EFFECTIVENESS OF COUGH ASSIST IN THE EXTUBATION OF ADULT PATIENTS: SYSTEMATIC REVIEW AND META-ANALYSIS

Giulia Montigiani [1]; Davide Papi[1]; Lorenzo Proietti[1]; Beatrice Meucci [2]; Mara Taddei[1]; Luca Bucciardini[3]; Mauro Di Bari[4].

[1]*PT - Rehabilitation Service, Department of Healthcare Professionals, Azienda Ospedaliero-Universitaria Careggi, Florence – Italy*
[2]*RN - Neuro Intensive Care Unit, department of Anesthesia and Intensive Care,Azienda Ospedaliero-Universitaria Careggi, Florence – Italy*
[3]*MD - Neuro Intensive Care Unit, department of Anesthesia and Intensive Care,Azienda Ospedaliero-Universitaria Careg gi, Florence – Italy*
[4]*MD, PhD, - Geriatric Intensive Care Unit, Department of Medicine and Geriatrics, AziendaOspedaliero-UniversitariaCareggi, Florence – Italy*

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ABSTRACT

In Intensive Care Unit (ICU), failure of extubation, resulting in the need for reintubation, mayoccur in 2-25% of Patients undergoing extubation[1].
The purpose of this review and meta-analysiswas to determine the effectiveness of cough assist in improving success rates of extubation compared with standard treatment.
Inclusion criteria were; Randomized Control Trials, which compared cough assist and conventional therapy in adult population in intensive care unit whith conventional therapy only. Outcomes representing the efficacy of the cough assist were: quantity and quality of secretions (weight, volume, and density), number of reintubation, indices of thoraco-pulmonary function.
The search string produced 764 studies, and only 5 studies eligible for review. Overall, a total of 331 Participants were enrolled in the five studies selected.
Of the meta-analyzed outcomes, the calculation of the effect size for the weight of secretions is the one that gave the best results, while no statistical difference was found in the other outcomes. In none of the meta-analysis studies were observed adverse effects in the use of in-exsufflator.
Our systematically review edsuggest sthatcough assist might be feasible and effective in patients intubated in ICU, but studies with larger sample sizes and well-defined outcomes are still required to obtain conclusive evidence.

INTRODUCTION

Removal of an endotracheal tube, even if conducted with standard techniques, may present significant complications, at the time of the procedure as well as subsequently. Extubation failure, resulting in the need for reintubation, may occur in 2-25% of patients undergoing extubation [1]. It has been shown that ineffective cough and abundance of secretions are frequent causes of extubation failure, which may occur in spite of a successful outcome of the spontaneous breath test [2]. Prolonged bed rest, administration of sedatives, and persistence of airway inflammation may concur to bronchial encumbrance, thus reducing the chances of successful extubation [3].

Cough assist is an airway clearance device that, thanks to the inspiratory and expiratory flow, may represent a valuable aid to help patients with ineffective cough eliminate secretions and facilitate bronchial clearance, replacing physiological cough.

Although this technology has been introduced in the routine management of many chronic respiratory diseases, its use in the acute setting, and specifically in critical area to ease extubation, has been poorly explored. A few studies examining this topic were limited by thesmall sample size:therefore, this technique has not been established in current guidelines of extubation.

The purpose of this review and meta-analysis was to determine the effectiveness of cough assist in improving success rates of extubation of Intensive Care Unit (ICU) adult patients, comparedwith standard treatment with only conventional therapy: bronchoaspiration, respiratory rehabilitation, and post-extubation Non-Invasive Mechanical Ventilation(NIV).

METHODS

Data sources and search strategy

The study followedthe PRISMA checklist. The quality of the included studies was assessed with the Cochrane risk of bias (ROB2) tool for randomized trials.

A systematic literature search of medical literature was undertaken, consulting the Pubmed (MEDLINE), EMBASE, Cochrane database of systematic reviews, CINAHL, and PROSPERO databases for studies published until 31July 2021.

The research string included a combination of the following keywords and connectors:
("Cough * assist *" OR "cough * augment *" OR "in-exsufflat *" OR "insufflat * exsufflat *" OR "MI-E" OR "mechanic * insufflat * exsufflat *" OR "airway clearance device" OR "mechanic * insufflat *" OR "mechanic * exsufflat *" OR "mechanic * cough" OR "cough * aid *") AND (extubat * OR "intensive care unit" OR "artificial air way" OR "ventilat * weaning" OR "impaired air way clearance "OR" endotracheal tube "OR intubat *) NOT pediatr * NOT child *

Study selection

Two authors (LP and GM)examined independently the studies for eligibility, according to the following criteria:

- Randomized Clinical Trial (RCT) design, with either parallel arms or crossover.
- Participants aged ≥18 years.
- Admissiontoan Intensive Care Setting.
- Presence of orotracheal tube.
- Mechanical ventilation for at least > 24 h.
- Experimental intervention represented by cough assist, alone or in addition to conventional therapy.
- Control treatment represented by chest physical therapy and/or endotracheal suctioning and/or NIV.

Except for COVID-19, which was considered as an exclusion criterion, all diagnoses were accepted.

Outcomes

Outcomes representing the efficacy of the cough assist were selected: quantity and quality of secretions (weight, volume, and density), reintubation, and indices of thoraco-pulmonary function, such as airway resistance and static compliance.

Statistical analysis

Crossover studies were analyzed as parallel arms RCT. Outcome measures represented by continuous variables, collected at the end of the intervention, were extracted as mean±SD, separately for the experimental and the control groups, and reported on an electronic form. Where measures were reported as median and interquartile range, mean and standard deviation were calculated as (q1+median+q3)/3 and (q3-q1)/1.35, respectively. Cohen's d estimator, representing the effect size (ES) of the intervention as the difference in the final values in each study group divided by their pooled SD, was calculated, together with its 95% confidence interval (CI). For the dichotomous outcome "reintubation", the relative risk (RR) was calculated, with corresponding 95% CI.
The results of the different studies were combined according to the Der Simonian-Laird random effects model. Non-cumulability (heterogeneity) of results between different studies was assessed using the Cochran Q test.
Data analysis was conducted with the Stats direct software. Protection against type I error was set at α = 0.05.

RESULTS

The search string produced 764 studies, of which 737 were excluded after reading title and abstract, with full agreement between the two independent researchers. Out of the 27 studies examined in full-text, the same researchers fully agreed on exclusion of22 articles, because they did not fulfil the selection criteria: thus,5 studies were eventually considered eligible for the review (Figure 1).

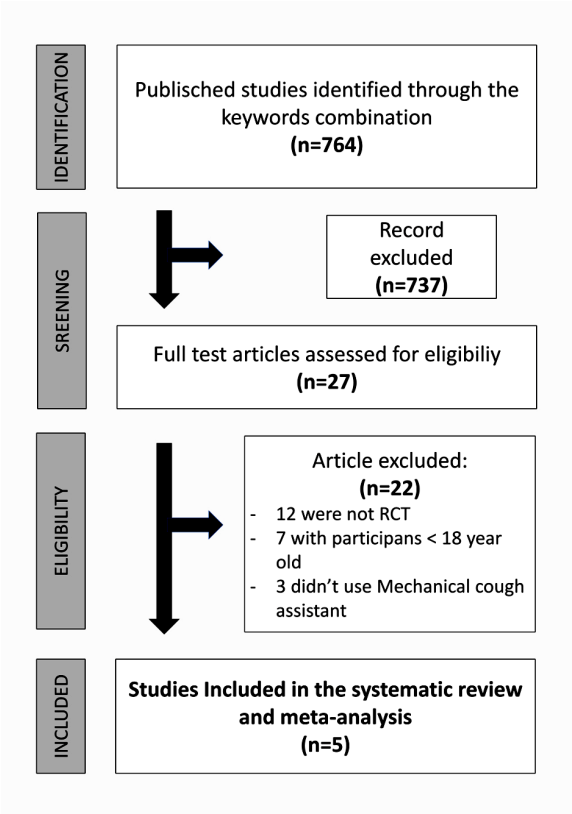

Figure 1: flowchart of literature search and included studies based on inclusion criteria.

The 5 studies selected for the meta-analysis were published between 2016 and 2018 and included 3 parallel arms RCTs [4, 5, 6] and 2 crossover studies [7,8].Overall, they enrolled a total of 331 participants (Table1), with sample sizes ranging from 10 and 180 individuals in the individual studies.
All patients were aspirated as needed and after cough assistant treatment. Participants in the control group received respiratory physiotherapy and manual cough assistance in all studies but one [8], in which only bronchial aspiration was performed. Moreover, Goncalves performed non-invasive ventilation as needed in both groups (Table1).

Of the different outcomes considered the five included studies, secretion weight or volume,reintubation, airway resistance, and static compliance were evaluated in this review (Table 1).

AUTHOR	YEAR	n. PARTICIPANTS		MV	INTERVENTION	CONTROL	UTCOME				
		Inter.	Contr.				secretions		reintubation	airways resistance	Static compliance
							Weight	Volume			
Alejoss	2016	10	10	48	CPT + BA + MCA: IpEp± 40 cm H_2O It 3" Et 2" B 1" 4 series of 5 cycles	CPT + BA		X		X	X
Coutinho	2016	43	43	48	BA + MCA: IpEp± 40 cm H_2O It 3" Et 3" no B 5 series of 4 cycles	BA	X				
De Camillis	2018	90	90	24	BA + MCA: IpEp± 40 cm H_2O It 3" Et 2" B 2" 3 series of 10 cycles	CPT + BA	X			X	X
Goncalves	2012	35	40	48	NIV* + BA + MCA: IpEp± 40 cm H_2O It 3" Et 2" B 3" 3 session/day *when necessary	CPT + BA NIV*			X		
Wibart	2016	61	62	48	CPT + BA + MCA: Non specified: IpEp, It, Et, B, series	CPT + BA			X		

MV: minimal duration of Mechanical Ventilation, in hours – **CPT**: Chest Physical Therapy – **BA**: Bronchial Aspiration – **NIV**: Non Invasive Ventilation
IpEp: inspiratory and Espiratory pressure – **It**: Inspiratory time – **Et**: Espiratory time – **B**: Break time

Table 1 *Summary table of the characteristics of the included studies with: population, intervention, control, outcome.*

The methodological quality of the studies (Figure 2) was assessed with the Cochrane risk of bias tool for RCTs.No study clearly specified blinding of the investigator. Four studies [4, 5, 7, 8] were free of attrition bias, whereas again four [4, 5, 6, 8] were found to be at low risk of reporting bias.In one study [8] results on dynamic lung compliance outcomes and pulmonary resistance were notdescribed completely. No study provided information to evaluate other types of bias, so that the evaluation in this case was "unclear".

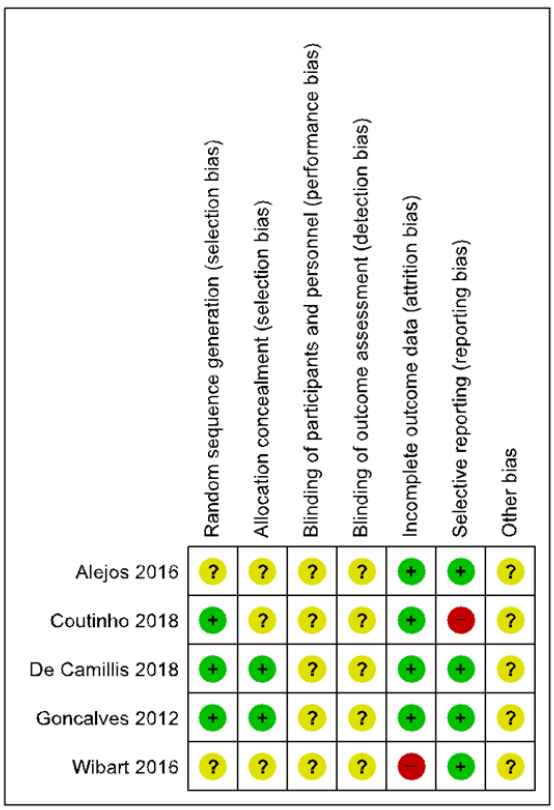

Figure 2*: risk of bias*

Meta-analysis

Assignment to treatment with cough assist, evaluated in 3 studies, increased significantly secretion weight, as indicated by an ES (95% CI) of 0.49 (0.25, 0.72), which was associated with a p value <0.001 and low heterogeneity (Q = 0.99, p = 0.600) (Figure 3). On the contrary, cough assist did not reduce the risk of reintubation, considered in 2 studies, as assessed from a pooled relative risk of 0.73 (0.14, 3.89), with p = 0.71 and some heterogeneity (Q = 3.41, p = 0.06) (Figure 4). Also the results on airway resistance and compliance, both considered in 2 studies, were non-significant, as indicated by ESs of -0.25 (-0.53, 0.02) with p = 0.07 and no heterogeneity (Q = 0.04, p = 0.83) and of 0.05 (-0.22, 0.33) with p = 0.71 and no heterogeneity (Q = 0.18, p = 0.67), respectively.

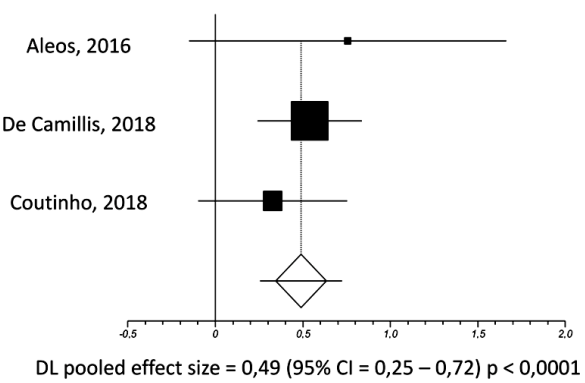

Figure 3*.Metanalysis of the weight of secretions.*

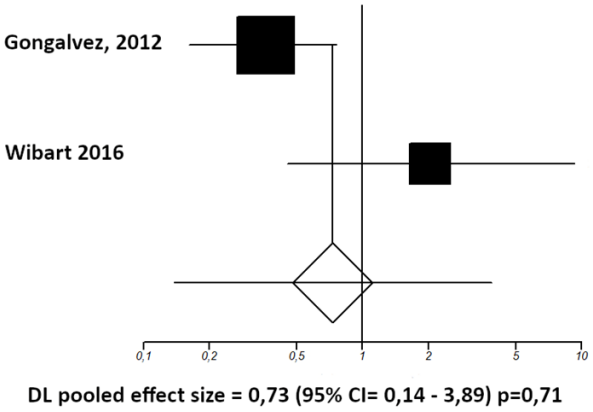

Figure 4.Metanalysis of the risk of reintubation.

DISCUSSION

This meta-analysis of 5 RCTs shows that the cough assist device is effective in increasing the amount of secretions removed from the bronchial tree in adult patients with prolonged intubation and mechanical ventilation.Decrease in airway resistance was close to statistical significance, whereas no significant difference was observed in change in compliance and in risk of reintubation.

The search for predictors of extubation failure is a majortopic in ICU research. It is estimated that, among patients with prolonged ICU stay, about 85% have failed extubation, with a consequent increase in comorbidity and costs [9].Excess secretions has been lengthy recognized as an important factor in the outcome of extubation[10, 11].Mokhlesiet al. [12] wrote that the evaluation of endotracheal secretions, patient's mental state and pre-extubation PaCO2 could be used to predict extubation failure even in patients who had successfully passed a spontaneous breathing trial. In substantial agreement, Kulkarni et al.[13] stated that the efficacy of coughing, the reduced amount of secretions and an adequate state of vigilance are necessary prerequisites for successful extubation, andSmina et al.[14]reported that cough capacity, measured objectively, is a major predictor of extubationfailure.Other studiesunderlined that extubation failure is often mediated by an ICU-associated "acquired weakness", which is frequently observed in individuals undergoing prolonged mechanical ventilation and limits at the same time the ability to mobilize adequate air volumes through the lungs and to clear the airways through effective coughing [15].

To overcome the problems associated with poor airways clearance,mechanical cough assist devices have been introduced, with time adapting to a growing range of applicationsin different rehabilitation areas [16,17].In a recent review [9], the utility of cough stimulator toolshas been emphasized, to either prevent orotracheal intubation or avoid intubation.

On the other hand, evidence is more limited on the use of the cough assist in mechanically ventilated patients. Yet, this issue is increasingly debated, also because of the variety of techniques and applications that have been developed.The device was initially used only in patients unable to produce effective cough because of neuromuscular disorders [18], in whom it represented a real prosthesis, as it completely replaced an absent function. Nowadays, a new and broader vision of cough assist stems from its use in the ICU area, where its task has become supporting a deficient function. Therefore, the time has come to understand if cough assist can be really useful in improving patient's clinical status and reducing the risk of reintubation [17, 19, 20].

This work was done with this goal in mind.Only five articles, all published between 2012 and 2018,fulfilled our selective search string with no time limit, confirming that the topic has gained relevance only in recent years. The selected articles shared a limited number of outcomes, of which only the amount of secretions gave fully satisfactory results, showing that cough assists effectively improves airways clearance. Airways resistance, which is somehow associated with bronchial secretions, had a positive trend, whereas compliance and reintubation were far from statistical significance.Since reintubation is a major clinical event that must be prevented, it is highly recommended that it be included as an outcome measure in future studies.

It should be noted that insufflation and exsufflation pressures were set in a very wide range,between +40 and -40 cmH2O. This variability might have contributed to the heterogeneity of the findings across the study selected. None of the studies included in the meta-analysis reported adverse effects from the use of the cough assist.

Limitations of this study mostly stem from those of the available literature, such as the small number of studies on the topic, the different outcomes across the studies, and the unclear protocol for cough assistapplication in some studies. Yet, our study represents a first step towards rigorous evaluation on cough assist devices, applied to promote successful extubation in ICU patients: as such, our work drawscurrent state of the art and suggests the need for future, high quality studies.

CONCLUSIONS

New methods and techniques are nowadays actively searched in many centers around the world to improve the outcome of extubation and avoid reintubation. The available literature, systematically reviewed and meta-analyzed in this study, suggests that cough assistant might contribute to successful extubation in ICU patients, by improving airway clearance. Studies with larger sample sizes,clearly-defined protocols and outcomes are required to obtain conclusive evidence. We hope that this meta-analysis will stimulate research on this field.

REFERENCES

1. *Epstein, S. Decision to extubate. Intensive Care Med. 2002; 28: 535-46.*
2. *Khamiees M. et al. Predictors of extubation outcome in patients who have successfully completed a spontaneous breathing trial. Chest. 2001: 1262-70.*
3. *ArtimeC. Tracheal extubation.Resèir Care. 2014; 59:991-1002.*
4. *De Camillis M. L. F. et al. Effects of mechanical insufflation-exsufflation on airway mucus clearance among mechanically ventilated ICU subjects. Respir Care. 2018; 63: 1471-7.*
5. *Gonçalves, M. R., Honrado, T., Winck, J. C., & Paiva, J. A. Effects of mechanical insufflation-exsufflation in preventing respiratory failure after extubation: a randomized controlled trial. Critical Care. 2021; 12: 16.*
6. *Wibart, P. Contribution of mechanical in-exsufflation (MI-E) device in preventing post-extubation respiratory failure in patient with critical illness polyneuromyopathy (CIP) neuromie. Am J Respir Crit Care Med. 2016; 193: A7652.*
7. *Martinez Alejos, R. et al.Effects of mechanical insufflation-exsufflation on sputum volume in mechanically ventilated critically ill subjects. Respir Care. 2021. 08641.*
8. *Coutinho W. et al. Comparison of mechanical insufflation–Exsufflation and endotracheal suctioning in mechanically ventilated patients: Effects on respiratory mechanics, hemodynamics, and volume of secretions. Indian J Crit Care Care Med. 2018; 22: 485-90.*
9. *Swingwood E., Stilma W. The use of mechanical insufflations-exsufflation in invasively ventilated critically ill adults:a scoping review protocol. Syst Rev. 2020; 8: 287.*
10. *Salam A., Tilluckdharry L., Amoateng-Adjepong Y., Manthous C.A. Neurologic status, cough, secretions and extubationoutcomes. Int Care Med. 2004; 30: 1334-9.*
11. *El Solh A.A. et al. Extubation failure in the elderly. Respir Med. 2004; 98:661-8.*
12. *Mokhlesi B. et al. Predicting extubation failure after successful completionof a spontaneous breathing trial. Respir Care. 2007;52: 1710 –17.*
13. *Kulkarni Atul, P. Extubation failure in intensive care unit: Predictorsand management. Indian J Crit Care Care Med. 2008; 12: 1-9.*
14. *Smina M. et al. Cough peak flows and extubation outcomes. Chest. 2003; 124: 262-8.*
15. *Bittner A. et al. Measurement of muscle strength in the intensive care unit. Crit Care Med. 2009; 37:221-30.*
16. *Salam A., Tilluckdharry L., Amoateng-Adjepong Y., Manthous C.A. Neurologic status, cough, secretions and extubationoutcomes. Int Care Med. 2004; 30: 1334-9.*
17. *El Solh A.A. et al. Extubation failure in the elderly. Respir Med. 2004; 98:661-8.*
18. *Mokhlesi B. et al. Predicting extubation failure after successful completionof a spontaneous breathing trial. Respir Care. 2007;52:1710 –17.*
19. *Andrani F. et al. Cough, a vital reflex. mechanisms, determinants and measurements. Acta Biomed. 2019; 15: 477-80.*
20. *Epstein S. K., &Ciubotaru R. L. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. Am J Respir Crit Care Med. 1998; 158: 489-93.*
21. *Bach J. R., Ishikawa Y., & Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. Chest. 1997; 112:1024-8.*
22. *BolesJ.-M. et al. Weaning from mechanical ventilation. Eur Respir J; 29:1033-56.*
23. *Roeseler J. et al. Chest physiotherapy in intensive care. Reanimation; 16: 33-41.*