissett et al. (2016) and subscales of the SF-36 in Postma et al. (2014). The difference in significance between the articles can possibly be explained by the different measured aspects of the QoL, the sensitivity and specificity of the measurement instruments and the difference between patient populations. The patient populations investigated by Bissett et al. (2016) and had more acute pathologies than those investigated in Postma et al. (2014).

In the article of Tonella et al. (2017) electronic inspiratory muscle training was used in tracheostomized patients. The results of this article are in line with the others five articles which used threshold spirometry. The only exception was the Tobin index. In the article of Tonella et al. (2017), no significant difference was found in the Tobin index while Cader et al. (2010) and Cader et al. (2012) found a significant between- (2010) and within-group (2012) difference. The difference in results could be explained by the difference in patient populations. Cader et al. (2010) and Cader et al. (2012) included mechanically ventilated elderly while Tonella et al. (2017) included patients who were already weaned from ventilation.

Two articles investigated the effect of incentive spirometry. No significant improvements were found in the article of Gosselink et al. (2000), in contrast to Sah et al. (2017). The difference between the articles can possibly be explained by the treatment administered to the control group. The control group of Gosselink et al. (2000) received respiratory physiotherapy. This treatment included breathing exercises, postural drainage, endotracheal suctioning, forced expiration and coughing. The patients in the control group of Sah et al. (2017) were treated with CPAP for only five minutes per hour or administered extra oxygen via an oronasal. Another possible explanation for the difference in significance is the treatment duration. The patients of Sah et al. (2017) were treated until six hours after the operation, while Gosselink et al. (2000) treated their patients until they were discharged from the hospital.

However, the place of incentive spirometry within the group of inspiratory muscle training can be taken in doubt. The focus of a treatment with incentive spirometry is on facilitating a slow, sustained deep breath to increase the overall lung volume of the patients. The main objective is to prevent and treat atelectasis, not to strengthen the inspiratory muscles.

5.2.3. Chest compression

All three included articles had a short follow-up period, going from the moment suctioning took place as a part of the intervention to 25 minutes afterwards. Due to this short follow-up period, there is no clear evidence of the long-term effects of thoracic squeezing combined with suctioning.

The articles used a crossover design with a washout period of three to six hours. By choosing this design, the researchers already assumed before the start of the studies that there would not be long-term effects of the intervention. Otherwise, they would have chosen a longer washout period between the interventions.

There was an insufficient reporting of the data from the interventions and the included patient populations. Whether the patients were dependent on mechanical ventilation, Yousefnia-Darzi et al. (2016) did not report any demographic characteristics of their patients. Furthermore, Naue Wda et al. (2014) and Yousefnia-Darzi et al. (2016) didn't mention the exact duration of treatment in the intervention groups, which made the comparison of results across the articles difficult.

In the articles of Naue Wda et al. (2014) and Yousefnia-Darzi et al. (2016), a significant difference in aspirated secretions was found in the intervention group. Unoki et al. (2005) did not find a significant difference for this outcome measure. This difference in results can possibly be explained by the fact that the measurements of the aspirated secretions happened immediately after the intervention in the studies of Naue Wda et al. (2014) and Yousefnia-Darzi et al. (2016), while Unoki et al. (2005) measured this for the first time 25 minutes after the intervention. This could indicate that chest compression only has a short-term effect on the amount of aspirated secretions.

When Yousefnia-Darzi et al. (2016) assigned their patients to either a cerebral or an internal pathology group to investigate the sputum weight, they only found a significant between-group difference in the group with cerebral diseases. The other two articles also included patients with both cerebral and internal diseases, but did not investigate the results for these groups separately. This could cause them to miss significant treatment effects in both articles.

5.2.4. Intrapulmonary Percussive Ventilation

Three articles with similar patient populations were included in the Intrapulmonary Percussive Ventilation (IPV) group. The articles found significant treatment effects in the intervention groups treated with IPV for respiratory, hemodynamic and other outcome measures. A significant difference in the outcome measure $PaCO_2$ was found in the articles of Vargas et al. (2005) and Antonaglia et al. (2006) but not in Clini et al. (2006). This difference could possibly be explained by the difference in health status of the patient populations. The patients in the article of Clini et al. (2006) were independently breathing for at least 72 hours, while in the other studies, the patients were admitted to the ICU for an acute

exacerbation. It is known that an acute exacerbation leads to an increase of PaCO2, with a reduced pH as a result. However, other results were found in the article of Vargas et al. (2005). There was no significant difference found in the outcome measures pH and HCO3-. This may be explained by the fact that the patients of this article were in a healthier range with less extra room for improvement.
In the article of Antonaglia et al. (2006), there was no significant difference found for the incidence of complications, in contrast to the article of Clini et al. (2006). The intervention group of Clini et al. (2006) had a lower incidence of nosocomial pneumonia than the control group. The patient population of this article may have had more contact with external influences in comparison with the patients of Antonaglia et al. (2006), who underwent helmet noninvasive positive-pressure ventilation (NPPV). This helmet was used in both control and intervention groups and may have induced a sterile setting for the patients.

5.2.5. Multimodal chest physiotherapy

Significant between-group differences in the mortality rate were found in the article of Pattanshetty and Gaude (2010) while no significant difference for this outcome measure was found in the other two articles. The difference between the articles can possibly be explained by the fact that only the patients in the intervention group of Pattanshetty and Gaude (2010) were treated with chest wall vibrations. Templeton and Palazzo (2007) found a significant within-group difference in the duration of mechanical ventilation. No significant difference was found in Patman et al. (2009). The difference in this outcome measure may can be explained by the difference between included patient populations. Patman et al. (2009) only included patients with acquired brain injury who suffered ventilator-associated pneumonia. Templeton and Palazzo (2007) included a larger range of pathologies, including respiratory and cardiac insufficiency, head trauma, intra-cerebral hemorrhage, sepsis, and seizures. Another aspect that has to be taken into account for this outcome measure is that the article of Templeton and Palazzo (2007) didn't used a uniform intervention. The treatment within the intervention group varied from none to twice daily and several techniques were used based on the judgment of the therapists. Due to this variability within the intervention group, it is not possible to determine the exact effect of the intervention on the outcome measures.

5.2.6. Chest wall vibrations

Only one included article investigated the effect of chest wall vibrations. Beyond the fact that the sample size was small, there was a risk of a selection bias in the article of Kuyrukluyildiz et al. (2016). Patient allocation to the control or intervention group was based on the appropriateness of the used devices. The results of the article were poorly reported. No clear differentiation between within-group and between-group differences was made. Therefore, it was not possible to draw any conclusion about the long-term effects of chest wall oscillations due to the short follow-up period of 72 hours. Due to these limitations and the fact that only one randomized controlled trial was included, the results were not generalizable for the evidence of chest wall oscillations at other intensive care units across the world.

5.2.7. Positive expiratory pressure devices

The three included articles all used different expiratory devices. Chicayban et al. (2011) was the only article with mechanically ventilated patients. The Flutter Valve was connected to the exhalation port of the mechanical ventilator. Bellone et al. (2002) used a Positive Expiratory Pressure (PEP) mask while Urell et al. (2011) used a PEP device. The fact that every article used a different device made the comparison of results across the articles difficult.

Chicayban et al. (2011) found a significant treatment effect of the intervention with the Flutter Valve in mechanically ventilated patients. The respiratory and hemodynamic outcome measures significantly improved. The article used a crossover design. By choosing this design, the intervention was only performed once and the follow-up period was short. No results were reported for the outcome measures blood pressure and PaO2, which can create a reporting bias. Bellone et al. (2002) found a significant between group effect for the outcome measure aspired sputum weight. The treatment effect was maintained one hour after the intervention. The patients in this article underwent an acute COPD exacerbation. These exacerbations are usually accompanied with an increase of mucus secretions, which can possibly explain the higher weight of aspirated sputum.

The length of follow-up in the article of Urell et al. (2011) was short and ended at the second postoperative day. The patients were excluded from the article when they were too tired to obtain a valid lung function test. This can create an attribution bias.

5.3. Reflections on the strengths and weaknesses of the literature study

An extended literature search based on a search strategy which combined two components was used in this literature study. Respiratory physiotherapy consists of various forms at the intensive care unit. The extended search is a strength of the literature study so no important articles could be missed. The search was executed in January 2018 and repeated in April 2018. The new search resulted in only one additional relevant article (Tonella, 2017.). A limitation of the literature study is the fact that only two databanks were used (Web of Science and PubMed).

All included articles had a high level of evidence. Only randomized controlled trials, the golden standard of clinical trials, were included in this literature study. No articles of a lower level of evidence were included to keep the quality of the review as high as possible. It was found that for some topics, for example chest wall vibrations, few studies with this high level of evidence were available. It was difficult to draw a generalizable conclusion of results. This was a limitation of the review. The abstract and text screening was executed by two independent assessors. Afterwards, the articles that passed this screening were compared to each other. The quality assessments were done by the two assessors together, so critical input of both is presented. The broad variety of outcome measures in the different articles made a comparison across the articles difficult. Also, there wasn't a homogenous patient population across the articles. Both facts made it difficult to find a general answer to the research question.

5.4. Recommendations for further research

This review provides an overview of the respiratory physiotherapeutic techniques most used in the ICU and currently available evidence for their application. The included articles were divided into seven groups based on used intervention. Due to the fact that only randomized controlled trials were included, some groups consisted of only a few articles.

Based on the evidence found in this article, it is recommended to use inspiratory muscle training, intrapulmonary percussive ventilation, positive expiratory pressure devices and chest compression combined with suctioning in the clinical practice for both mechanically ventilated and independently breathing patients. The use of incentive spirometry is not recommend due to the conflicting evidence. A larger amount of randomized of controlled trials needs to be published to prove the evidence of the other techniques and answer the research question more correctly.

Several recommendations can be made to improve the future studies on respiratory physiotherapy. To reach a higher level of evidence and prevent a bias, more assessors of the study results in the randomized controlled trials need to blinded. A larger sample size should be included. Furthermore, the outcome measures of the included articles in this review differ a lot. This variation made it difficult to make a conclusion of the comparison across the articles. It is recommended that future articles, make use of a set of common outcome measures. A future review should use a more homogenous patient population. This can be done by making the selection criteria more precise. To make the results more generalizable, it is recommended to distinguish between patients who breathe independently and patients who require mechanical ventilation. A better checklist needs to be used for the quality assessment, so the possible presence of a bias can be detected in an earlier phase. This way, time spent on an additional analysis of the articles' strengths and weaknesses can be saved. The CONSORT checklist for randomized controlled trials is recommended.

6. Conclusion

Based on several randomized controlled trails, this literature study shows the significant treatment effects of inspiratory muscle training, intrapulmonary percussive ventilation, positive expiratory pressure devices and chest compression combined with suctioning in the patient population of the ICU, but further research is needed to draw a conclusion of the evidence of the other respiratory physiotherapeutic techniques.

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8. Appendices part I - overview of the literature

Table 1: Overview of the used search terms, combinations and obtained hits in PubMed and Web of Science

		Term PubMed	Term WoS	PubMed				Web of Science			
				Hits individual term	A	B	C	Hits individual term	A	B	C
		intensive care units[MeSH Terms]	intensive care units	71 512	71 512		71 512	176 228	176 228		176 228
		Intensive care units[Title/Abstract])		20 305	81 980		81 980				
	OR	respiratory care units[MeSH Terms]	respiratory care units	518	81 980		81 980	40 462	182 158		182 158
		respiratory care units[Title/Abstract]		20	81 991		81 991				
		ICU[Title/Abstract]	ICU	44 729	105 071		105 071	66 235	204 321		204 321
		Intensive care[Title/Abstract]	"Intensive care"	121 287	162 073		162 073	212 673	241 503		241 503
		physical therapy modalities[MeSH Terms]	physical therapy modalities	134 445		134 445	926	46 166		46 166	617
		Physical therapy modalities[Title/Abstract]		304		134 605	932				
		breathing exercises[MeSH Terms]	breathing NEAR/5 exercises	3 180		134 605	932	6 605		52 341	707
		Breathing exercises[Title/Abstract]		844		134 895	939				
		Respiratory physiotherapy[Title/Abstract]	respiratory NEAR/5 physiotherapy	283		135 056	964	627		52 740	769
		Respiratory physical therapy[Title/Abstract]	respiratory NEAR/5 "physical therapy"	50		135 081	968	236		52 884	778
		Respiratory rehabilitation[Title/Abstract]	respiratory NEAR/5 rehabilitation	355		135 338	981	1 281		53 968	855
AND		Intrapulmonary percussive ventilation[Title/Abstract]	"Intrapulmonary percussive ventilation"	65		135 386	990	125		54 063	868
		Incentive spirometry[Title/Abstract]	incentive spirometry	257		135 550	1 002	535		54 398	900
		Patient positioning[Title/Abstract]		2 329		137 861	1 054				
	OR	patient positioning[MeSH Terms]		5 086		142 402	1 275				
		Airway clearance[Title/Abstract]	airway clearance	707		142 936	1 301	6 788		60 903	1 046
		Manual lung inflation[Title/Abstract]	manual lung hyperinflation	7		142 943	1 303	124		60 977	1 073
		postural drainage[MeSH Terms]	postural drainage	351		143 072	1 312	791		61 440	1 102
		Postural drainage[Title/Abstract]		232		143 072	1 312				
		Chest wall vibration[Title/Abstract]	chest wall vibration	39		143 104	1 313	369		61 745	1 110
		Chest wall percussion[Title/Abstract]	chest wall percussion	10		143 108	1 313	90		61 785	1 111
		Inspiratory muscle training[Title/Abstract]	"inspiratory muscle" NEAR training	513		143 281	1 320	894		62 285	1 126
		chest wall oscillation[MeSH Terms]	chest wall oscillation	276		143 484	1 326	714		62 777	1 144
		Chest wall oscillation[Title/Abstract]		86		143 503	1 327				
		pediatrics[MeSH Terms]	pediatric	52 902	52 902	143 256	1 320	385 046	220 276	61 584	1 056
		pediatric[Title/Abstract]		221 504	221 504	141 832	1 266				
NOT		"child"[MeSH Terms]	child	1 760 221	139 687	131 762	1 204	3 292 399	199 051	54 874	978
		"infant"[MeSH Terms]	infant	1 059 765	119 603	129 664	1 001	1 426 157	175 202	54 199	903
		intensive care units, pediatric[MeSH Terms]	pediatric intensive care units	18 388	188 516	129 663	1 000	17 214	175 202	54 199	903
		intensive care units, neonatal[MeSH Terms]	neonatal intensive care units	12 343	188 516	129 663	1 000	29 565	171 284	54 195	899

Setting (OR) AND Interventions (OR)

A B

C

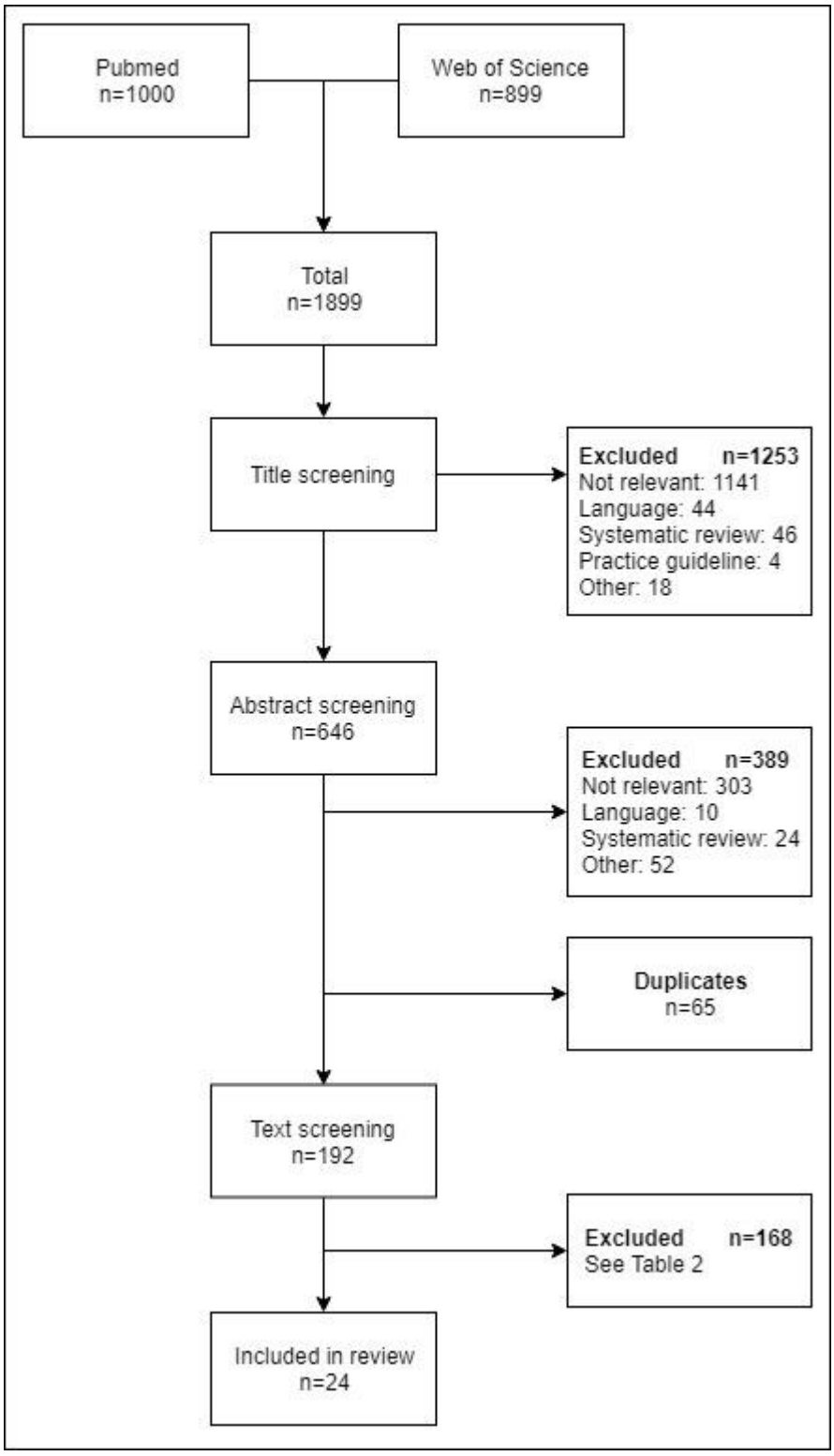


Fig. 1: Flowchart of study selection process

Table 2: Overview of the excluded articles and reason for exclusion

No RCT design	69	(al-Saady et al., 1995) (S. Berney, Denehy, & Pretto, 2004) (B. Bissett, Leditschke, & Green, 2012) (Blattner et al., 2017) (Borges et al., 2016) (Caruso et al., 2005) (A. A. Castro & E. F. Porto, 2015) (Cerqueira-Neto et al., 2010) (Cerqueira Neto et al., 2013) (Cordeiro de Souza et al., 2014) (Costa Fermiano, Cavenaghi, Correia, Camargo de Brito, & Ferreira, 2017) (A. T. Chang, Boots, Henderson, Paratz, & Hodges, 2005) (Chen et al., 2009) (Chuang, Chou, Lee, & Huang, 2017) (da Silva Fernandes et al., 2016) (Dimassi et al., 2011) (dos Santos et al., 2014) (Elay et al., 2015) (Elkins & Dentice, 2015) (Fehrenbach, Werner, Demirci, Zahn, & Grueneberg, 2016) (Franco de Godoy, Yokota, Muglia Araujo, & Pedreira de Freitas, 2011) (Genc, Ikiz, Guneri, & Gunerli, 2008) (Guimaraes et al., 2014) (Gundogdu et al., 2017) (Gungen et al., 2017) (C. Hodgson, Denehy, Ntoumenopoulos, Santamaria, & Carroll, 2000) (Carol Hodgson, Ntoumenopoulos, Dawson, & Paratz, 2007) (Inal-Ince, Savci, Topeli, & Arikan, 2004) (Jellema et al., 2000) (D. Johnson, Kelm, Thomson, Burbridge, & Mayers, 1996) (Jones, Thomas, & Paratz, 2009) (Kikukawa, Ogura, Harasawa, Suzuki, & Nakano, 2016) (Lamar, 2012) (Lee et al., 2011) (Leech, Bissett, Kot, & Ntoumenopoulos, 2015) (Leelarungrayub, Pinkaew, Wonglangka, Eungpinichpong, & Klaphajone, 2016) (Liu et al., 2014) (Maggiorelli et al., 2015) (Moreira, Teixeira, Savi, & Xavier, 2015) (Moss et al., 2016) (Nava, 1998) (Ntoumenopoulos, Gild, & Cooper, 1998) (Ntoumenopoulos, Presneill, McElholum, & Cade, 2002) (Ntoumenopoulos & Glickman, 2012) (Olper et al., 2017) (Pattanshetty & Gaude, 2011) (Paulus, Binnekade, Vermeulen, Vroom, & Schultz, 2010) (Preuss, Schmitt, Soares, Albuquerque, & Trevisan, 2015) (Rance, 2005) (Raoof et al., 1999) (Saad et al., 2014) (Saleem, Khan, Kabir, & Baig, 2017; Santos et al., 2010) (Senduran, Yurdalan, Karadibak, & Gunerli, 2010) (Elizabeth H. Skinner, 2016) (Singer, Vermaat, Hall, Latter, & Patel, 1994) (Smith, Gabrielli, Davenport, & Martin, 2014) (Sprague & Hopkins, 2003) (Suh, Heitkemper, & Smi, 2011) (van Aswegen et al., 2013) (Van der Touw, Mudaliar, & Nayyar, 1998) (Vargas & Hilbert, 2006) (Weindler & Kiefer, 2001) (Westerdahl et al., 2005) (Wong, 2000) (Yosef-Brauner, Adi, Ben Shahar, Yehezkel, & Carmeli, 2015) (Zencir & Eser, 2016) (Zeng, Zhang, Gong, & Chen, 2017) (Zeppos et al., 2007)
Review	11	(Alessandri, Pugliese, & Ranieri, 2018; Ciesla, 1996) (Fischer, Kaese, & Lebiedz, 2016) (Mohamed D. Hashem, Nelliot, & Needham, 2016) (M. D. Hashem, Parker, & Needham, 2016) (Kallet, 2013) (Lesage, Gravier, Medrinal, & Bonnevie, 2016) (Makhabah, Martino, & Ambrosino, 2013) (Nessizius, 2014) (Parker, Sricharoenchai, & Needham, 2013) (Sommers et al., 2015)

Did not have ICU setting	8	(Ali, Talwar, & Jain, 2014) (Gruther et al., 2017) (M. J. Johnson et al., 2015) (Manzano, Carvalho, Saraiva-Romanholo, & Vieira, 2008) (Nyland et al., 2016) (Vagvolgyi, Rozgonyi, Kerti, Vadasz, & Varga, 2017) (van Adrichem, Meulenbroek, Plukker, Groen, & van Weert, 2014) (Ventura Nepomuceno et al., 2017)
Other text type (e.g. letter, editorial)	6	(Annoni, Buttignol, & Pires Neto Rde, 2015) (B. M. Bissett, Leditschke, Paratz, & Boots, 2012) (A. A. M. Castro & E. F. Porto, 2015) (Copotoiu, Chis, & Copotoiu, 2014) (Ntoumenopoulos, 2007) (Spijkstra & van der Spoel, 2016)
Use of non-respiratory and/or non-physiotherapeutic techniques	43	(Bein, Metz, Eberl, Pfeifer, & Taeger, 1994) (S. Berney & Denehy, 2003) (Bolotova, Shul'zhenko, Sholin, Ezugbaya, & Porkhanov, 2016) (Burk & Grap, 2012) (A. T. Chang, Boots, Hodges, & Paratz, 2004) (M. Y. Chang, Chang, Huang, Lin, & Cheng, 2011) (Davis et al., 2001) (Dellamonica et al., 2013) (D. M. Dennis, Duncan, Pinder, Budgeon, & Jacob, 2016) (Dong et al., 2016) (Fujita et al., 2008) (Guner & Korkmaz, 2015) (Hale et al., 2012) (Hammon, Connors, & McCaffree, 1992) (C. L. Hodgson et al., 2016) (Hongrattana, Reungjui, & Jones, 2014) (Lemes, Zin, & Guimarães, 2009) (Karsten, Stueber, Voigt, Teschner, & Heinze, 2016) (Maffei et al., 2017) (Martinez et al., 2015) (McGrath, 2014) (Paternot, Repesse, & Vieillard-Baron, 2016) (Poelaert et al., 1991) (Porta et al., 2005) (Roche-Campo, Aguirre-Bermeo, & Mancebo, 2011) (Setten, Plotnikow, & Accoce, 2016) (Staudinger et al., 2010) (Sutyak, Wohltmann, & Larson, 2007) (Suzuki & Takasaki, 2014) (Taniguchi et al., 2015) (P. Thomas, Paratz, & Lipman, 2014) (P. J. Thomas, 2015) (K. Thomas et al., 2015) (Toccolini et al., 2015) (Toyama et al., 1997) (Traver, Tyler, Hudson, Sherrill, & Quan, 1995) (Umei et al., 2016) (Vianello et al., 2005) (Vitacca, Bianchi, Sarva, Paneroni, & Balbi, 2006) (J. Y. Wang, Chuang, Lin, Yu, & Yang, 2003) (J. Wang et al., 2017) (Wutzler et al., 2017) (Yang et al., 2010)
Does not answer the research question or does not correspond to PICO	13	(S. Berney & Denehy, 2002) (Blattner et al., 2017) (D. Dennis, Jacob, & Budgeon, 2012) (Hanlon et al., 2014) (Kelly & Georgiou, 2014) (Luedike et al., 2014) (Milgrom et al., 2004) (Naue et al., 2011) (Oliveira, Neto, & Aras Junior, 2017) (Ortiz et al., 2013) (Riedel, Richards, & Schibler, 2005) (Riffard, Buzenet, & Guerin, 2014) (Savian, Paratz, & Davies, 2005)
Not available in English or Dutch	2	(Plotnikov, Malakhov, Hayes, Grigoryev, & Barbarash, 2009) (Sandoval Moreno, Casas Quiroga, Wilches Luna, & Garcia, 2018)

Overview of available/used techniques without discussing effectiveness	15	(Schwabbauer, 2014) (van der Lee, Hill, & Patman, 2017) (Bhat, Chakravarthy, & Rao, 2014) (Rose, Adhikari, Poon, Leasa, & McKim, 2016) (Campbell, 2017) (Bonnevie et al., 2015) (Morar & van Aswegen, 2016) (Susan Berney, Haines, & Denehy, 2012) (Lottering & van Aswegen, 2016) (Baidya, Acharya, & Coppieters, 2016) (Yeole, Chand, Nandi, Gawali, & Adkitte, 2015) (Tadyanemhandu & Manie, 2015) (Ntoumenopoulos et al., 2017) (Al Mohammedali, O'Dwyer, & Broderick, 2016) (E. H. Skinner et al., 2015)
Insufficient quality	1	(Cirak, Karahan, Yelvar, Erden, & Demirkilic, 2015)

Table 3: Critical assessment of the included RCT's (n=24) via the PEDro checklist

	1. Eligibility criteria	2. Random allocation of subjects	3. Concealed allocation	4. Comparable groups at start	5. Blinding of all subjects	6. Blinding of all therapists	7. Blinding of assessors	8. Outcome measures for more than 85% of subjects	9. All subjects analysed in group as allocated	10. Results of between-group statistical comparisons for at least one key outcome	11. Both point measures and measures of variability for at least one key outcome	Score (/11)
Manual hyperinflation												
Barker, Adams, 2002	Y	Y	Y	Y	N	N	?	Y	Y	Y	Y	8
Berti, Tonon et al., 2012	Y	Y	Y	Y	N	N	?	N	Y	Y	Y	7
Paulus, Veelo et al., 2011	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9
Inspiratory muscle training												
Sah, Ackil et al., 2017	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9
Cader, Vale et al., 2012	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	7
Gosselink, Schrever et al., 2000	N	Y	?	N	N	N	N	Y	Y	Y	Y	5
Cader, Vale et al., 2010	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	7
Bisset, Leditschke et al., 2016	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	8
Postma, Haisma et al., 2014	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9
Savci, Degirmenci et al., 2011	Y	Y	Y	Y	N	N	?	Y	Y	Y	Y	8
Tonella, Ratti et al., 2017	Y	Y	Y	Y	N	N	?	Y	Y	Y	Y	8
Chest compression												
Naue, Forgiarini Junior et al., 2013	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9
Takeshi, Kawaski et al., 2005	N	Y	Y	Y	N	N	?	Y	Y	Y	Y	7
Yousefnia-Darzi, Hasarvi et al., 2016	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9

Intrapulmonary Percussive Ventilation												
Antonaglia, Lucangelo et al., 2006	Y	Y	Y	Y	N	N	?	Y	Y	Y	Y	8
Vargas, Bui et al., 2005	Y	Y	Y	Y	N	N	?	Y	Y	Y	Y	8
Clini, Antoni et al., 2006	Y	Y	Y	Y	N	Y	?	Y	Y	Y	Y	9
Multimodal chest physiotherapy												
Templeton, Palazzo, 2007	Y	Y	Y	Y	N	N	?	Y	Y	Y	Y	8
Pattanshetty, Gaude, 2010	Y	Y	Y	Y	N	N	?	Y	Y	Y	Y	8
Patman, Jenkins et al., 2008	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	10
Chest wall vibrations												
Kuyrukluyildiz, Binici et al., 2016	Y	N	N	Y	N	N	Y	Y	Y	Y	Y	7
Positive expiratory pressure (PEP) devices												
Luciano, Walter et al., 2011	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	8
Bellone, Spagnolatti et al., 2002	Y	Y	Y	Y	N	N	?	Y	Y	Y	Y	8
Urell, Emtner et al., 2010	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9

PEDro Checklist for RCT's

1. Were eligibility criteria specified?
2. Were subjects randomly allocated to groups?
3. Was allocation concealed?
4. At baseline, were the groups similar regarding the most important prognostic factors?
5. Was there blinding of all subjects?
6. Was there blinding of all therapists who administered the therapy?
7. Was there blinding of all assessors who measured at least one key outcome?
8. Were measures of at least one key outcome obtained for more than 85% of the subjects initially allocated to groups?
9. Did all subjects for whom outcome measures where available receive the treatment or control condition as allocated?
10. Are the results of between-group statistical comparisons reported for at least one key outcome?
11. Does the study provide both point measures and measures of variability for at least one key outcome?

Table 4: Strengths-weaknesses analysis of the included RCT's

	Strengths	Limitations
Group 1: Manual hyperinflation		
Barker and Adams (2002)	− No selective loss to follow-up: only 1 drop out due to an a systolic cardiac arrest − Clearly defined inclusion and exclusion criteria and treatment procedures − No risk for performance bias, same two therapists for every treatment: one to perform manual hyperinflation, one to perform the suction − Results and measures of variability reported for every outcome measure, including within-group and between-group comparisons	− Small sample size, total n = 18 (group 1: n=5, group 2: n=5, group 3: n=7) − Blinding methods not described − Selection bias: no equal baseline characteristics: patients not matched at randomization, group 2 higher lung injury scores on McMurray scale − Low external validity
Berti et al. (2012)	− Homogeneous groups regarding most of the baseline characteristics − Clearly defined inclusion and exclusion criteria and treatment procedures − Follow-up: 30 days after ICU discharge − No risk for selection or performance bias − All patients analyzed in randomized group − Reasons for withdrawal reported − Results and point measures reported for every outcome measure, including within-group and between-group comparisons	− Small size: n = 24 in exp. group, n = 25 in con. group − Loss to follow-up: n = 6 in exp. group, n = 8 in con. group − No blinding of patients, physiotherapists or assessors
Paulus et al. (2011)	− Large sample size: n = 93 (n = 46 in exp. group, n = 47 in con. group) − No loss to follow-up − Cleary defined time line depicting trial investigations, interventions and outcome measures − No difference in demographic baseline characteristics between participants − Clearly defined inclusion and exclusion criteria and treatment procedures − Graphs and/or tables provides clear representation of results − Results and point measures reported for every outcome measure, including within-group and between-group comparisons − Blinding of assessors	− No blinding of patients or physiotherapists − Bedside functional residual capacity was used to measure lung ventilation while there are more suited parameters to represent this outcome measure (Paulus et al., 2011) − Parameters of treatment that determine efficacy of manual hyperinflation were not recorded. (Paulus et al., 2011) − Low external validity: single-centre trial, generalization to other hospitals with different methods is limited.
Group 2: Inspiratory muscle training		
Sah et al. (2017)	− Large sample size: n = 79 − Clear explanation of the dropout rate of patients − Extended description of the intervention and results − Sample size calculations based on other study	− Underpowered for the secondary outcomes − Follow-up only lasted for 24h postoperatively − No imaging techniques used to assess lungs
Cader et al. (2012)	− Potential for placebo and Hawthorne effects reduced because of the fact that relatives signed the informed consent − Extended description of the intervention − Cleary defined inclusion and exclusion criteria	− Lack of blinding of patients, physiotherapists or assessors − 198 patients eligible but many not included because of mortality − Small sample size: n = 20 − Loss to follow-up because of high dropout rate: 8 of the 20 patients − Results with high sensitivity and low specificity for outcome measures − Different use of cut-off values

Gosselink et al. (2000)	− Large sample size for main parameters: n = 67 − Recalculation of the power − Clearly defined limitations of the study − Blinded observer for one parameter	− Different definitions of parameters used by literature − Selection bias: patient characteristics may have influenced the outcome − Intervention data was not quantified − No clearly defined inclusion and exclusion criteria − No clear description of intervention
Cader et al. (2010)	− Clear description of the design and flow of participants through the trial − Informed consent signed by the relatives − Clear figures − Clear description of intervention and outcome measures − Clear defined inclusion and exclusion criteria − No difference in demographic baseline characteristics between participants	− High dropout rate → small sample size − Lack of blinding of patients, physiotherapists or assessors
Bissett et al. (2016)	− Clear figure to describe flow of participants − Graphs and/or tables provide clear representation of results − Blinding of assessors − Cleary defined intervention and outcome measures − Cleary defined inclusion and exclusion criteria	− Possible learning effect − Loss to follow-up: high dropout rate (n = 6 in exp. group, n = 6 in control group) − Lack of follow-up of primary outcomes − Ceiling effect for two participants because of characteristics of the device → participants probably had higher values but these were not measured by the device
Postma et al. (2014)	− Long follow-up period: 1 year after inpatient rehabilitation − Clearly defined inclusion and exclusion criteria and treatment procedures − Graphs and/or tables provides clear view of the results − Flowchart of the participants in the study − No difference in demographic baseline characteristics between participants	− Selection bias: uneven distribution of people with premorbid respiratory diseases between groups, all were allocated to control group − Loss to follow-up: relatively large amount of drop outs one year after inpatient rehabilitation caused a loss of power (n = 6 in exp. group, n = 6 in con. group) → long term effects not clear − Used a subjective measuring instrument: questionnaire for the evaluation of respiratory function, limitations in daily life and respiratory complications → may not be valid or not sensitive enough to detect differences between groups
Savci et al. (2011)	− Clearly defined inclusion and exclusion criteria and treatment procedures − No difference in demographic baseline characteristics between participants − Results include within-group and between-group comparisons − Graphs and/or tables provide clear overview of the results − Flowchart of the participants in the study	− Population not specifically ICU bound, only one parameter ICU related (length of ICU stay) − Blinding methods not described − Possible performance bias: pre-operative inspiratory muscle training may affect results − Small sample size: n = 43 (n = 22 in exp. group, n = 21 in con. group) − Long term effects of intervention (inspiratory muscle training) not monitored − Used a subjective, generic measuring instrument: questionnaire for the evaluation quality of life
Tonella et al. (2017)	− Clearly defined inclusion and exclusion criteria and treatment procedures − Flowchart of the participants in the study − No difference in demographic baseline characteristics between participants − Treatment procedures of experimental group were supported by findings of other studies − Results and point measures reported for every outcome measure, including within-group and between-group comparisons	− Small sample size: n = 21 (n = 10 in exp. group, n = 11 in con. group) − Pilot RCT

Group 3: Chest compression		
Naue Wda et al. (2014)	− Assessor was blinded − Randomised allocation	− No blinding of patients or therapists − Only limited demographics reported
Unoki et al. (2005)	− Randomised allocation	− No blinding of therapist − Exclusion criteria not clearly reported − Of 144 eligible patients, only 31 were included
Yousefnia-Darzi et al. (2016)	− Assessors were blinded − Clear description of used intervention	− There was a time span of only three hours between administering of the intervention and the control intervention in this study with cross-over design − The intervention was performed only once − Although the aim of the study was to assess the effect on secretion removal, only sputum weight was used as outcome measure for this variable.
Group 4: Intrapulmonary percussive ventilation		
Antonaglia et al. (2006)	− Inclusion and exclusion criteria clearly reported − Group allocation was randomised and blinded	− Small sample (n=20 per group)
Vargas et al. (2005)	− Randomised group allocation − Groups were comparable at baseline	− Small sample (n=33 in total) − No blinding of patients or therapists
Clini et al. (2006)	− Therapists were blinded − Sample size calculation: n=22 for each group with power of 90% to detect a difference of 30 points in PaO_2/FiO_2 − All results reported.	− No placebo intervention
Group 5: Multimodal chest physiotherapy		
Templeton and Palazzo (2007)	− Groups were comparable at baseline − Large sample size (n=180) − Medical and nursing staff were blinded to allocation − Power analysis: 76 patients in each group for power=80%	− No uniform intervention: treatment within intervention group varied from none to twice daily and there were several used techniques based on judgement of the therapist. − Heterogenous group − Therapists providing treatment were not blinded
Pattanshetty and Gaude (2010)	− Groups were comparable at baseline − Clearly described intervention	− No blinding of therapist or patients
Patman et al. (2009)	− Power calculated: n=17 per group, power=80% and alpha=0,05 − Randomised allocation for both parts of the study − Tester was blinded − Clearly described intervention	− Groups were not comparable for gender and BMI − Chance of selective loss-to-follow-up
Group 6: Chest wall vibrations		
Kuyrukluyildiz et al. (2016)	− Groups were comparable at baseline − Clearly described intervention − Sample size estimation conducted: n=30 to detect clinically relevant reduction of pulmonary secretion with power = 0.91 and alpha = 5%	− Small sample size (n=30) − Patient allocation based on appropriateness of device: risk of selection bias − Results are poorly reported: the study does not differentiate between between-group and within-group differences

Group 7: Positive expiratory pressure devices		
Bellone et al. (2002)	− Clear description of intervention − Randomised allocation − Decision to wean taken by blinded physician to prevent bias	− No placebo treatment − Blinding of patients and therapist not possible − Small sample size (n=27)
Chicayban et al. (2011)	− Cleary defined inclusion and exclusion criteria − No performance bias: not biased by different sizes of endotracheal tubes because of the crossover trial − Crossover trial − Treatment procedure is clearly explained with the use of a figure − Table with the description of the study variables − Graphs and/or tables provides clear representation of results	− Small sample size: n = 10 − Lack of blinding of patients, physiotherapists or assessors − Power calculation done but not met in the study − Absence of measurements after 30 minutes post intervention − Outcome parameters such as length of stay, duration of mechanical ventilation and mortality were not studied.
Urell et al. (2011)	− Groups were comparable at baseline − Large sample (n=107) − Used techniques clearly documented − Power calculated: n=63 for power of 80% to detect a difference of 0,5 kPa in PaO_2	− Patients did exercises independently, no control by therapists − Therapists who performed testing are reported to be blinded, however they also gave the instructions of the intervention or control intervention. − Patients were excluded when too tired to obtain a valid lung function test. This might create an attrition bias.

Table 5: List of the used abbreviations in Table 6

Abbreviation	Full term
APACHE II	Acute Physiology and Chronic Health Evaluation II
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CCI	Charlson Comorbidity Index
COPD	Chronic Obstructive Pulmonary Disease
CPIS Score	Clinical Pulmonary Infection Score
EIMT	Electronic Inspiratory Muscle Training
ES	Esophageal surgery
ETI	Endotracheal Intubation
FEV1	Forced Expiratory Volume in 1 second
FiO2	Fractional Inspired Oxygen Concentration
FVC	Forced Vital Capacity
HADS	Hospital Anxiety and Depression Scale
HR	Heart Rate
IC	Inspiratory Capacity
I/E	Inspiration-to-expiration ratio
I.i.a.	Included in analysis
IPV	Intrapulmonary Percussive Ventilation
IMT	Inspiratory Muscle Training
INP	Intermittent Nebulization Program
IS	Incentive Spirometry
LS	Lung Surgery
MAP	Mean Arterial Pressure
MD	Mean Difference
MEP	Maximal Expiratory Pressure
MIP	Maximal Inspiratory Pressure
MV	Mechanical Ventilation
NaCl	Natrium Chloride

NIPPV	Noninvasive Positive Pressure Ventilation
NIV	Noninvasive Ventilation
PaCO2	Arterial Carbon Dioxide Pressure
PaO2	Arterial Oxygen Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PEEP	Positive End Expiratory Pressure
PEP	Positive Expiratory Pressure
QoL	Quality of Life
RR	Respiratory Rate
RSBI	Rapid Shallow Breathing Index
SaO2	Oxygen Saturation
SAPS II	Simplified Acute Physiologic Score II
SD	Standard Deviation
SF-36	36-Item Short Form Health Survey
SOFA	Sequential Organ Failure Assessment
SvO2	Mixed Venous Oxygenation Saturation
VAP	Ventilator-Associated Pneumonia
VC	Vital Capacity
Vt	Tidal volume
Yrs	Years
6MWT	6 Minute Walk Test

Table 6: Data extraction of the included RCT's

Group 1: Manual hyperinflation					
Study	*Design*	*Participants*	*Intervention*	*Outcome measures*	*Results*
Barker, Adams, 2002	RCT	Inclusion criteria: − Intubated via endotracheal tube due to acute lung injury, ventilated mechanically on pressure support ventilation − Murray score 0-2.5 − Adequately sedated − Hemodynamically stable (MAP >60 mmHg, no acute cardiac arrhythmias) − Has intra-arterial catheter and pulmonary artery catheter Exp 1: n = 5 Age (yr) = 73 (SD ± 2.6) Days in study = 2.8 (SD ± 2.4) Exp 2: n = 5 Age (yr) = 70 (SD ± 7.4) Days in study = 4.4 (SD ± 1.1) Exp 3: n = 7 Age (yr) = 70 (SD ± 16.3) Days in study = 4.1 (SD ± 4.5)	Exp. 1: − Positioned in supine position (30° head-up) − Pre-oxygenation and endotracheal suction Exp. 2: − Positioned in both left and right lateral decubitus positions (0° elevation of the head) − Pre-oxygenation and endotracheal suction Exp. 3: − Positioned in both left and right lateral decubitus positions (0° elevation of the head) − 6 manual hyperinflation breaths before suctioning − Endotracheal suctioning	− Arterial blood gases − FiO2 − Vt − Peak airway pressure − PEEP − HR − BP − PCWP − SvO2 Measurements before treatment and at 10, 30 and 60 minutes after treatment.	SvO2: − No significantly change over time (p = 0.106) − Significant difference between groups (p = 0.03) with a lower SvO2 in exp 2 PaCO2: − Significant difference over time (p = 0.026): increases at 10-min post-treatment, return to baseline at 60-min post-treatment PaO2/FiO2 + PCWP: − No significant difference in any group Dynamic compliance: − Significant difference over time (p = 0.019), decreases at 10-min post-treatment HR + BP: − Statistically significant (HR p = 0.012, BP p = 0.002)), but no clinically significant differences over time
Berti, Tonon et al., 2012	RCT	Inclusion criteria: − Intubated via endotracheal tube − Mechanically ventilated for 24-72 h Exclusion criteria: − Age <18 yrs − Length of ICU/ER stay ≤24 hrs − Referral to another ICU − PEEP > 8 cmH_2O − Severe asthma − ARDS − Invasive bronchoscopy procedure − (History of) pneumothorax − Chest trauma − Brain swelling − (Potential to develop pathologically) raised intracranial pressure − Unstable cardiovascular status on inotropic support − Obesity − Spinal cord injury − Do-not-resuscitate status Exp: n = 16 Age (yr) = 58.06 (SD ± 13.81) APACHE II score = 15.81 (SD ± 4.29) Murray score = 1.04 (SD ± 0.44) Con: n = 19 Age (yr) = 55.42 (SD ± 16.99) APACHE II score = 17.21 (SD ± 7.47) Murray score = 1.04 (SD ± 0.48)	Exp.: − Manual percussion on chest wall in side lying position (10 min, 2x/day) − Manual hyperinflation (MH) with expiratory rib cage compression (ERCC) (2x/day) followed by endotracheal suctioning − Standard nursing care: positioning (every 2h) + pre-oxygenation via manual resuscitation bag and endotracheal suctioning (4x/day) Con.: − Standard nursing care: positioning (every 2h) + pre-oxygenation via manual resuscitation bag and endotracheal suctioning (6x/day)	Primary: − ICU discharge − Weaning success Secondary: − 30-day mortality − Murray-score − APACHE II − Charlson comorbidity index (CCI) − Daily measurements	Duration of MV: − Shorter in exp. group : day 2 37.5% weaned − Significant differences between groups on days 2 and 3 (p < 0.01 for both) and on days 4 and 5 (p < 0.05 for both) Length of ICU stay: − Shorter in exp. group: from day 3, 25% of exp. discharged (p < 0.05) → proportion increased to 31% on day 4 and 5 (p < 0.01) APACHE II: − No effect of exp. on scores. Murray: − Scores were lower on day 5 than on day 1 in both groups − Scores on day 5 were significantly lower in the exp. group than in the con. group (p < 0.01) 30-day mortality: − No significant difference between groups

Paulus, Veelo et al., 2011	RCT	Inclusion criteria: − Patients after elective coronary artery bypass graft and/or valve surgery Exclusion criteria: − Previous lung surgery − Moderate to severe COPD: FEV1 <80%pred en FEV1/FVC < 0.7 − Repeated cardiac surgery within 48 hours after index surgery − Requirement of prolonged post-operative mechanical ventilation (>36 hours) Exp. n=50, i.i.a. 47 Age (yr) = 65 (SD ± 10.2) FEV1,% = 95 (SD ± 14) FVC, % = 101 (SD ± 14) Control n=50, i.i.a. 46 Age (yr) = 60.3 (SD ± 13.5) FEV1,% = 99 (SD ± 16) FVC, % = 101 (SD ± 15)	Exp.: − MH manoeuvre within 30 min. after connection to ICU-ventilator, repeated every 6 hours and directly before tracheal extubation − Additional MH manoeuvre in case of ○ Perceptible sputum which could not be removed from the larger airways with endotracheal suctioning ○ SpO2 < 95% − Standard procedures Con.: − MH manoeuvre in case of ○ Perceptible sputum which could not be removed from the larger airways with endotracheal. suctioning ○ SpO2 < 95% − Standard procedures	Primary: − FRC change 1,3, 5 days after tracheal extubation Secondary: − SpO2 (1) First 5 days after tracheal extubation − atelectasis (2) − pulmonary infiltrate (2) − extra-vascular lung fluid (2) − Pleural fluid (2) − pneumothorax (2) (1) First 5 days after tracheal extubation (2) As evaluated on chest radiographs pre-operative and on the third post-op. day.	Changes in FRC: − FRC sign. reduced after cardiac surgery in both groups (P<0.001) − FRC decreased more in con. group on first post-op. day than in exp. group (400 ml diff., P=0.002) − Lower absolute reduction FRC at day 3 in exp. group (306 ml diff., P=0.04) − Difference in decrease FRC between groups no longer significant at day 5 Oxygenation (PaO2/FiO2): − No significant differences between groups at any point Chest radiographs: − At day 3 more patients in con. group with atelectasis, but no difference in atelectasis score between groups − No significant differences between groups
Group 2: Inspiratory muscle training					
Sah et al. (2017)	RCT	Inclusion criteria: − ASA I-II patients − 18-70 years − Scheduled for elective supratentorial craniotomy Exclusion criteria: − Neurological disorders hindering communication − Obstructive/restrictive lung disease − Heart failure − Raised intracranial pressure − Lower cranial nerve palsy − Smoking − Drug/alcohol addiction − Dementia − Patients still intubated/unconscious at the end of the study Group IS: n = 20 Age (yrs): 37.85 (SD ± 12.06) Group CPAP: n = 20 Age (yrs): 38.90 (SD ± 12.80) Group Control: n = 20 Age (yrs): 35.50 (SD ± 14.46)	Group IS: − Incentive spirometry 5x in 1 min 5 min/hour during first 6 hrs post-op Group CPAP: − CPAP, 10 cmH_20 pressure, 0.4 FiO_2 5 min/hour during first 6 hrs post-op Group Control: O2 with oronasal mask during first 6 hrs post-op	Primary outcome measures: − FVC Secondary outcome measures: − FEV1 − FEV/FVC − [$HCO3^-$] − PaO_2 − $PaCO_2$ − Base excess − PaO_2/FiO_2 Measurements before induction anaesthesia (baseline), 30 mins after surgery, 6 h and 24 h after surgery	Between groups: − FEV1 sign. lower at 24 h in control icw IS Within groups: − All groups − FVC sign. reduced at 30 min p-o icw baseline ○ FVC sign. increased at 24 h p-o icw 30 min ○ FEV1 sign. reduced at 30 min icw baseline − IS ○ FEV1 sign. increased at 24 h icw 30 min ○ FEV1/FVC: sign. difference* − CPAP ○ FEV1 sign. increased at 24 h icw 30 min ○ [$HCO3^-$]: sign. difference* ○ Base excess: sign. difference* − Control ○ $PaCO_2$: sign. difference* ○ [$HCO3^-$]: sign. difference* * But not clinically important
Cader et al. (2012)	RCT	Inclusion criteria: − Intubated elderly patients who required mechanical ventilation for at least 48h due to acute respiratory failure − Maximum inspiratory pressure cut off point: -20 cm H_2O − Tobin index cut off point: 100 ipm/L Exp: n = 14 Age (yr) = 82 (SD ± 4) APACHE II score = 19 (SD ± 8) Con: n = 14 Age (yr) = 82 (SD ± 4) APACHE II score = 19 (SD ± 8)	Exp.: − Threshold device at 30% MIP − Pressure increased daily by 10% of initial MIP − 5 min, 2x/day, 7 days/week − From beginning of mechanical ventilation weaning until extubation − Supplemental oxygen as needed − Stopped if adverse signs − Conventional physiotherapy (same as con. group) Con.: conventional physiotherapy − Reduction in support pressure to 8cm H_2O, no specific training for respiratory musculature − Passive-assisted tot active-assisted mobilization − Chest compression − Decompression traction chest − Aspiration of endotracheal tube − Positioning	− MIP − Tobin index (rate of breath/tidal volume in litters) − Extubation success − Weaning time	MIP: − Significant increase (p = 0.001: 95% CI 4.67 - 10.19) in exp. group compared to con. Group Tobin index: − Significant increase in con. group (p = 0.002: 95% CI -4.47 to -24.44) − Significant reduction in exp. group post-treatment (p = 0.001: 95% CI -26.33 to -6.05) Extubation success: − No significant difference between groups (p = 0.20) Weaning times: − Shorter in exp. group (3.64 ± 1.50 days) compared to con. group (5.36 ± 1.87 days)

Gosselink et al. (2000)	RCT	Inclusion criteria: − Patients who underwent elective thoracic surgery for lung (n = 40) or oesophagus resection (n = 27) − Ability to perform IS adequately and to follow and understand preoperative instructions Exp: n = 35 (LS = 20, ES = 15) Age (yr) = 61 (SD ± 14) Weight = 71 (SD ± 13) * FEV_1 = 87 (SD ± 25) * Con: n = 33 (LS = 20, ES = 12) Age (yr) = 58 (SD ± 13) Weight = 79 (SD ± 15) * FEV_1 = 99 (SD ± 17) * * $p < 0.05$: significant difference between groups	Exp.: physiotherapy + incentive spirometry − IS: every hour 2 x 5-10 maximal inspiratory manoeuvres with volume feedback IS − Followed by breath holding, forced expiration and coughing − Postural drainage − Endotracheal suctioning Con.: physiotherapy alone − Breathing exercise: every hour 2 x 5-10 maximal inspiratory manoeuvres − Followed by breath holding, forced expiration and coughing − Postural drainage − Endotracheal suctioning	− Lung function o FEV1 o FVC o MIP o MEP − Body temperature − Chest radiograph o Atelectasis score − Pulmonary complication score o White blood cell count − Number of hospital and ICU days Spirometry: pre-operatively and post-operatively every other day Body temperature: daily Other measurements: as frequently as judged relevant by the pulmonary physician	No significant difference in outcome measures between exp. and con. group
Cader et al. (2010)	RCT	Inclusion criteria: − Intubated via endotracheal tube due to acute respiratory failure − Mechanically ventilated in controlled mode for at least 48h − Aged at least 70 yrs − MIP < 20 cm H_2O Exclusion criteria: − Condition that could compromise weaning − Condition that could prevent adequate performance of inspiratory muscle training − Tracheostomy before commencement of weaning − Major neurological co-morbidity − Morbid obesity − Use of medication that could cause a disorder of attention Exp: n = 21 (9 male) Age (yr) = 83 (SD ± 3) APACHE II = 20 (SD ± 6) Con: n = 20 (10 male) Age (yr) = 82 (SD ± 7) APACHE II = 20 (SD ± 7)	Exp.: − Threshold device at 30% MIP in supine 45° − Pressure increased by 10% of initial MIP daily − 5 min, 2x/day, 7 days/week throughout weaning period − Supplemental oxygen as needed − Stopped if adverse signs − Usual care Con.: − No training of respiratory muscles − Usual care: o Passive to active-assisted mobilisation o Chest compression with quick release at end-expiration o Aspiration of endotracheal tube o Positioning	Primary: − MIP Secondary: − Tobin index − Weaning time − Weaning duration − Duration of MV − Measurements daily before any physiotherapy or training	MIP: − Increased significantly more in exp. group than con. group (MD 7.6 cmH_2O, 95% CI 5.8 to 9.4) Tobin index: − Increased in both groups over weaning period → Significantly less increase by the inspiratory muscle training (exp. group) (MD 8.3 br/min/L, 95% CI 2.9 to 13.7) Weaning duration: − Significantly shorter in exp. group → effect of inspiratory muscle training: weaning period reduced by 1.7 days (95% CI 0.4 to 3.0) Duration of controlled MV: − No significant different between groups
Bissett et al. (2016)	RCT	Inclusion criteria: − Mechanically ventilated ≥7 days − Successfully weaned from mechanical ventilation (>48 hours) − Alert or able to participate with training Exp: n = 34 Age (yrs): 59 (SD ± 16) APACHE II score: 21.1 (SD ± 7.8) Con: n = 36 Age (yrs): 59 (SD ± 13) APACHE II score: 22.9 (SD ± 8.3)	Exp.: − Same usual care as con. Group − IMT at highest tolerable intensity of MIP − IMT at highest tolerable intensity of MIP for 6 breaths -> 5 x 6 breaths,< 1 min rest between sets − Pressure increased daily − 1x/day, 5 days/week, for 2 weeks Con.: usual care − Assisted mobilisation − Secretion clearance treatments: → PEP techniques − Deep breathing exercises (without resistance device) − Upper and lower limb exercises	Primary: − Inspiratory muscle strength (MIP) − Fatigue resistance index (FRI) Secondary: − Dyspnoea (Modified Borg scale) − Physical function (ACIF) − Quality of life (SF-36 + EQ-5D-3L) − Post-intensive care length of stay − In-hospital mortality − Reintubation − ICU readmission Measurements at baseline and after 2 weeks	MIP: − Improved in both groups, significantly greater increase in exp. group compared to con. group (17% in exp. group vs 6% in con., M: 11%, p = 0.024) Quality of life: − Significant greater in the exp. group (14% vs 2%, MD 12%, p = 0.03) In-hospital mortality: − Higher in exp. group (4 vs 0, 12% vs 0%, p = 0.051. No significant differences in... − FRI: no significant change in both groups (0.03 vs 0.02, p = 0.81) − Physical function (0.25 vs 0.25, p = 0.97) − Dyspnoea (−0.5 vs 0.2, p = 0.22) − Post-ICU length of stay, reintubation rate, ICU admission

Postma et al. (2014)	RCT	Inclusion criteria: − Patients with spinal cord injury admitted for initial inpatient rehabilitation − Motor level T12 or higher − AIS grade A, B, C, or D − Age 18-70 years − Impaired pulmonary function: FEV1 < 80% predicted Exclusion criteria: − Progressive diseases − Psychiatric condition that interfered with constructive participation − Insufficient comprehension of the Dutch language − Medical instability − Ventilator dependency − Tracheostomy Exp.: n=19 Age (yrs): 47.1 (SD ± 14.1) Con.: n=21 Age (yrs): 46.6 (SD ± 14.9)	Exp.: − IMT treshold trainer 8 weeks, 5x/week Interval based, high-intensity protocol Start load: 60%MIP 7 sets of 2 minutes, 1 min break − Recommendation to continue IMT training after discharge − Usual care − 2 standardized educational lessons Con.: − Usual care (passive range of motion, muscle strength ex., functional training) 2 standardized educational lessons on respiratory function and complications	Primary outcome measures: − MIP − MEP − FVC − FEV1 − PEF − MVV: maximum ventilation volume − PCF: peak cough flow − Limitations with breathing, talking, coughing, clearing one's nose (questionnaire) Secondary outcome measures: − HR − QoL − Perceived limitations in daily life − Subscales of SF-36 on perceived general health, vitality, and mental health − Respiratory complications Measurements at baseline, within 1 week after intervention period, 9 weeks after intervention period and 1 year after discharge	MIP: − Significant between-group difference during intervention period, no longer sign. at follow-up Mental health: − Greater improvement in exp. group after intervention period (between-group difference) Significant improvement over time in all parameters except for HRQoL for both groups (within-group differences) No significant between-group differences in any of the other outcome measures
Savci et al. (2011)	RCT	Inclusion criteria: − Confirmed diagnosis of coronary artery diseases − Scheduled to undergo CABG surgery − Low risk group for preoperative risk (Euro Score) Exclusion criteria: − Pulmonary disease − Atrial fibrillation − Stroke − Previous cardiac surgery − Valvular diseases Exp.: n=22 Age (yrs): 62.82 (SD ± 8.69) Con.: n=21 Age (yrs): 57.48 (SD ± 11.48)	Exp.: − IMT 2x/d, 30min/session 10 d. (5 d. pre-op, 5 d. post-op) initial resistance 15% MIP, progression to 15-45%MIP − Usual care: mobilization, active exercises of UL & LL, post-op chest physiotherapy (breathing ex. and coughing techniques) Con.: − Usual care: mobilization, active exercises of UL & LL, post-op chest physiotherapy (breathing ex. and coughing techniques)	− Presence of atelectasis, pleural effusion, and/or lung consolidation (X-ray) − Preoperative risk of death (Euro Score) − FVC, FEV1, FEV1/FVC (spirometry) − MIP, MEP − Functional exercise capacity (6MWT) − QoL (Nottingham Health Profile) − Anxiety and depression (HADS) − Length of ICU stay Measurements at baseline and on fifth postoperative day.	Between groups: − Length of ICU stay sign. longer in control group − Sign. increase in distance in 6MWT in exp. group − Sign. better sleep dimension of Nottingham Health Profile in exp. group − Sign. lower anxiety scores of HADS in exp. group Within group (exp. group): − Sign. increase MIP
Tonella et al. (2017)	Pilot RCT	Inclusion criteria: − Mechanically ventilated via tracheostomy − Weaning success defined as breathing without MV for 48 consecutive hours − Physical therapy (bronchial hygiene therapy, tracheal and oral cavity aspiration, positioning in bed with head at 30°) prior to data collection Exclusion criteria: − Presented injury of phrenic nerve − Neuromuscular disease − Musculoskeletal disorders − Necessity of > 1 aspiration per hour − Used home MV before hospitalization Exp.: n = 11 (8 male) Median age (yr) = 58.0 APACHE II = 20.9 (SD ± 5.4) SOFA = 7.13 (SD ± 5.8) Con.: n = 8 (7 male) Median age (yr) = 46.5 APACHE II = 20.2 (SD ± 7.2) SOFA = 7.7(SD ± 4.4)	Exp.: − EIMT with POWER Breathe® in manual mode − 2x/day with resistive load of 30% of initial MIP, increase with 10% on each training day − 3 x 10 repetitions with 1 minute break between sets Con.: − INP: patients subjected to INP using a T-piece for progressively increasing duration until patients completed 48 hours of respiratory autonomy on continuous nebulization	− MIP: three times daily − RSBI: daily − Duration of MV − Total weaning time	MIP: − Significant increase after training in exp. group ($p < 0.017$) RSBI: − No significant differences con. and exp. group either before or after respective treatment ($p = 0.049$ vs. $p = 0.249$) Duration of MV: − No significant difference between con. and exp. group (21.8 ± 9.8 vs. 14.5 ± 10 days, $p = 0.082$) Total weaning time: − Significant shorter in exp. than in con. group (3.5 ± 1.6 vs. 9.4 ± 6.47, $p = 0.0192$)

Group 3: Chest compression					
Naue Wda et al. (2014)	RCT: cross-over design	Inclusion criteria: − Mechanically ventilated for more than 48h − Not diagnosed with ventilator-associated pneumonia − PEEP ≤ 10 cm H_2O − Had an adequate respiratory drive − Respiratory stable (MAP ≥ 60 cm H_2O) Exclusion criteria: − Undrained pneumothorax or haemothorax or subcutaneous emphysema (forming contraindication to increasing positive pressure) − Osteoporosis − Peak pressure > 40 cmH_2O − Being a neurosurgical patient n = 34 Age: 64.2 (SD ± 14.6) APACHE II: 25.5 (SD ± 6.6) Duration of mechanical ventilation (days): 8.2 (SD ± 4.9)	All participants were placed in supine position, head of the bed elevated 30° + underwent a single aspiration 2h prior treatment Exp.: − Chest compression accompanied by a 10 cm H_2O increase in baseline inspiratory pressure on pressure support ventilation − Aspiration (suctioning) for 15s, 3x Con.: − Ventilated with 100% FiO2 for 1 min → disconnected from ventilator → aspiration (suctioning) for 15s, 3x	− Hemodynamic parameters: HR, RR, MAP, SpO_2 − Respiratory mechanics parameters: peak inspiratory pressure, expiratory tidal volume, dynamic compliance − Amount of secretions collected: sputum weight Measurements at baseline and one minute after application of the techniques.	Hemodynamic + respiratory parameters: − HR: increase in exp. group but not clinically relevant − RR: no significant difference between groups − Expiratory tidal volume in :comparison with con. group significant increase in exp. group (16 ± 69 mL vs. 56 ± 69 mL; p = 0.005) − Dynamic compliance: in comparison with con. group significant increase in exp. group (0.1 ± 4.9 cm H_2O vs. 2.9 ± 4.5 cm H_2O; p = 0.018) Amount of secretions: − In comparison with con. group significant increase in exp. group (1.9 g vs. 2.3 g; p = 0.004)
Unoki et al. (2005)	RCT: cross-over design	Inclusion criteria: − Mechanically ventilated and arterial cannulation for > 48 hours − Hemodynamically stable Exclusion criteria: − Rib fracture − Presence of chest tube − Hemodynamic instability − Inadequate human resources Included patients were excluded when ventilatory settings changed during the study n = 31 Age: 56.7 (SD ± 17.6) Simplified Acute Physiology Score: 59.4 (SD ± 10.7)	Exp.: − Patients positioned with the most affected lung region uppermost − Rib cage compression performed for 5 minutes → applied 5 minutes before endotracheal suctioning → therapist used both hands to gradually squeeze during expiration on the part of the rib cage that included the most affected lung region Con.: − Patients positioned with the most affected lung region uppermost − Endotracheal suctioning alone Interval of minimum 3 hours between interventions	− Arterial blood gases: PaO2, PaCO2, PaO2/FiO2 − Respiratory mechanics: dynamic lung compliance, Vt − Airway-secretion clearance: sputum weight − Measured 5 min before and 25 min after suctioning	Arterial blood gases: − PaO2/FiO2: no significant differences between 2 periods → no beneficial effect on oxygenation − PaCO2: no significant difference between 2 post-intervention periods or before and after treatment Respiratory mechanics: − Dynamic lung compliance: no significant difference between 2 post-intervention periods or before and after treatment Sputum weight: − No significant differences in both periods
Yousefnia-Darzi et al. (2016)	RCT: cross-over design	Inclusion criteria: − Mechanically ventilated in volume controlled mode via endotracheal tube for at least 48h − Hemodynamically stable − Aged between 18 and 65 yr − No chest tube, thorax injury or surgery, rib fracture, pneumothorax, embolus, subcutaneous emphysema, metastatic cancer, burn, skin graft or reconstructive surgery in the thorax − No spinal fusions, pregnancy, obesity, cardiac pacemaker, severe scoliosis, unstable thorax, lung abscess or cyst, − infiltration and atelectasis as identified by an anaesthesiologist on chest radiographs − Score of -4 or -5 on the Richmond Agitation and Sedation Scale Exclusion criteria: − Use of mucolytics or neuromuscular blocking drugs − Change of use of bronchodilation agents during the study − Receiving endotracheal suctioning within an hour of the study − Use of a closed suctioning system − Occurrence of severe bronchospasm − Raised ICP − Fragile vasculature n = 50 − No demographics reported	Exp.: − Thoracic squeezing during expiration → expiratory tidal volume increased by 30% → 10 x with interval of 3 respiratory cycles after every compression − Suctioning: preoxygenated with 100% oxygen first (1min) − Positioned based on the pulmonary radiologic findings Con.: − Suctioning alone → 2x 10s → preoxygenated with 100% oxygen first (1min) Treatment in both groups changed after 3h	− Mean weight of aspirated secretions	Mean weight of secretions: − Significant higher weight in exp. group than in con. group (1.94 g vs 1.35 g, p = 0.003) → can be used as an effective method Evaluation of effect of sex and disease: − Significant difference only in patients with cerebral problems, not in patients with internal problems

Group 4: Intrapulmonary Percussive Ventilation					
Antonaglia et al. (2006)	**RCT**	Inclusion criteria: − Admitted to ICU due to acute exacerbation of COPD − RR > 25 breaths/min, pH = 7.10 - 7.35, PaCO2 > 50 mm Hg Exclusion criteria: − Glasgow coma scale < 8 − Failure > 2 additional organs − ECG instability + evidence of ischemia or significant ventricular arrhythmia − Sudden intubation for CPR Exp: n = 40 − Phys group: n = 20 Age (yr) = 69 (SD ± 7.0) PaO2/FiO2 = 163 (SD ± 33.3) APACHE II = 22 (SD ± 20-26) − IPV group: n = 20 age (yr) = 72 (SD ± 7.0) PaO2/FiO2 = 173 (SD ±, 27.1) APACHE II = 22 (SD ± 20-26) Con: n = 40 Age (yr) = 69 (SD±6.0) PaO2/FiO2 = 181 (SD ± 29) APACHE II = 22 (SD ±21-24)	Exp.: − Phys group: Standard helmet-NPPV and respiratory physiotherapy Day 1: ○ Helmet-NPPV and medical treatment to reduce RR <30 breaths/min and eliminate accessory muscle activity ○ Flow trigger = 15-20 L/min ○ After first 2 hrs in the first day: they lower the RR to <25 breaths/min Day 2 : ○ Periods of 3-4 hrs ventilation with 2-3 hrs of spontaneous breathing combined with 25- to 30-min standard respiratory physiotherapy → chest clapping, mobilization and postural drainage, and expiration with the glottis open in the lateral posture, 10 mins each − IPV group: Helmet-NPPV and noninvasive IPV via a mouthpiece Day 1: ○ Helmet-NPPV and medical treatment to reduce RR <30 breaths/min and eliminate accessory muscle activity. ○ Flow trigger = 15-20 L/min ○ After first 2 hrs in the first day: they lower the RR to <25 breaths/min Day 2: ○ Periods of 3-4 hrs ventilation with 2-3 hrs of spontaneous breathing combined with 25- to 30-min IPV ○ High-flow mini bursts at rates of 225 cycles per minute with peak delivery pressure < 40 cm H2O Con.: − Treated with facial mask NPPV delivered by the same ventilator and similar settings − Underwent respiratory physiotherapy − Were clinically treated as those in the other two groups	Physiologic variables: − PaCO2 − FiO2 − RR − Heart rate Other outcome variables: − Need for intubation − Ventilatory assistance − Length of intensive care unit stay − Complications	Physiologic variables: − PaCO2: significantly lower in the IPV group compared to the Phys and control groups (mean ± SD, − 58 ± 5.4 vs. 64 ± 5.2 mm Hg, 67.4 ± 4.2 mm Hg, p <0.01) − PaO2/FIO2= significant higher in IPV (274 ± 15) than the other groups (Phys, 218 ± 34; control, 237 ± 20; p <0 .01) Other outcome variable: − Time of noninvasive ventilation (hrs): significantly lower in IPV group (median, 25th–75th percentile: 61, 60–71) than in other groups (Phys, 89, 82–96; control, 87, 75–91; p<0.01) − Length of ICU stay (days): significantly lower in IPV group (median, 25th–75th percentile: 7, 6-8) than other groups (Phys, 9, 8–9; control, 10, 9–11; p<0.01)
Vargas et al. (2005)	RCT	Inclusion criteria: − Admitted to ICU due to acute exacerbation of COPD, breathed air room: → RR ≥ 25/min, PaCO2 > 45 Torr, 7.35 ≤ pH ≤ 7.38 → hemodynamically stable Exclusion criteria: − Emergency intubation for CPR, respiratory arrest, or GCS <8 − Hemodynamic instability − ECG evidence of ischemia or significant ventricular arrhythmias − Failure of > 2 additional organs − Tracheotomy, pneumothorax, facial deformity − Recent history of oral, oesophageal or gastric surgery Exp.: n = 16 Age (yr) = 69.2 (SD ± 6.0) SAPS II = 25.4 (SD ± 6.0) pH = 7.37 (SD ± 0.01) Con.: n = 17 Age (yr) = 70.2 (SD ± 5.0 SAPS II = 25.4 (SD ± 4.0) − pH = 7.37 (SD ± 0.01)	Exp.: − Standard drug protocol − IPV through face mask → initial frequency of percussion at 250/min, initially peak pressure at 20 cm H_2O, but adjusted for each patient → I/E : 1 / 2.5 → 0.9% NaCL delivered by nebulizer → oxygen fed into mask to maintain SaO_2 between 88% to 92% ○ Stopped if adverse signs ○ 2x/day, 30 min − Breathed oxygen spontaneously between treatments Con.: − Received oxygen with nasal cannula to maintain target SaO_2 between 88% to 92% − Head of bed elevated at a 45° angle Standard drug protocol	Primary: − Avoidance of worsening of acute exacerbation → pH < 7.35 − Need of non-invasive ventilation Secondary: − Hospital stay → discharged from ICI when pH > 7.38 → discharged from hospital clinical status + gas exchange stable Measurements at baseline, at the end of the first IPV session, once daily during the morning.	IPV: − Significant decrease in RR and $PaCO_2$ − Significant increase in PaO_2 − No significant difference between group in pH Need of NIV: − Significant difference between con. group: 6 out of 17 (35.3%) vs exp. group: 0 out of 16, p < 0.05 Hospital stay: − Significantly shorter in exp. group than in con. group (6.8 ± 1.0 vs. 7.9 ± 1.3 days, p < 0.05)

Clini et al. (2006)	RCT	Inclusion criteria: − Tracheostomized patients weaned from mechanical ventilation → were mechanically ventilated for ≥ 14 days − Had been on spontaneous unassisted breathing for ≥ 72 h − Showed excessive production and retention of secretions − Stable and conscious Exp.: n = 24 (15 male) Age (yr) = 68 (SD ± 10) APACHE II = 13 (SD ± 3) PaO_2/FiO_2 238 (SD ± 51) Con.: n = 22 (13 male) Age (yr) = 70 (SD ± 8) APACHE II = 13 (SD ± 5) PaO_2/FiO_2 = 240 (SD ± 34)	Exp.: − IPV → 10min, 2x/day − Chest physiotherapy → 1h, 2x/day Con.: − Chest physiotherapy → 1h, 2x/day	Primary: − Physiological effectiveness of IPV → gas exchange, MEP Secondary: − Short- + long-term rate of respiratory complications associated with treatments	Effectiveness of IPV: − Significant improvement in both PaO_2/FiO_2 and MEP in exp. group compared to con. group → analysis of group differences: PaO_2/FiO_2: -11.75 to 55.05, MD 21.65, p = 0.038 MEP: 1.98 to 16.54, MD 9.26, p = 0.014 Respiratory complications: − Exp. group significant lower incidence of pneumonia (p ≤ 0.05)
Group 5: Multimodal chest physiotherapy					
Templeton and Palazzo (2007)	RCT	Inclusion criteria: − Intubated and ventilated for > 48h − Likely to remain ventilated Exclusion criteria − Previously ventilated during current ICU stay − Ventilatory failure due to neuromuscular dysfunction Exp.: n = 87 (53 male) Age (yr) = 57.7 (SD ± 16.5) APACHE II = 49 Smokers (%) = 55.2 Tracheostomised (%) = 36.7 Con.: n = 85 (58 male) Age (yr) = 58.2 (SD ± 18.0) APACHE II = 41 Smokers (%) = 48.2 Tracheostomised (%) = 25.8	Exp.: − Thoracic and pulmonary expansion by positioning − Rib springing − Manual hyperinflation − General mobilisation when possible, incl. sitting out of bed − Secretion removal: manual pulmonary hyperinflation with vibration, positioning, tracheal suctioning Intensity, frequency and used techniques as considered appropriate by physiotherapists Con.: − Tracheal suctioning − Decubitus care − General mobilisation	Primary: − Initial time to become ventilator-free Secondary: − ICU and hospital mortality − ICU length of stay − Incidence of ventilator-associated pneumonia (VAP)	Time to become ventilator-free: − Significant prolongation of median time among exp. group vs con. group (15 vs 11 days, p = 0.047) No significant differences between groups in: − ICU or hospital mortality rates − Length of ICU stay − VAP (35 in exp, 25 in con, p = 0.13)
Pattanshetty and Gaude (2010)	RCT	Inclusion criteria: − Intubated and mechanically ventilated for > 48 h Exclusion criteria: − ARDS − Acute pulmonary oedema − Untreated pneumothorax − Requiring high-respiratory support (FiO_2 > 0.70) − Acute myocardial infarction − Cardiac arrhythmias − Hypovolemia − Haemodialysis − Community-acquired pneumonia − Unstable cardiovascular or neurological function − Injury preventing positioning for chest physiotherapy − Open heart surgery − Tracheostomy − HIV Exp: n = 50 (37 male) Age (yr) = 47.8 (SD ± 14.72) CPIS at baseline = 7.6 (SD ± 1.15) Con: n = 51 (40 male) Age (yr) = 51.6 (SD ± 17.47) CPIS at baseline = 7.6 (SD ± 1.75) −	Exp.: − Manual hyperinflation ○ 20 min/session, 2x/day, 8-13 breaths/min. − Chest wall vibrations: manual application of fine oscillatory movement combined with compression to patient's chest wall → helps to loosen and mobilize secretions ○ Positioned to side lying in bed ○ 3 repetitions in upper, middle, and lower zone of chest − Endotracheal suctioning for 15s − Positioning: head of the bed positioned at angle of 30-45° elevation for at least 30 min. − 2x/day Con.: − Manual hyperinflation − Endotracheal suctioning for 15s − Standard care	Primary: − Prevalence of VAP: CPIS Score Secondary: − Mortality rate − Duration of mechanical ventilation − Length of ICU stay	Prevalence of VAP (CPIS Score): − Mean reduction in the CPIS Scores between both the groups was highly significant at end of extubation/successful outcome or discharge as compared to the baseline CPIS Score (p = 0.000) − CPIS Score reduction was more prominent in the study group (3.9 ± 1.69) with significant reduction (p = 0.000) when compared with the baseline data in both the groups (p = 0.000) − Reduction in CPIS Score was higher in the exp. group (3.4 ± 4.4) as compared to the con. group (1.9 ± 2.9) Mortality rate: − Significant decrease in mortality rate noted in exp. group as compared to the con. group (24% vs. 49%, p = 0.007) Duration of mechanical ventilation + length of ICU stay: − No statistical difference (p = 0.986 and p = 0.102, respectively)

Patman et al. (2009)	**RCT**	***Part A:*** Inclusion criteria: − Adults in ICU with acquired brain injury − ≥16 years − Admission GCS ≤ 9 − ICP monitor or drain in situ − Requiring invasive MV for >24 hrs Exclusion criteria: − Not suitable for active therapy − Requiring excessive respiratory support i.e. any of the following o nitric oxide ventilation o FiO2 > 0.8 o PEEP > 10 cm H2O − Unstable haemodynamic status i.e. any of the following o mean arterial pressure > 120 or < 60 mmHg o heart rate > 120 or < 60 bpm o labile mean arterial pressure or heart rate o new cardiac arrhythmias requiring definitive intervention o noradrenaline/adrenaline infusion > 30 mg/hr − Unstable neurological status i.e. any of the following o labile ICP or CPP o sustained ICP > 25 mmHg o sustained CPP < 70 mmHg − Development of any of the exclusion criteria for a sustained period of ≥ 12 h after inclusion Exp.: n=72 Age (yrs): 45.8 (SD ± 19.0) GCS: 5.4 (SD ± 2.0) APACHE II score: 20.3 (SD ±5.7) Con.: n=72 Age (yrs): 41.1 (SD ±20.0) GCS: 4.9 (SD ±2.0) APACHE II score: 20.5 (SD ± 5.6) ***Part B:*** Inclusion criteria: − Patients included in part 1 who fulfilled a diagnosis of ventilator associated pneumonia (VAP) Exp.: n=17 Age (yrs): 34.1 (SD ± 16.3) GCS: 4.5 (SD ± 2.0) APACHE II score: 21.0 (SD ± 6.2) Con.: n=16 Age (yrs): 37.9 (SD ± 17.8) GCS: 4.9 (SD ± 1.9) APACHE II score: 18.2 (SD ± 6.4)	***Part A:*** Exp.: 6 respiratory physiotherapy treatments/24 hrs − Positioning − Manual hyperinflation − Airway suctioning − Routine nursing care Con.: − Routine nursing care	***Part A:*** Primary outcome measures: − Incidence of VAP Secondary outcome measures: − Duration of MV − Length of ICU/hospital stay − Withdrawal rates − Incidence of lobar collapse − Bronchoscopy − Reventilating/ reintubation − Re-admission to ICU − Mortality − Daily CPIS (clinical pulmonary infection score) − Best/worst PaO2/FiO2 ***Part B:*** Primary outcome measures: − Duration of MV − Length of ICU stay Secondary outcome measures: idem to part A	***Part A:*** − No significant differences for any of the outcome measures ***Part B:*** − No significant differences for any of the outcome measures
6. Chest wall vibrations					
Kuyrukluyildiz et al. (2016)	RCT	Inclusion criteria: − Patients in critical care unit − > 3d intubation Exclusion criteria: − Rib fracture − Acute haemorrhage − Unstable intracranial pressure − Chest drainage tube − History of spinal history − Skin infection in the back and chest area Exp.: n =15 (male n=10) Age (yr) = 74.7 (SD ± 11.5) APACHE II score = 26.5 (SD ± 6.1)	Exp.: − High frequency chest wall oscillation (The Vest Model 205) 4x15min/day for 72 hours freq. 7-10 Hz. − Position giving technique − Chest wall percussion − Airway aspiration every 3 hours − Postural drainage when extubated Con: − Position giving technique − Chest wall percussion − Airway aspiration every 3 hours − Postural drainage when extubated	At 0 hrs, 24 hrs, 48 hrs, 72 hrs − Dry sputum weight (DSW) − Lung collapse index (LCI) − PO2 − Blood lactate − Chest X-ray At 0 hrs and 72 hrs − Endotracheal aspirate culture Days intubated Days in ICU	DSW − Significant decrease at 72 hrs LCI − Significant decrease at 48 and 72 hrs PO2 − Significant elevation in exp. group at 72 hrs Lactate − Significant increase at 24 hrs in exp. group − Significant decrease at 72 hrs in exp. Group No significant differences between groups for days intubated or days in ICU

		Con.: n=15 (male n=9) Age (yr) = 73.1 (SD ± 11.9) APACHE II score = 27.9 (SD ± 7.4)	Settings of the mechanical ventilators were the same for all the patients. Secretions were aspirated when deemed necessary.		
7. Positive expiratory pressure devices					
Chicayban et al. (2011)	RCT: cross-over design	Inclusion criteria: − Mechanically ventilated − > 18 years old − Clinical and radiologic diagnosis of pulmonary infection and hypersecretion (defined as need for endotracheal suctioning in <2h) Exclusion criteria: − Absence of cough reflex − Hemodynamic instability (mean arterial pressure < 60 mmHg) − Pneumothorax or nontreated pleural effusion − Intracranial hypertension (> 20 mmHg) − Acute respiratory distress syndrome − Acute bronchospasm or discomfort during experimental protocol n = 20 (male n=10) Age (yr) = 48.4 (SD ± 4.3) BMI = 27.1 (SD ± 1.3) PaO2/FiO2 = 298.3 (SD ± 22.8) APACHE II score = 21.7 (SD ± 2.3) Mechanical ventilation length = 21.6 (SD ± 4.9)	Exp.: FLUTTER intervention − Connecting the Flutter Valve to the exhalation port of the mechanical ventilator (30° angle) − 2 x 15 minutes series with FLUTTER − Subjects were under pressure controlled ventilation with inspiratory pressure of 25 cmH2O, inspiratory time of 1.2 seconds, respiratory rate of 15 bpm Con.: − Normal ventilation in pressure controlled mode with inspiratory pressure of 25 cmH2O, inspiratory time of 1.2 seconds, respiratory rate of 15 bpm − No oscillatory device connected to the exhalation port of the mechanical ventilator Washout period of 6h between interventions	− Sputum production − Respiratory mechanics: ○ Respiratory system static compliance ○ Total and homogenous resistances ○ Peak expiratory flow ○ Expiratory flow at 75% tidal volume − Hemodynamic ○ SBP and DBP ○ Mean airway pressure ○ SPO_2 ○ $PetCO_2$ ○ MAP ○ HR − Gas exchange ○ PaO_2 ○ $PaCO_2$ ○ PaO_2/FiO_2 Measurements immediately before and after both interventions	Sputum production: − Significantly higher in exp. group compared to con. group (5.1 ± 0 .5 mL vs 3.3 ± 0 .3 mL, p < .001) Comparing pre- and post-intervention data, significantly increases in exp. group compared to con. group in: − Respiratory system static compliance (p < 0.001) − Peak expiratory flow (p = 0 .048) − Expiratory flow at 75% of tidal volume (p = 0.005) − Arterial PO2-to-inspired oxygen concentration ratio (p < .001). − Mean airway pressure Respiratory resistance, heart rate, and mean arterial pressure remained unaltered during the interventions (p > 0.05)
Bellone et al. (2002)	RCT	Inclusion criteria: − Admitted to ICU because of hypercapnic respiratory failure due to exacerbation of COPD − pH: 7.25 - 7.35 − $PaCO_2$ < 6.5 kPa − Required NIPPV − Large amounts of bronchial secretions − Mild acidosis Exp.: n = 13 (men n = 8) Age (yr) = 65 (SD ± 7.8) APACHE II score = 16.6 (SD ± 1.1) pH = 7.33 (SD ± 0.2) Con.: n = 14 (men n = 9) Age (yr) = 64 (SD ± 7.7) APACHE II score = 17 (SD ± 1.2) pH = 7.33 (SD ± 1.1)	Exp.: − 3 sessions of 30-40 minutes each ○ 2 min of tidal volume breathing with PEP mask → PEP of 10-15 cm H_2O → receiving oxygen through mask ○ Assisted coughing ○ 2 min undisturbed breathing ➔ 5-7 cycles for a total of 30-40 minutes per session Con.: 30-40 min/session, 3 sessions/day − Assisted coughing → compressing the trachea just above sternal notch − Huffing	Primary: − Total wet sputum weight − Assess feasibility of the PEP mask Secondary: − Time required for weaning from NIPPV − Treatment failure → mortality within 2 months after ICU discharge, need for ETI	Total wet sputum weight: − Baseline sputum production in two groups of patients was not significantly different (2.1 ± 2.4 g in exp. group, 2.6 ± 3.8 g in con. group) − At the end of treatment sputum production was significantly (p < 0.01) higher in exp. group (9.6 ± 3.9 g) compared with group B (4.7 ± 2.5 g) − One hour later sputum had increased significantly (p < 0.05) in exp. group (from 9.6 ± 3.9 g to 13.2 ± 4.1 g), no change was seen in con. group (from 4.7 ± 2.5 g to 5.2 ± 1.9 g) The total length of weaning time: − Significantly lower in exp. group (4.9 ± 0.8 days) vs con. group (7.0 ± 0.7 days), p < 0.01 Mortality and ETI: − Not significantly different in two groups (0 versus 1 and 0 versus 1, resp.)
Urell et al. (2011)	RCT	Inclusion criteria: − Received general anaesthesia and underwent open-heart surgery through a median sternotomy − Postoperatively artificially ventilated with a positive end-expiratory pressure of 5-12 cmH_2O Exclusion criteria: − Preoperative angina pectoris at rest − Insufficient understanding of the Swedish language − Postoperative artificial ventilation > 15 hrs − Receiving CPAP treatment Exp.: n = 63 (men n = 42) Age (yr) = 69 (SD ± 9) Con.: n = 56 (men n = 56) Age (yr) = 68 (SD ± 9)	Patients sat at bedside or upright position Exp.: − 30 deep breaths/h with PEP device → 3 x 10 breaths, 30-60s pause between sets Con.: − 10 deep breaths/h with PEP device → 1 x 10 breaths Expiratory pressure of 10-15 cm H_2O. Average of 20 sessions during study period per patient Treatment started 1 hr after extubation and ended in the morning of the second postoperative day	Primary: − Arterial blood gases: PaO_2, $PaCO_2$, SaO_2 ➔ Measured on the second post-operative day Secondary: − Pulmonary function: IC, VC, FVC, FEV1 ➔ Measured pre-operatively and on the second post-operative day	Arterial blood gases: − PaO_2: significant difference between exp. group and con. group (exp. 8.9 ± 1.7 kPa vs con. 8.1 ± 1.4 kPa, p = 0.004) − SaO_2: significant difference between exp. group and con. group (exp. 92. 7± 3.7% vs con. 91.1 ± 3.8%, p = 0.016 − $PaCO_2$: no significant difference Pulmonary function: − No significant differences in measured lung function between groups

Table 7: Inspiratory muscle training: study characteristics and results

	Sah et al. (2017)	Cader et al. (2012)	Gosselink et al. (2000)	Cader et al. (2010)	Bissett et al. (2016)	Postma et al. (2014)	Savci et al. (2011)	Tonella et al. (2017)
Used technique	Incentive spirometry	Threshold spirometry	Incentive spirometry	Threshold spirometry	Threshold spirometry	Threshold spirometry	Threshold spirometry	EIMT: resistive IMT
Study characteristics								
Intervention	5x in 1 minute, 5 minutes/hour, first 6 postoperative hours	5 min, 2x/day, 7days/week, 30% MIP, until extubation	2x5-10 maximal inspiratory maneuvers every hour, duration intervention not reported	30%MIP, 5 minutes, 2x/day, 7days/week, until successfully weaned	1x/day, 5days/week, 6 breaths at highest tolerable intensity, for 2 weeks	5x/week, 60% MIP, 8 weeks	2x/day, 15-45% MIP	2x/day, 30%MIP, until discharge
Control	CPAP or O_2 with oronasal mask	Standard physiotherapy	Breathing exercises, forced expiration, postural drainage, suction	Usual care	Usual care (including PEP and deep breathing)	Usual care + education	Usual care (including breathing exercises + coughing technique.), 5 d pre-op, 5 d post-op	Intermittent nebulization program
Follow-up	30 minutes, 6 hours and 24 hours after surgery	Not reported	Every other day until discharge	Daily until discharge	After 2 weeks	1 – 9 weeks after intervention period, 1 year after discharge	Fifth postoperative day	Daily until discharge
Results								
Respiratory parameters								
-> peak expiratory flow						WG both groups		
-> expiratory flow at 75% tidal volume								
-> FVC	WG all groups		NS			WG both groups	NS	
-> FEV_1	WG+BG		NS			WG both groups	NS	
-> FEV_1/FVC	WG in favor of exp. group						NS	
-> MIP		WG in favor of exp. group	NS	BG in favor of exp. group	BG in favor of exp. group	WG+BG WG both groups BG: exp. group	WG exp. group	WG exp. group
-> MEP			NS			WG both groups	NS	
-> MVV						WG both groups		
-> PCF: peak cough flow						WG both groups		
-> Tobin index		WG con. group (incr.) + exp. group (decr.)		BG in favor of exp. group				
-> Atelectasis score (RXThorax)			NS					
-> Pulmonary complication score			NS					
-> Limitations with breathing, talking, coughing, clearing one's nose						WG both groups		
-> Presence of atelectasis, pleural effusion, and/or lung consolidation (RX)							NS	
-> Rapid shallow breathing index								NS
Blood gases								
-> PaO_2	NS							
-> $PaCO_2$	WG con. group							
-> PaO_2/FiO_2	NS							
-> $[HCO_3^-]$	NS							
Other								
-> Extubation succes		NS						
-> Weaning time		BG in favor of exp. group		BG in favor of exp. group				BG in favor of exp. group
-> Duration of MV				NS				NS
-> Time in hospital			NS		NS			
-> Time in ICU			NS				BG in favor of exp. group	
-> In-hospital mortality					NS			
-> Reintubation					NS			
-> ICU readmission					NS			
-> Respiratory complications						WG both groups		
-> Body temperature			NS					
-> WBC count			NS					
-> Fatigue resistance index					NS			
-> Dyspnea (Borg)					NS			
-> Physical function					WG both groups			
-> QoL					WG+BG WG exp. group BG in favor of exp. group	NS	BG in favor of exp. group	
-> Euro Score								
-> Perceived limitations in daily life						WG both groups		
-> perceived general health, vitality, and mental health						WG+BG WG both groups BG: in favor of exp. group		
-> Functional exercise capacity (6MWT)							BG in favor of exp. group	
-> Anxiety and depression (HADS)							BG in favor of exp. group	

PART TWO – RESEARCH PROTOCOL

1. Introduction

A significant proportion of the patients in the Intensive Care Unit (ICU) require Mechanical Ventilation (MV) via endotracheal intubation or tracheostomy. MV preserves a stable airway, the patients work of breathing has the opportunity to become normal and the gas exchange maintenance stable (Ciesla, 1996; Naue Wda, Forgiarini Junior, Dias, & Vieira, 2014). However, in this population, there is an increase of the prevalence of respiratory complications. An adverse effect of MV is weakening of the inspiratory muscles (Tobin, Laghi, & Jubran, 2010) and the cough reflex (Yousefnia-Darzi, Hasavari, Khaleghdoost, Kazemnezhad-Leyli, & Khalili, 2016), which leads to an impairment of the mucociliary transport with retained secretions as a result (Branson, 2007). Other complications are atelectasis due to decreased aeration of distal lung units and ventilator-associated pneumonia (Kalanuria, Ziai, & Mirski, 2014). These respiratory complications often results in a prolonged stay at the ICU. The findings of Loss et al. (Loss et al., 2015) suggest that patients who underwent MV spent more days at the ICU which leads to a higher hospital cost. These patients also have an increase in hospital mortality.

Chest physiotherapy composes of several interventions to prevent and minimalize respiratory complications. Intrapulmonary Percussive Ventilation (IPV) is one of these treatments used for the ICU population. IPV uses a breathing circuit called a Phasitron®. The Phasitron® is a pressure-flow converter which sends small, rapid bursts of gas into the lungs. These bursts are called percussions and are delivered into the lungs at rates of 60 to 600 cycles per minute (2 to 5 Hz). The percussions, which delivers a positive pressure of 10 to 30 cm H_2O, opens the airway and expands the lungs. The airway walls vibrate in synchrony with these percussions which allows air going behind the obstruction. Simultaneously therapeutic aerosols of saline (NaCl) with or without a bronchodilator are added to prevent secretions for drying out. Secretions are mobilized towards the upper airways and oral pharynx by the expiratory flow created in the expiratory phase of each percussion. (Antonaglia et al., 2006; Langenderfer, 1998; Marks, 2007; Reychler et al., 2004; Vargas et al., 2005). IPV has been successfully used to remove secretions in patients with neuromuscular diseases (Duchenne dystrophy) (Toussaint, De Win, Steens, & Soudon, 2003) and Cystic Fibrosis (Varekojis et al., 2003), but also to enhance gas exchange parameters in patients with Chronic Obstructive Pulmonary Disease (Testa et al., 2015) and tracheostomized patients (Clini et al., 2006). IPV has been used for alveolar recruitment in obese patients with compression atelectasis (Tsuruta, Kasaoka, Okabayashi, & Maekawa, 2006). These findings show the increased amount of collected secretions but also the improved respiratory and hemodynamic parameters after treatment with IPV. However, these parameters doesn't show the effect of IPV on the aeriation inside the lungs. By having an insight in the lung ventilation, treatment can be applied more specific which has a positive effect on lung recruitment.

To our knowledge, there is only one study published that uses medical imaging that investigated changes in lung ventilation induced through IPV. Patients in the study of Godet et al. (Godet et al., 2018) are for one hour ventilated with Volumetric Diffusive Respirator 4 (VDR-4, Percussionaire Corporation). The VDR-4 works with the same principle as IPV and with a combination of high frequency small bursts of air and low frequency of ventilation, so high frequency bursts are applied during both inspiratory and expiratory phase. In this study the VDR-4 is used for eight patients with early non-focal acute respiratory distress syndrome. The findings of this study, assessed by a computed tomography (CT) scan, suggest alveolar recruitment significantly increases in the posterior lung regions.

2. Aim of the study

2.1. Research questions related to the master thesis

The research questions related to the master thesis are formulated in the following aims. The primary aim of this study is to investigate the influence of respiratory physiotherapy including IPV and assisted autogenic drainage on the distribution of ventilation in a heterogenous group of sedated patients requiring MV. Can a difference in distribution of ventilation be found before and after the treatment? The secondary aims are to investigate the dynamic changes of lung ventilation during treatment and the influence of treatment on gas exchange parameters. Can a specific dynamic of changes in lung ventilation be found during treatment? Can changes in gas exchange parameters be found immediately after treatment? Can the changes in distribution of ventilation and gas exchange parameters be maintained 60 minutes after treatment or can they be decreased to their original values?

2.2. Hypotheses

The hypothesis for the primary aim is that the distribution of ventilation after treatment will be increased in the regional lung areas of patients requiring MV. For the secondary aims the following hypotheses are suggested. At a certain time within treatment dynamic changes will happen. In this study the exact time to this dynamic changes need to be investigated, so a guideline for time of treatment can be set. Gas exchange parameters will be increased after treatment. Distribution of ventilation and gas exchange parameters will be decreased 60 minutes after compared with values immediately after treatment, but still be higher than baseline values.

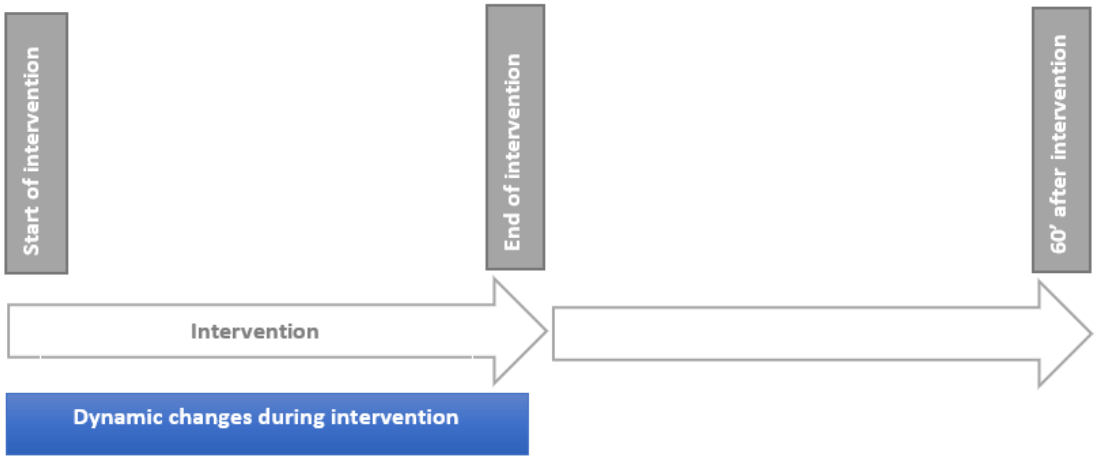
3. Methods

3.1. Research design

This will be an interventional study with a pre-post design which investigates the routine care intervention (Thiese, 2014). The study will take place at the Intensive Care Unit of Ziekenhuis Oost-Limburg (ZOL), campus Sint-Jan, located in Genk, Belgium. A heterogeneous group of sedated patients requiring MV will be recruited for this study. The intervention will be performed by a senior physiotherapist, who has a lot of experience with respiratory physiotherapy in the ICU population. All the patients will be treated with the same Intrapulmonary Percussive Ventilator (IPV2C®).

The measurements will be taking before, immediately after and 60 minutes after the treatment. The dynamic of changes in the ventilation will be continuously monitored during the treatment and will be analyzed afterwards. The distribution of ventilation and hemodynamic values will be stored at the defined measurement moments (Figure 1).

Figure 1: Study Design



3.2. Participants

3.2.1. Inclusion criteria

Patients with all kinds of pathologies are eligible for inclusion in this study if they:

1) Receive respiratory physiotherapy including IPV
2) Are aged 18 years or older
3) Are full sedated
4) Have received 24 hours or more of MV

3.2.2. Exclusion criteria

Patients are excluded from the study if they:

1) Don't receive chest physiotherapy including IPV
2) Are aged younger than 18 years
3) Are mentioned unstable
    a) Based on the clinical experiences of the physiotherapist
    b) Or defined as
        i) Systolic blood pressure (SBP) < 100 mmHg or > 180 mmHg
        ii) Mean arterial pressure (MAP) < 70 mmHg or > 110 mmHg
        iii) Heart rate (HR) < 60 bpm or > 120 bpm
4) Have a length of ICU stay ≤ 24 hours and don't receive MV
5) Receive extracorporeal membrane oxygenation (ECMO)
6) Have a do-not-resuscitate (DNR) status

3.2.3. Patient recruitment

The aim is to recruit 20 patients to this study. Patients will be recruited at the ICU of ZOL, Genk. The ICU consisted of two wards and had a total of 38 beds. The physiotherapy team comprised three physiotherapists working in a day shift. All ICU patients, who require MV and receive the routine care intervention including IPV, will be screened daily for study eligibility by the physiotherapists. The senior physiotherapist together with the patients doctor will be making the final decision to enroll the patients in the study.

3.3. Medical ethics

Approval for this protocol will be obtained from the Medical Ethics Committee of Ziekenhuis Oost-Limburg and the University of Hasselt. Written informed consent will be signed by patient's family before their participation in the study.

3.4. Intervention

The intervention includes routine care respiratory physiotherapy which will be performed by a skilled respiratory physiotherapist. The respiratory physiotherapy will consist of IPV, assisted autogenic drainage and secretion clearance. The routine care treatment will occur once a day. After being preoxygenated, patients will be disconnected from MV and the IPV will be attached to the end of the endotracheal tube or tracheostomy. The patients will receive the same amount of oxygen through the IPV as required on MV. For each patient, time of treatment, frequency and pressure settings of the IPV will be adjusted to their individual needs. The physiotherapist will be sure that the entire lungs will be percussed if patient's total thorax will be making small vibrating movements. Secretions will be hydrated with saline (NaCl) delivered by the aerosol of the IPV. Assisted autogenic drainage will be giving during inspiration and expiration at the areas where the physiotherapist feels secretions are being retained. Secretion clearance will occur through suctioning. Patient's safety will require attention and monitoring of hemodynamic and respiratory changes. Treatment will be stopped when the patient shows adverse signs of hemodynamic instability.

3.5. Outcome measures

Before the start of the intervention, master students will assist the physiotherapist to put a flexible silicone belt around the patient's chest. This belt has 16 integrated electrodes. This whole technique is called Electrical Impedance Tomography® (EIT, Dräger). Recent findings (Karsten, Stueber, Voigt, Teschner, & Heinze, 2016) suggest that the best position to place the belt is between the fourth and fifth intercostal place. In this study, the positioning will be different. The EIT belt will be placed around the thorax at the height of the problem region of the lungs. This region will be based on a standardized interpretation of daily chest X-ray findings made in a multidisciplinary council between doctors, physiotherapist and nurses.

The belt is connected to the PulmoVista 500® (Dräger) (Teschner, Imhoff, & Leonhardt, 2015). The PulmoVista 500® is a lung function monitor which can measure the distribution of ventilation based on cross-sectional images of the lung function by connection with EIT. It can also measure the short-term changes in end-expiratory lung volumes. The effect of therapeutic interventions will be showed and measured over time. Measurements of hemodynamic parameters (heart rate (HR), mean arterial pressure (MAP), arterial oxygen saturation (SaO_2)) will be continuously monitored.

3.5.1. Primary outcome measures

The primary outcome measures are the data collected with PulmoVista 500®. The data will include the effect of the intervention with IPV.

- Distribution of ventilation (before, after and during the intervention)
  The PulmoVista 500® represents this data with use of the following color scale (Karsten et al., 2016; Teschner et al., 2015):
  - Black: non-ventilated regions
  - White: best-ventilated regions
  - Blue: partial-ventilated regions
    How darker the blue color is, the less ventilation there is in that region.
- Changes in end-expiratory lung volumes

3.5.2. Secondary outcome measures

The secondary outcome measures will include:

- Arterial blood gasses: partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), oxygen saturation (SaO_2), mean arterial pressure (MAP), pH
- Heart rate (HR)

3.6. Data analysis

The data from the patients hemodynamic values are continuous, quantitative variables and will be stored anonymously in Word and Excel. The data collected with the PulmoVista 500® are ordinal, categorical variables. The used colors represent the degree of ventilation at the lung region where the belt is placed. To detect the dynamic changes in the ventilation during the intervention, the PulmoVista 500® continuously monitors these colors and records this data as a video. This data will be saved and transferred to a computer in the hospital to be analyzed afterwards. SAS JMP will be used for statistical tests and analysis. Further details of the statics to analyze the data will be discussed with all the partners of the protocol in the following months.

4. Time planning

The measurements and data collection of this study will be conducted between July and December 2018, if medical ethics is approved. Data analysis will start between January and March 2019. The plan is to finish the paper with all the results in June 2019.

	July 2018	August 2018	September 2018	November 2018	December 2018	January 2019	February 2019	March 2019	April 2019	May 2019
Data acquisition	X	X	X	X	X	X				
Data analysis						X	X	X		
Writing								X	X	X

5. List of references

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VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
26/10/2017	Bespreking onderwerp en mogelijke onderzoeksvragen	Promotor: Copromotor: Student(e): B[illegible] Student(e):
08/11/2017	Afbijnen zoekstrategie	Promotor: Copromotor: Student(e): B[illegible] Student(e):
10/01/2018	Brainstormen over protocol met David Schramme + bespreken tekstscreening	Promotor: Copromotor: Student(e): B[illegible] Student(e):
29/01/2018	Bespreken protocol + resultaten tekst-screening	Promotor: Copromotor: Student(e): B[illegible] Student(e):
05/03/2018	Afbijnen methode + aanpak data extractie	Promotor: Copromotor: Student(e): B[illegible] Student(e):
28/03/2018	Bespreken resultaten van data extractie	Promotor: Copromotor: Student(e): B[illegible] Student(e):
17/04/2018	Afbijning resultaten	Promotor: Copromotor: Student(e): B[illegible] Student(e):
08/05/2018	Bespreken inhoud van de discussie	Promotor: Copromotor: Student(e): B[illegible] Student(e):
30/05/2018	Bespreken geheel MP 1 deel 1	Promotor: Copromotor: Student(e): B[illegible] Student(e):
		Promotor: Copromotor: Student(e): Student(e):

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ZELFEVALUATIERAPPORT **WETENSCHAPPELIJKE STAGE - DEEL 1** **RWK**

Naam & Voornaam STUDENT: Broeders Leenne, Engelen Annick

Naam & Voornaam (CO)PROMOTOR & PROMOTOR: Dr. Burtin Chris

TITEL masterproef (Nederlandstalig of Engels): The use of respiratory physiotherapy in the Intensive Care Unit

LITERATUURSTUDIE	Gestelde deadline	Behaald op	Reflectie
De belangrijkste concepten en conceptuele kaders van het onderzoekdomein uitdiepen en verwerken	Oktober 2017	Oktober 2017	Behaald
De belangrijkste informatie opzoeken als inleiding op de onderzoeksvraag van de literatuurstudie	November 2017	November 2017	Behaald
De opzoekbare onderzoeksvraag identificeren en helder formuleren in functie van de literatuurstudie	November 2017	November 2017	Behaald
De zoekstrategie op systematische wijze uitvoeren in relevante databanken	December 2017	Januari 2018	Zoekstrategie aantal keer verbreed voor definitieve beslissing
De kwaliteitsbeoordeling van de artikels diepgaand uitvoeren	Maart 2018	April 2018	Bijkomende sterkte-zwakte analyse uitgevoerd
De data-extractie grondig uitvoeren	Maart 2018	Mei 2018	Meer tijd voor nodig gehad dan gepland
De bevindingen ïntegreren tot een synthese	Mei 2018	Mei 2018	Behaald

ONDERZOEKSPROTOCOL	Gestelde deadline	Behaald op	Reflectie
De onderzoeksvraag in functie van het onderzoeksprotocol identificeren	Eind januari 2018	Eind januari 2018	Behaald
Het onderzoeksdesign bepalen en/of kritisch reflecteren over bestaande onderzoeksdesign	Eind januari 2018	Eind januari 2018	Behaald
De methodesectie (participanten, interventie, uitkomstmaten, data-analyse) uitwerken	Eind januari 2018	Eind januari 2018	Behaald

ACADEMISCHE SCHRIJVEN	Gestelde deadline	Behaald op	Reflectie
Het abstract tot the point schrijven	Juni 2018	Juni 2018	Behaald
De inleiding van de literatuurstudie logisch opbouwen	Mei 2018	Mei 2018	Behaald
De methodesectie van de literatuurstudie transparant weergegeven	April 2018	April 2018	Behaald
De resultatensectie afstemmen op de onderzoeksvragen	April 2018	Mei 2018	Meer tijd voor nodig gehad dan gepland
In de discussiesectie de bekomen resultaten in een wetenschappelijke tekst integreren en synthetiseren	Mei 2018	Mei 2018	Behaald
Het onderzoeksprotocol deskundig technisch uitschrijven	Februari 2018	Februari 2018	Behaald
Referenties correct en volledig weergeven	Juni 2018	Juni 2018	Behaald

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ZELFSTUREND EN WETENSCHAPPELIJK DENLEN EN HANDELEN	**Aanvangsfase**	**Tussentijdse fase**	**Eindfase**
Een realistische planning opmaken, deadlines stellen en opvolgen	G	V	G
Initiatief en verantwoordelijkheid opnemen ten aanzien van de realisatie van de wetenschappelijke stage	G	ZG	G
Kritisch wetenschappelijk denken	G	ZG	G
De contacten met de promotor voorbereiden en efficiënt benutten	ZG	ZG	ZG
De richtlijnen van de wetenschappelijke stage autonoom opvolgen en toepassen	G	ZG	ZG
De communicatie met de medestudent helder en transparant voeren	ZG	G	ZG
De communicatie met de promotor/copromotor helder en transparant voeren	ZG	ZG	ZG
Andere verdiensten:			